Uttar Pradesh Rajarshi Tandon Open University

Bachelor of Science

DCEZY- 108

Developmental Biology

DCEZY-108

Developmental Biology

Uttar Pradesh Rajarshi Tandon

Open University

Bachelor of Science

Block

1 Developmental Biology - I

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COURSE INTRODUCTION

The objective of this course deals basic introduction to developmental biology in concerned to asexual reproduction, metamorphosis, regeneration and growth & ageing. The aim is to provide brief introduction of different concepts of sexual reproduction and practical aspects of parthenogenesis. The course is organized into following two blocks.

Block-I & Block II

Block I has four units in which you are going to study developmental biology I (fission, budding, gemmule formation, gametogenesis, parthenogenesis, metamorphosis).

Block II has four units in which you are going to study developmental biology II (Moulting, Regeneration Growth and aging)

Block I (Developmental Biology- I)

The block 1st is organized into following four units as under:

Unit-1

It covers the asexual reproduction (fission, budding, gemmule formation). The division of the cells into two daughter cells is known as binary fission. The formation of new bnd from the parent organism in known as budding. Gemmules are internal buds found in sponges and are involved in asexual reproduction.

Unit-2

It deals the basic concepts of sexual reproduction (spermetogenesis, oogenesis and vitellogenesis). Spermatogenesis and oogenesis are both forms of gametogenesis, the production of sperm (spermatogenesis) and eggs (oogenesis). Spermatogenesis is the process by which haploid spermatozoa develop from germ cells in the seminiferous tubules of the testis. Oogenesis is the process of producing the female gametes. It is the type of gametogenesis through which ova or the female gametes are formed. Vitellogenesis is the process of yolk formation

Unit-3

It describes the basic properties parthenogenesis. Parthenogenesis is the type of asexual reproduction involving the development of female gametes without any fertilization.

Unit-4

It covers the metamorphosis (morphogenetic processes and tissue reactivity). Metamorphosis is a biological process by which an animal physically develops after birth or hatching, involving a conspicuous and relatively abrupt charge in the animal body, metamorphosis occurs in animals such as amphibians insects and fish.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about developmental processes
- To discuss about sexual and asexual reproduction
- To know about morphogenetic processes
- To discuss about spermatogenesis and oogenesis
- To discuss about vitellogenesis and types of parthenogenesis**,** metamorphosis

Unit-1 Asexual reproduction (fission, budding, gemmule formation)

Structure

1.1 Introduction

Developmental biology is the study of the process by which animals and plants grow and develop. Developmental biology also encompasses the biology of regeneration, asexual reproduction, metamorphosis, and the growth and differentiation of stem cells in the adult organism. Developmental biology is a great field for scientists who want to integrate different levels of biology. We can take a problem and study it on the molecular and chemical levels (e.g., How are globin genes transcribed, and how do the factors activating their transcription interact with one another on the DNA), on the cellular and tissue levels (Which cells are able to make globin, and how does globin mRNA leave the nucleus), on the organ and organ system levels (How do the capillaries form in each tissue, and how are they instructed to branch and connect), and even at the ecological and evolutionary levels (How do differences in globin gene activation enable oxygen to flow from mother to fetus, and how do environmental factors trigger the differentiation of more red blood cells).

Developmental biology is one of the fastest growing and most exciting fields in biology, creating a framework that integrates molecular biology, physiology, cell biology, anatomy, cancer research, neurobiology, immunology, ecology, and evolutionary biology. The study of development has become essential for understanding any other area of biology.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about developmental processes
- To discuss about asexual reproduction
- To know about morphogenetic processes
- To discuss about gemmule formation
- To know about fission, budding, blastogenesis and embryogenesis

The main processes involved in the embryonic development of animals are: tissue patterning (via regional specification and patterned cell differentiation); tissue growth; and tissue morphogenesis.

- Regional specification refers to the processes that create spatial pattern in a ball or sheet of initially similar cells. This generally involves the action of cytoplasmic determinants,

located within parts of the fertilized egg, and of inductive signals emitted from signaling centers in the embryo. The early stages of regional specification do not generate functional differentiated cells, but cell populations committed to develop to a specific region or part of the organism. These are defined by the expression of specific combinations of transcription factors.

- Cell differentiation relates specifically to the formation of functional cell types such as nerve, muscle, secretory epithelia etc. Differentiated cells contain large amounts of specific proteins associated with the cell function.
- Morphogenesis relates to the formation of three-dimensional shape. It mainly involves the orchestrated movements of cell sheets and of individual cells. Morphogenesis is important for creating the three germ layers of the early embryo (ectoderm, mesoderm and endoderm) and for building up complex structures during organ development.
- Tissue growth involves both an overall increase in tissue size, and also the differential growth of parts (allometry) which contributes to morphogenesis. Growth mostly occurs through cell proliferation but also through changes of cell size or the deposition of extracellular materials.

The development of plants involves similar processes to that of animals. However plant cells are mostly immotile so morphogenesis is achieved by differential growth, without cell movements. Also, the inductive signals and the genes involved are different from those that control animal development.

1.2 Developmental processes

1.2.1 Cell differentiation

Cell differentiation is the process whereby different functional cell types arise in development. For example, neurons, muscle fibers and hepatocytes (liver cells) are well known types of differentiated cells. Differentiated cells usually produce large amounts of a few proteins that are required for their specific function and this gives them the characteristic appearance that enables them to be recognized under the light microscope. The genes encoding these proteins are highly active. Typically their chromatin structure is very open, allowing access for the transcription enzymes, and specific transcription factors bind to regulatory sequences in the DNA in order to activate gene expression. For

example, NeuroD is a key transcription factor for neuronal differentiation, myogenin for muscle differentiation, and HNF4 for hepatocyte differentiation.

Cell differentiation is usually the final stage of development, preceded by several states of commitment which are not visibly differentiated. A single tissue, formed from a single type of progenitor cell or stem cell, often consists of several differentiated cell types. Control of their formation involves a process of lateral inhibition, based on the properties of the Notch signaling pathway. For example, in the neural plate of the embryo this system operates to generate a population of neuronal precursor cells in which NeuroD is highly expressed.

1.2.2 Regeneration

Regeneration indicates the ability to regrow a missing part. This is very prevalent amongst plants, which show continuous growth, and also among colonial animals such as hydroids and ascidians. But most interest by developmental biologists has been shown in the regeneration of parts in free living animals. In particular four models have been the subject of much investigation. Two of these have the ability to regenerate whole bodies: *Hydra*, which can regenerate any part of the polyp from a small fragment, and planarian worms, which can usually regenerate both heads and tails. Both of these examples have continuous cell turnover fed by stem cells and, at least in planaria, at least some of the stem cells have been shown to be pluripotent.

The other two models show only distal regeneration of appendages. These are the insect appendages, usually the legs of hemimetabolous insects such as the cricket, and the limbs of urodele amphibians. Considerable information is now available about amphibian limb regeneration and it is known that each cell type regenerates itself, except for connective tissues where there is considerable interconversion between cartilage, dermis and tendons. In terms of the pattern of structures, this is controlled by a re-activation of signals active in the embryo. There is still debate about the old question of whether regeneration is a "pristine" or an "adaptive" property. If the former is the case, with improved knowledge, we might expect to be able to improve regenerative ability in humans. If the latter, then each instance of regeneration is presumed to have arisen by natural selection in circumstances particular to the species, so no general rules would be expected.

1.2.3 Asexual reproduction

Asexual reproduction is a mode of reproduction in which a new offspring is produced by a single parent. The new individuals produced are genetically and physically identical to each other, i.e., they are the clones of their parent. Asexual reproduction is observed in both multicellular and unicellular organisms. This process does not involve any kind of gamete fusion and there won't be any change in the number of chromosomes either. It will inherit the same genes as the parent, except for some cases where there is a chance of rare mutation to occur.It can be defined as;

"Asexual reproduction is the mode of reproduction that is involved in the production of offsprings by a single parent."

1.3 Characteristics of Asexual Reproduction

Following are the important features of asexual reproduction:

- ✓ Single parent involved.
- ✓ No fertilization or gamete formation takes place.
- ✓ This process of reproduction occurs in a very short time.
- ✓ The organisms multiply and grow rapidly.
- ✓ The offspring is genetically similar.

1.3.1 Types of Asexual Reproduction

There are different types of asexual reproduction:

- Binary Fission
- Budding
- Fragmentation
- Vegetative Propagation
- Sporogenesis

1.3.2 Morphogenetic process

Morphogenesis (from the Greek *morphê* shape and *genesis* creation, literally "the generation of form") is the biological process that causes a cell, tissue or organism to develop its shape. It is one of three fundamental aspects of developmental biology along with the control of tissue growth and patterning of cellular differentiation. The process controls the organized spatial distribution of cells during the embryonic development of an organism. Morphogenesis can take place also in a mature organism, such as in the normal maintenance

of tissue by stem cells or in regeneration of tissues after damage. Cancer is an example of highly abnormal and pathological tissue morphogenesis.

Morphogenesis also describes the development of unicellular life forms that do not have an embryonic stage in their life cycle. Morphogenesis is essential for the evolution of new forms. Morphogenesis is a mechanical process involving forces that generate mechanical stress, strain, and movement of cells, and can be induced by genetic programs according to the spatial patterning of cells within tissues.

Morphogenesis**,** the shaping of an organism by embryological processes of differentiation of cells, tissues, and organs and the development of organ systems according to the genetic "blueprint" of the potential organism and environmental conditions. Plant morphogenesis is brought about chiefly through differential growth. Permanent embryonic tissue results in a morphogenetic potential that varies greatly with the environment and continues to produce new organs throughout the life of the plant. Animal morphogenesis is accomplished by growth and by cell movement. A fixed pattern is established early; the organism is determined as to shape, size, and organ complement. Once organs are formed, no new ones (with few exceptions) are produced.

1.4 History

Some of the earliest ideas and mathematical descriptions on how physical processes and constraints affect biological growth, and hence natural patterns such as the spirals of phyllotaxis, were written by D'Arcy Wentworth Thompson in his 1917 book On Growth and Form and Alan Turing in his The Chemical Basis of Morphogenesis (1952). Where Thompson explained animal body shapes as being created by varying rates of growth in different directions, for instance to create the spiral shell of a snail, Turing correctly predicted a mechanism of morphogenesis, the diffusion of two different chemical signals, one activating and one deactivating growth, to set up patterns of development, decades before the formation of such patterns was observed. The fuller understanding of the mechanisms involved in actual organisms required the discovery of the structure of DNA in 1953, and the development of molecular biology and biochemistry.

1.4.1 Blastema

Blastema, also called Regeneration Bud, in zoology, a mass of undifferentiated cells that has the capability to develop into an organ or an appendage. In lower vertebrates the blastema is particularly important in the regeneration of severed limbs. In the salamander, for example,

tissues in the stump of a limb dedifferentiate—that is, they lose their individual characteristics—and revert to an embryonic appearance. Under the influence of regenerating nerve fibres, they will form a blastema, a mound of cells resembling the original limb bud, from which the replacement limb gradually emerges.

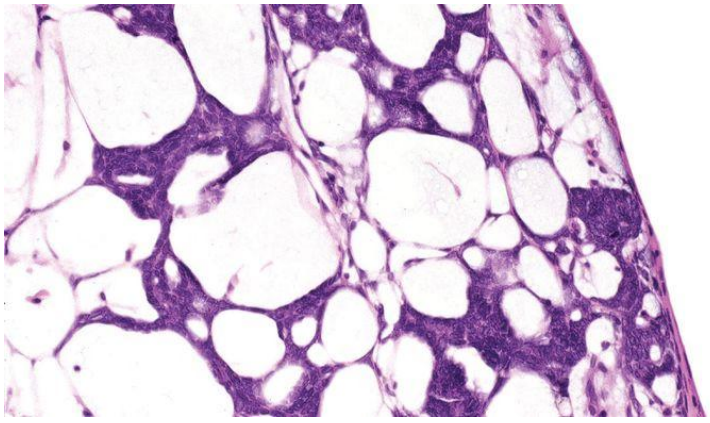


Fig. 1 Blastema cells surrounded by transparent cystic spaces

In some invertebrates, such as flatworms, reserve cells scattered throughout the body supply the cells of blastemas. In vertebrates, dedifferentiated skin and muscle cells at the site of a wound constitute the developing blastema. If for any reason the regenerating nerve fibres are damaged or destroyed, the blastema will fail to develop and scar tissue will form instead.

1.4.2 Blastogenesis

Normal human development begins with blastogenesis in the first 4 weeks after fertilization. This is followed by 4–5 weeks of organogenesis, which involves both morphogenesis and histogenesis. These embryonic organs continue to grow and differentiate during subsequent fetal development. These processes are regulated by a finite number of developmental genes and pathways, the temporal and spatial expression of which are tightly regulated through control of gene expression at different developmental time points in different tissues or organs although there are some redundancies due to the presence of paralogous genes. Mutations in these developmental genes result in a variety of congenital malformations that may be explained through an understanding of the functions and the timing of the expression of these genes. Most organs that are malformed are histologically normal and hence not at risk of malignancies; however, abnormal histogenesis in a dysmorphogenetic organ might result in malignancy.

1.4.3 Blastozooids

It is a member of a colony of animals which are produced by asexual budding. Asexual reproduction occurs in prokaryotic microorganisms (bacteria) and in some eukaryotic single-

celled and multi-celled organisms. Asexual reproduction produces offspring that are genetically identical to the parent because the offspring are all clones of the original parent. A single individual can produce offspring asexually and large numbers of offspring can be produced quickly.

In a stable or predictable environment, asexual reproduction is an effective means of reproduction because all the offspring will be adapted to that environment. In an unstable or unpredictable environment asexually-reproducing species may be at a disadvantage because all the offspring are genetically identical and may not have the genetic variation to survive in new or different conditions. On the other hand, the rapid rates of asexual reproduction may allow for a speedy response to environmental changes if individuals have mutations. An additional advantage of asexual reproduction is that colonization of new habitats may be easier when an individual does not need to find a mate to reproduce. There are a number of ways that animals reproduce asexually.

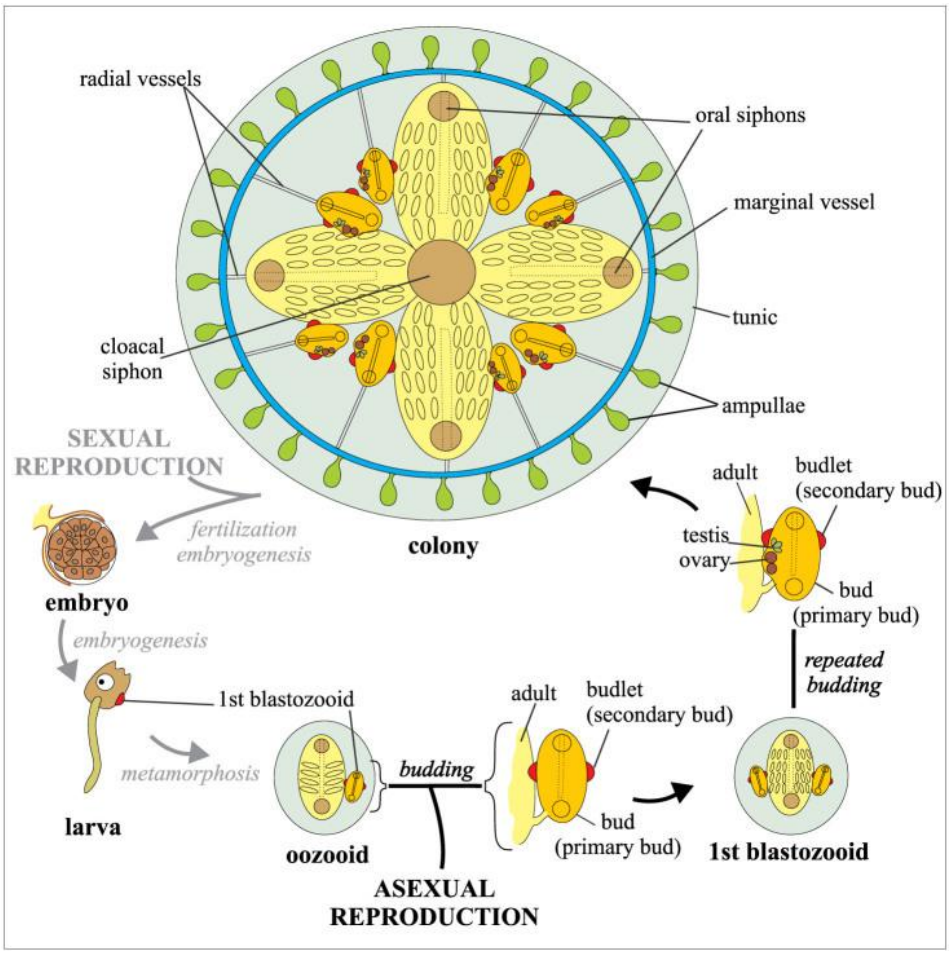


Fig. 2 Ozooid and blastozooids are shown in a dorsal view. A colony is represented as formed by a single system of four adult blastozooids each bearing two buds, that in turn bear two budlets

1.4.4 Fission

The term “fission” means “to divide”. During binary fission, the parent cell divides into two cells. The cell division patterns vary in different organisms, i.e., some are directional while others are non-directional. Amoeba and euglena exhibit binary fission. It is one of the simplest and uncomplicated methods of asexual reproduction. The parent cell divides into two, each daughter cell carrying a nucleus of its own that is genetically identical to the parent. The cytoplasm also divides leading to two equal-sized daughter cells. The process repeats itself and the daughter cells grow and further divide.

1.5 Fission of prokaryotes

The single DNA molecule first replicates, then attaches each copy to a different part of the cell membrane. When the cell begins to pull apart, the replicated and original chromosomes are separated. The consequence of this asexual method of reproduction is that all the cells are genetically identical, meaning that they have the same genetic material (barring random mutations). Unlike the processes of mitosis and meiosis used by eukaryotic cells, binary fission takes place without the formation of a spindle apparatus on the cell. Like in mitosis (and unlike in meiosis), the parental identity is lost.

1.5.1 Process of FtsZ-dependent fission

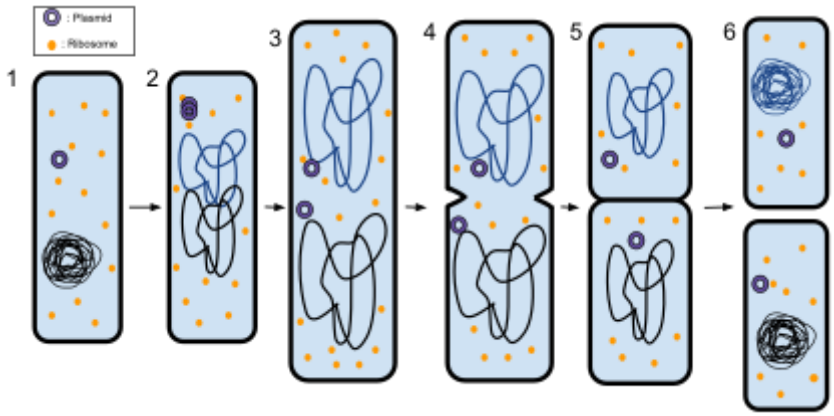


Fig. 3 Binary fission in a prokaryote

FtsZ is homologous to β-tubulin, the building block of the microtubule cytoskeleton used during mitosis in eukaryotes. FtsZ is thought to be the first protein to localize to the site of future division in bacteria, and it assembles into a Z ring, anchored by FtsZ-binding proteins and defines the division plane between the two daughter cells. MinC and MinD function

together as division inhibitors, blocking formation of the FtsZ ring. MinE stops the MinCD activity midcell, allowing FtsZ to take over for binary fission.

More specifically, the following steps occur:

1. The bacterium before binary fission is when the DNA is tightly coiled.
2. The DNA of the bacterium has uncoiled and duplicated.
3. The DNA is pulled to the separate poles of the bacterium as it increases the size to prepare for splitting.
4. The growth of a new cell wall begins to separate the bacterium (triggered by FtsZ polymerization and "Z-ring" formation)[7]
5. The new cell wall (septum) fully develops, resulting in the complete split of the bacterium.
6. The new daughter cells have tightly coiled DNA rods, ribosomes, and plasmids; these are now brand-new organisms.

Studies of bacteria made to not produce a cell wall, called L-form bacteria, shows that FtsZ requires a cell wall to work. Little is known about how bacteria that naturally don't grow a cell wall divides, but it is thought to resemble the L-form's budding-like division process of extrusion and separation.

1.6 Budding

Budding is a type of asexual reproduction in which a new organism develops from an outgrowth or bud due to cell division at one particular site. For example, the small bulb-like projection coming out from the yeast cell is known as a bud. Since the reproduction is asexual, the newly created organism is a clone and excepting mutations is genetically identical to the parent organism. Organisms such as hydra use regenerative cells for reproduction in the process of budding.

In hydra, a bud develops as an outgrowth due to repeated cell division at one specific site. These buds develop into tiny individuals and, when fully mature, detach from the parent body and become new independent individuals. Internal budding or endodyogeny is a process of asexual reproduction, favored by parasites such as *Toxoplasma gondii*. It involves an unusual process in which two daughter cells are produced inside a mother cell, which is then consumed by the offspring prior to their separation.

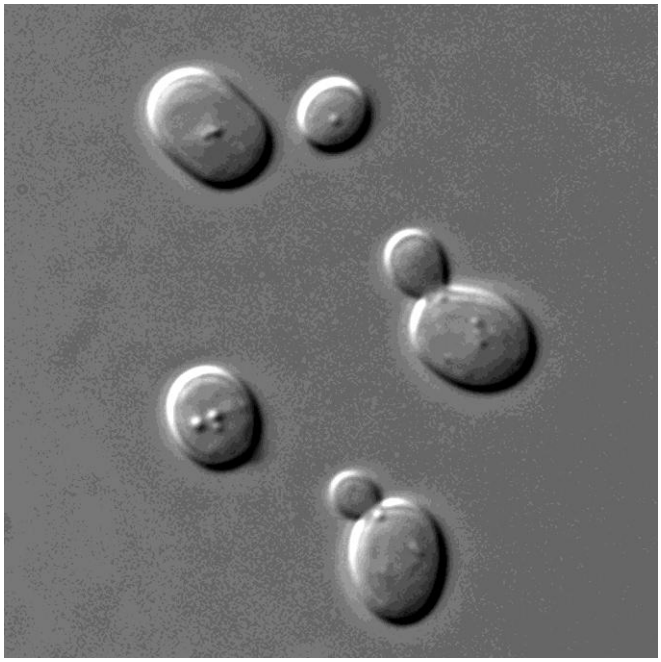


Fig. 4 Saccharomyces cerevisiae reproducing by budding

The new individual may separate to exist independently, or the buds may remain attached, forming aggregates or colonies. Budding is characteristic of a few unicellular organisms (e.g., certain bacteria, yeasts, and protozoans). However, a number of metazoan animals (e.g., certain cnidarian species) regularly reproduce by budding. In horticulture the term *budding* refers to a method of plant propagation in which a bud of the plant to be propagated is grafted onto the stem of another plant.

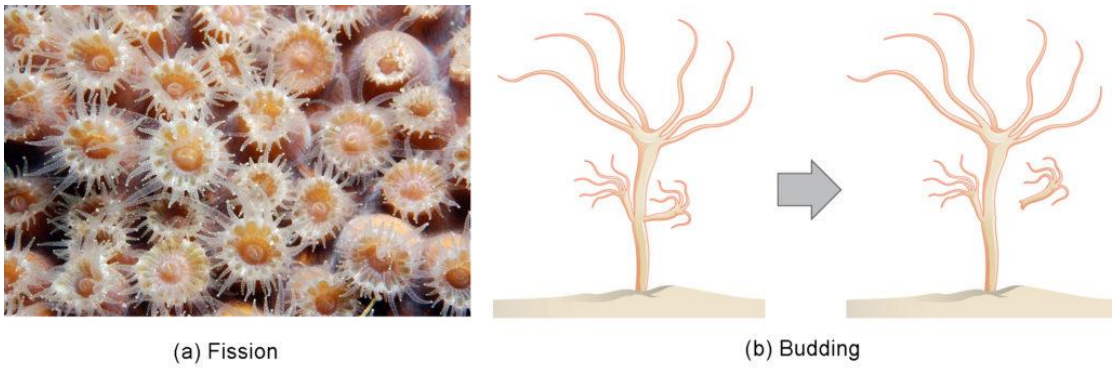


Fig. 5 Coral polyps reproduce asexually by fission. (b) Hydra reproduce asexually through budding

1.7 Gemmule

An asexually produced mass of cells, which are capable of developing into a new organism or into an adult freshwater sponge is termed as a Gemmule. They are small bud-like cells, which are formed by sponges to withstand unfavourable environmental conditions. A freshwater

sponge reproduces both by sexually and asexually. Asexual reproduction is mainly carried out by budding and also by gemmulation. The internal buds, which are formed by the freshwater sponges are called gemmules. These gemmules are tough and coated with a dormant cluster of embryonic cells. Freshwater sponges are multicellular, marine living species of a Kingdom Phylum – Porifera. The species of this kingdom includes sponges, Ficulina ficus, sea sponges and much more. All the species related to the same kingdom and carry the same characteristic features.

Fig. 6 The Role of Gemmule in Sponge Reproduction

The internal buds, gemmules are resistant to dehydration, freezing and can survive even without an oxygen supply. The outer layer of the gemmule is enclosed and protected with the endospore that is surrounded by a layer of spicules, which helps the gemmule from all other unfavourable environmental conditions and also helps gemmules in growing into an adult freshwater sponge.

Fig. 7. Gemmules are usually found in a round or a ball-like structure, along with a central mass of amoeboid cells and a thick peripheral layer of a small siliceous spicule.

The structure of Gemmules includes Micropyle, Spicule, Inner layer, Archaeocytes and an Outer pneumatic layer. The micropyle is an outer coat of a cell with a minute opening and the peripheral layer is made up of a thick pneumatic layer and air chambers, which helps gemmules to float in water bodies. The Archaeocytes are reproductive cells and the spicule is the sharp-pointed structure, which is involved in protecting the gemmules from predators and also provide structural support to the gemmules.

1.8 How are gemmule produced?

Gemmule is produced by few genus of freshwater sponges such as Spongilla and some marine species including ficulina ficus, sea sponges, and other poriferans, which produces gemmules to survive in the unfavourable conditions and to germinate and produce new sponges. During gemmule formation, the archaeocytes- totipotent cells, which are loaded with food material in the form of glycoprotein or lipoprotein get combined into a mass. An amoebocyte – a cell with motility, move and surround the central mass of archaeocytes and starts to secrete thick solid chitin around archaeocytes and forms a layer around it. Amphidisc spicules are secreted by sclera oblasts in between the internal and external membranes.

A completely formed gemmule is normal in size, hardball like structure, having a mass of food loaded with reproductive cells, which are embedded in a double membrane layered thick envelope with amphidisc spicules in between. There is a minute opening called Micropyle through which the cells come out during development in favourable conditions. During autumn, freshwater sponges die by leaving behind numerous gemmules. These gemmules produced by the sponges remain active by withstanding unfavourable environmental conditions both in winter and summer season. Gemmules begin to develop into new sponges when there is an availability of an abundance of water.

1.9 Blastogenesis

Normal human development begins with blastogenesis in the first 4 weeks after fertilization. This is followed by 4–5 weeks of organogenesis, which involves both morphogenesis and histogenesis. These embryonic organs continue to grow and differentiate during subsequent fetal development. These processes are regulated by a finite number of developmental genes and pathways, the temporal and spatial expression of which are tightly regulated through control of gene expression at different developmental time points in different tissues or organs although there are some redundancies due to the presence of paralogous genes. Mutations in these developmental genes result in a variety of congenital malformations that

may be explained through an understanding of the functions and the timing of the expression of these genes. Most organs that are malformed are histologically normal and hence not at risk of malignancies; however, abnormal histogenesis in a dysmorphogenetic organ might result in malignancy.

1.10 Embryogenesis

In developmental biology, animal embryonic development, also known as embryogenesis, is the developmental stage of an animal embryo. Embryonic development starts with the fertilization of an egg cell (ovum) by a sperm cell, (spermatozoon). Once fertilized, the ovum becomes a single diploid cell known as a zygote. The zygote undergoes mitotic divisions with no significant growth (a process known as cleavage) and cellular differentiation, leading to development of a multicellular embryo after passing through an organizational checkpoint during mid-embryogenesis.[3] In mammals, the term refers chiefly to the early stages of prenatal development, whereas the terms fetus and fetal development describe later stages.

The main stages of animal embryonic development are as follows:

- The zygote undergoes a series of cell divisions (called cleavage) to form a structure called a morula.
- The morula develops into a structure called a blastula through a process called blastulation.
- The blastula develops into a structure called a gastrula through a process called gastrulation.
- The gastrula then undergoes further development, including the formation of organs (organogenesis).

The embryo then transforms into the next stage of development, the nature of which varies between different animal species (examples of possible next stages include a fetus and a larva).

1.11 Differences between blastogenesis and embryogenesis

Blastogenesis is the formation of daughter individuals through budding, gemmation and other means of asexual reproduction. Embryogenesis is the production of individuals through fertilization of ovum and development of embryo. Embryology deals with the study of changes that involve embryogenesis or formation of zygote and its development upto the

birth of young one. The various steps of embryonic development are gametogenesis, gametes, fertilization, cleavage, blastulation, gastrulation, organogenesis, etc.

1.12 Summary

In this unit we summarize that the term morphogenesis generally refers to the processes by which order is created in the developing organism. This order is achieved as differentiated cells carefully organize into tissues, organs, organ systems, and ultimately the organism as a whole. Questions centered on morphogenesis have aimed to uncover the mechanisms responsible for this organization, and developmental biology textbooks have identified morphogenesis as one of the main challenges in the field. The concept of morphogenesis is intertwined with those of differentiation, growth, and reproduction. Each comprises the fundamental components of development that have commonly been used to categorize the problems that motivate developmental biology.

Fission is stated as the division of a single unit or cell into two or more parts. These parts regenerate to form a complete structure and resemble their parents. It is used mainly about the cell, but sometimes may also be used for organisms, species, etc. Binary fission is usually found in Bacteria but it is also present in a few eukaryotic organisms. It is of various types depending upon the direction of the fission. It may be irregular (fission takes place at any plane), longitudinal (fission occurs along the longitudinal axis), transverse (fission occurs along a transverse axis), and oblique (fission occurs obliquely).

New buds form externally on the body surface of the parent in budding, which is an asexual method of reproduction in yeasts, hydra and scypha. Gemmule formation, also known as internal budding, involves the formation of a mass of cells or gemmules inside the parent organism. Gemmule formation is a characteristic feature of sponges. The key difference between budding and gemmule formation is that buds develop externally while gemmules develop internally.

The basic developmental similarities between blastogenesis (development after asexual reproduction) and embryogenesis (development from the egg) are demonstrated. The development of different animals (Cnidaria, Bryozoa and Tunicata) was analyzed to show that such general embryological concepts as preformation, epigenesis, embryonic induction, recapitulation, phyloembryogenesis, palingenesis, coenogenesis, heterochrony, heterotropy, etc., apply to asexual reproduction as well.

1.13 Terminal questions

Q.1 What do you mean by asexual reproduction?

Answer:----------

Q.2 Describe blastema and blastogenesis stages.

Answer:----------

Q.3 Write a short note on fission and budding.

Answer:----------

Q.4 What do you mean by gemmule formation?

Answer:----------

Q.5 Compare between blastogenesis and embryogenesis?

Answer:----------

Q.6 Write a short note on blastozoides.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner
3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit 2 - Basic concepts of sexual reproduction (spermetogenesis, oogenesis and vitellogenesis)

Structure

2.1 Introduction

Sexual reproduction is a type of reproduction that involves a complex life cycle in which a gamete (such as a sperm or egg cell) with a single set of chromosomes (haploid) combines with another to produce a zygote that develops into an organism composed of cells with two sets of chromosomes (diploid). Sexual reproduction is the most common life cycle in multicellular eukaryotes, such as animals, fungi and plants. Sexual reproduction does not occur in prokaryotes (organisms without cell nuclei), but they have processes with similar effects such as bacterial conjugation, transformation and transduction, which may have been precursors to sexual reproduction in early eukaryotes.

Objectives

This is the second unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about sexual reproduction
- To discuss about spermatogenesis and oogenesis
- To know about maturation of gametes
- To discuss about vitellogenesis

In the production of sex cells in eukaryotes, diploid mother cells divide to produce haploid cells known as gametes in a process called meiosis that involves genetic recombination. The homologous chromosomes pair up so that their DNA sequences are aligned with each other, and this is followed by exchange of genetic information between them. Two rounds of cell division then produce four haploid gametes, each with half the number of chromosomes from each parent cell, but with the genetic information in the parental chromosomes recombined. Two haploid gametes combine into one diploid cell known as a zygote in a process called fertilisation. The zygote incorporates genetic material from both gametes. Multiple cell divisions, without change of the number of chromosomes, then form a multicellular diploid phase or generation.

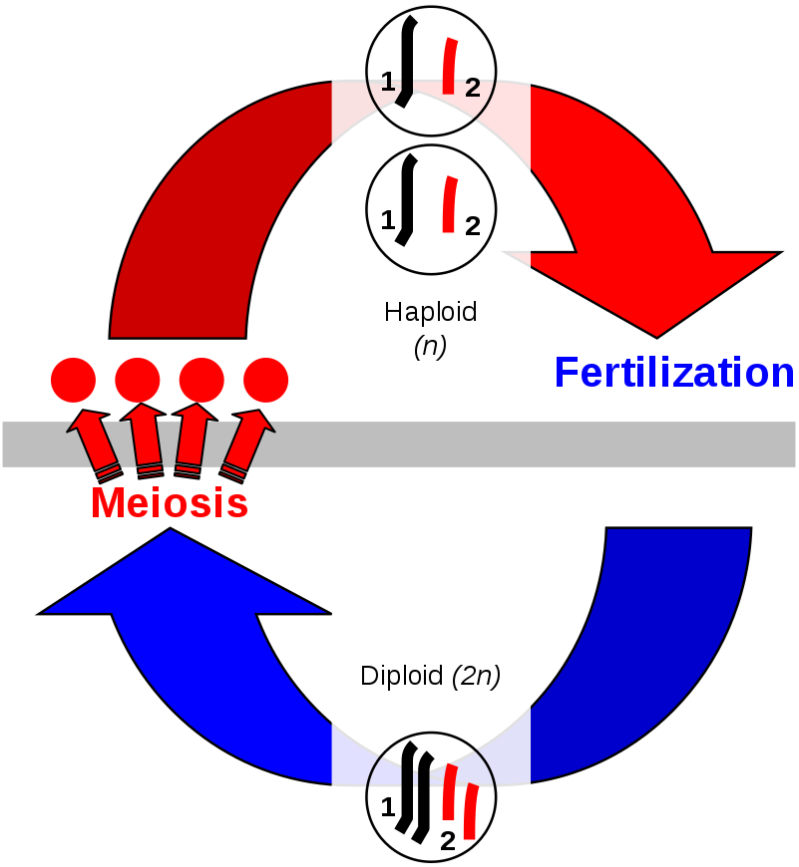


Fig. 1 In the first stage of sexual reproduction, "meiosis", the number of chromosomes is reduced from a diploid number (2n) to a haploid number (n).

In human reproduction, each cell contains 46 chromosomes in 23 pairs. Meiosis in the parents' gonads produces gametes that each contains only 23 chromosomes that are genetic recombinants of the DNA sequences contained in the parental chromosomes. When the nuclei of the gametes come together to form a fertilized egg or zygote, each cell of the resulting child will have 23 chromosomes from each parent, or 46 in total. In plants only, the diploid phase, known as the sporophyte, produces spores by meiosis that germinate and then divide by mitosis to form a haploid multicellular phase, the gametophyte, that produces gametes directly by mitosis. This type of life cycle, involving alternation between two multicellular phases, the sexual haploid gametophyte and asexual diploid sporophyte, is known as alternation of generations.

The evolution of sexual reproduction is considered paradoxical, because asexual reproduction should be able to outperform it as every young organism created can bear its own young. This implies that an asexual population has an intrinsic capacity to grow more rapidly with each generation. This 50% cost is a fitness disadvantage of sexual reproduction.

The two-fold cost of sex includes this cost and the fact that any organism can only pass on 50% of its own genes to its offspring. One definite advantage of sexual reproduction is that it impedes the accumulation of genetic mutations. Sexual selection is a mode of natural selection in which some individuals out-reproduce others of a population because they are better at securing mates for sexual reproduction. It has been described as "a powerful evolutionary force that does not exist in asexual populations."

2.2 Evolution

The first fossilized evidence of sexual reproduction in eukaryotes is from the Stenian period, about 1.05 billion years ago. Biologists studying evolution propose several explanations for the development of sexual reproduction and its maintenance. These reasons include reducing the likelihood of the accumulation of deleterious mutations, increasing rate of adaptation to changing environments, dealing with competition, DNA repair and masking deleterious mutations. All of these ideas about why sexual reproduction has been maintained are generally supported, but ultimately the size of the population determines if sexual reproduction is entirely beneficial. Larger populations appear to respond more quickly to some of the benefits obtained through sexual reproduction than do smaller population sizes.

Maintenance of sexual reproduction has been explained by theories that work at several levels of selection, though some of these models remain controversial. However, newer models presented in recent years suggest a basic advantage for sexual reproduction in slowly reproducing complex organisms. Sexual reproduction allows these species to exhibit characteristics that depend on the specific environment that they inhabit, and the particular survival strategies that they employ.

2.3 Sexual selection

In order to reproduce sexually, both males and females need to find a mate. Generally in animals mate choice is made by females while males compete to be chosen. This can lead organisms to extreme efforts in order to reproduce, such as combat and display, or produce extreme features caused by a positive feedback known as a Fisherian runaway. Thus sexual reproduction, as a form of natural selection, has an effect on evolution. Sexual dimorphism is where the basic phenotypic traits vary between males and females of the same species. Dimorphism is found in both sex organs and in secondary sex characteristics, body size, physical strength and morphology, biological ornamentation, behavior and other

bodily traits. However, sexual selection is only implied over an extended period of time leading to sexual dimorphism.

2.4 Animals

Insect species make up more than two-thirds of all extant animal species. Most insect species reproduce sexually, though some species are facultatively parthenogenetic. Many insects species have sexual dimorphism, while in others the sexes look nearly identical. Typically they have two sexes with males producing spermatozoa and females ova. The ova develop into eggs that have a covering called the chorion, which forms before internal fertilization. Insects have very diverse mating and reproductive strategies most often resulting in the male depositing spermatophore within the female, which she stores until she is ready for egg fertilization. After fertilization, and the formation of a zygote, and varying degrees of development, in many species the eggs are deposited outside the female; while in others, they develop further within the female and are born live.

2.5 Gametogenesis

Gametogenesis**,** in embryology, the process by which gametes, or germ cells, are produced in an organism. The formation of egg cells, or ova, is technically called oogenesis, and the formation of sperm cells, or spermatozoa, is called spermatogenesis. Gamete**,** sex, or reproductive, cell containing only one set of dissimilar chromosomes, or half the genetic material necessary to form a complete organism (i.e., haploid). Gametes are formed through meiosis (reduction division), in which a germ cell undergoes two fissions, resulting in the production of four gametes. During fertilization, male and female gametes fuse, producing a diploid (i.e., containing paired chromosomes) zygote.

Gametes may be identical in form (isogamy), as in certain species of algae, fungi, and protozoans, or there may be more than one morphological type (heterogamy, or anisogamy), as with many green algae of the genus *Chlamydomonas*. Gametes of animals, some algae and fungi, and all higher plants exhibit an advanced form of heterogamy called oogamy. In oogamy one of the gametes is small and motile (the sperm), and the other is large and nonmotile (the egg).

Gametogenesis is the production of gametes from haploid precursor cells. In animals and higher plants, two morphologically distinct types of gametes are produced (male and female) via distinct differentiation programs. Animals produce a tissue that is dedicated to forming gametes, called the germ line. Individual germline cells are called germ cells. During the process of gametogenesis, a germ cell undergoes meiosis to produce haploid cells that directly develop into gametes. Hence, in animals, meiosis is an integral part of gametogenesis. In plants, some fungi, and some algae, meiosis is temporally separated from gametogenesis. Diploid cells undergo meiosis to produce haploid spores, which give rise to a haploid generation called the 'gametophyte'.

Cells in the latter eventually develop into gametes, sometimes in response to environmental or chemical stimuli. Many unicellular and simple multicellular eukaryotes produce gametes from haploid cells many generations after meiosis or, in some species, immediately following meiosis. Although of opposite mating types, gametes in fungi, multicellular algae, and some protists are usually not morphologically distinct and are designated (+) or (–) rather than as egg or sperm.

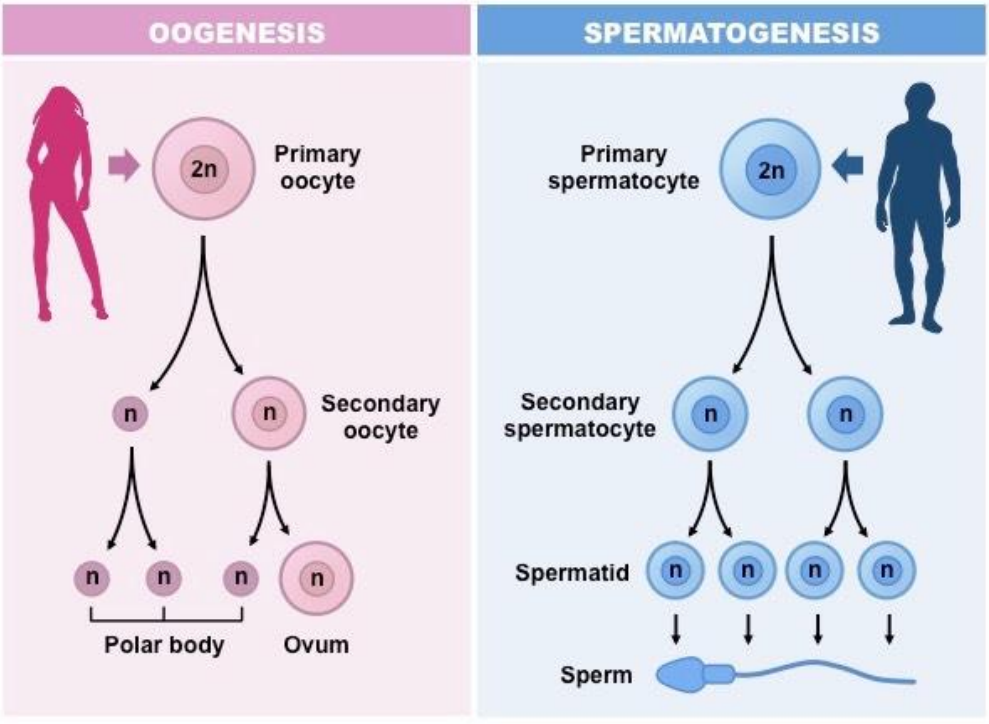


Fig. 2 Gametogenesis

Gametogenesis and intra-gonadal nutrient storage and utilization are linked processes in sea urchin reproduction. These processes involve the two cellular populations that make up the germinal epithelium of the sea urchin gonad. Uniquely, sea urchin gonads grow in size not

only because gametogenesis increases the size and/or numbers of germinal cells present but also because somatic cells within the germinal epithelium, the nutritive phagocytes, store extensive nutrient reserves before gametogenesis begins. Knowledge of these phenomena has lead to successful manipulation of sea urchin reproduction. A thorough understanding of sea urchin reproduction will provide increased opportunities for aquaculture.

2.6 Spermatogenesis

Spermatogenesis is the process by which haploid spermatozoa develop from germ cells in the seminiferous tubules of the testis. This process starts with the mitotic division of the stem cells located close to the basement membrane of the tubules. These cells are called spermatogonial stem cells. The mitotic division of these produces two types of cells. Type A cells replenish the stem cells, and type B cells differentiate into primary spermatocytes. The primary spermatocyte divides meiotically (Meiosis I) into two secondary spermatocytes; each secondary spermatocyte divides into two equal haploid spermatids by Meiosis II. The spermatids are transformed into spermatozoa (sperm) by the process of spermiogenesis. These develop into mature spermatozoa, also known as sperm cells. Thus, the primary spermatocyte gives rise to two cells, the secondary spermatocytes, and the two secondary spermatocytes by their subdivision produce four spermatozoa and four haploid cells.

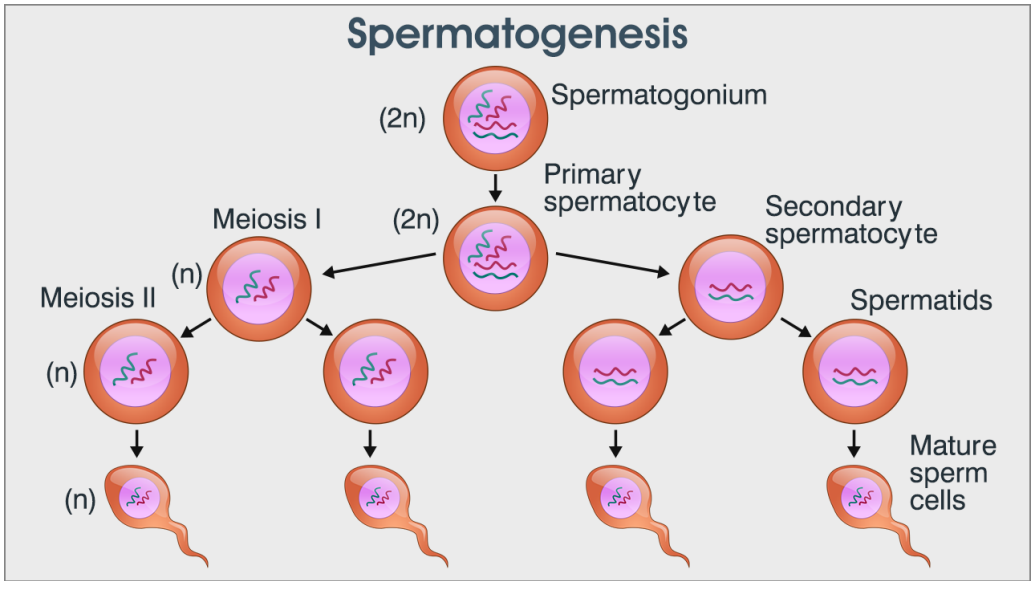


Fig. 3 The process of spermatogenesis

Spermatozoa are the mature male gametes in many sexually reproducing organisms. Thus, spermatogenesis is the male version of gametogenesis, of which the female equivalent

is oogenesis. In mammals it occurs in the seminiferous tubules of the male testes in a stepwise fashion. Spermatogenesis is highly dependent upon optimal conditions for the process to occur correctly, and is essential for sexual reproduction. DNA methylation and histone modification have been implicated in the regulation of this process. It starts at puberty and usually continues uninterrupted until death, although a slight decrease can be discerned in the quantity of produced sperm with increase in age.

Spermatogenesis starts in the bottom part of seminiferous tubes and, progressively, cells go deeper into tubes and moving along it until mature spermatozoa reaches the lumen, where mature spermatozoa are deposited. The division happens asynchronically; if the tube is cut transversally one could observe different maturation states. A group of cells with different maturation states that are being generated at the same time is called a spermatogenic wave.

2.7 Purpose

Spermatogenesis produces mature male gametes, commonly called *sperm* but more specifically known as *spermatozoa*, which are able to fertilize the counterpart female gamete, the oocyte, during conception to produce a single-celled individual known as a zygote. This is the cornerstone of sexual reproduction and involves the two gametes both contributing half the normal set of chromosomes (haploid) to result in a chromosomally normal (diploid) zygote.

To preserve the number of chromosomes in the offspring – which differs between species – one of each gamete must have half the usual number of chromosomes present in other body cells. Otherwise, the offspring will have twice the normal number of chromosomes, and serious abnormalities may result. In humans, chromosomal abnormalities arising from incorrect spermatogenesis results in congenital defects and abnormal birth defects (Down syndrome, Klinefelter syndrome) and in most cases, spontaneous abortion of the developing foetus.

2.8 Location in humans

Spermatogenesis takes place within several structures of the male reproductive system. The initial stages occur within the testes and progress to the epididymis where the developing gametes mature and are stored until ejaculation. The seminiferous tubules of the testes are the starting point for the process, where spermatogonial stem cells adjacent to the inner tubule wall divide in a centripetal direction—beginning at the walls and proceeding into the innermost part, or *lumen*—to produce immature sperm. Maturation occurs in the epididymis.

The location [Testes/Scrotum] is specifically important as the process of spermatogenesis requires a lower temperature to produce viable sperm, specifically 1°-8 °C lower than normal body temperature of 37 °C (98.6 °F). Clinically, small fluctuations in temperature such as from an athletic support strap, causes no impairment in sperm viability or count.

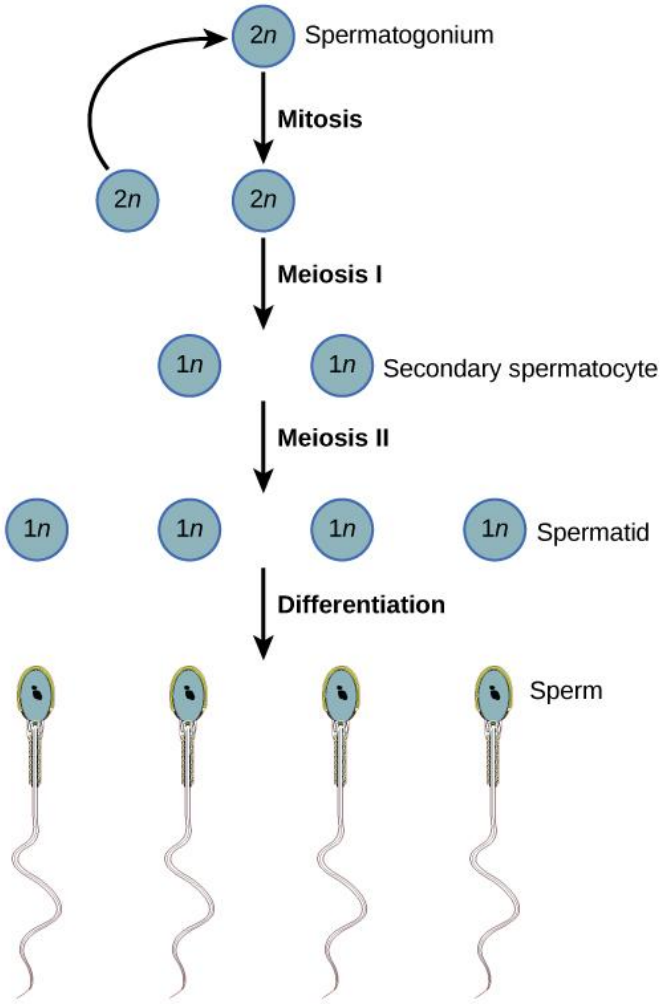


Fig. 4 During spermatogenesis, four sperm result from each primary spermatocyte, which divides into two haploid secondary spermatocytes

2.8.1 Duration

For humans, the entire process of spermatogenesis is variously estimated as taking 74 days (according to tritium-labelled biopsies) and approximately 120 days (according to DNA clock measurements). Including the transport on ductal system, it takes 3 months. Testes produce 200 to 300 million spermatozoa daily. However, only about half or 100 million of these become viable sperm.

2.8.2 Stages

The entire process of spermatogenesis can be broken up into several distinct stages, each corresponding to a particular type of cell in humans. In the following table, ploidy, copy number and chromosome/chromatid counts are for one cell, generally prior to DNA synthesis and division (in G1 if applicable). The primary spermatocyte is arrested after DNA synthesis and prior to division.

2.9 Oogenesis

Oogenesis, in the human female reproductive system, growth process in which the primary egg cell (or ovum) becomes a mature ovum. In any one human generation, the egg's development starts before the female that carries it is even born; 8 to 20 weeks after the fetus has started to grow, cells that are to become mature ova have been multiplying, and by the time that the female is born, all of the egg cells that the ovaries will release during the active reproductive years of the female are already present in the ovaries. These cells, known as the primary ova, number around 400,000. The primary ova remain dormant until just prior to ovulation, when an egg is released from the ovary. Some egg cells may not mature for 40 years; others degenerate and never mature.

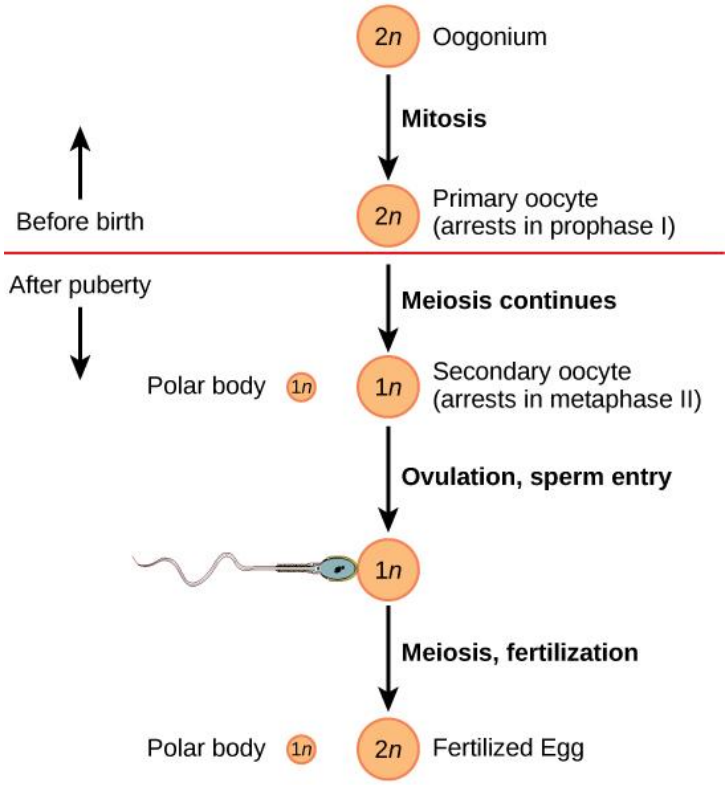


Fig. 5 The process of oogenesis occurs in the ovary's outermost layer

The egg cell remains as a primary ovum until the time for its release from the ovary arrives. The egg then undergoes a cell division. The nucleus splits so that half of its chromosomes go to one cell and half to another. One of these two new cells is usually larger than the other and is known as the secondary ovum; the smaller cell is known as a polar body. The secondary ovum grows in the ovary until it reaches maturation; it then breaks loose and is carried into the fallopian tubes. Once in the fallopian tubes, the secondary egg cell is suitable for fertilization by the male sperm cells.

2.9.1 Gamete

Oogenesis is the process of female gamete formation in animals. This process involves meiosis (including meiotic recombination) occurring in the diploid primary oocyte to produce the haploid ovum. Spermatogenesis is the process of male gamete formation in animals. This process also involves meiosis occurring in the diploid primary spermatocyte to produce the haploid spermatozoon. Gamete is a haploid cell that fuses with another haploid cell during fertilization in organisms that reproduce sexually.

Gametes are an organism's reproductive cells, also referred to as sex cells. In species that produce two morphologically distinct types of gametes, and in which each individual produces only one type, a female is any individual that produces the larger type of gamete- called an ovum; and a male produces the smaller type- called a sperm. Sperm cells or spermatozoa are small and motile due to the flagellum, a tail-shaped structure that allows the cell to propel and move. In contrast, each egg cell or ovum is relatively large and non-motile. In short a gamete is an egg cell (female gamete) or a sperm (male gamete).

In animals, ova mature in the ovaries of females and sperm develop in the testes of males. During fertilization, a spermatozoon and ovum unite to form a new diploid organism. Gametes carry half the genetic information of an individual, one ploidy of each type, and are created through meiosis, in which a germ cell undergoes two fissions, resulting in the production of four gametes. In biology, the type of gamete an organism produces determines the classification of its sex

This is an example of anisogamy or heterogamy, the condition in which females and males produce gametes of different sizes (this is the case in humans; the human ovum has approximately 100,000 times the volume of a single human sperm cell). In contrast, isogamy is the state of gametes from both sexes being the same size and shape, and

given arbitrary designators for mating type. The name gamete was introduced by the German cytologist Eduard Strasburger. Male and female gametes set the basis for the sexual roles and sexual selection.

2.10 Evolution of gametes

It is generally accepted that isogamy is the ancestral state from which anisogamy evolved, although its evolution has left no fossil records. Oogamy also evolved from isogamy through anisogamy. There are almost invariably only two gamete types, all analyses showing that intermediate gamete sizes are eliminated due to selection. Intermediate sized gametes do not have same advantages as small or large ones; they do worse than small ones in mobility and numbers, and worse than large ones in supply.

2.11 Artificial gametes

Artificial gametes, also known as In vitro derived gametes (IVD), stem cell-derived gametes (SCDGs), and In vitro generated gametes (IVG), are gametes derived from stem cells. Research shows that artificial gametes may be a reproductive technique for same-sex male couples, although a surrogate mother would still be required for the gestation period. Women who have passed menopause may be able to produce eggs and bear genetically related children with artificial gametes. Robert Sparrow wrote, in the Journal of Medical Ethics, that embryos derived from artificial gametes could be used to derive new gametes and this process could be repeated to create multiple human generations in the laboratory. This technique could be used to create cell lines for medical applications and for studying the heredity of genetic disorders. Additionally, this technique could be used for human enhancement by selectively breeding for a desired genome or by using recombinant DNA technology to create enhancements that have not arisen in nature.

2.12 Male & female gametes

Gametes can be described as sex cells of plants. Like humans, plants have sperm and egg cells that need to fuse in order to produce a zygote, or fertilized egg. Unlike humans, however, plants produce both types of these cells.

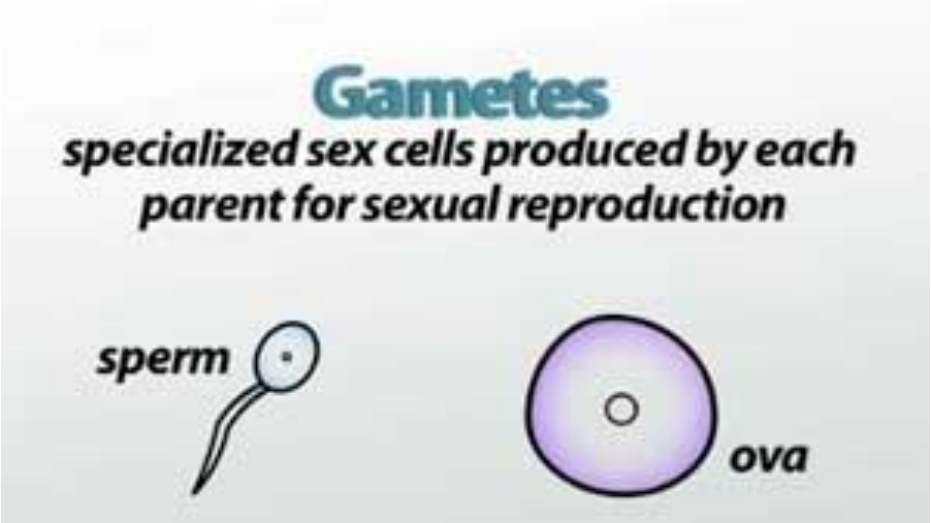


Fig. 6 Male and female gametes

The ovary of the plant produces the female ovule, or egg cell. The male sperm cell is generally encased by some sort of enclosure, like a pollen grain. This allows the egg and sperm cells to stay moist and safe from destruction.

The complexity of the different types of gametes will be seen shortly. However, they do have some commonalities; for example, each contains a sperm cell or, in some cases, multiple sperm cells. These sperm cells are all formed by a specialized cell division and, in the case of vascular plants, are usually encased by some sort of protective shell that also contains nutrients for the cell.

Female gametes are also known as eggs or ova. They are haploid cells that, when fused during sexual reproduction with a male gamete (sperm), form a zygote. Let's break this down a little more. During sexual reproduction, two cells - one from a female organism and one from a male organism - fuse together to create a zygote, or a fertilized cell. This zygote will mature into a new individual of the same species as the mother and father. The female gamete is considered a haploid cell because it only has a half-set of chromosomes. When it fuses with the sperm of another haploid cell, their chromosomes come together to complete the set, resulting in a diploid zygote, which has a full set of chromosomes.

2.13 Formation of the Female Gamete

Gametes (both male and female) are the products of a special type of cellular reproduction called meiosis. Meiosis is special or different due to the number of chromosomes that results from it. During normal cell reproduction, **mitosis**, the resulting cells have the same number of chromosomes as the original cells. In **meiosis**, however, the resulting cell only has half of the original number of chromosomes. There are a lot of phases and processes that occur during

meiosis, but there are two main stages: meiosis I and meiosis II. At the end of meiosis I, two cells result, each with a full set of chromosomes. These cells again go through a process of duplicating and splitting, but this time, the resulting cells only have half of the chromosomes. The resulting cells of meiosis are the gametes.

2.14 Maturation of gametes

Gametes (germ cells) are produced in the gonads. In females, this is called oogenesis and, in males, spermatogenesis. Most new mutations occur during gametogenesis, but there is a higher mutation rate in males, especially with increased paternal age. In females, meiosis I begins about 4 weeks before birth and then arrests in prophase, resulting in a primary oocyte. The primary oocyte persists in this stage until ovulation (after puberty). The arrest of meiosis I may contribute to the increased rate of chromosomal nondisjunction with advanced maternal age.

Gamete maturation occurs at the end of gametogenesis, with the formation of mature cells that are competent for fertilization, but in a state of meiotic and metabolic quiescence that can be reciprocally resumed by interaction with a partner. In fact, mutual activation of the gametes is an essential pre-requisite for fertilization, a process that involves numerous molecules, ions, cellular structures and metabolic pathways.

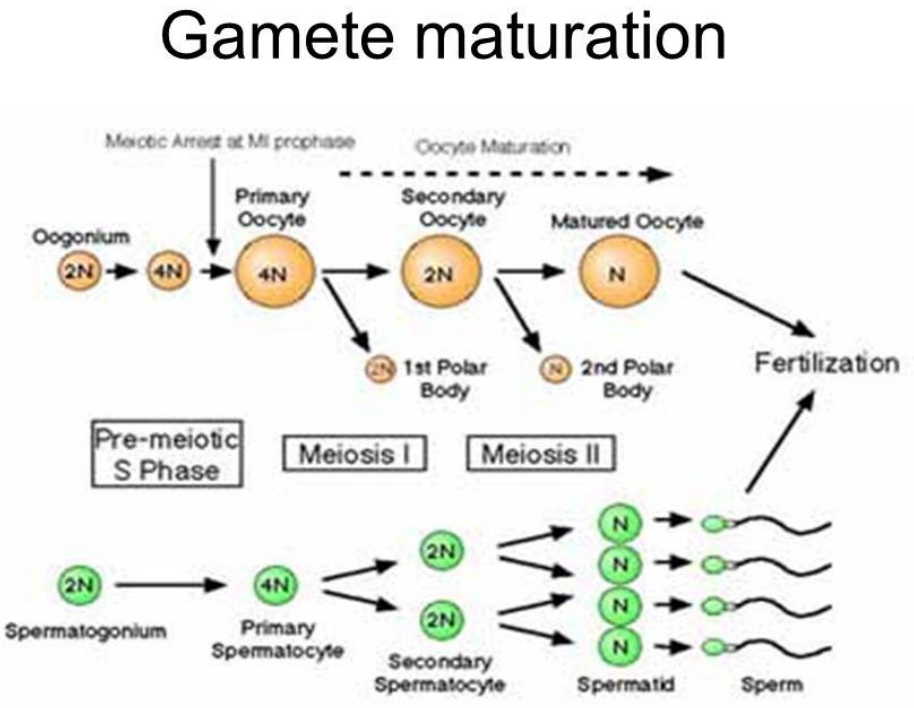


Fig. 7 Maturation of gametes

2.15 Difference between oogensis and spermatogenesis

Female oogenesis	Male spermatogenesis
• Meiosis initiated once in a finite population of cells	• Meiosis initiated continuously in a mitotically dividing stem cell population
• One gamete produced per meiosis	• Four gametes produced per meiosis
• Completion of meiosis delayed for months or years	• Meiosis completed in days or weeks
• Meiosis arrested at first meiotic prophase and reinitiated in a smaller population of cells	• Meiosis and differentiation proceed continuously without cell cycle arrest
• Differentiation of gamete occurs while diploid, in first meiotic prophase	• Differentiation of gamete occurs while haploid, after meiosis ends
• All chromosomes exhibit equivalent transcription and recombination during meiotic prophase	• Sex chromosomes excluded from recombination and transcription during first meiotic prophase

2.16 Vitellogenesis

Vitellogenesis (also known as yolk deposition) is the process of yolk formation via nutrients being deposited in the oocyte, or female germ cell involved in reproduction of lecithotrophic organisms. In insects, it starts when the fat body stimulates the release of juvenile hormones and produces vitellogenin protein. It occurs in all animal groups other than the mammals. In cockroaches, for example, vitellogenesis can be stimulated by injection of juvenile hormone into immature females and mature males. Chemically yolk is lipoprotein composed of proteins, phospholipids and neutral fats along with a small amount of glycogen. The yolk is synthesised in the liver of the female parent in soluble form. Through circulation it is transported to the follicle cells that surround the maturing ovum, and is deposited in the form of yolk platelets and granules in the ooplasm. The mitochondria and Golgi complex are said to bring about the conversion of the soluble form of yolk into insoluble granules or platelets.

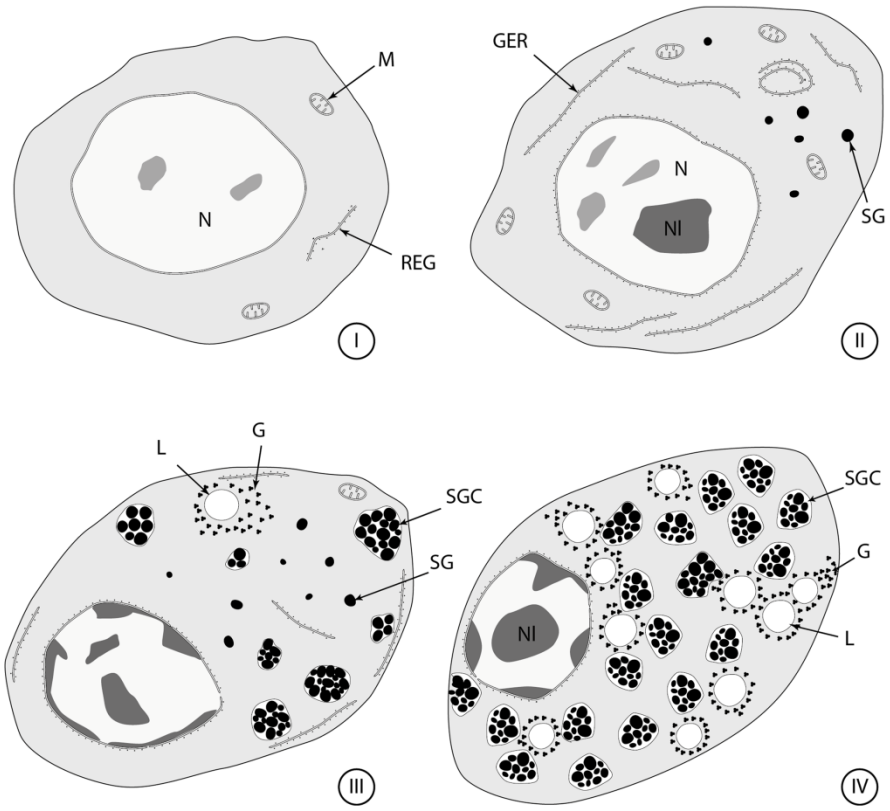


Fig. 8 Diagram of vitellogenesis in the digenean *Crepidostomum metoecus*

In mosquitoes infected with *Plasmodium*, vitellogenesis may be manipulated by the parasites to reduce fecundity. In mammalian vitellogenesis, vitellogenin is the major protein, produced by the Vit gene and regulated by oestrogen. The yolk consists of lipids (triglycerides, cholesterol etc.) and proteins, mainly vitellogenin. The term *vitellogenesis* comes from the Latin *vitellus* ("egg yolk").

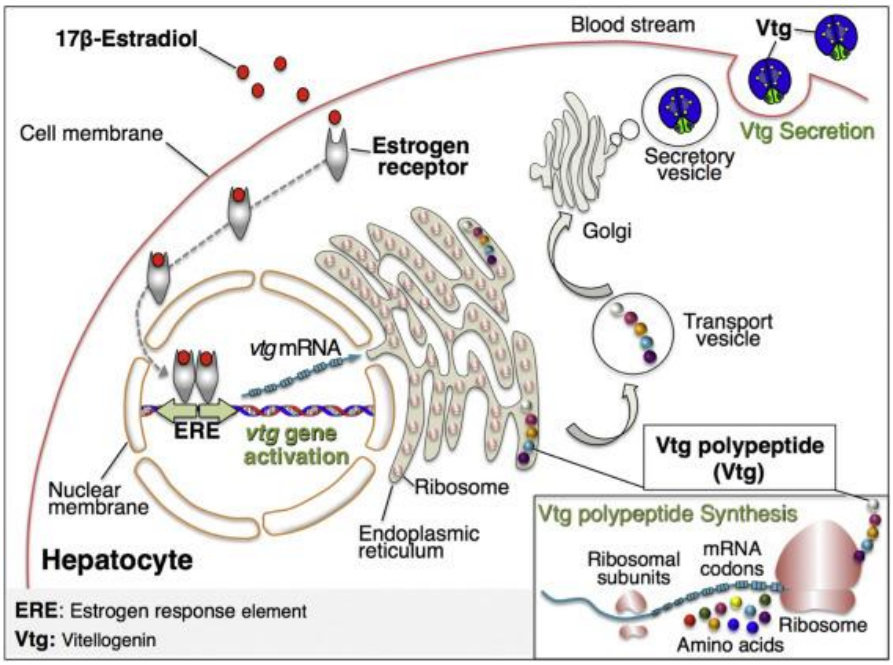


Fig. 9 Vitellogenesis - An overview

Yolk proteins provide embryos with nutrients essential for growth within the egg. Most are phosphoglycoproteins and provide amino acids, phosphate, lipids, and carbohydrates. The major yolk proteins are derived from vitellogenins, which are produced by the fat body and secreted for uptake by maturing oocytes. Yolk proteins in *Drosophila* consist of three polypeptides: YP1, YP2, and YP3. YP1 is expressed by the fat body and, after post-translational processing and glycosylation, the proteins are secreted into the hemolymph and delivered to the oocyte. YP2 is expressed in ovaries. The production and delivery of the three proteins is coordinately regulated and under the control of two hormones, 20-hydroxyecdysone and juvenile hormone. These two hormones regulate molting and metamorphosis during development, as well.

Production of yolk proteins begins during the first day of *Drosophila* adult life. The production rate is high, with yolk proteins representing about one-third of total proteins in hemolymph. YP1 and YP2 are closely linked genes on the X chromosome, while YP3 is sex-linked but more distant. YP1 and YP2 show much sequence homology and probably resulted from a fairly recent gene duplication event. Only one small intron is found in YP1 and YP2; there are two in YP3. Extensive yolk-protein synthesis in *Drosophila* is achieved because tissues are polytene and polyploid.

2.17 Summary

Under this unit, we have summarized that sexual reproduction is the production of new organisms by the combination of genetic information of two individuals of different sexes. In most species the genetic information is carried on chromosomes in the nucleus of reproductive cells called gametes, which then fuse to form a diploid zygote. The zygote develops into a new individual. Sexual reproduction is the dominant form of reproduction in living beings. Gametes are an organism's reproductive cells. These reproductive cells are produced through a type of cell division called meiosis. During meiosis, a diploid parent cell, which has two copies of each chromosome, undergoes one round of DNA replication followed by two separate cycles of nuclear division to produce four haploid cells. These cells develop into sperm or ova.

The ova mature in the ovaries of females, and the sperm develop in the testes of males. Each sperm cell, or spermatozoon, is small and motile. The spermatozoon has a flagellum, which is a tail-shaped structure that allows the cell to propel and move. In contrast, each egg cell, or ovum, is relatively large and non-motile. During fertilization, a spermatozoon and ovum unite to form a new diploid organism. Gametogenesis, the production of sperm (spermatogenesis) and eggs (oogenesis), takes place through the process of meiosis.

In oogenesis, diploid oogonium go through mitosis until one develops into a primary oocyte, which will begin the first meiotic division, but then arrest; it will finish this division as it develops in the follicle, giving rise to a haploid secondary oocyte and a smaller polar body. The secondary oocyte begins the second meiotic division and then arrests again; it will not finish this division unless it is fertilized by a sperm; if this occurs, a mature ovum and another polar body is produced. In spermatogenesis, diploid spermatogonia go through mitosis until they begin to develop into gametes; eventually, one develops into a primary spermatocyte that will go through the first meiotic division to form two haploid secondary spermatocytes. The secondary spermatocytes will go through a second meiotic division to each produce two spermatids; these cells will eventually develop flagella and become mature sperm.

2.18 Terminal questions

Q.1. Describe gametogenesis with diagram?

Answer:----------

Q.2. What do you mean by spermatogenesis? Explain it.

Answer:----------

Q.3. What do you mean by oogenesis? Explain it.

Answer:----------

Q.4. Describe vitellogenesis with diagram.

Answer:----------

Q.5. Describe maturation of gametes.

Answer:----------

Q.6. Discuss between spermatogenesis and oogenesis.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner
3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit-3 Parthenogenesis

Structure

3.1 Introduction

Parthenogenesis is a natural form of asexual reproduction in which growth and development of embryos occur without fertilization by sperm. In animals, parthenogenesis means development of an embryo from an unfertilized egg cell. In plants parthenogenesis is a component process of apomixis. Parthenogenesis occurs naturally in some plants, some invertebrate animal species (including nematodes, some tardigrades, water fleas, some scorpions, aphids, some mites, some bees, some Phasmatodea and parasitic wasps) and a few vertebrates (such as some fish, amphibians, reptiles and very rarely birds. This type of reproduction has been induced artificially in a few species including fish and amphibians.

Normal egg cells form in the process of meiosis and are haploid, with half as many chromosomes as their mother's body cells. Haploid individuals, however, are usually non-viable, and parthenogenetic offspring usually have the diploid chromosome number. Depending on the mechanism involved in restoring the diploid number of chromosomes, parthenogenetic offspring may have anywhere between all and half of the mother's alleles. The offspring having all of the mother's genetic material are called full clones and those having only half are called half clones. Full clones are usually formed without meiosis. If meiosis occurs, the offspring will get only a fraction of the mother's alleles since crossing over of DNA takes place during meiosis, creating variation.

Objectives

This is the third unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about parthenogenesis.
- To discuss the mechanism of parthenogenesis.
- To know the types of parthenogenesis.
- To discuss the parthenogenesis in human, birds and reptiles
- To know the significance and disadvantages of parthenogenesis.

3.2 Parthenogenesis

Parthenogenetic offspring in species that use either the XY or the X0 sex-determination system have two X chromosomes and are female. In species that use the ZW sex-determination system, they have either two Z chromosomes (male) or two W chromosomes

(mostly non-viable but rarely a female), or they could have one Z and one W chromosome (female).

Parthenogenesis is a form of reproduction in which an egg can develop into an embryo without being fertilized by a sperm. Parthenogenesis is derived from the Greek words for "virgin birth," and several insect species including aphids, bees, and ants are known to reproduce by parthenogenesis. Recently, parthenogenesis has received considerable attention as a tool for the production of stem cells. Human stem cells derived from embryos, fetal primordial germ cells, umbilical cord blood, and adult tissues provide potential cell based therapies for repair of degenerating or damaged tissues. Twenty years ago in the mouse model, the pluripotency of the cells and the efficacy of their derivatives were poorly explored. The possibility of deriving stem cells from parthenogenetic embryos could eliminate the requirement to produce and destroy viable embryos and may reduce the ethical concerns surrounding stem cell research. Because parthenogenetic stem cells contain only maternal genes, their use of may reduce the occurrence of immune-mediated rejection following graft transplantation.

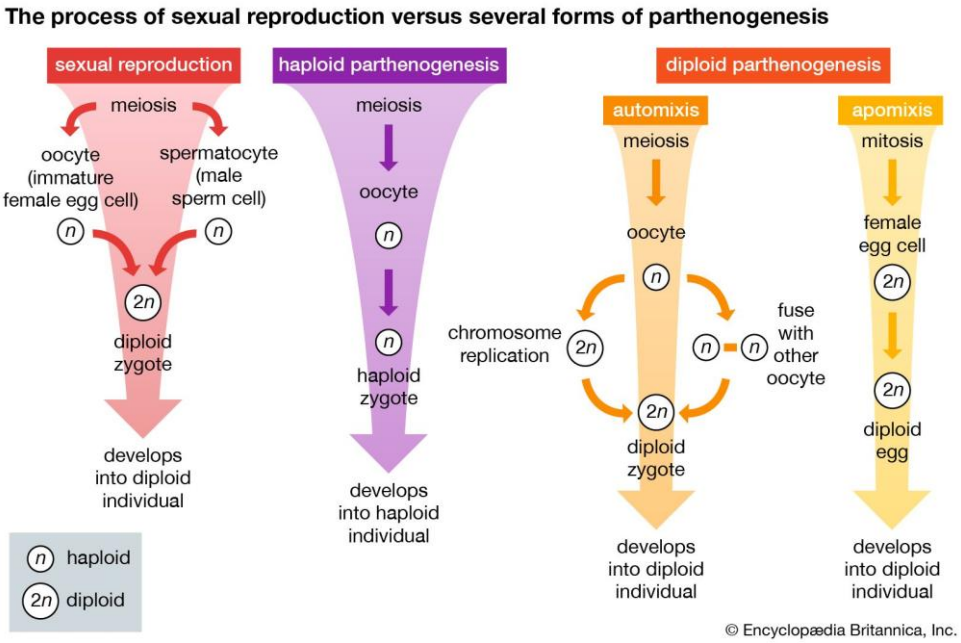


Fig. 1 Sexual reproduction and parthenogenesis compared

It is a reproductive strategy that involves development of a female (rarely a male) gamete (sex cell) without fertilization. It occurs commonly among lower plants and invertebrate animals (particularly rotifers, aphids, ants, wasps, and bees) and rarely among higher vertebrates. An egg produced parthenogenetically may be either haploid (i.e., with one set of dissimilar chromosomes) or diploid (i.e., with a paired set of

chromosomes). Parthenogenic species may be obligate (that is, incapable of sexual reproduction) or facultative (that is, capable of switching between parthenogenesis and sexual reproduction depending upon environmental conditions). The term *parthenogenesis* is taken from the Greek words *parthenos*, meaning "virgin," and *genesis*, meaning "origin." More than 2,000 species are thought to reproduce parthenogenically.

Fig. 2 Parthenogenetic New Mexico whiptail, flanked on either side by whiptails that reproduce sexually

3.3 Mechanisms

Parthenogenesis is sometimes considered to be an asexual form of reproduction; however, it may be more accurately described as an "incomplete form of sexual reproduction," since offspring of parthenogenic species develop from gametes. Gametes are reproductive cells that result from meiosis (or reduction division)—in which a specialized cell with a (diploid) double set of chromosomes undergoes two fissions of its nucleus. Meiosis gives rise to four gametes, or sex cells, which are haploid—in that each possesses half the number of chromosomes of the original cell.

Parthenogenesis can operate on either a haploid or a diploid cell. In haploid parthenogenesis, a rare form of parthenogenesis that occurs in a few species of bees, nematodes, and plants, offspring develop from haploid eggs to produce haploid adults. On the other hand, the process of diploid parthenogenesis, a more common and varied form of the phenomenon, may proceed along two pathways. Automixis (automictic parthenogenesis) is a postmeiotic process in which a haploid cell may either duplicate its chromosomes or join with another haploid cell. In both cases, diploid zygotes develop and grow into diploid adults.

Such organisms are not true clones of the mother, however, because the meiotic process separates and recombines the genetic material. A second form of diploid parthenogenesis, apomixis (apomicitic parthenogenesis), forgoes complete meiosis

altogether. Instead, two genetically identical diploid egg cells are produced from a parent cell through mitosis (the process of cell duplication), and one or more of these daughter cells, which are both diploid and clones (that is, genetically identical) of the original parent cell, develop into a diploid offspring. Diploid parthenogenesis occurs in insects such as aphids as well as in some rotifers and flowering plants (*see* animal reproductive system and plant reproductive system).

3.4 Parthenogenesis in order Hymenoptera

In the insect order Hymenoptera (which includes bees, wasps, and ants), parthenogenesis can take one of three forms: arrhenotoky, thelytoky, and deuterotoky. In arrhenotoky, haploid males are produced from unfertilized eggs laid by mated (impregnated) females or by so-called secondary, or supplementary, queens, which have not been impregnated. In thelytoky, which occurs in many species of the suborder Symphyta (a group that includes the sawflies, the horntails, and the wood wasps), unmated females produce males. In deuterotoky, unmated females of some Symphyta produce females as well as males. The occurrence of these forms is not always mutually exclusive. For example, in *Apis* (bees), about 1 percent of the eggs laid by secondary queens may be female.

Sometimes associated with arrhenotoky, thelytoky, and deuterotoky is pseudoarrhenotoky (or paternal genome elimination). Pseudoarrhenotoky is a nonparthenogenic form of reproduction that occurs in the hymenopteran superfamily Chalcidoidea (a group of small parasitic wasps) and in some mites, Like arrhenotoky, pseudoarrhenotoky results in the production of haploid males. In this process, development begins as diploid organisms within fertilized eggs; however, as development progresses, males become haploid after the paternal contribution to the genome has been lost, eliminated, or deactivated.

3.5 Variations

A number of parthenogenic variations have been observed. Some aphids and water fleas undergo a type of parthenogenesis called heterogony or cyclic parthenogenesis. In these species, generations of offspring produced from fertilized eggs may alternate with those produced from unfertilized ones. Such an alternation of generations in both groups of insects is thought to result partly from seasonal temperature changes, with eggs produced through sexual reproduction having a greater ability to withstand the winter cold. They lie dormant until temperatures rise.

Pseudogamy (gynogenesis, or sperm-dependent parthenogenesis) is another variation, which appears in the life cycle of a few insects, mites, and salamanders as well as the

flatworm *Schmidtea polychroa*. *S. polychroa* is hermaphroditic and may be diploid (which can reproduce sexually) or polyploid (that is, with one or more additional sets of chromosomes). Whereas sexual reproduction requires sperm for fertilization, parthenogenic reproduction in this species involves sperm only to stimulate the initial development of the egg; the sperm's genetic material is not used.

3.6 Types of parthenogenesis

There are two types of parthenogenesis as under:

- Natural Parthenogenesis
- Artificial Parthenogenesis

3.6.1 Natural Parthenogenesis

In certain animals, parthenogenesis occurs naturally in their life cycles. This is known as natural parthenogenesis. Natural parthenogenesis can be further divided into:

3.6.2 Complete Parthenogenesis

A few insects have no males and no sexual phase. Such organisms depend upon self-reproduction. This is known as complete parthenogenesis.

3.6.3 Incomplete Parthenogenesis

The life cycle of a few insects involves two generations:

- Sexual generation
- Parthenogenesis generation

In this, the unfertilised eggs produce males and the diploid eggs produce females. This type of parthenogenesis is called partial or incomplete parthenogenesis.

3.7 Artificial Parthenogenesis

The fertilised eggs might sometimes develop parthenogenetically by various chemical and physical means. This is known as artificial parthenogenesis.

3.7.1 Physical Means

- ✓ Temperature induces parthenogenesis in eggs. For eg., parthenogenesis is induced if an egg is transferred from -30 to -10°C.
- ✓ Parthenogenesis is caused by ultraviolet light.

- ✓ Electrical shocks cause parthenogenesis.
- ✓ When an egg is pricked by a needle, the development occurs parthenogenetically.

3.7.2 Chemical Means

The chemicals that are responsible for the parthenogenesis of eggs are:

- ✓ Chloroform
- ✓ Urea and Sucrose
- ✓ Strychnine
- ✓ Fat solvents
- ✓ Acids
- ✓ Chlorides

3.8 Parthenogenesis in invertebrates

Parthenogenesis can be defined as the production of an embryo from a female gamete without any genetic contribution from a male gamete, with or without the eventual development into an adult. It is distinct from asexual reproduction since it involves the production of egg cells. Parthenogenesis is a normal method of reproduction in many lower organisms, but does not lead to viable mammalian offspring. Parthenogenetic development can proceed by various routes depending on whether meiosis has occurred or has been supressed, in which case the egg develops as as result of mitotic divisions. Whenever sex is determined by chromosome constitution, parthenogenetic offspring, in the absence of effective meiosis, all will be, mostly female. In birds, however (see below), the offspring are male as in this case females are the heterogametic sex.

In bees, males originate by haploid parthenogenesis while diploid females are produced by fertilization in the normal way. Other aphids, such as greenfly (Hemiptera) have generations which alternate between parthenogenesis and fertilization, so called cyclical parthenogenesis. The formation of female parthenogenetic offspring is widespread among many order of insects. For example in *Drosophila parthenogenetica,* a small proportion of eggs laid by virgin females develop to produce viable adults. Another example is the parthenogenetic grasshopper *Warramaba virgo*, a species which consists of females only. Parthenogenesis is also successful in some Crustaceae such as the brine shrimp, *Artemia*

salina. Animals such as bees, wasps, ants have no sex chromosomes. These organisms reproduce by parthenogenesis. A few plants, reptiles and fish are also capable of reproducing in this manner. A few organisms such as crayfish, snakes, komodo dragons and sharks can reproduce sexually as well as by parthenogenesis. This is known as facultative parthenogenesis.

3.9 Parthenogenesis in humans

Parthenogenesis is common in some vertebrates including the whiptail lizard where the offspring develops from an oocyte without being fertilized by a sperm. So, no paternal inheritance occurs and the offspring genome is completely inherited from the mother. Parthenogenesis in humans, as well as androgenetic events, may spontaneously occur in humans. However, they can only produce tumors such as ovarian teratoma. The production of a parthenogenesis human depends on several factors including activation of the oocyte, meiosis, and genetic imprinting.

It is not naturally a common type of reproduction in mammals. However, artificial induction of parthenogenesis in mammals included stimulation of the mammalian oocyte; The oocyte was activated and developed into an embryo by parthenogenesis. However, the resulting embryo will not develop further due to a lack of paternal genes, which are responsible for the establishment of the normal placenta. On the other hand, creating a fully fertile animal by parthenogenesis is possible by the technology of genetic modification, which manipulates the genome of the produced animal from an activated oocyte.

Asexual reproduction in humans is not common. Therefore, the parthenogenetic activation of a human oocyte is facing legal and ethical issues. However, this method of reproduction has medical, scientific, and economic reasons. For example, parthenogenesis may be used in different fields. Human stem cells have been studied for their regulatory mechanisms which are responsible for the development of an embryo or cloning experiments in different researches using the oocyte. Therefore, clinical human parthenogenesis in humans may reproduce cells such as embryonic stem cells that can be used in the favor of many patients. It can be used in organ transplantation with minimal risk of organ rejection.

Human oocyte activation is a complex process that requires several stimuli at different phases of the cell division cycle. At metaphase II, the unfertilized oocyte will not develop without a

stimulus. The stimulus may occur due to the fertilization by a spermatozoon or using an artificial agent. The artificial agent permits the transition to anaphase, sister chromatids segregation, and expels the second polar body. The artificial agent must mimic the action of the sperm to trigger the development of an embryo. Oocyte parthenogenetic activation can be performed by different types of stimuli. These stimuli are divided into chemical and physical stimuli. Even though different methods provide oocyte stimulation, however, they have different degrees of embryonic development and activation rates which affect the degree of success.

The produced embryo is a *pseudodiploid*, which contains the two maternal sister chromatids chromosomes in the oocyte. Spontaneous diploidization occurs since the resulting embryo contains one copy of sister chromatids in order to develop into a homozygous embryo. Then, the activating agent induced the extrusion of the second polar body and transition from metaphase II without performing diploidization. Therefore, the resulting embryo from this stage is a haploid embryo. Activation of the human oocyte by parthenogenesis to treat infertility is now of great interest since it can be used to produce embryos in areas such as assisted reproduction technologies itself, somatic cell, and nuclear transfer experiments and for the derivation of clinical-grade pluripotent embryonic stem cells for regenerative medicine. Different methods have been employed to activate human and nonhuman female gametes with different degrees of embryonic development.

3.10 Parthenogenesis in birds

Parthenogenesis may occur naturally in some birds. However, surrounding conditions may affect the development of the unfertilized egg so it is usually abortive. Birds may reproduce by *facultative parthenogenesis*, producing diploid males only. The mechanism of parthenogenesis in birds is not clear yet, however, some researchers suggest that parthenogenesis may affect the normal fertilization as well as the natural development of an embryo. For example, *turkey* and *virgin quail* that reproduce by parthenogenesis have shown less reproductive performance after sexual mating. Environmental factors, as well as genetic selection such as exposure to virus vaccines, may initiate parthenogenesis in birds.

Parthenogenesis in avian species can be studied to get more information about parthenogenesis among vertebrates. This information is useful in understanding the pathogenesis of ovarian cancers that develop from mammalian oocytes by

parthenogenesis. Avian species represent a great model for such studies due to their small size, the short interval of generations, and earlier sexual maturity in comparison with chickens and turkeys. On the other hand, parthenogenesis is abortive in most birds such as pigeons, quail, turkeys, and zebra finches. However, when they were exposed to genetic selection, researchers were able to hatch a small percentage of turkey's unfertilized eggs.

In parthenogenesis, the meiotic early stage is similar to fertilized egg where the number of chromosomes is reduced. Consequently, to restore the diploid number of chromosomes, the haploid egg nucleus and the haploid second polar body are fused or by endomitosis. As a result, the produced parthenogen has the same diploid chromosome number.

3.11 Parthenogenesis in reptiles

Many snake species reproduce sexually but there are other snake species that are capable of reproducing asexually. Apart from snakes, other reptiles that reproduce asexually are certain species of lizards. Both the snake and lizard asexual reproductions may be in the form of facultative or obligate parthenogenesis. In *facultative parthenogenesis*, a sexually reproducing reptile becomes parthenogenetic when males are lacking in their population. In this case, their population consists of members that may or may not be a clone of the mother's genome as they reproduce by mating as well when an opportunity presents. In *obligate parthenogenesis*, such as rock lizard and certain groups of geckos, they reproduce by parthenogenesis alone.

In these species, the female egg develops into a new offspring without the contribution of the male in fertilization. There are about 50 lizard species and only 1 snake species that reproduce by obligate parthenogenesis. Parthenogenesis in reptiles may produce either full clones that carry all the mother's genes or produce a half-clone that combines a haploid genome of the reptile egg. Full clones are produced due to a certain modification in the normal process of haploid egg production where the genome of a female's germ cell is doubled in a process known as *pre-meiotic genome doubling*.

In this process, two-division cycles of meiosis produce a diploid egg instead of a haploid egg where two similar sister chromosomes produced during premeiotic genome doubling are

separated during *meiosis I*. Identical chromosomes pair instead of the two homologous chromosomes that pair in sexual reproduction. Then, two identical sister chromatids are separated during *meiosis II*. Full clones are found among obligate parthenotes, like *Lacerta*, as well as facultative parthenotes such as the Burmese python.

Other species produce half clones.

These usually reproduce by facultative parthenogenesis. Terminal fusion takes place between an egg cell and a haploid polar body. The polar body is a byproduct of meiosis. The fusion between the egg and polar body produces a diploid nucleus that develops into a diploid offspring. This method is similar to the fusion of an egg and sperm in sexual reproduction since it forms a diploid nucleus from the fusion of two different cells. The resulting offspring is a homozygote and gets about half of its mother's genetic variation.

This type of parthenogenesis could produce either a female or a male. Since the meiosis process takes place normally in individuals produced by this type of parthenogenesis, these individuals can reproduce either sexually or asexually such as some species of snakes and Komodo dragons. Several types of Lizards are parthenogenetic such as Caucasian rock lizard species of genus *Lacerta*. *Lacerta* is true parthenotes, therefore, their egg is not fertilized by a sperm. Another genus is the *Teiid* of whiptail lizards, which is the most known evolutionarily type of reptiles that reproduce by parthenogenesis.

SAQs

Choose the best answer from the given options.

1. Which of the following is parthenogenesis?
   - **(a)** Reproduction by means of mating between male and female.
   - **(b)** Reproducing offspring in the absence of a male gamete.
   - **(c)** Reproducing offspring in the absence of a female gamete.
2. Parthenogenesis is a form of…
   - **(a)** Asexual reproduction.
   - **(b)** Sexual reproduction.
   - **(c)** Either asexual or sexual reproduction.
3. Parthenogenesis that produces a full clone of the mother

(a) Apomixis parthenogenesis.

(b) Automixis parthenogenesis.

(c) Facultative parthenogenesis.

4. Which of the following is generally a disadvantage of parthenogenesis as a form of reproduction?

(a) Conserve time in finding a mate.

(b) Relatively a quicker way to reproduce offspring.

(c) Offspring are predisposed to the same diseases inflicting the present.

3.12 Examples of parthenogenesis

Parthenogenesis takes place spontaneously in rotifers, daphnia, nematodes, aphids, as well as other invertebrates and plants. Among vertebrates, birds, snakes, sharks, and lizards are the only species that can reproduce by strict parthenogenesis. While other amphibians, fish, and reptiles can perform different forms of hybridogenesis, which is a form of *incomplete parthenogenesis*. Other species such as the blacktip and hammerhead sharks as well as the Komodo dragon usually reproduce sexually; however, these species may sometimes reproduce asexually by parthenogenesis. Parthenogenesis may be artificially induced in mammals to produce animal clones, i.e., the offspring is genetically identical to the mother. In this process, the egg cell is artificially stimulated to undergo mitosis in order to produce a new organism.

3.13 Significance of Parthenogenesis

Parthenogenesis is important for the following reasons:

- Parthenogenesis helps in determining the sex of an individual in honey bees, wasps, etc.
- It supports the chromosomal theory of inheritance.
- Variations from populations are eliminated by parthenogenesis.
- It is the simplest, most stable and easy process of reproduction.
- Polyploidy in organisms is caused by parthenogenesis.
- It helps in the development of advantageous mutant characters.
- Non-adaptive combination of genes is controlled.
- There are no sterile races.

However, the organisms produced by parthenogenesis cannot survive for long due to no recombination of genetic material.

3.14 Disadvantages of Parthenogenesis as a Form of Reproduction

Parthenogenesis is a form of asexual reproduction. Thus, it is characterized by a lack of genetic diversity since the offspring gets all genetic material from one parent only. Lack of genetic diversity predisposes the offspring to the same diseases and same conditions as its parent. Moreover, negative mutations, as well as unfavorable traits, will persist in many generations. Furthermore, the offspring produced by parthenogenesis is a clone of the parent so it cannot adapt easily or survive when the condition changes and becomes unfavorable. That's why parthenogenesis may produce a large number of organisms that cannot survive through any slight change in their environment.

3.15 Summary

Parthenogenesis is a method of self-reproduction in which the egg cells develop into offspring in the absence of a mate. Thus, parthenogenetic animals and plants may still reproduce their own kind without the need to exert time and effort in looking for a suitable mate. The female can then use this time to search for food and shelter where these resources are available. For example, aphids reproduce asexually by parthenogenesis during summer since green leaves are available and the daytime is longer. Asexual parthenogenesis enables a population to grow as twice faster as a population that reproduces sexually. Parthenogenesis enables rapid reproduction and increases in population size without the need for fertilization. Therefore, parthenogenesis is faster and easier than sexual reproduction since it does not depend on the presence of a male. In fact, females that reproduce by parthenogenesis can produce the same number of offspring as sexually reproduced females but with only half the size of the population saving more resources.

In parthenogenetic species, one individual is capable of forming a colony without mating, producing female offspring that may grow and reproduce again to provide a large number of offspring in a short period of time. Moreover, some parthenogens can maintain the ability to incorporate new genes during the cycle of sexual reproduction. Therefore, they can maintain their evolutionary process while producing a great number of offspring.

Sexual reproduction does have greater genetic diversity than parthenogenesis. However, parthenogenesis may prove beneficial in a way that it produces clones having the same genes for favorable traits as inherited from their parents. So, if the mother lives in a habitat to which she has adapted, her offspring will carry the same genes to ensure their survival in such an environment. Parthenogenesis is now being tested on human eggs to stimulate the egg to

develop without fertilization. This approach may help researchers to find a new method of producing human stem cells from an unfertilized egg or even to clone humans.

3.16 Terminal questions

Q.1 What do you mean by parthenogenesis?

Answer:----------

Q.2 Describe significance of parthenogenesis..

Answer:----------

Q.3 Write a short note on

Answer:----------

Q.4 What do you mean by parthenogenesis in birds?

Answer:----------

Q.5 What do you mean by parthenogenesis in reptiles?

Answer:----------

Q.6 Write a short note on parthenogenesis in invertebrates.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner

3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit-4 – Metamorphosis (morphogenetic processes and tissue reactivity)

Structure

4.1 Introduction

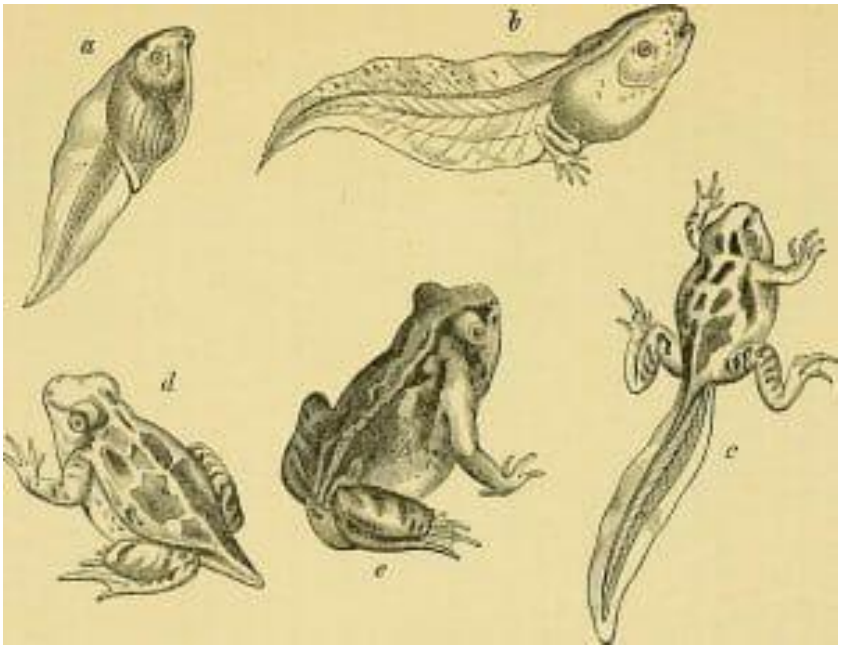
Metamorphosis is a process by which animals undergo extreme, rapid physical changes some time after birth. The result of metamorphosis may be change to the organism's entire body plan, such as a change in the animal's number of legs, its means of eating, or its means of breathing. In species that use metamorphosis, metamorphosis is also typically required for sexual maturity. Pre-metamorphic members of these species are typically unable to mate or reproduce. Commonly known examples of metamorphosis include the process undergone by most insects, and the transformation of tadpoles into frogs. The diagram below shows the stages of this change, wherein the small fish-like tadpoles transform into what seems a completely different animal.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about metamorphosis
- To discuss types of metamorphosis
- To discuss metamorphosis in butterflies, frogs and fish
- To know tissue reactivity and protein adsorption

Animals that you may not know undergo metamorphosis include fish, mollusks, and many other types of sea creatures which are related to insects, mollusks, or fish. Lobsters, for example, which are closely related to insects, do undergo metamorphosis as part of their life cycle. Metamorphosis is a remarkable process. The speed and extent of cell growth and differentiation is astonishing. In most species, such rapid growth and such sweeping changes to cell type only happen during embryonic development. Indeed, some scientists believe that the process of metamorphosis involves a sort of re-activating of genes that allow animal cells to change from one cell type to another.



The changes leading to metamorphosis are triggered by hormones, which the animal's body releases as the right conditions for metamorphosis approach. In some animals a hormone cascade follows, with the trigger hormone causing the release of several other hormones that act on different parts of the animal's body. The hormones cause drastic changes to the functioning of cells, and even behavioral changes such as the caterpillar spinning its cocoon. The effects of hormones on metamorphosis can be studied by artificially administering these hormones to pre-metamorphic animals. Tadpoles, for example, can be triggered to begin losing their tails and growing limbs early by the addition of thyroid hormones to their water supply. Unfortunately this has a detrimental effect on the animal's health.

4.2 Function of metamorphosis

Scientists remain uncertain why metamorphosis evolved. For the animals of today, its purpose is obvious: if metamorphosis did not occur, tadpoles could not become frogs and larvae could not become full-grown adults capable of reproduction. Without reproductively mature members, these species would quickly die off. But why would these species evolve to need this extra step in the first place? Why not just hatch full-grown butterflies or frogs from eggs?

At least some metamorphosing species did not start out that way: the earliest insects basically did hatch as full-grown adults. But a few hundred million years ago, some species stumbled upon the trick of metamorphosis. It was apparently wildly successful; it is thought that almost

two-thirds of species alive today use metamorphosis to accomplish large changes between their adult and juvenile forms.

The benefit of metamorphosis may lie in its ability to reduce competition. Pre-metamorphic animals typically consume completely different resources from their adult forms. Tadpoles live in water, eating algae and plants. Frogs live on land, breathing air and eating insects. Caterpillars eat leaves; butterflies live off of nectar. Etc. This effectively prevents older members of the species from competing with younger members. This may lead more members of the species to successfully reach sexual maturity, without the risk of being out-competed by older members of their species.

4.3 Types of metamorphosis

4.3.1 Complete Metamorphosis

In complete metamorphosis, a larva completely changes its body plan to become an adult. The most famous example is that of the butterfly, which starts out as a worm-like, leaf-eating caterpillar and transforms into a flying, nectar-drinking creature with an exoskeleton. Organisms that undergo complete metamorphosis are called "holometabolous," from the Greek words "holo" for "complete" or "whole," "meta" for "change," and the noun "bole" for "to throw." "Holometabolous," then, means "completely changing," or "wholly changing."

This transformation is so swift and complete that the caterpillar must spin a cocoon and lie dormant for weeks while its body undergoes these radical changes. Other animals which transform from a worm-like larval stage into an animal that looks completely different include beetles, flies, moths, ants, and bees. Some scientists believe that the larval stage of complete metamorphosis may have evolved from insects which hatched from their eggs without developing properly. Some of these embryos may have survived long enough to find food in the outside world; and this may have ended up giving them an advantage, as they would be able to feed longer and gain more strength than their peers before metamorphosing into the adult stage.

4.3.2 Incomplete Metamorphosis

In incomplete metamorphosis, only some parts of the animal's body change during metamorphosis. Animals that only partially change their bodies as they mature are called "hemimetabolous," from the Greek words "hemi" for "half," "meta," for "change," and the verb "bole" for "to throw." "Hemimetabolous," then, is a word meaning "half-changing." Cockroaches, grasshoppers, and dragonflies, for example, hatch from eggs looking a lot like their adult selves. They do acquire wings and functioning reproductive organs as they grow, but they do not completely remake their bodies like their completely metamorphosing cousins do.

4.3.3 Examples of Metamorphosis

4.3.3.1 Butterflies

Many of us may have witnessed the process of metamorphosis first hand, by raising caterpillars into butterflies in school. The idea of a worm-like caterpillar wrapping itself in a cocoon for weeks and then emerging as a beautiful butterfly is certainly strange. But the obvious changes of appearance, such as the growth of wings, don't do justice to just how strange this process is. In the cocoon, caterpillars don't simply gain legs, wings, and an exoskeleton. They also grow new eyes, lose their leaf-eating mouth parts and replace them with nectar-sucking proboscises, and gain mature reproductive organs. To accomplish this drastic change, a metamorphosing caterpillar basically digests itself.

A great deal of energy and raw materials are required to turn a caterpillar into a butterfly. So to make it possible, caterpillars release enzymes that dissolve most of their bodies! Indeed, the hard shell of the cocoon is required not just to protect the metamorphosing insect from attack: it is required to keep its liquefying body bound together, lest it ooze away! Not all of the caterpillar's cells are dissolved by these enzymes. Special tissues called imaginal discs survive – and they use the soup that used to be the rest of the caterpillar's body for nutrition. By consuming the proteins, vitamins, and minerals – everything you need to build a butterfly – these imaginal discs are able to grow incredibly quickly, developing into the butterfly's mature body parts. The new body has almost nothing in common with the old body. It has new legs, new sensory organs, a new exoskeleton, a new reproductive system. Even its digestive system does not work the same way, since it must now digest nectar instead of leaves. That's all in addition to the beautiful wings.

This radical change allows butterflies to complete their life cycle very efficiently, with no competition between adult butterflies and caterpillars for food. Many other insects pass through a similar process. They hatch as worm-like larva, eventually encase themselves in hard pupas, and emerge as adults with legs, exoskeletons, and other features that have little in common with the larva they once were. Bees, beetles, ants, and flies all use this strategy.

4.3.3.2 Frogs

The metamorphosis of a tadpole into a frog is a little less violent than that of a caterpillar into a butterfly, but the processes share some important common features. Tadpoles do not dissolve their bodies into mush; but they do "digest" them in a less spectacular way. Using the process of apoptosis – or "programmed cell death" – the tadpoles "order" the cells they don't need anymore to shred their DNA and die. The dead cells are then cannibalized for energy and raw materials to make other cells. The cells of their tails are broken down and used to make their developing legs; a similar process happens with the gills, which disappear as the tadpole begins to develop air-breathing lungs. One interesting thing to note is that tadpole metamorphosis and insect metamorphosis likely developed separately; the common ancestor of insects and amphibians diverged long ago, and the ancestors of modern insects are not thought to have used metamorphosis. When the same phenomenon evolves twice in radically different organisms, that's a sure sign that it is a useful adaptation.

4.3.3.3 Fish

Some species of fish undergo metamorphoses similar to those of the tadpole. Though those changes are not so dramatic, they can result in changes in the fish's food source, its body plan, and where it's able to live. Just like the more drastic forms of evolution, this may function to prevent adults from competing with juveniles for food. The salmon, for example, is a freshwater fish in its juvenile form. After undergoing a partial metamorphosis, it becomes a saltwater fish. When thinking about this process it is important to keep in mind that all organisms must regulate their salt/water balance. This is why humans can't drink seawater without dying: the salt would overwhelm our cellular chemistry, and our cells would not function properly. In just the same way, freshwater fish typically cannot live in saltwater. To become saltwater fish, then, salmon must develop new organs and cellular mechanisms to cope with the salt water.

That's why salmon must perform their annual migration upstream; adult salmon live in the ocean, but their eggs must hatch in fresh water in order for the juveniles to survive. That means that adult salmon must leave their homes in the ocean for freshwater rivers, and swim as far upstream as possible before laying their eggs! Flounders, bizarrely, undergo a metamorphosis in which one of their eyes and nostrils move from one side of the head to the other. As juveniles, flounder look much like most fish: they swim vertical relative to the current, with one eye and one nostril on each side of their bladelike body. This body type allows them to swim fast like most other species of fish.

But in adulthood, flounder are flat fish which camouflage themselves by swimming on their bellies, pressed against the sea bed. To accomplish this lifestyle change, juvenile flounder essentially flip over on their sides and make one side of their body into their belly. Through cellular changes, the eye and nostril from the belly side actually migrate to join the other eye and nostril on what is now the "top" side of the fish.

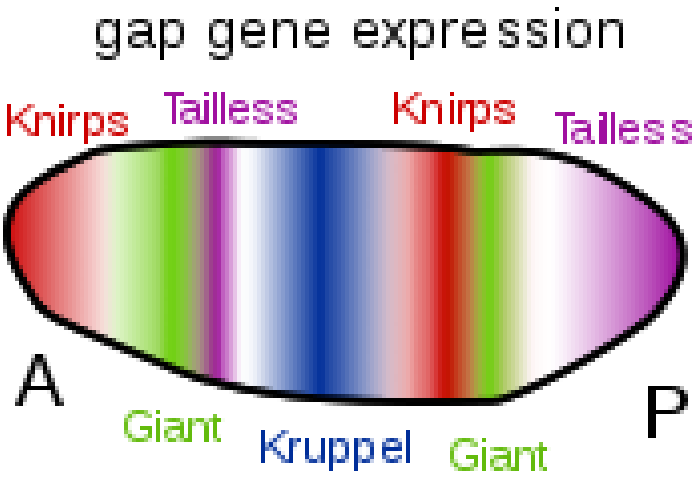
4.4 Morphogenesis

Morphogenesis is the biological process that causes a cell, tissue or organism to develop its shape. It is one of three fundamental aspects of developmental biology along with the control of tissue growth and patterning of cellular differentiation. The process controls the organized spatial distribution of cells during the embryonic development of an organism. Morphogenesis can take place also in a mature organism, such as in the normal maintenance of tissue by stem cells or in regeneration of tissues after damage. Cancer is an example of highly abnormal and pathological tissue morphogenesis. Morphogenesis also describes the development of unicellular life forms that do not have an embryonic stage in their life cycle. Morphogenesis is essential for the evolution of new forms.

Morphogenesis is a mechanical process involving forces that generate mechanical stress, strain, and movement of cells, and can be induced by genetic programs according to the spatial patterning of cells within tissues. Some of the earliest ideas and mathematical descriptions on how physical processes and constraints affect biological growth, and hence natural patterns such as the spirals of phyllotaxis, were written by D'Arcy Wentworth Thompson in his 1917 book *On Growth and Form* and Alan Turing in his *The Chemical Basis of Morphogenesis* (1952).

Where Thompson explained animal body shapes as being created by varying rates of growth in different directions, for instance to create the spiral shell of a snail, Turing correctly predicted a mechanism of morphogenesis, the diffusion of two different chemical signals, one activating and one deactivating growth, to set up patterns of development, decades before the formation of such patterns was observed. The fuller understanding of the mechanisms involved in actual organisms required the discovery of the structure of DNA in 1953, and the development of molecular biology and biochemistry.

4.5 Genetic and molecular basis



Morphogenesis is controlled by a "toolkit" of genes which switch development on and off at precise times and places.

Several types of molecules are important in morphogenesis. Morphogens are soluble molecules that can diffuse and carry signals that control cell differentiation via concentration gradients. Morphogens typically act through binding to specific protein receptors. An important class of molecules involved in morphogenesis are transcription factor proteins that determine the fate of cells by interacting with DNA. These can be coded for by master regulatory genes, and either activate or deactivate the transcription of other genes; in turn, these secondary gene products can regulate the expression of still other genes in a regulatory cascade of gene regulatory networks. At the end of this cascade are classes of molecules that control cellular behaviors such as cell migration, or, more generally, their properties, such as cell adhesion or cell contractility.

For example, during gastrulation, clumps of stem cells switch off their cell-to-cell adhesion, become migratory, and take up new positions within an embryo where they again activate

specific cell adhesion proteins and form new tissues and organs. Developmental signaling pathways implicated in morphogenesis include Wnt, Hedgehog, and ephrins.

4.6 Branching morphogenesis

In the development of the lung a bronchus branches into bronchioles forming the respiratory tree. The branching is a result of the tip of each bronchiolar tube bifurcating, and the process of branching morphogenesis forms the bronchi, bronchioles, and ultimately the alveoli. Branching morphogenesis is also evident in the ductal formation of the mammary gland. Primitive duct formation begins in development, but the branching formation of the duct system begins later in response to estrogen during puberty and is further refined in line with mammary gland development.

4.6.1 Cancer morphogenesis

Cancer can result from disruption of normal morphogenesis, including both tumor formation and tumor metastasis. Mitochondrial dysfunction can result in increased cancer risk due to disturbed morphogen signaling.

4.6.2 Virus morphogenesis

During assembly of the bacteriophage (phage) T4 virion, the morphogenetic proteins encoded by the phage genes interact with each other in a characteristic sequence. Maintaining an appropriate balance in the amounts of each of these proteins produced during viral infection appears to be critical for normal phage T4 morphogenesis. Phage T4 encoded proteins that determine virion structures include major structural components, minor structural components and non-structural proteins that catalyze specific steps in the morphogenesis sequence. Phage T4 morphogenesis is divided into three independent pathways: the head, the tail and the long tail fibres as detailed by Yap and Rossman.

4.7 Amphibians

There are more than 6,000 species of amphibians living today. This animal class includes toads and frogs, salamanders and newts, and caecilians. Almost all amphibians have thin, moist skin that helps them breathe. No other group of animals has this special skin. Most amphibians undergo a unique change from larvae to adults, called metamorphosis. All amphibians are ectotherms (what used to be called "cold-blooded"), a trait they share with invertebrates, fish, and reptiles.

4.8 Thin-skinned

Most amphibians have thin skin that is very permeable (allowing liquids and gases to pass through it easily). This is important for two reasons. First, it means that their skin helps them breathe, since oxygen passes easily through it. Second, it means that amphibians lose a lot of water through their skin. This is why most amphibians are found in moist or humid environments, where they can re-load their water reserves.

4.9 Leading a Double-Double Life

The word amphibian comes from the Greek word *amphibios,* meaning "a being with a double life." Some say their name refers to the fact that amphibians live in two places -- on land and in water. While dual residence is the rule for most amphibians, some species are strictly aquatic (water-dwelling) and some are strictly terrestrial (land-dwelling).

More accurately, amphibians' "double life" refers to two distinct life stages -- a larval stage and an adult stage. Most amphibians lay eggs, which hatch into larvae and undergo an amazing transformation (or metamorphosis) as they move from larval to adult stages. For instance, tadpoles (the larval stage of frogs) have gills and a tail -- features that enable them to live underwater. During metamorphosis, tadpoles lose their gills and develop lungs so they can breathe out of water. At the same time, they begin to grow limbs and lose their tails. The end result: adult frogs who spend much of their time on land.

4.10 Just the Right Temperature

Amphibians, like reptiles, are ectotherms. This means that they cannot produce sufficient internal heat to maintain a constant body temperature. Instead, amphibians' body temperature varies, depending on the surrounding temperature. So what does this mean for amphibians? It means that they're responsible for regulating their own body temperature. When it's cold outside and they need to warm up, amphibians often bask in the sun to raise their body temperature. When it's too cold to even bask, amphibians may brumate**.** This means they're in a hibernation-like state, but they may have periods of wakefulness and even drink when necessary. When it's hot outside, amphibians spend much of the time burrowing during the day, becoming active only at night.

4.11 Amphibians in Danger: The Extinction Crisis

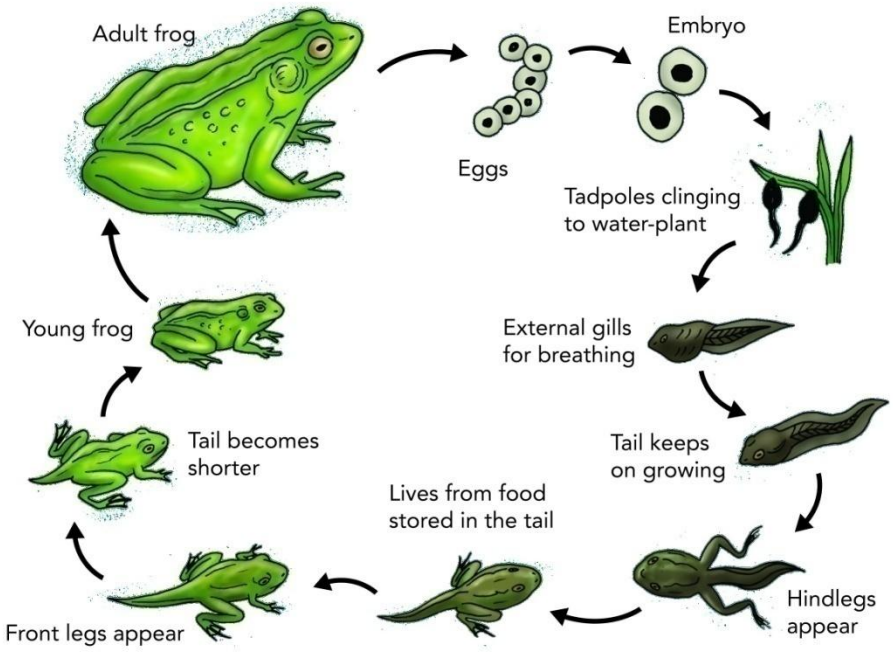
At this very moment, amphibians are facing an extinction crisis. More than 160 species of amphibians may already be extinct. More than 1,800 amphibian species are threatened with extinction – that’s 32% of all known amphibian species. And at least 43% of all species have

undergone population declines, while less than one percent show population increases. The greatest threat facing amphibians is habitat loss and degradation. Other significant threats include pollution, climate change, introduced species, and over-collection. Perhaps the most sinister threat is a newly-recognized fungal disease, which can cause rapid and severe amphibian declines. What is being done to help amphibians? As a first step, hundreds of experts have contributed to a Global Amphibian Assessment, an ongoing project that looks at the distribution and conservation status of all known species.

In addition, amphibian specialists around the world are working on understanding the causes of the declines, developing long-term conservation programs, and responding to immediate crises. Amphibians have been referred to as "canaries in the global coalmine" and "nature's indicators" because they are some of the first living things to be affected by environmental changes. When amphibians show a decline, it serves as a warning to other species, including humans. By helping amphibians, we are helping the world.

4.12Metamorphosis in amphibians

Metamorphosis in amphibians is the transformation of the larva to a miniature adult replicate, and usually from an aquatic to a terrestrial or semi-terrestrial lifestyle. Metamorphosis marks the beginning of the end of larval life. Once begun, metamorphosis usually proceeds rapidly, which reduces the transforming amphibian's exposure to predation or other potential stresses when it is neither fully aquatic nor fully terrestrial.



Different stages of metamorphosis in frog

Metamorphosis is initiated internally and maintained by the hormone thyroxine (TH), and the process is obligatory. TH elicits extensive cellular, biochemical, and morphological changes to occur during metamorphosis. Events that occur during metamorphosis, including altered gene expression, morphogenesis, tissue restructuring, and extensive cell death, result from differential response of tissues to TH. The genetically determined developmental program is in place prior to the release of TH. The key element determining the response to the hormone is determined by the nuclear thyroid hormone receptor (TR). As in most vertebrates, two thyroid hormone receptors, TRα and TRβ, repress transcription in the absence of the TH, and whose concentration of TR in tissues is directly modulated by TH. Nevertheless, environmental factors can initiate early thyroxine release if a larva has completed certain morphogenic events.

For example, crowding, reduced food or oxygen, drying of water bodies, or increased predation can result in TH release. Although TH and its derivatives promote metamorphosis, they do not operate alone. The thyroid is present early in larval life, but its secretory activity is apparently inhibited by corticoid hormones, such as corticosterone. Furthermore, prolactin is abundant in early larval stages and makes the body tissues insensitive to TH. When these inhibitions are removed, the thyroid secretes TH, effecting transformation.

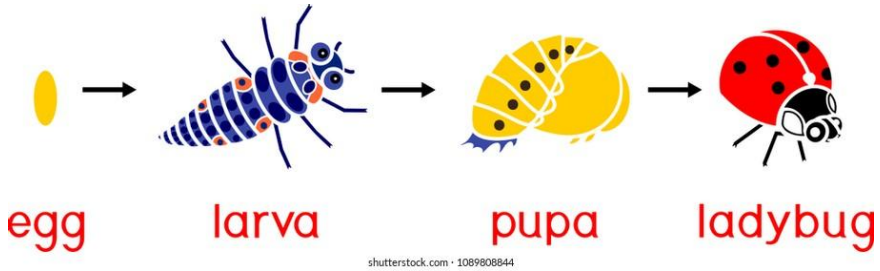
Metamorphosis signals the completion of embryogenesis. Some developmental processes, such as maturation of gonads, continue through the juvenile stage, but the major structural and physiological features are in place at the conclusion of metamorphosis. Metamorphosis is

nearly imperceptible in caecilians and salamanders but dramatic in frogs. Anuran larvae require major structural and physiological reorganization because of the striking differences between the larval and the juvenile–adult stages. Change does not occur all at once but gradually, each step leading to the next level of transformation. Unlike insect pupae, metamorphosing tadpoles remain active, capable of avoiding predators and environmental stresses.

4.13 Metamorphosis in insects

Amphibians and insects provide most people with their first contact with metamorphosis. The striking transformation of a tadpole into a frog is relatively rapid but one can track its progression from day to day as its limbs extend and its tail is resorbed. Metamorphosis in insects, though, seems more mysterious as their external exoskeleton hides the gradual changes occurring inside, and one only sees the results when the old outer cuticle is abruptly shed, such as when the butterfly emerges from its chrysalis. Metamorphosis is an ancient life history trait that extends deep to the roots of the amphibians and many groups of invertebrates.

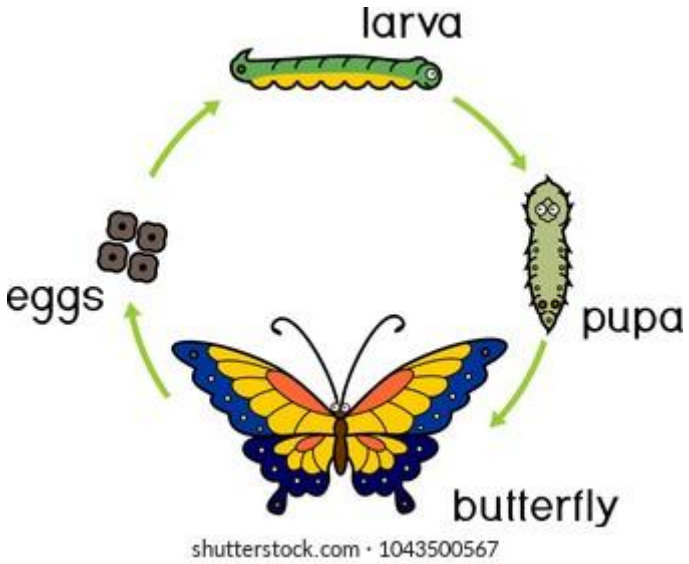
Insects are unusual, though, in that their metamorphosis is a derived trait that evolved well after they colonized the land. Insect orders approximating different steps in the evolution of metamorphosis exist today, so that comparative studies allow a piecing together of the molecular, developmental and endocrine changes that accompanied this transition. Insect metamorphosis is under hormonal control, which has been a subject of experimental study for almost a century. The importance of insects as competitors for food and fiber as well as their impact on human and animal health spurred extensive research into their physiology and development, and especially into how they control their metamorphosis.



The early stages of this research typically used large insects which facilitated surgical manipulations and the isolation of sufficient amounts of tissue for hormone extraction and chemical characterization. Ensuing genetic and molecular studies, though, gradually shifted to *Drosophila melanogaster*, which still serves as an unrivaled platform for gene discovery. However, many derived features of *Drosophila*, such as an invariant number of

larval instars and an almost complete replacement of larval cells by those of the adult at metamorphosis, have resulted in a de-emphasis or loss of some aspects of the hormonal control seen in less derived insects.

Consequently, despite the fact that work on *Drosophila* is responsible for the discovery of virtually all the genes involved in hormone reception, their downstream effects, and stage specificity of action, the broader functions of such genes often remained obscure for decades and were finally shown in insects with less derived life history patterns. For example, work on the flour beetle, *Tribolium castaneum*, provided the proof that the *Methoprene tolerant* gene (*Met*) does, indeed, encode the receptor for juvenile hormone (JH), a key hormone that suppresses metamorphosis. Also, studies on this beetle and the cockroach *Blattella germanica* showed that the helix-turn-helix transcription factor Eip93F (E93) is a master stage-specifying gene that stands on top of a gene cascade that produces the adult phenotype. Besides *Drosophila*, this discussion draws on other insect model systems such as *Bombyx mori*, *Manduca sexta*, *Tribolium castaneum*, *Oncopeltus fasciatus*, *Pyrrhocoris apterus* and *Blattella germanica*, for which genomic information and gene suppression techniques can be woven into a rich history of endocrine experimentation.



Although these few systems do not begin to cover the amazing range of variation that one sees in the insects, it is heartening that highly derived life history strategies, such as female neoteny in Strepsiptera and scale insects or the complete metamorphosis that evolved in parallel in thrips, utilize the same molecular switches that regulate more traditional life history patterns. This unit explores the developmental changes that accompanied the

evolution of the insect larval and pupal stages. It then focuses on the two main hormonal systems that regulate insect molting and metamorphosis and considers how these systems evolved to support the increasing complexity of insect life histories. Finally, it examines our growing knowledge of the function of the stage specification genes that regulate the phenotype of each major life stage and how these genes and their control have changed with the increasing complexity of insect life histories.

4.14 Tissue reactivity

A foreign body reaction (FBR) is a typical tissue response to a foreign body within biological tissue. It usually includes the formation of a foreign body granuloma. Tissue-encapsulation of an implant is an example, as is inflammation around a splinter. Foreign body granuloma formation consists of protein adsorption, macrophages, multinucleated foreign body giant cells (macrophage fusion), fibroblasts, and angiogenesis. It has also been proposed that the mechanical property of the interface between an implant and its surrounding tissues is critical for the host response.

In the long term, the foreign body reaction results in encapsulation of the foreign body within a calcified shell. For example, a *lithopedion* is a rare phenomenon which occurs most commonly when a fetus dies during an abdominal pregnancy, is too large to be reabsorbed by the body, and calcifies.

4.15 Foreign body reaction to biomaterial implantation

Following biomaterial implantation, blood and body fluids contact the implant surface. Host blood proteins adsorb onto the implant surface and a fibrin matrix forms. Acute and chronic inflammation follow the initial blood protein deposition and matrix formation. Macrophages at the implant site fuse to form foreign body giant cells. Following the inflammatory response, granulation tissue form. The end stage of the foreign body reaction is the fibrous capsule formation around the implanted biomaterial. The biocompatibility of the device affects the severity of the foreign body reaction. The foreign body reaction can lead to device failure.

4.16 Protein adsorption

During blood-biomaterial interaction, blood proteins spontaneously adsorb to the biomaterial surface. The biomaterial surface properties affect the types, concentrations, and conformation of proteins that adsorb to the surface. The Vroman effect can describe the time-dependent

behavior of this protein adsorption. Surface-adsorbed proteins regulate inflammatory cell interaction and adhesion. The deposited proteins allow inflammatory cells to attach via integrins. The biomaterial surface can also recruit and activate complement proteins.

4.17 Immune recruitment

The composition and conformation of adsorbed proteins on the implant surface is critical to the foreign body reaction. For the first two days, neutrophils are the primary cell type that deposit on the implant surface. Neutrophils release degradative enzymes and reactive oxygen intermediates that damage the implant. Platelets from the blood-biomaterial interaction release inflammatory cytokines that cause monocytes and macrophages to extravasate and migrate to the implant site. The degranulation and release of histamine from mast cells further recruits macrophages to the biomaterial. Macrophages adhere to the biomaterial surface based on the surface protein deposits and produce cytokines that further recruit macrophages. Foreign body granuloma forms as immune cells accumulate on the biomaterial surface in an attempt to eliminate the biomaterial.

4.18 Macrophage fusion

Adherent macrophages at the implant site can fuse into a multinucleated cell called foreign body giant cell. Foreign body giant cell formation depends on the biomaterial surface properties and on the presence of interleukin-4 and interleukin-13. Foreign body giant cells release reactive oxygen intermediates, degradative enzymes, and acid onto the biomaterial surface. Foreign body giant cells also attempt to engulf the biomaterial for degradation. Adherent macrophages and foreign body giant cells degrade biomaterials and can lead to device failure. Foreign body giant cells remain on the surface of the implanted device throughout the device's lifetime.

4.19 Biological properties

Biocompatibility of suture materials describes how sutures, which are foreign materials to the body, could affect surrounding tissues and how the surrounding tissues could affect the properties of sutures. Thus, biocompatibility is a two-way relationship. The extent of tissue reaction to sutures depends largely on the chemical nature of the suture and its degradation products, if it is absorbable. Sutures from natural sources like catgut and silk usually provoke

more tissue reaction than synthetic sutures because of the availability of enzymes to react with natural biopolymers.

Besides chemical factors, physical form, the amount and stiffness of suture materials have also been reported to elicit different levels of tissue reactions. For example, a stiff suture would result in stiff projecting ends in a knot where cut. These stiff ends could irritate surrounding tissues mechanically, a problem associated with some monofilament sutures but generally not found in braided multifilament sutures. Because the extent of a reaction relates to the quantity of the buried structure, it is a well-known practice in surgery that one should use as little suture material as possible, such as a smaller knot and a smaller size, to close wounds. The use of a smaller size suture which provides adequate support to wounds and does not cut through tissue is preferred as a small decrease in diameter would lead to a large decrease in buried suture volume. There are two basic ways to study biocompatibility of suture materials:

- Cellular response and
- Enzyme histo-chemistry

The former is the most frequently used and provides information about the type and density of inflammatory cells at a suture site. In this approach, sutures without tension are implanted in small animals, e.g. the gluteal muscle of rats. This implantation site has given a very consistent reproducible cellular response for comparisons. However, Walton (1989) raised the question of using this common test procedure, particularly for sutures used in orthopedic surgery due to the observed inflamed nature of the postoperative synovial tissue and the mechanically stressed nature of the suture.

Normal tissue reaction to sutures can be grouped into the following stages, according to the time taken for the appearance of inflammatory cells. They are:

- Initial infiltration of polymorphonuclear leukocytes;
- Lymphocytes and monocytes during the first 3–4 days (i.e., acute response);
- Appearance of macrophages and fibroblasts from day 4 to day 7; and
- Maturation of fibrous connective tissue formation with chronic inflammation after the 7th to the 10th day.

During the first 7 days post-implantation, there is virtually no difference in normal tissue reaction between synthetic absorbable and nonabsorbable sutures. However, a slightly higher inflammatory reaction to synthetic absorbable sutures could persist for an extended period

until they are completely absorbed and metabolized, while synthetic nonabsorbable sutures, in general, produce a minimal chronic inflammatory reaction with a thin fibrous connective tissue capsule surrounding the suture usually by 28 days post-implantation. In addition to the tissue reactions that are normal to all sutures, there are several reactions that are suture and site specific. Some examples include urinary stone or calci formation, granuloma formation, thrombogenicity, propensity toward wound infection and recurrence of tumor after radiation treatment and allergy.

Monofilament sutures are considered to be a better choice than multifilament ones in closing contaminated wounds. Multifilament sutures elicit more tissue reactions which may lessen tissue ability to deal with wound infections. They also have a capillary effect which could transport microorganisms from one region of the wound to another. The reason that multifilament sutures generally elicit more tissue reactions than their monofilament counterparts is because inflammatory cells are able to penetrate into the interstitial space within a multifilament suture and invade each filament. Multifilament sutures also have a larger surface area in contact with tissues which should be expected to elicit more tissue reaction.

4.20 Summary

Under this unit we have summarized metamorphosis and its types with examples. Metamorphosis is the change in the body form and habits during the development cycle of animals. Complete metamorphosis and incomplete metamorphosis are two growth types of insects where the body form of insects changes during their lifecycle. Both complete and incomplete metamorphosis extend from the egg stage to the adult stage. Complete metamorphosis consists of four stages: egg, larva, pupa, and adult. However, the incomplete metamorphosis consists of three stages: egg, nymph, and adult. The main difference between complete metamorphosis and incomplete metamorphosis is that complete metamorphosis consists of a very active, ravenously eating larva and an inactive pupa whereas incomplete metamorphosis consists of a nymph, which resembles a miniature adult. Complete metamorphosis occurs in wasps, ants, and fleas while incomplete metamorphosis occurs in termites, praying mantis, and cockroaches

Complete metamorphosis is the type of insect development that includes egg, larva, pupal, and adult stages, which differ greatly in morphology. The lifecycle of butterflies, ants, fleas, bees, beetles, moths, and wasps are examples of the complete metamorphosis. Complete and incomplete metamorphosis are two types of growth forms in insects. The complete

metamorphosis occurs through four stages: egg, larva, pupa, and adult. The incomplete metamorphosis occurs through three stages: egg, nymph, and adult. The pupa stage is not developed during incomplete metamorphosis. Therefore, the main difference between complete and incomplete metamorphosis is the differential stages developed during each type of growth.

4.21 Terminal questions

Q.7. What do you mean by metamorphosis?

Answer:----------

Q.8. Describe metamorphosis in amphibians.

Answer:----------

Q.9. Write a short note on tissue reactivity.

Answer:----------

Q.10. What do you mean by metamorphosis in insects?

Answer:----------

Further readings

6. Vertebrate Endocrinology- David O. Norris

7. Invertebrate Zoology –Robert W. Hegner

8. Textbook of Biotechnology –B. D. Singh

9. Textbook of Biochemistry for Undergraduates - Rafi, M.D.

10. Biochemistry and molecular biology- Wilson Walker.

DCEZY-108

Developmental Biology

Uttar Pradesh Rajarshi Tandon

Open University

Bachelor of Science

Block

2 Developmental Biology - II

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Block-II

In the previous block you have studies half part of developmental biology. In this block you will study remaining part of developmental biology, which is divided into four units (units 5 to 8).

The block 2nd is organized into further following four units as under:

Unit-5

It deals the induction process (factors controlling moulting in insects). The process of moulting in insects beings with the separation of the cuticle from the underlying epidermal cells and formation of its replacement. Moulting which is regulated by harmons. Moulting known technically as ecdysis, is literally a period of growth for insects.

Unit-6

It describes regeneration (Ability of regeneration, amphibian limb regeneration). Regeneration is the natural process of replacing or restoring damaged or missing cells, tissues and organs or regeneration is one of the processes in which if an organism is cut into several pieces, each of its parts regrows to the original state.

Unit-7

It covers the growth and ageing (concepts of growth and mechanism of growth). Growth and aging appear to be opposites, growth is the progressive increase in the size of a child or parts of a child. Aging is the sequential or progressive , physiological change in an organism.

Unit-8

It covers the growth curve and its interpretation (types of cell growth, ageing). Aging changes occur in all of the body's cells, tissues and organs and these changes affect the functioning of all body system.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about genetic specificity
- To discuss moulting, regeneration

- To discuss about cellular molecular fundamentals (tissue, arthropods, planaria, humans and reptiles)
- To know about histology of regeneration process
- To know about concept of ageing and degrowth
- To know about mechanism of growth and cell growth
- To know about cancer cell growth and exponential growth
- To discuss about the factors that regulate growth

Unit-5 - Induction process (factors controlling moulting in insects)

Structure

5.1 Introduction

Organs are complex structures composed of numerous types of tissues. In the vertebrate eye, for example, light is transmitted through the transparent corneal tissue and focused by the lens tissue (the diameter of which is controlled by muscle tissue), eventually impinging on the tissue of the neural retina. The precise arrangement of tissues in this organ cannot be disturbed without impairing its function. Such coordination in the construction of organs is accomplished by one group of cells changing the behavior of an adjacent set of cells, thereby causing them to change their shape, mitotic rate, or fate. This kind of interaction at close range between two or more cells or tissues of different history and properties is called proximate interaction, or induction. There are at least two components to every inductive interaction. The first component is the inducer: the tissue that produces a signal (or signals) that changes the cellular behavior of the other tissue. The second component, the tissue being induced, is the responder.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about induction
- To know about genetic specificity
- To discuss moulting
- To understand the process of moulting

Not all tissues can respond to the signal being produced by the inducer. For instance, if the optic vesicle (presumptive retina) of *Xenopus laevis* is placed in an ectopic location (i.e., in a different place from where it normally forms) underneath the head ectoderm, it will induce that ectoderm to form lens tissue. Only the optic vesicle appears to be able to do this; therefore, it is an inducer. However, if the optic vesicle is placed beneath ectoderm in the flank or abdomen of the same organism, that ectoderm will not be able to respond. Only the head ectoderm is competent to respond to the signals from the optic vesicle by producing a lens.

5.2 Genetic specificity of induction

The second property of epithelial-mesenchymal interactions is the genetic specificity of induction. Whereas the mesenchyme may instruct the epithelium as to what sets of genes to

activate, the responding epithelium can comply with these instructions only so far as its genome permits. This property was discovered through experiments involving the transplantation of tissues from one species to another. In one of the most dramatic examples of interspecific induction, Hans Spemann and Oscar Schotté (1932) transplanted flank ectoderm from an early frog gastrula to the region of a newt gastrula destined to become parts of the mouth. Similarly, they placed presumptive flank ectodermal tissue from a newt gastrula into the presumptive oral regions of frog embryos. The structures of the mouth region differ greatly between salamander and frog larvae.

The salamander larva has club-shaped balancers beneath its mouth, whereas the frog tadpole produces mucus-secreting glands and suckers. The frog tadpole also has a horny jaw without teeth, whereas the salamander has a set of calcareous teeth in its jaw. The larvae resulting from the transplants were chimeras. The salamander larvae had froglike mouths, and the frog tadpoles had salamander teeth and balancers. In other words, the mesodermal cells instructed the ectoderm to make a mouth, but the ectoderm responded by making the only kind of mouth it "knew" how to make, no matter how inappropriate.

5.3 Moulting

In biology, moulting (British English), or molting (American English), also known as sloughing, shedding, or in many invertebrates, ecdysis, is the manner in which an animal routinely casts off a part of its body (often, but not always, an outer layer or covering), either at specific times of the year, or at specific points in its life cycle. Moulting can involve shedding the epidermis (skin), pelage (hair, feathers, fur, wool), or other external layer. In some groups, other body parts may be shed, for example, the entire exoskeleton in arthropods, including the wings in some insects. It is also known as Ecdysis or Shedding. The periodic shedding of old cuticle and the subsequent formation of new one is called moulting or ecdysis moulting are accuring periodically till maturation of insects. The molting process is triggered by hormones released when an insect's growth reaches the physical limits of its exoskeleton. Each molt represents the end of one growth stage (instar) and the beginning of another. In some insect species the number of instars is constant (typically from 3 to 15), but in others it may vary in response to temperature, food availability, or other environmental factors.

An insect is known as an imago (adult) when it becomes sexually mature. At this point, molting stops and energy for growth is channeled into production of eggs or sperm. An insect cannot survive without the support and protection of its exoskeleton, so a new, larger replacement must be constructed inside the old one -- much like putting an overcoat under a sweater! The molting process begins when epidermal cells respond to hormonal changes by increasing their rate of protein synthesis. This quickly leads to apolysis -- physical separation of the epidermis from the old endocuticle. Epidermal cells fill the resulting gap with an inactive molting fluid and then secrete a special lipoprotein (the cuticulin layer) that insulates and protects them from the molting fluid's digestive action. This cuticulin layer becomes part of the new exoskeleton's epicuticle.

After formation of the cuticulin layer, molting fluid becomes activated and chemically "digests" the endocuticle of the old exoskeleton. Break-down products (amino acids and chitin microfibrils) pass through the cuticulin layer where they are recycled by the epidermal cells and secreted under the cuticulin layer as new procuticle (soft and wrinkled). Pore canals within the procuticle allow movement of lipids and proteins toward the new epicuticle where wax and cement layers form. When the new exoskeleton is ready, muscular contractions and intake of air cause the insect's body to swell until the old exoskeleton splits open along lines of weakness (ecdysial sutures). The insect sheds its old exoskeleton (ecdysis) and continues to fully expand the new one. Over the next few hours, sclerites will harden and darken as quinone cross- linkages form within the exocuticle.

This process (called sclerotization or tanning) gives the exoskeleton its final texture and appearance. An insect that is actively constructing new exoskeleton is said to be in a pharate condition. During the days or weeks of this process there may be very little evidence of change. Ecdysis, however, occurs quickly (in minutes to hours). A newly molted insect is soft and largely unpigmented (white or ivory). It is said to be in a teneralcondition until the process of tanning is completed (usually a day or two).

Molting, known technically as ecdysis, is literally a period of growth for insects. In humans, an analogy can be drawn to molting as a period of personal transformation, such as the shedding of one's old self and the emergence of a new and improved person. Insects grow in increments. Each stage of growth ends with molting, the process of shedding and replacing the rigid exoskeleton. People often think molting is the simple act of an insect breaking out of its skin and leaving it behind. In truth, the process is complex and involves several parts.

5.4 When insects molt

After egg hatches, the immature insect feeds and grows. Its exoskeleton is like a shell. Eventually, the larva or nymph must shed its unyielding overcoat to continue its development.

The exoskeleton which serves as its external backbone is used for protection and support. Without an exoskeleton, the insect could not survive. An old exoskeleton is shed when a new one is ready underneath, a process that can take days or weeks.

5.5 Understanding the exoskeleton

To understand how molting occurs, it helps to know the three layers of the insect exoskeleton. The outermost layer is called the cuticle. The cuticle protects the insect against physical injury and water loss, as well as provides rigidity for muscle. It is this outermost layer that sheds during a molt. Underneath the cuticle is the epidermis. It is responsible for secreting a new cuticle when it is time to shed the old one. Underneath the epidermis is the basement membrane. This membrane is what separates the insect's main body from its exoskeleton.

5.6 The process of molting

In molting, the epidermis separates from the outermost cuticle. Then, the epidermis forms a protective layer around itself and secretes chemicals that break down the insides of the old cuticle. That protective layer becomes part of the new cuticle. When the epidermis has formed the new cuticle, muscular contractions and air intake cause the insect's body to swell, thus splitting open the remains of the old cuticle. Finally, the new cuticle hardens. The bug squeezes out from the outgrown exoskeleton. The insect must continue to swell and expand the new cuticle, so it is large enough to allow room for more growth. The new overcoat is soft and much paler than the former one, but over a few hours, it becomes darker and begins to harden. Within a few days, the insect appears to be a slightly larger copy of its former self.

5.7 Pros and cons of molting

For some insects, a big benefit to having a system of molting for growth is that it allows damaged tissue and missing limbs to be regenerated or substantially reformed. Complete regeneration may require a series of molts, the stump becoming a little larger with each molt until it is a normal or nearly back to normal size. A major disadvantage to having to molt as a system of growth is that the animal in question is entirely incapacitated during the process. An insect is completely vulnerable to a predator attack while undergoing molting.

5.8 Summary

This unit summarizes molting that is the process of producing a new cuticle and the subsequent shedding of the old cuticle. The cuticle is the outer covering of the insect and is its exoskeleton to which the muscles are attached. The outermost layer is called the epicuticle; under this is the exocuticle followed by the endocuticle. In some systems, the exo- and endocuticle are classed together as the procuticle. In some insects, only the epi- and exocuticle are deposited before ecdysis, with the endocuticle following ecdysis, whereas in others, some endocuticle may be deposited before ecdysis. The epicuticle is composed of only protein, whereas the exo- and endocuticle contain both chitin and protein in varying proportions depending on the type of cuticle, that is, whether rigid or flexible. Chitin is a polymer of *N*-acetylglucosamine and can be cross-linked to the protein components of the cuticle in a process called sclerotization. After sclerotization the insect is able to move, feed, fly, etc. The rigid parts of the cuticle are then set and cannot be expanded, whereas flexible cuticle may expand either by a simple unfolding of the new epicuticle or in response to hormonal signals. When the epicuticle has completely unfolded, further expansion is impossible and the larva must molt in order to grow further. Molting is also necessary at the end of larval life for metamorphosis.

5.9 Terminal questions

Q.1 What do you mean by induction process?

Answer:----------

Q.2 Describe moulting in insects.

Answer:----------

Q.3 Write a short note on moulting.

Answer:----------

Q.4 Write a short note on insects.

Answer:----------

Q.5 Describe controlling factors of moulting.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner
3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit-6 - Regeneration (Ability of regeneration, amphibian limb regeneration)

Structure

6.1 Introduction

Morphogenesis is the developmental process by which tissues and organs acquire the shape that is critical to their function. Here, we review recent advances in our understanding of the mechanisms that drive morphogenesis in the developing eye. These investigations have shown that regulation of the actin cytoskeleton is central to shaping the presumptive lens and retinal epithelia that are the major components of the eye. Regulation of the actin cytoskeleton is mediated by Rho family GTPases, by signaling pathways and indirectly, by transcription factors that govern the expression of critical genes. Changes in the actin cytoskeleton can shape cells through the generation of filopodia (that, in the eye, connect adjacent epithelia) or through apical constriction, a process that produces a wedge-shaped cell. We have also learned that one tissue can influence the shape of an adjacent one, probably by direct force transmission, in a process we term inductive morphogenesis. Though these mechanisms of morphogenesis have been identified using the eye as a model system, they are likely to apply broadly where epithelia influence the shape of organs during development.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about regeneration
- To discuss about cellular molecular fundamentals (tissue, arthropods, planaria, humans and reptiles)
- To know about amphibian limb generation
- To know about histology of regeneration process

Morphogenesis is the developmental cascade of pattern formation and body plan establishment, resulting in the final form of the organism. Morphogenesis is the basis of the fields of tissue engineering and regenerative medicine that is founded on the basis of morphogenetic signals, responding stem cells, and the extracellular matrix scaffolds. The goal of tissue engineering is the design and construction of spare parts for the human body to restore function to bone and articular cartilage and other tissues. Although bone has a high potential for regeneration, the adjacent articular cartilage is feeble in its capacity for repair and regeneration. Implantation of demineralized extracellular matrix from bone into subcutaneous sites induces local new bone induction. This experimental model permits the

isolation and identification of bone morphogenetic proteins (BMPs), the morphogenetic signals for bone and cartilage morphogenesis. BMPs initiate and promote bone formation and a variety of tissues including articular cartilage, brain, eye, heart, and kidney, leading to the concept of BMPs as body morphogenetic proteins. This chapter will discuss the role of BMPs in bone and articular cartilage regenerative medicine and the remaining challenges. The rules of tissue morphogenesis gleaned from BMPs and bone may be applied universally to morphogenesis and regeneration of other organs and tissues, ushering us into the brave new world of the creation of spare parts for the human body based on signals, stem cells, and scaffolds of extracellular matrix.

Many biological organisms can regenerate some of their tissues and organs. Some species, such as hydra or planarian, can regenerate the whole organism from its small parts. Other organisms, among them mammals, have more limited regeneration potential that includes wound healing but also regeneration of complex structures such as antlers, and fingertips.

Physiological mechanisms of regeneration are very complex and in many cases they are not completely known. However, the biggest knowledge gap concerns the overall dynamics of a large-scale anatomy which allows it to be maintained, remodelled, or regenerated toward a specific shape. Our goal is to understand what algorithm is used by cell networks to decide which activity brings the morphology closer to the correct state, and to know when that state has been reached so that growth can stop. We can group these mechanisms in two classes that can be related to large pattern formation and to cell (or tissue) memory. By pattern formation we understand here the tissue organization due to the molecular process of cell-cell communication, processes of cell growth, division and motion and other processes which use the information available at current time. Contrary to that, cell memory implies the existence of the information about some former states of the tissue, which orchestrates cellular activity towards restoring a particular anatomical configuration and allows growth and remodelling to stop when a particular goal-state has been reached.

Let us illustrate these mechanisms on the example of wound healing, in which some cytokines are produced at the injury site, they diffuse in the tissue and attract some special cells (e.g., fibroblasts) which divide and regenerate the tissue. Morphogenetic gradients, organizing centres and activator-inhibitor interaction can be involved in pattern formation and tissue regeneration. If, for example, tissue formation is controlled by an organizing

centre, we can expect that the same centre will provide its regeneration assuming that the centre itself is preserved.

Experiments on planarian regeneration allow us to assume that its tissues can keep some information about their former states. Due to alteration of normal electrical connectivity among its cells, a planarian with two heads can be obtained from a normal one-headed animal. If two heads are amputated, then both of them will regenerate in subsequent rounds of regeneration. Hence, regenerations of one or two heads are possible. The choice between them is not determined at the genetic level because the genomic sequence is the same, and because any "reprogrammed" (epigenetically) tissues are discarded at each cut. Therefore the information about the number of heads is kept in the remaining tissue. Moreover, this memory is preserved in any part of the tissue since the amputated part can vary. There are other examples of regeneration that suggest the existence of tissue memory.

A model of tissue regeneration based on cell memory is suggested in our previous work, where we consider a tissue as an ensemble of points on the plane, each point corresponding to a single cell. Each cell produces a signal that spreads in space and decays as a function of distance from the cell. At the same time, each cell receives the signals produced by all other cells, and consequently the total signal received by a cell depends on its location with respect to the other cells. Hence, the distribution of the total signal depends on the geometry of cell structure. We suppose that each cell keeps the value of the total signal that it receives from the other cells (memory). If a part of the cell structure is amputated, the signal distribution changes, and the difference between the old and the new signals stimulates cell proliferation. Under some additional conditions on the location of proliferation cells, the initial cell structure will be regenerated. This mechanism works for a local tissue regeneration with the characteristic size determined by the rate of signal decay in space.

In the current work we continue to model regeneration of cell structures. We suggest a model which allows a more distant regeneration. It contains two submodels – one global and one local. The main assumptions of the first submodel are similar to those in the previous work: cells exchange signals, keep the information about the values of these signals and react when these values are changed. In comparison with the previous work, we do not amputate a part of the cell structure but instead alter the positions of cells. The difference between the initial signal distribution and the new one after cell displacement initiates cell motion and returns them to the initial positions.

One of the important characteristics of multicellular regeneration is the minimal information necessary to restore the initial structure after its modification. In, all cells produce and receive the same signal. Hence, each cell is supposed to keep only one real number: the value of the total initial signal. It appears that this information is sufficient for the regeneration of cell structure when a part of it is amputated. The difference between the old and the new signals stimulate cell proliferation, and we can exactly restore the initial cell structure. In the current work we consider a more complex biological structure consisting of several different tissues, and we change its geometry. In this case, if all cells produce and receive the same signal, in general they will not return to their initial configuration. In order to characterise such structures, a more detailed pair wise cell communication is required, where each cell produces its own signal and distinguishes the signals from other cells.

Hence, we consider that only the cells of the first (global) submodel communicate by different signals. Those cells can be some special cells or groups of cells of the corresponding tissue (e.g. stem cells, instructor cells, or organizers. Then the number of such cells corresponds to the number of tissues or organs and it is much more limited than the number of cells in the whole structure. In this case we need to complete the first (global) submodel by the second (local) submodel, which describes tissue growth around the cells of the first submodel. While a more complete and biologically realistic models can be considered, here we choose a simple and schematic mechanism of circular tissue growth in order to illustrate the principle.

Therefore, the global submodel provides configuration of tissue centres, while the local submodel creates the tissues around the centres. If some parts of the tissues are amputated but their centres are preserved, then the tissues will be regenerated. If some centres are amputated, then they should be restored by some other mechanisms which we do not consider here. The same model is able to describe morphogenesis, assuming the cells of the global submodel emerge in the embryo. In this case the tissue centres move to their equilibrium positions and generate their corresponding tissues.

6.2 Regeneration

In biology, regeneration is the process of renewal, restoration, and tissue growth that makes genomes, cells, organisms, and ecosystems resilient to natural fluctuations or events that cause disturbance or damage. Every species is capable of regeneration, from bacteria to

humans. Regeneration can either be complete where the new tissue is the same as the lost tissue, or incomplete where after the necrotic tissue comes fibrosis.

At its most elementary level, regeneration is mediated by the molecular processes of gene regulation and involves the cellular processes of cell proliferation, morphogenesis and cell differentiation. Regeneration in biology, however, mainly refers to the morphogenic processes that characterize the phenotypic plasticity of traits allowing multi-cellular organisms to repair and maintain the integrity of their physiological and morphological states. Above the genetic level, regeneration is fundamentally regulated by asexual cellular processes. Regeneration is different from reproduction. For example, hydra perform regeneration but reproduce by the method of budding.

The hydra and the planarian flatworm have long served as model organisms for their highly adaptive regenerative capabilities. Once wounded, their cells become activated and restore the organs back to their pre-existing state. The Caudata , an order of tailed amphibians, is possibly the most adept vertebrate group at regeneration, given their capability of regenerating limbs, tails, jaws, eyes and a variety of internal structures. The regeneration of organs is a common and widespread adaptive capability among metazoan creatures. In a related context, some animals are able to reproduce asexually through fragmentation, budding, or fission. A planarian parent, for example, will constrict, split in the middle, and each half generates a new end to form two clones of the original.

Echinoderms (such as the sea star), crayfish, many reptiles, and amphibians exhibit remarkable examples of tissue regeneration. The case of autotomy, for example, serves as a defensive function as the animal detaches a limb or tail to avoid capture. After the limb or tail has been autotomized, cells move into action and the tissues will regenerate. In some cases a shed limb can itself regenerate a new individual. Limited regeneration of limbs occurs in most fishes and salamanders, and tail regeneration takes place in larval frogs and toads (but not adults). The whole limb of a salamander or a triton will grow again and again after amputation. In reptiles, chelonians, crocodilians and snakes are unable to regenerate lost parts, but many (not all) kinds of lizards, geckos and iguanas possess regeneration capacity in a high degree. Usually, it involves dropping a section of their tail and regenerating it as part of a defense mechanism. While escaping a predator, if the predator catches the tail, it will disconnect.

6.3 Ecosystems

Ecosystems can be regenerative. Following a disturbance, such as a fire or pest outbreak in a forest, pioneering species will occupy, compete for space, and establish themselves in the newly opened habitat. The new growth of seedlings and community assembly process is known as regeneration in ecology.

6.4 Cellular molecular fundamentals

Pattern formation in the morphogenesis of an animal is regulated by genetic induction factors that put cells to work after damage has occurred. Neural cells, for example, express growth-associated proteins, such as GAP-43, tubulin, actin, an array of novel neuropeptides, and cytokines that induce a cellular physiological response to regenerate from the damage. Many of the genes that are involved in the original development of tissues are reinitialized during the regenerative process. Cells in the primordia of zebrafish fins, for example, express four genes from the homeobox *msx* family during development and regeneration.

6.4.1 Tissues

Strategies include the rearrangement of pre-existing tissue, the use of adult somatic stem cells and the dedifferentiation and/or transdifferentiation of cells, and more than one mode can operate in different tissues of the same animal. All these strategies result in the re-establishment of appropriate tissue polarity, structure and form. During the developmental process, genes are activated that serve to modify the properties of cell as they differentiate into different tissues. Development and regeneration involves the coordination and organization of populations cells into a blastema, which is "a mound of stem cells from which regeneration begins. Dedifferentiation of cells means that they lose their tissue-specific characteristics as tissues remodel during the regeneration process. This should not be confused with the transdifferentiation of cells which is when they lose their tissue-specific characteristics during the regeneration process, and then re-differentiate to a different kind of cell.

6.5 In animals

6.5.1 Arthropods

Arthropods are known to regenerate appendages following loss or autotomy. Regeneration among arthropods is restricted by molting such that hemimetabolous insects are capable of regeneration only until their final molt whereas most crustaceans can regenerate throughout their lifetimes. Molting cycles are hormonally regulated in arthropods, although premature molting can be induced by autotomy. Mechanisms underlying appendage regeneration in

hemimetabolous insects and crustaceans are highly conserved. During limb regeneration species in both taxa form a blastema following autotomy with regeneration of the excised limb occurring during proecdysis. Limb regeneration is also present in insects that undergo metamorphosis, such as beetles, although the cost of said regeneration is a delayed pupal stage. Arachnids, including scorpions, are known to regenerate their venom, although the content of the regenerated venom is different from the original venom during its regeneration, as the venom volume is replaced before the active proteins are all replenished.

6.5.2 Annelids

Many annelids (segmented worms) are capable of regeneration. For example, Chaetopterus variopedatus and Branchiomma nigromaculata can regenerate both anterior and posterior body parts after latitudinal bisection. The relationship between somatic and germline stem cell regeneration has been studied at the molecular level in the annelid Capitella teleta. Leeches, however, appear incapable of segmental regeneration. Furthermore, their close relatives, the branchiobdellids, are also incapable of segmental regeneration. However, certain individuals, like the lumbriculids, can regenerate from only a few segments. Segmental regeneration in these animals is epimorphic and occurs through blastema formation. Segmental regeneration has been gained and lost during annelid evolution, as seen in oligochaetes, where head regeneration has been lost three separate times.

Along with epimorphosis, some polychaetes like Sabella pavonina experience morphallactic regeneration. Morphallaxis involves the de-differentiation, transformation, and re-differentation of cells to regenerate tissues. How prominent morphallactic regeneration is in oligochaetes is currently not well understood. Although relatively under-reported, it is possible that morphallaxis is a common mode of inter-segment regeneration in annelids. Following regeneration in *L. variegatus*, past posterior segments sometimes become anterior in the new body orientation, consistent with morphallaxis.

Following amputation, most annelids are capable of sealing their body via rapid muscular contraction. Constriction of body muscle can lead to infection prevention. In certain species, such as Limnodrilus, autolysis can be seen within hours after amputation in the ectoderm and mesoderm. Amputation is also thought to cause a large migration of cells to the injury site, and these form a wound plug.

6.5.3 Echinoderms

Tissue regeneration is widespread among echinoderms and has been well documented in starfish *(Asteroidea)*, sea cucumbers *(Holothuroidea)*, and sea urchins *(Echinoidea).* Appendage regeneration in echinoderms has been studied since at least the 19th century. In addition to appendages, some species can regenerate internal organs and parts of their central nervous system. In response to injury starfish can autotomize damaged appendages. Autotomy is the self-amputation of a body part, usually an appendage. Depending on severity, starfish will then go through a four-week process where the appendage will be regenerated. Some species must retain mouth cells to regenerate an appendage, due to the need for energy. The first organs to regenerate, in all species documented to date, are associated with the digestive tract. Thus, most knowledge about visceral regeneration in holothurians concerns this system.

6.5.4 Planaria (Platyhelminthes)

Regeneration research using Planarians began in the late 1800s and was popularized by T.H. Morgan at the beginning of the 20th century. Alejandro Sanchez-Alvarado and Philip Newmark transformed planarians into a model genetic organism in the beginning of the 20th century to study the molecular mechanisms underlying regeneration in these animals. Planarians exhibit an extraordinary ability to regenerate lost body parts. For example, a planarian split lengthwise or crosswise will regenerate into two separate individuals. In one experiment, T.H. Morgan found that a piece corresponding to 1/279th of a planarian or a fragment with as few as 10,000 cells can successfully regenerate into a new worm within one to two weeks. After amputation, stump cells form a blastema formed from neoblasts, pluripotent cells found throughout the planarian body. New tissue grows from neoblasts with neoblasts comprising between 20 and 30% of all planarian cells. Recent work has confirmed that neoblasts are totipotent since one single neoblast can regenerate an entire irradiated animal that has been rendered incapable of regeneration. In order to prevent starvation a planarian will use their own cells for energy, this phenomenon is known as de-growth.

6.5.5 Aves (birds)

Owing to a limited literature on the subject, birds are believed to have very limited regenerative abilities as adults. Some studies on roosters have suggested that birds can adequately regenerate some parts of the limbs and depending on the conditions in which

regeneration takes place, such as age of the animal, the inter-relationship of the injured tissue with other muscles, and the type of operation, can involve complete regeneration of some musculoskeletal structure. Werber and Goldschmidt (1909) found that the goose and duck were capable of regenerating their beaks after partial amputation and Sidorova (1962) observed liver regeneration via hypertrophy in roosters. Birds are also capable of regenerating the hair cells in their cochlea following noise damage or ototoxic drug damage. Despite this evidence, contemporary studies suggest reparative regeneration in avian species is limited to periods during embryonic development.

An array of molecular biology techniques have been successful in manipulating cellular pathways known to contribute to spontaneous regeneration in chick embryos. For instance, removing a portion of the elbow joint in a chick embryo via window excision or slice excision and comparing joint tissue specific markers and cartilage markers showed that window excision allowed 10 out of 20 limbs to regenerate and expressed joint genes similarly to a developing embryo. In contrast, slice excision did not allow the joint to regenerate due to the fusion of the skeletal elements seen by an expression of cartilage markers.

Similar to the physiological regeneration of hair in mammals, birds can regenerate their feathers in order to repair damaged feathers or to attract mates with their plumage. Typically, seasonal changes that are associated with breeding seasons will prompt a hormonal signal for birds to begin regenerating feathers. This has been experimentally induced using thyroid hormones in the Rhode Island Red Fowls.

6.5.6 Mammals

Fig. 1 Spiny mice (*Acomys cahirinus* pictured here) can regenerate skin, cartilage, nerves and muscle.

Mammals are capable of cellular and physiological regeneration, but have generally poor reparative regenerative ability across the group. Examples of physiological regeneration in mammals include epithelial renewal (e.g., skin and intestinal tract), red blood cell replacement, antler regeneration and hair cycling. Male deer lose their antlers annually during the months of January to April then through regeneration are able to regrow them as an example of physiological regeneration. A deer antler is the only appendage of a mammal that can be regrown every year. While reparative regeneration is a rare phenomenon in mammals, it does occur. A well-documented example is regeneration of the digit tip distal to the nail bed. Reparative regeneration has also been observed in rabbits, pikas and African spiny mice. In 2012, researchers discovered that two species of African Spiny Mice, *Acomys kempi* and *Acomys percivali*, were capable of completely regenerating the autotomically released or otherwise damaged tissue. These species can regrow hair follicles, skin, sweat glands, fur and cartilage. In addition to these two species, subsequent studies demonstrated that *Acomys cahirinus* could regenerate skin and excised tissue in the ear pinna.

Despite these examples, it is generally accepted that adult mammals have limited regenerative capacity compared to most vertebrate embryos/larvae, adult salamanders and fish. But the regeneration therapy approach of Robert O. Becker, using electrical stimulation, has shown promising results for rats and mammals in general.

Some researchers have also claimed that the MRL mouse strain exhibits enhanced regenerative abilities. Work comparing the differential gene expression of scarless healing MRL mice and a poorly-healing C57BL/6 mouse strain, identified 36 genes differentiating the healing process between MRL mice and other mice. Study of the regenerative process in these animals is aimed at discovering how to duplicate them in humans, such as deactivation of the p21 gene. However, recent work has shown that MRL mice actually close small ear holes with scar tissue, rather than regeneration as originally claimed.

MRL mice are not protected against myocardial infarction; heart regeneration in adult mammals (neocardiogenesis) is limited, because heart muscle cells are nearly all terminally differentiated. MRL mice show the same amount of cardiac injury and scar formation as normal mice after a heart attack. However, recent studies provide evidence that this may not always be the case, and that MRL mice can regenerate after heart damage.

6.5.7 Humans

The regrowth of lost tissues or organs in the human body is being researched. Some tissues such as skin regrow quite readily; others have been thought to have little or no capacity for regeneration, but ongoing research suggests that there is some hope for a variety of tissues and organs. Human organs that have been regenerated include the bladder, vagina and the penis.

As are all metazoans, humans are capable of physiological regeneration (i.e. the replacement of cells during homeostatic maintenance that does not necessitate injury). For example, the regeneration of red blood cells via erythropoiesis occurs through the maturation of erythrocytes from hematopoietic stem cells in the bone marrow, their subsequent circulation for around 90 days in the blood stream, and their eventual cell-death in the spleen. Another example of physiological regeneration is the sloughing and rebuilding of a functional endometrium during each menstrual cycle in females in response to varying levels of circulating estrogen and progesterone.

However, humans are limited in their capacity for reparative regeneration, which occurs in response to injury. One of the most studied regenerative responses in humans is the hypertrophy of the liver following liver injury. For example, the original mass of the liver is re-established in direct proportion to the amount of liver removed following partial hepatectomy, which indicates that signals from the body regulate liver mass precisely, both positively and negatively, until the desired mass is reached. This response is considered cellular regeneration (a form of compensatory hypertrophy) where the function and mass of the liver is regenerated through the proliferation of existing mature hepatic cells (mainly hepatocytes), but the exact morphology of the liver is not regained. This process is driven by growth factor and cytokine regulated pathways. The normal sequence of inflammation and regeneration does not function accurately in cancer. Specifically, cytokine stimulation of cells leads to expression of genes that change cellular functions and suppress the immune response.

Adult neurogenesis is also a form of cellular regeneration. For example, hippocampal neuron renewal occurs in normal adult humans at an annual turnover rate of 1.75% of neurons. Cardiac myocyte renewal has been found to occur in normal adult humans, and at a higher rate in adults following acute heart injury such as infarction. Even in adult myocardium following infarction, proliferation is only found in around 1% of myocytes around the area of injury, which is not enough to restore function of cardiac muscle.

However, this may be an important target for regenerative medicine as it implies that regeneration of cardiomyocytes, and consequently of myocardium, can be induced.

Another example of reparative regeneration in humans is fingertip regeneration, which occurs after phalange amputation distal to the nail bed (especially in children) and rib regeneration, which occurs following osteotomy for scoliosis treatment (though usually regeneration is only partial and may take up to one year). Yet another example of regeneration in humans is vas deferens regeneration, which occurs after a vasectomy and which results in vasectomy failure.

6.5.8 Reptiles

The ability and degree of regeneration in reptiles differs among the various species, but the most notable and well-studied occurrence is tail-regeneration in lizards. In addition to lizards, regeneration has been observed in the tails and maxillary bone of crocodiles and adult neurogenesis has also been noted. Tail regeneration has never been observed in snakes. Lizards possess the highest regenerative capacity as a group. Following autotomous tail loss, epimorphic regeneration of a new tail proceeds through a blastema-mediated process that results in a functionally and morphologically similar structure.

6.5.9 Chondrichthyes

Studies have shown that some chondrichthyans can regenerate rhodopsin by cellular regeneration, micro RNA organ regeneration, teeth physiological teeth regeneration, and reparative skin regeneration. Rhodopsin regeneration has been studied in skates and rays. After complete photo-bleaching, rhodopsin can completely regenerate within 2 hours in the retina. White bamboo sharks can regenerate at least two-thirds of their liver and this has been linked to three micro RNAs, xtr-miR-125b, fru-miR-204, and has-miR-142-3p_R-. In one study, two-thirds of the liver was removed and within 24 hours more than half of the liver had undergone hypertrophy. Leopard sharks routinely replace their teeth every 9–12 days and this is an example of physiological regeneration. This can occur because shark teeth are not attached to a bone, but instead are developed within a bony cavity. It has been estimated that the average shark loses about 30,000 to 40,000 teeth in a lifetime. Some sharks can regenerate scales and even skin following damage. Within two weeks of skin wounding the mucus is secreted into the wound and this initiates the healing process. One study showed

that the majority of the wounded area was regenerated within 4 months, but the regenerated area also showed a high degree of variability.

6.5.10 Amphibians limb regeneration

Limb regeneration in the axolotl and newt has been extensively studied and researched. The nineteenth century studies of this subject are reviewed in Holland (2021). Urodele amphibians, such as salamanders and newts, display the highest regenerative ability among tetrapods. As such, they can fully regenerate their limbs, tail, jaws, and retina via epimorphic regeneration leading to functional replacement with new tissue. Salamander limb regeneration occurs in two main steps. First, the local cells dedifferentiate at the wound site into progenitor to form a blastema. Second, the blastemal cells will undergo cell proliferation, patterning, cell differentiation and tissue growth using similar genetic mechanisms that deployed during embryonic development. Ultimately, blastemal cells will generate all the cells for the new structure.

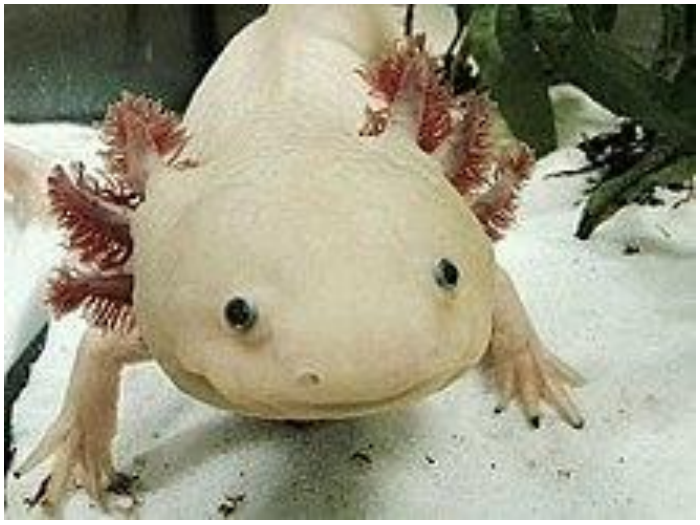

Fig. 2 Axolotls can regenerate a variety of structures, including their limbs

After amputation, the epidermis migrates to cover the stump in 1–2 hours, forming a structure called the wound epithelium (WE). Epidermal cells continue to migrate over the WE, resulting in a thickened, specialized signaling center called the apical epithelial cap (AEC). Over the next several days there are changes in the underlying stump tissues that result in the formation of a blastema (a mass of dedifferentiated proliferating cells). As the blastema forms, pattern formation genes – such as HoxA and HoxD – are activated as they were when the limb was formed in the embryo. The positional identity of the distal tip of the limb (i.e. the autopod, which is the hand or foot) is formed first in the blastema. Intermediate

positional identities between the stump and the distal tip are then filled in through a process called intercalation. Motor neurons, muscle, and blood vessels grow with the regenerated limb, and reestablish the connections that were present prior to amputation. The time that this entire process takes varies according to the age of the animal, ranging from about a month to around three months in the adult and then the limb becomes fully functional.

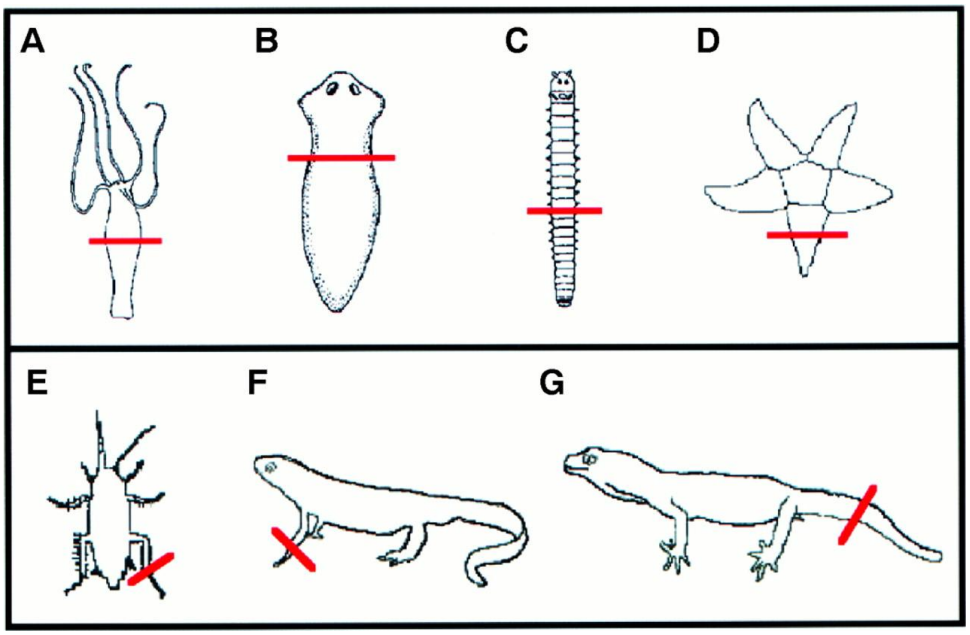

Fig. 3 Amphibian Limb Regeneration: Rebuilding a Complex Structure

In spite of the historically few researchers studying limb regeneration, remarkable progress has been made recently in establishing the neotenous amphibian the axolotl (*Ambystoma mexicanum*) as a model genetic organism. This progress has been facilitated by advances in genomics, bioinformatics, and somatic cell transgenesis in other fields, that have created the opportunity to investigate the mechanisms of important biological properties, such as limb regeneration, in the axolotl. The Ambystoma Genetic Stock Center (AGSC) is a self-sustaining, breeding colony of the axolotl supported by the National Science Foundation as a Living Stock Collection. Located at the University of Kentucky, the AGSC is dedicated to supplying genetically well-characterized axolotl embryos, larvae, and adults to laboratories throughout the United States and abroad. An NIH-funded NCRR grant has led to the establishment of the Ambystoma EST database, the Salamander Genome Project (SGP) that has led to the creation of the first amphibian gene map and several annotated molecular data bases, and the creation of the research community web portal.

Anurans can only regenerate their limbs during embryonic development. Once the limb skeleton has developed regeneration does not occur (Xenopus can grow a cartilaginous spike

after amputation). Reactive oxygen species (ROS) appear to be required for a regeneration response in the anuran larvae. ROS production is essential to activate the Wnt signaling pathway, which has been associated with regeneration in other systems. Limb regeneration in salamanders occurs in two major steps. First, adult cells de-differentiate into progenitor cells which will replace the tissues they are derived from. Second, these progenitor cells then proliferate and differentiate until they have completely replaced the missing structure.

6.5.12 Hydra

Hydra, a primitive metazoan, has a simple structure consisting of a head, body column, and foot aligned along a single oral–aboral axis. The body column has a high capacity for regeneration of both the head and foot. Because of the tissue dynamics that take place in adult *Hydra*, the processes governing axial patterning are continuously active to maintain the form of the animal. Regeneration in hydra is morphallactic and closely related to these axial patterning processes. As might be expected, analysis at the molecular level indicates that the same set of genes are involved in head regeneration and the maintenance of the head in the context of the tissue dynamics of the adult. The genes analyzed so far play roles in axial patterning processes in bilaterians.

Hydra is a genus of freshwater polyp in the phylum Cnidaria with highly proliferative stem cells that gives them the ability to regenerate their entire body. Any fragment larger than a few hundred epithelial cells that is isolated from the body has the ability to regenerate into a smaller version of itself. The high proportion of stem cells in the hydra supports its efficient regenerative ability.

6.5.13 Structure and tissue dynamics of Hydra

The simple body plan of a *Hydra* is shown in given fig. The single axis consists of a cylindrical shell surrounding a gastric cavity that extends throughout the body column. The head consists of two parts. The apical part is the hypostome, or mouth region, whereas the basal part is the tentacle zone from which a ring of tentacles emerge. At the opposite end, the body column ends in the foot, or basal disk, with which the animal attaches itself to surfaces in its freshwater environment.

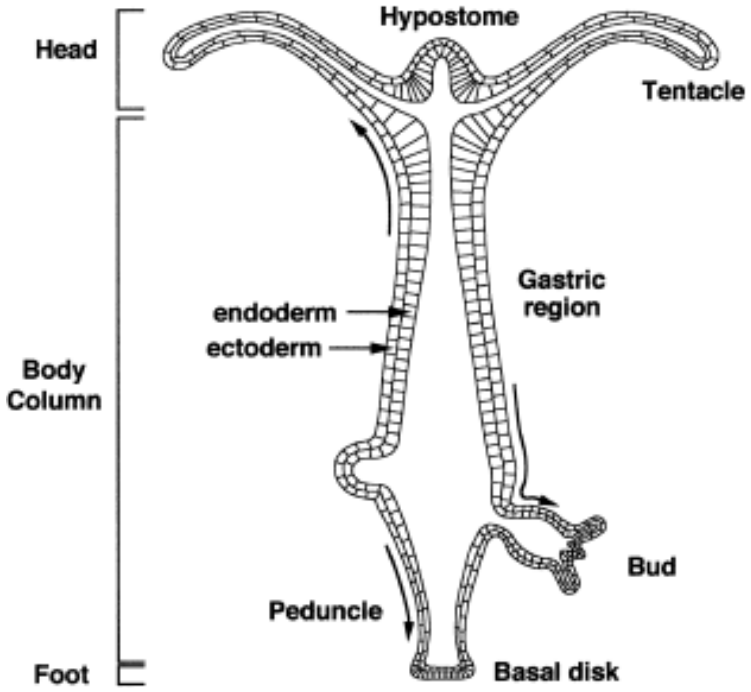

Fig. 4 Longitudinal cross-section of an adult *Hydra*.

Regeneration among hydra occurs as foot regeneration arising from the basal part of the body, and head regeneration, arising from the apical region. Regeneration tissues that are cut from the gastric region contain polarity, which allows them to distinguish between regenerating a head in the apical end and a foot in the basal end so that both regions are present in the newly regenerated organism. Head regeneration requires complex reconstruction of the area, while foot regeneration is much simpler, similar to tissue repair. In both foot and head regeneration, however, there are two distinct molecular cascades that occur once the tissue is wounded: early injury response and a subsequent, signal-driven pathway of the regenerating tissue that leads to cellular differentiation. This early-injury response includes epithelial cell stretching for wound closure, the migration of interstitial progenitors towards the wound, cell death, phagocytosis of cell debris, and reconstruction of the extracellular matrix.

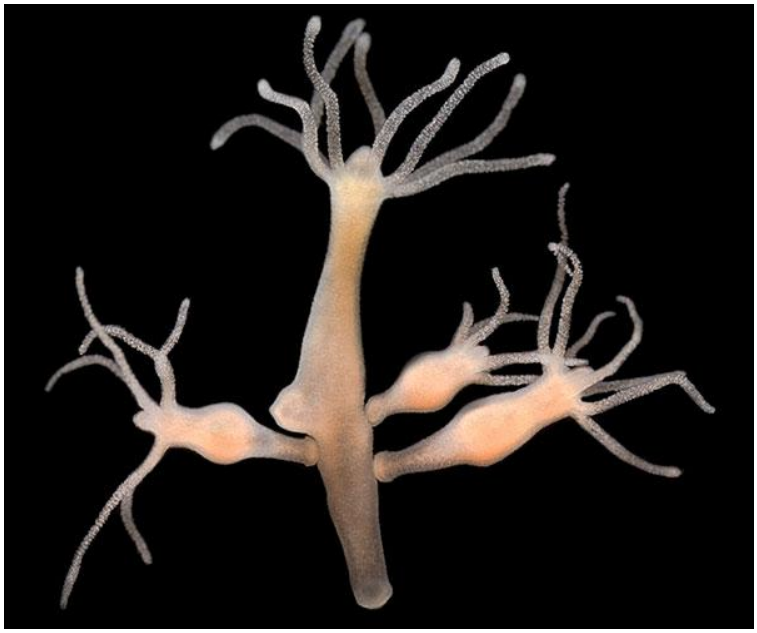

Fig. 5 This tiny freshwater animal hydra can form two whole bodies after being cut in half

Regeneration in hydra has been defined as morphallaxis, the process where regeneration results from remodeling of existing material without cellular proliferation. If a hydra is cut into two pieces, the remaining severed sections form two fully functional and independent hydra, approximately the same size as the two smaller severed sections. This occurs through the exchange and rearrangement of soft tissues without the formation of new material.

6.6 Characteristics of regeneration

The head regeneration process is quite rapid. After bisection of the body column, head regeneration in the lower part consists of the following. The epithelia at the wounded upper end of the lower piece stretch to cover and close the wound, which takes place in 3 to 6 hr. Within 30 to 36 hr, tentacles begin to emerge, and by 48 to 72 hr, a fully regenerated head has formed. Foot regeneration is a similar process in that the epithelia stretch to close the wound, and then a foot begins to form. As measured by the reappearance of a foot-specific peroxidase as well as the ability of the piece of tissue to stick to a surface, a foot regenerates in approximately 30 hr.

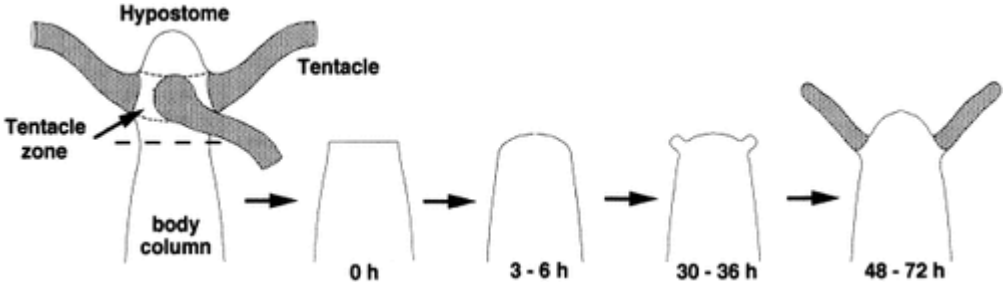

Fig. 6 Morphologic changes during head regeneration after decapitation.

Regeneration processes are of two kinds. In epimorphic regeneration, cell division takes place at and near the cut surface to provide tissue from which the removed structure regenerates. The regenerated structure, such as a limb, is the same size as the normal limb. In contrast, during morphallactic regeneration, cell division is unnecessary as the remaining tissue is remodeled to build the missing structures. In *Hydra*, regeneration is morphallactic, as illustrated by the regeneration of a complete, albeit much smaller, animal from a piece of the body column. That cell division is unnecessary for regeneration in *Hydra* was demonstrated by blocking cell division with γ-irradiation or hydroxyurea, bisecting the body column, and allowing regeneration to occur. The rates and extent of regeneration in pieces in which cell division was blocked were very similar in treated and untreated controls.

Another issue concerns which of the three cell lineages are responsible for head and foot regeneration, and what roles do they play. Obviously, the epithelial cells of both layers are involved. However, the interstitial cell lineage is not required. The interstitial cell lineage can be removed from hydra in several ways. Because of the shorter cell cycle time [1 day vs. 3 days], treatment with hydroxyurea or colchicine selectively reduces and eventually removes the interstitial cell population. Thereafter, the tissue displacement patterns coupled with sloughing at the extremities leads to the loss of all the interstitial cell differentiation products. Such animals, termed "epithelial animals" can be maintained indefinitely by hand-feeding, and will reproduce by budding as do normal animals. Epithelial animals maintained for over a year, when bisected, will regenerate a head and foot on the lower and upper parts, respectively, as do normal animals. Similar results were obtained with nf-1, a mutant of *Hydra magnipapillata* devoid of cells of the interstitial cell lineage. When bisected, animals of this strain regenerated a head at the same rate as a strain containing interstitial cells.

Although both epithelial lineages are required for head and foot regeneration simply for structural purposes, the question arises as to whether the control, or patterning, of the head during head regeneration is controlled by one or both layers. A similar question exists for foot regeneration. Smid and Tardent examined this issue by removing head and foot, separating the two epithelial layers, and generating chimeras by recombining the two layers either with the same head-foot polarity, or with an opposite polarity. Those chimeras with the same head-foot polarity all regenerated normally. However, the majority of those chimeras in which the ectoderm and endoderm had opposite polarities, formed a new axis that was perpendicular to

the original axis, indicating that neither layer alone controlled where head and foot formed during regeneration. Instead, both layers play a role in determining the head/foot polarity.

Do the two layers provide the same or different information during head or foot regeneration? This question was examined by Zeretzke and Berking who made use of mh-1, a mutant of *Hydra magnipapillata* that forms ectopic heads along the body column. In addition, upon bisection, mh-1 animals regenerate a foot at a slower rate than does the 105 strain, which is the wild-type. By making ectoderm/endoderm chimeras [same head–foot polarity for both layers), they generated mh-1 ecto/105 endo and 105 ecto/mh-1 endo chimeras. They found that the mh-1 ecto/105 endo chimeras formed ectopic heads along the body column, whereas the 105 ecto/mh-1 endo chimeras regenerated feet at a reduced rate. These results suggest that, in this situation, the ectoderm influences head formation, whereas the endoderm affects foot formation. Whether this is generally true, will require a similar analysis using mutants with alterations in different characteristics of head and foot.

6.6.1 Patterning process governing axial patterning in hydra

Because an adult *Hydra* is in a steady state of production and loss of tissue coupled with continual displacement of tissue along the body axis, the processes governing axial patterning need to be constantly active to maintain the morphology of the animal. These same processes are also involved in head regeneration.

6.6.2 Histology of regeneration process (Metaplasia)

Metaplasia is the replacement of one differentiated cell type with another mature differentiated cell type that is not normally present in a specific tissue. It is important to distinguish metaplasia from transdifferentiation. Transdifferentiation is a process in which one differentiated cell type converts into a completely different cell type present in the tissue[2]. Although the change from one type of cell to another in metaplasia might be a part of the normal adult maturation processes, as will be discussed later, it is not known to occur during embryonic development. Metaplasia may be induced or accelerated by some sort of abnormal stimulus (for example, acid or base, and hence a change in pH; hormones; cigarette smoke; and alcohol). In the context of an abnormal stimulus, the original cells adapt to the environmental stress by changing identity. If the stimulus that caused metaplasia is removed, it is not clear whether the tissues can return to their normal pattern of differentiation. However, if the condition promoting metaplasia persists, metaplasia can progress to dysplasia and occasionally malignancy, as will be discussed later (for example, in the oesophagus).

It is not realistically possible to determine the prevalence or incidence of tissue metaplasia of any type in the general population, as that information would require comprehensive and longitudinal monitoring, but one can glean some information about metaplasia and progression to dysplasia and cancer in the oesophagus, which has been studied more than metaplasia in other tissues. It is estimated that oesophageal intestinal metaplasia, termed Barrett oesophagus, will progress to cancer in 1 in 860 (0.12%) individuals with the condition.

The progression of metaplasia to dysplasia may be viewed as an 'oncogenic' phase, in contrast to the initial development of metaplasia, which is viewed as an 'adaptive' phase that occurs in response to environmental stress. While insights into the mechanisms leading to metaplasia are key to understanding tissue homeostasis as well as adaptation to stress, studying metaplasia progression to low-grade dysplasia and high-grade dysplasia can reveal major contributors to malignancy at early stages. The wide prevalence of tissue metaplasia and the limited progression to dysplasia and cancer, there is tremendous intersection of this topic with cancer prevention, early detection, risk stratification, prognosis and therapy. This unit focuses on the types of metaplasia, the potential cellular origins of metaplasia, the ways to model certain types of metaplasia and the potential opportunities for intervention to either reverse or arrest it.

6.6.3 Tissue metaplasia

Metaplasia tends to occur in tissues constantly exposed to environmental agents, which are often injurious in nature. For example, the pulmonary system (lungs and trachea) and the gastrointestinal tract are common sites of metaplasia owing to their contacts with air and food, respectively. As a result, the tissue epithelial structure adapts through metaplasia, with definitive morphological changes. The type of metaplasia depends upon the resident tissue. Metaplasia may be categorized broadly as squamous metaplasia, intestinal metaplasia or acinar–ductal metaplasia (ADM).

6.6.4 Polarity and gradient

Each living thing exhibits polarity, one example of which is the differentiation of an organism into a head, or forward part, and a tail, or hind part. Regenerating parts are no exception; they exhibit polarity by always growing in a distal direction (away from the main part of the body). Among the lower invertebrates, however, the distinction between proximal (near, or toward the body) and distal is not always clear cut. It is not difficult, for example, to

reverse the polarity of "stems" in colonial hydroids. Normally a piece of the stem will grow a head end, or hydranth, at its free, or distal, end; if that is tied off, however, it regenerates a hydranth at the end that was originally proximal. The polarity in this system is apparently determined by an activity gradient in such a way that a hydranth regenerates wherever the metabolic rate is highest. Once a hydranth has begun to develop, it inhibits the production of others proximal to it by the diffusion of an inhibitory substance downward along the stem.

When planarian flatworms are cut in half, each piece grows back the end that is missing. Cells in essentially identical regions of the body where the cut was made form blastemas, which, in one case gives rise to a head and in the other becomes a tail. What each blastema regenerates depends entirely on whether it is on a front piece or a hind piece of flatworm: the real difference between the two pieces may be established by metabolic differentials. If a transverse piece of a flatworm is cut very thin—too narrow for an effective metabolic gradient to be set up—it may regenerate two heads, one at either end. If the metabolic activity at the anterior end of a flatworm is artificially reduced by exposure to certain drugs, then the former posterior end of the worm may develop a head.

Appendage regeneration poses a different problem from that of whole organisms. The fin of a fish and the limb of a salamander have proximal and distal ends. By various manipulations, it is possible to make them regenerate in a proximal direction, however. If a square hole is cut in the fin of a fish, regeneration takes place as expected from the inner margin, but may also occur from the distal edge. In the latter case, the regenerating fin is actually a distal structure except that it happens to be growing in a proximal direction.

Amphibian limbs react in a similar manner. It is possible to graft the hand of a newt to the nearby body wall, and once a sufficient blood flow has been established, to sever the arm between the shoulder and elbow. This creates two stumps, a short one consisting of part of the upper arm, and a longer one made up of the rest of the arm protruding in the wrong direction from the side of the animal. Both stumps regenerate the same thing, namely, everything normally lying distal to the level of amputation, regardless of which way the stump was facing. The reversed arm therefore regenerates a mirror image of itself.

Clearly, when a structure regenerates it can only produce parts that normally lie distal to the level of amputation. The participating cells contain information needed to develop everything

"downstream," but can never become more proximal structures. Regeneration, like embryonic development, occurs in a definite sequence.

6.6.5 Regulation of regeneration

There are certain prerequisites without which regeneration cannot occur. First and foremost, there must be a wound, although the original appendage need not have been lost in the process. Second, there must be a source of blastema cells derived from remnants of the original structure or an associated one. Finally, regeneration must be stimulated by some external force. The stimuli often involve the nervous system. An adequate nerve supply is required for the regeneration of fish fins, taste barbels, and amphibian limbs. In the case of many tail regenerations, the spinal cord provides the necessary stimulus. Lens regeneration in salamander eyes depends upon the presence of a retina. Arthropod appendages regenerate in the presence of molting hormones. Protozoan regeneration requires the presence of a nucleus. In case after case, regeneration depends on more than a healed wound and a source of blastema cells. It is often triggered by some physiological stimulus originating elsewhere in the body, a stimulus invariably associated with the very function of the structure to be regenerated. The conclusion is inescapable that regeneration is primarily the recovery of deficient functions rather than simply the replacement of lost structures. The imperative of need is of further importance in suppressing excess regeneration. To be able to regenerate is to run the risk of regenerating too much or too often. If regeneration did not depend upon a physiological stimulus, such as those mediated by nerves or hormones, there would be no reason why simple wounds should not sprout whole new appendages.

It is not known why regeneration fails to occur in many cases, as in the legs of frogs or the limbs and tails of mammals. The nerve supply might be inadequate, for when the number of nerves is artificially increased, regeneration is sometimes induced. This cannot be the whole answer, however, because not all appendages depend on nerves for their regeneration; newt jaws, salamander gills, and deer antlers do not require nerves to regenerate. Possibly the failure to regenerate relates to the ways in which wounds heal. In higher vertebrates there is a tendency to form thick scar tissue in healing wounds, which may act as a barrier between the epidermis and the underlying tissues of the stump. In the absence of direct contact between these two tissues, the stump may not be able to give rise to the blastema cells required for regeneration.

6.7 Summary

In this unit we summarize that regeneration is the natural process of replacing or restoring damaged or missing cells, tissues, organs, and even entire body parts to full function in plants and animals. Scientists are studying regeneration for its potential uses in medicine, such as treating a variety of injuries and diseases. Researchers also hope to learn more about the human aging process through studies of regeneration. This rapidly advancing field is called regenerative medicine.

All living organisms have some ability to regenerate as part of natural processes to maintain tissues and organs. Some animals have extensive regenerative abilities. For example, the tiny freshwater animal called Hydra can form two whole bodies after being cut in half. The axolotl, or Mexican salamander, is an animal with a backbone that can regenerate the form and function of almost any limb, organ, or other body part. More complex animals such as mammals have limited regenerative capacities. These include: Forming thick scars in tissues and skin to promote the healing of injured or amputated body parts, Regrowing hair and skin and Healing a bone fracture by using new tissue to knit the bone pieces together.

Organisms regenerate in different ways. Plants and some sea creatures, such as jellyfish, can replace missing parts by extensively remodeling their remaining tissues. Some animals such as lobsters, catfish, and lizards replace missing parts by first growing a blastema. The blastema cells rapidly divide to form the skin, scales, muscle, bone, or cartilage needed for creating the lost limb, fin, or tail. In other animals, including humans, organs such as the liver undergo what's called compensatory hypertrophy. When part of the liver is removed or destroyed, the remaining portion grows to the original size and allows the liver to function as it did before. Our kidneys, pancreas, thyroid, adrenal glands, and lungs compensate for organ loss in a similar, but more limited, way.

6.8 Terminal questions

Q.1 What do you mean by regeneration?

Answer:----------

Q. 2 Describe morphogenetic process of regeneration.

Answer:----------

Q. 3 Write a short note on ability of regeneration in different group of animal.

Answer:----------

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Q.4 What do you mean by limb generation?

Answer:----------

-

Q.5 Describe limb generation in amphibians.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner
3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit-7 - Growth and Ageing

Structure

7.1 Introduction

Growth, the increases in cell size and number that take place during the life history of an organism. It is seldom random. Rather, it occurs according to a plan that eventually determines the size and shape of the individual. Growth may be restricted to special regions of the organism, such as the layers of cells that divide and increase in size near the tip of the plant shoot. Or the cells engaged in growth may be widely distributed throughout the body of the organism, as in the human embryo. In the latter case, the rates of cell division and of the increase in cell size differ in different parts. That the pattern of growth is predetermined and regular in plants and animals can be seen in the forms of adults. In some organisms, however, notably the slime molds, no regular pattern of growth occurs, and a formless cytoplasmic mass is the result.

The rate of growth of various components of an organism may have important consequences in its ability to adapt to the environment and hence may play a role in evolution. For instance, an increase in the rate of growth of fleshy parts of the fish fin would provide an opportunity for the fish to adapt more easily to terrestrial locomotory life than could a fish without this modified fin. Without disproportionate growth of the fin- ultimately resulting from random changes in the genetic material (mutations); the evolution of limbs through natural selection might have been impossible.

7.2 Growth and development

Growth and development of the normal healthy breast is dependent on the sex steroid hormones, specifically estrogen and progesterone. This relationship is initially most evident in a woman's life during puberty, when undeveloped and quiescent breast tissue is exposed to increasing amounts of estrogen and progesterone, ultimately resulting in the development of the adult breast. Simply put, exposure to these hormones causes growth and development of the breast tissue. Throughout premenopausal life, during a normal menstrual cycling, physiological changes occur within the breast tissue in response to varying levels of the steroid hormones. Perhaps the most dramatic evidence for this change is during pregnancy, when the breast responds remarkably to the changing hormone milieu with breast enlargement, engorgement, lactation, and involution after breast-feeding has stopped. Finally, withdrawal of estrogen at menopause, either naturally or surgically, results in breast changes that are clinically measurable.

Biological development encompasses, therefore, all the processes concerned with implementing the instructions contained in the DNA. Those instructions can only be

carried out by an appropriate executive machinery, the first phase of which is provided by the cell that carries the DNA into the next generation: in animals and plants by the fertilized egg cell; in viruses by the cell infected. In life histories that have more than a minimal degree of complexity, the executive machinery itself becomes modified as the genetic instructions are gradually put into operation, and new mechanisms of protein synthesis are brought into functional condition. The fundamental problem of developmental biology is to understand the interplay between the genetic instructions and the mechanisms by which those instructions are carried out.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about concept of ageing and degrowth
- To discuss about programmed cell death, apoptosis and cell death
- To know about mechanism of growth and cell growth
- To know about sexual reproduction

Development and growth of bone are critically dependent on thyroid hormone, as evidenced by the typical short stature of adults when neonatal hypothyroidism remains untreated. The cell types that are involved in bone formation (osteoblasts) and bone resorption (osteoclasts) are both stimulated by T_3, with effects on several critical enzymes. In hyperthyroid patients, increased bone formation and resorption result in a net loss of bone thickness and increase in porosity, leading to greater risk of fractures. Little is known about the primary targets and mechanism of action of T_3 in bone cells, mainly because these cells are difficult to study in culture. Thyroid hormone is required for the effects of GH on bone growth and development, which involve the production of insulin-like growth factor 1. Some of the effects of T_3 may therefore result from this permissive action of thyroid hormone. However, studies using TR knockout mice indicate that many of the effects of T_3 on bone metabolism are nuclear mediated and independent of GH.

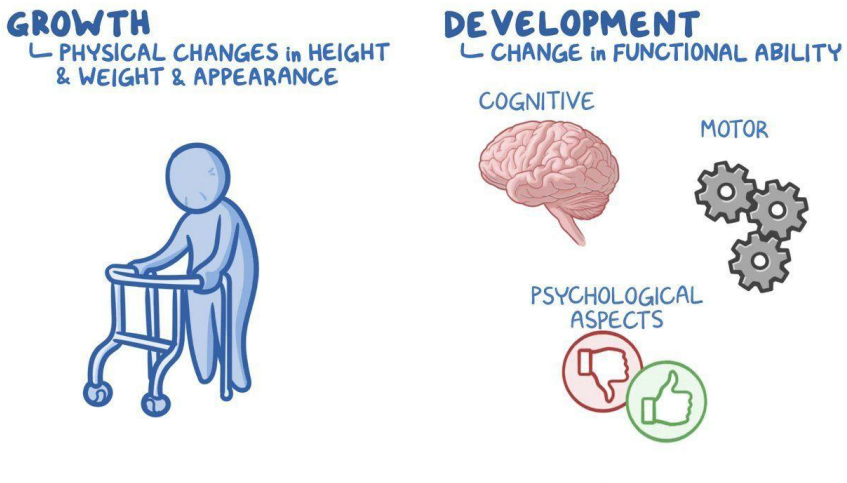


Fig. 1 Growth and development

The environment with all its potential toxins and pollutants may have a direct influence on growth and development, interfering with both physiologic and pathologic aspects. For the two past decades, we have known that programmed cell death (or apoptosis) is part of normal development and that triggering factors result from both evolutionary pathways and external influences. This occurs at both anatomic and functional levels and opens the potential for many and varied investigations. Neurogenesis, particularly in specific parts of the brain such as the hippocampus, has long been thought to occur only during development, but recent evidence has shown that it continues throughout human life and both genetics and inflammation may hold the keys to neurodegenerative disorders. Implications of an interaction between memory and its influence on degenerative neurologic diseases are now firmly established. Anesthetic drugs have been shown to adversely affect the developing brain in rodents and primates, but with the discovery of neurogenesis in adults, we now know that similar changes occur in adults as well. However, recent evidence suggests it is quite unlikely that anesthetics affect the neurobehavioral changes in human infants and toddlers.

Evidence has confirmed that the functional aspect of brain development in the fetus is far more complex than previously thought and is not limited just to the last weeks before birth. A waking-like brain state exists that is present earlier in gestation and inducible with maternal behavioural changes and external stimuli (e.g., music). These factors may have long-term neuro developmental effects and the beginning of memorization likely occurs earlier than previously thought. A mother's voice, heartbeat, speech, and language all impact the fetal neural plasticity.

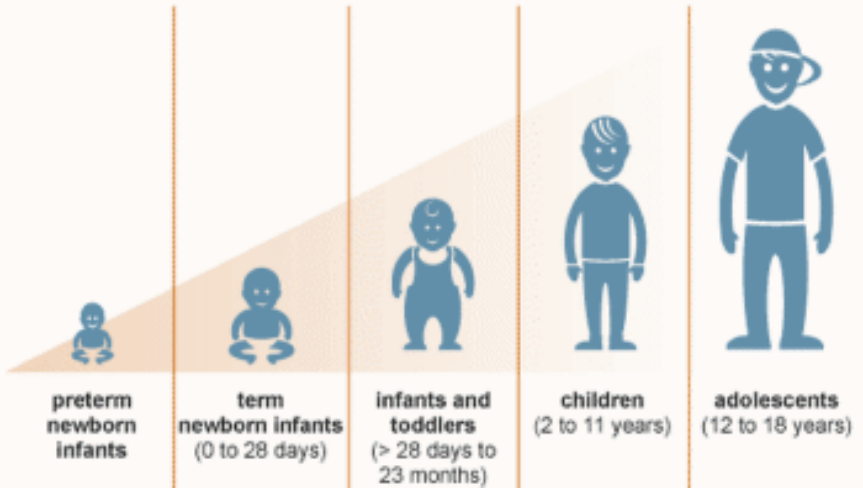
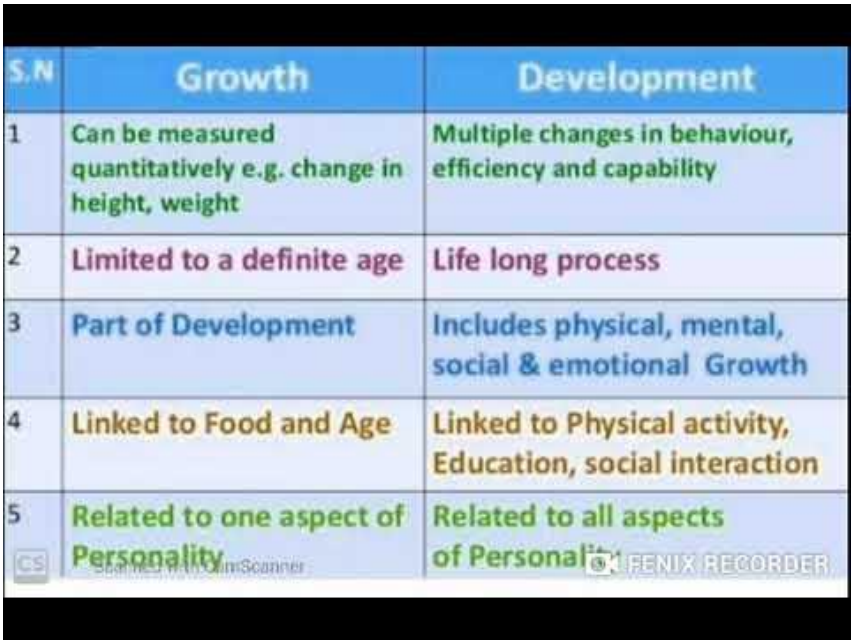


Fig. 2 Human Growth and Development

In addition, a large number of interactions between the neonate and the external world exist. The child has some direct influences on his or her external environment. The ethnologic concept of "baby schema" was proposed by Lorenz, who suggested that some type of positive features can result in a positive response in the human. Infantile physical features, such as a round face and big eyes, are perceived as cute and motivate care taking behavior in the human, with the evolutionary function of enhancing offspring survival. This has been observed across animal species. A baby's smile, for example, can increase the speed of the caring response and narrow the intentional focus of the mother independently of face recognition. Comparisons between neurophysiologic and neuropsychological studies are difficult but may prove an important confounding factor in our search to understand the complexities of human growth and development.

As medicine has progressed over the past several decades, so has the development of hormonal medications. Tremendous advancements have been achieved using these medications in the areas of pregnancy prevention and relief of vasomotor symptoms related to estrogen withdrawal. Hormonal contraception and hormone replacement are the two most common medications prescribed today in the United States.



S.N	Growth	Development
1	Can be measured quantitatively e.g. change in height, weight	Multiple changes in behaviour, efficiency and capability
2	Limited to a definite age	Life long process
3	Part of Development	Includes physical, mental, social & emotional Growth
4	Linked to Food and Age	Linked to Physical activity, Education, social interaction
5	Related to one aspect of Personality	Related to all aspects of Personal

Fig. 3 Difference between growth and development

Unfortunately, the most common cancer in U.S. women, affecting 1 in 8 women, is breast cancer. The incidence of breast cancer has risen over the past two decades, and there is mounting concern over the connection between exogenous hormone exposure and the development of breast cancer. This concern is not unfounded given that it stands to reason that the exposure of breast tissue to exogenous steroid hormones might affect breast physiology, including growth and development.

7.3 Ageing

Ageing or aging is the process of becoming older. The term refers mainly to humans, many other animals, and fungi, whereas for example, bacteria, perennial plants and some simple animals are potentially biologically immortal. Furthermore, ageing connotes a biological and social construct. It is usually associated with dynamic changes in the biological, psychological, physiological, environmental, behavioral and social processes. In the broader sense, ageing can refer to single cells within an organism which have ceased dividing or to the population of a species.

In humans, ageing represents the accumulation of changes in a human being over time and can encompass physical, psychological, and social changes. Reaction time, for example, may slow with age, while memories and general knowledge typically increase. Ageing increases the risk of human diseases such as cancer, Alzheimer's disease, diabetes, Cardiovascular

disease, stroke and many more. Of the roughly 150,000 people who die each day across the globe, about two-thirds die from age-related causes.

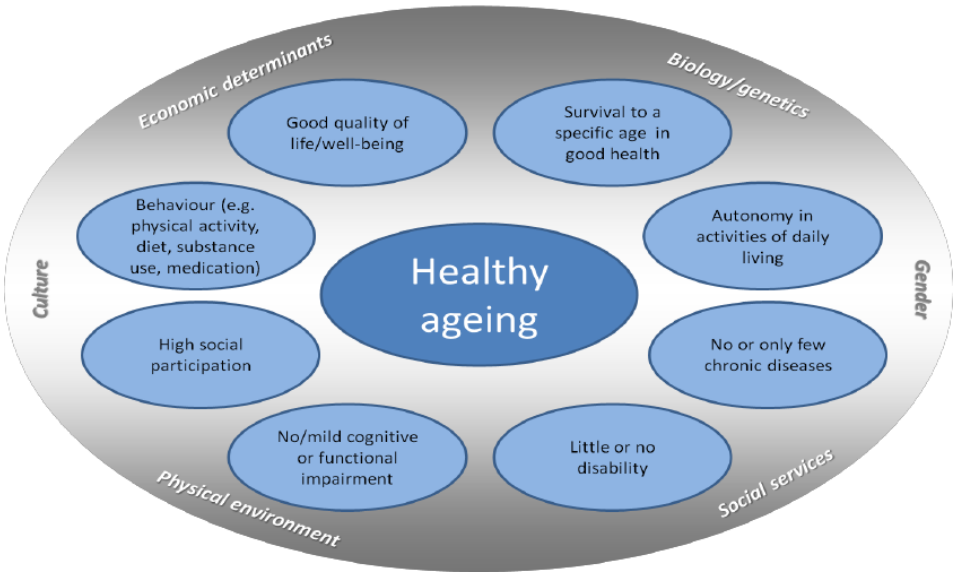


Fig. 4 Components of healthy ageing

Current ageing theories are assigned to the damage concept, whereby the accumulation of damage (such as DNA oxidation) may cause biological systems to fail, or to the programmed ageing concept, whereby problems with the internal processes (epigenetic maintenance such as DNA methylation) may cause ageing. Programmed ageing should not be confused with programmed cell death (apoptosis). Additionally, there can be other reasons, which can speed up the rate of ageing in organisms including human beings like obesity and compromised immune system.

Scientists have long known that dietary calorie restriction in non-primate animals slows ageing while maintaining good health and body functions. Rats and mice fed 30 to 50% fewer calories than they would freely eat beginning in early life shows various physiological health benefits, lower incidence of chronic diseases, and up to 50% increase in length of life. Though life-extending effects remain uncertain in primates (including humans), the diverse health benefits of limiting calorie intake are now well-established. They seem to result from a physiological response to food scarcity that evolved to enhance the body's capacity to survive adversity. Nevertheless, few people would be willing to maintain a substantially reduced diet for most of their lifespan. As a result, scientists have begun to explore calorie-restriction mimetics-natural and synthetic drug compounds that might yield the same health effects as calorie restriction, without dieting. These investigations are still in their early stages.

Biologically, ageing results from the impact of the accumulation of a wide range of molecular and cellular damage over time. Thus, this leads to a gradual decline in physical and mental capacity, a growing risk of diseases, and ultimately, death. These changes are usually consistent, and they are associated with a person's age in years. While some people aged 70 years may be strong and enjoy good health, others who are 70 years may be weak and require others to help them.

7.4 Degrowth

Degrowth is a term used for both a political, economic, and social movement as well as a set of theories that critiques the paradigm of economic growth. It is based on ideas from a diverse range of lines of thought such as political ecology, ecological economics, feminist political ecology, and environmental justice, pointing out the social and ecological harm caused by the pursuit of infinite growth and Western "development" imperatives. Degrowth emphasizes the need to reduce global consumption and production (social metabolism) and advocates a socially just and ecologically sustainable society with social and environmental well-being replacing GDP as the indicator of prosperity. Hence, although GDP is likely to shrink in a "Degrowth society", i.e. a society in which the objectives of the degrowth movement are achieved, this is not the primary objective of degrowth.

Degrowth thought is in opposition to all forms of productivism (the belief that economic productivity and growth is the purpose of human organization). It is, thus, opposed to the current form of sustainable development. While the concern for sustainability does not contradict degrowth, sustainable development is rooted in mainstream development ideas that aim to increase capitalist growth and consumption. Degrowth therefore sees sustainable development as an oxymoron, as any development based on growth in a finite and environmentally stressed world is seen as inherently unsustainable. Critics of degrowth argue that a slowing of economic growth would result in increased unemployment, increased poverty, and decreased income per capita.

Many who understand the devastating environmental consequences of growth still advocate for economic growth in the South, even if not in the North. But, a slowing of economic growth would fail to deliver the benefits of degrowth-self-sufficiency, material responsibility—and would indeed lead to decreased employment. Rather, degrowth proponents advocate the complete abandonment of the current (growth) economic model,

suggesting that relocalizing and abandoning the global economy in the Global South would allow people of the South to become more self-sufficient and would end the overconsumption and exploitation of Southern resources by the North. Proponents of degrowth see it as a possible path to preserve ecosystems from human pressures. The environment is communally cared for, integrating humans and nature; degrowth implies the perception of ecosystems as inherently valuable, not just as a source for resources.

7.5 Cell death

Cell death is the event of a biological cell ceasing to carry out its functions. This may be the result of the natural process of old cells dying and being replaced by new ones, or may result from such factors as disease, localized injury, or the death of the organism of which the cells are part. Apoptosis or Type I cell-death, and autophagy or Type II cell-death are both forms of programmed cell death, while necrosis is a non-physiological process that occurs as a result of infection or injury.

7.5.1 Programmed cell death

Programmed cell death (or PCD) is cell death mediated by an intracellular program. PCD is carried out in a regulated process, which usually confers advantage during an organism's life-cycle. For example, the differentiation of fingers and toes in a developing human embryo occurs because cells between the fingers apoptose; the result is that the digits separate. PCD serves fundamental functions during both plant and metazoa (multicellular animals) tissue development.

7.5.2 Apoptosis

Apoptosis is the process of programmed cell death (PCD) that may occur in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. It is now thought that – in a developmental context – cells are induced to positively commit suicide whilst in a homeostatic context; the absence of certain survival factors may provide the impetus for suicide. There appears to be some variation in the morphology and indeed the biochemistry of these suicide pathways; some treading the path of "apoptosis", others following a more generalized pathway to deletion, but both usually being genetically and synthetically motivated. There is some evidence that certain symptoms of "apoptosis" such as endonuclease activation can be spuriously induced without engaging a genetic cascade,

however, presumably true apoptosis and programmed cell death must be genetically mediated. It is also becoming clear that mitosis and apoptosis are toggled or linked in some way and that the balance achieved depends on signals received from appropriate growth or survival factors.

7.5.3 Autophagy

Autophagy is cytoplasmic, characterized by the formation of large vacuoles that eat away organelles in a specific sequence prior to the destruction of the nucleus. Macroautophagy, often referred to as autophagy, is a catabolic process that results in the autophagosomic-lysosomal degradation of bulk cytoplasmic contents, abnormal protein aggregates, and excess or damaged organelles. Autophagy is generally activated by conditions of nutrient deprivation but has also been associated with physiological as well as pathological processes such as development, differentiation, neurodegenerative diseases, stress, infection and cancer.

7.5.4 Other variations of PCD

Other pathways of programmed cell death have been discovered. Called "non-apoptotic programmed cell-death (or "caspase-independent programmed cell-death"), these alternative routes to death are as efficient as apoptosis and can function as either backup mechanisms or the main type of PCD. Some such forms of programmed cell death are anoikis, almost identical to apoptosis except in its induction; cornification, a form of cell death exclusive to the eyes; excitotoxicity; ferroptosis, an iron-dependent form of cell death and Wallerian degeneration. Plant cells undergo particular processes of PCD similar to autophagic cell death. However, some common features of PCD are highly conserved in both plants and metazoa.

Activation-induced cell death (AICD) is a programmed cell death caused by the interaction of Fas receptor (Fas, CD95)and Fas ligand (FasL, CD95 ligand). It occurs as a result of repeated stimulation of specific T-cell receptors (TCR) and it helps to maintain the periphery immune tolerance. Therefore, an alteration of the process may lead to autoimmune diseases. In the other words AICD is the negative regulator of activated T-lymphocytes.

Ischemic cell death, or oncosis, is a form of accidental or passive cell death that is often considered a lethal injury. The process is characterized

by mitochondrial swelling, cytoplasm vacuolization, and swelling of the nucleus and cytoplasm. Mitotic catastrophe is a mode of cell death that is due to premature or inappropriate entry of cells into mitosis. It is the most common mode of cell death in cancer cells exposed to ionizing radiation and many other anti-cancer treatments. Immunogenic cell death or immunogenic apoptosis is a form of cell death caused by some cytostatic agents such as anthracyclines, oxaliplatin and bortezomib, or radiotherapy and photodynamic therapy (PDT). Pyroptosis is a highly inflammatory form of programmed cell death that occurs most frequently upon infection with intracellular pathogens and is likely to form part of the antimicrobial response in myeloid cells.

7.5.5 Necrotic cell death

Necrosis is cell death where a cell has been badly damaged through external forces such as trauma or infection and occurs in several different forms. In necrosis, a cell undergoes swelling, followed by uncontrolled rupture of the cell membrane with cell contents being expelled. These cell contents often then go on to cause inflammation in nearby cells. A form of programmed necrosis, called necroptosis, has been recognized as an alternative form of programmed cell death. It is hypothesized that necroptosis can serve as a cell-death backup to apoptosis when the apoptosis signaling is blocked by endogenous or exogenous factors such as viruses or mutations. Necroptotic pathways are associated with death receptors such as the tumor necrosis factor receptor.

7.5.6 Mechanism of growth

Mechanistic research has been extremely successful in identifying the parts, operations, and basic organization of a vast range of biological mechanisms. It has been less successful, though, in understanding the implications of various forms of organization — especially the temporal dynamics that orchestrate the functioning of biological mechanisms. Biochemists' basic strategy has been to put together linear sequences of reactions, moving to cyclic organization (e.g., the Krebs cycle) only as necessary. By focusing on near-equilibrium steady-state conditions and summary statistics (e.g., mean concentration of a metabolite), traditionally biologists have screened themselves off from oscillatory phenomena. We have suggested that the resulting mechanistic accounts are blind to crucial dynamics of the systems they target. The new mechanistic philosophy of science has tended to parallel biology in this respect, emphasizing the discovery of component parts and operations and simple organizational schemes, and providing little systematic attention to orchestration.

Although explanation in biology remains primarily mechanistic, small clusters of investigators have confronted the complex dynamics that serve to orchestrate the functioning of biological mechanisms. We have discussed a few of these endeavors, focusing especially on explorations of the oscillatory dynamics that can result from some common types of cyclic organization. All of the cases we discussed were grounded in accounts of parts, operations, and organization of a particular biological mechanism but added concepts and tools of mathematical modeling and dynamical systems. Hence, they well exemplify the project of dynamic mechanistic explanation that we have endorsed.

Dynamic mechanistic explanation stands in contrast not only to purely mechanistic explanation but also to theoretical inquiries that emphasize complex dynamics in living systems conceived abstractly — at best neglecting but in some cases explicitly rejecting the mechanistic project. Artificial life research, for example, is conducted on a plane removed from research on actual biological mechanisms. While accounts oriented purely to complexity or dynamics can make unique and valuable contributions, they provide no understanding of how the dynamic relations are actually realized in living systems if they do not get anchored to component parts and operations of actual mechanisms.

Some theoretical biologists have not only preferred to work on an abstract plane, but also aspired to achieve a unified, law-based theoretical framework. In the spirit of cybernetics and general systems theory, they direct themselves to the big picture that seems to be neglected in reductionistic inquiry. Again, this endeavor has produced some ingenious and valuable directions for further inquiry, but does not in itself achieve the integration we regard as crucial. The most promising contributions for near-term integration probably come not from comprehensive systems, but from particular proposed principles of organization: self-organization through positive feedback in non-equilibrium conditions, small-world organization, scale-free networks, and so forth.

A characteristic feature of modern biology is its particularity. Biochemical pathways, while showing common patterns across phyla, also reveal substantial differences that matter to the functioning of particular organisms. The same is true of circadian oscillators. The resulting extrapolation from studied models to other systems is very different from the generalization achieved by universal quantifiers in laws. Researchers do not know in advance which features change and which remain constant (or nearly so) when extrapolating, and must be prepared to modify specific parts and operations in mechanisms as they move to new instances. The same is likely to apply to the tools of complex systems analysis. That is, the

general understanding of how small-worlds phenomena emerge from a few long-range connections in networks primarily constituted of short-range connections will need to be adapted given the particular long-range connections found in a given system. Complex systems analyses provide a rich toolkit for appreciating organization and orchestration of operations in biological mechanisms, and invoking these tools can illuminate how these mechanisms generate the rich phenomena biology seeks to explain.

Thus, we see an immediate future in which dynamic mechanistic researchers in biology will continue to offer piecemeal, context-specific accounts, even as they stretch them to incorporate dynamics. Systems biologists and philosophers of science can, and should, add insight and perspective while remaining grounded by examining a spectrum of these accounts. Such generalizations as we extract will be works in progress, with frequently modified contextual and other limitations, and will not readily be systematized — including those regarding cycles, oscillations and autonomy.

7.6 Mechanisms of cell growth

Cells can grow by increasing the overall rate of cellular biosynthesis such that production of biomolecules exceeds the overall rate of cellular degradation of biomolecules via the proteasome, lysosome or autophagy. Biosynthesis of biomolecules is initiated by expression of genes which encode RNAs and/or proteins, including enzymes that catalyse synthesis of lipids and carbohydrates.

Individual genes are generally expressed via transcription into messenger RNA (mRNA) and translation into proteins, and the expression of each gene occurs to various different levels in a cell-type specific fashion (in response to gene regulatory networks).

- To drive cell growth, the global rate of gene expression can be increased by enhancing the overall rate of transcription by RNA polymerase II (for active genes) or the overall rate of mRNA translation into protein by increasing the abundance of ribosomes and tRNA, whose biogenesis depends on RNA polymerase I and RNA polymerase III. The Myc transcription factor is an example of a regulatory protein that can induce the overall activity of RNA polymerase I, RNA polymerase II and RNA polymerase III to drive global transcription and translation and thereby cell growth. In addition, the activity of individual ribosomes can be increased to boost the global efficiency of mRNA translation via regulation of translation initiation factors,

including the 'translational elongation initiation factor 4E' (eIF4E) complex, which binds to and caps the 5' end of mRNAs. The protein TOR, part of the TORC1 complex, is an important upstream regulator of translation initiation as well as ribosome biogenesis. TOR is a serine/threonine kinase that can directly phosphorylate and inactivate a general inhibitor of eIF4E, named 4E-binding protein (4E-BP), to promote translation efficiency. TOR also directly phosphorylates and activates the ribosomal protein S6-kinase (S6K), which promotes ribosome biogenesis.

- To inhibit cell growth, the global rate of gene expression can be decreased or the global rate of biomolecular degradation can be increased by increasing the rate of autophagy. TOR normally directly inhibits the function of the autophagy inducing kinase Atg1/ULK1. Thus, reducing TOR activity both reduces the global rate of translation and increases the extent of autophagy to reduce cell growth.

7.6.1 Cell growth regulation in animals

Many of the signal molecules that control of cellular growth are called growth factors, many of which induce signal transduction via the PI3K/AKT/mTOR pathway, which includes upstream lipid kinase PI3K and the downstream serine/threonine protein kinase Akt, which is able to activate another protein kinase TOR, which promotes translation and inhibits autophagy to drive cell growth. Nutrient availability influences production of growth factors of the Insulin/IGF-1 family, which circulate as hormones in animals to activate the PI3K/AKT/mTOR pathway in cells to promote TOR activity so that when animals are well fed they will grow rapidly and when they are not able to receive sufficient nutrients they will reduce their growth rate. In addition, the availability of amino acids to individual cells also directly promotes TOR activity, although this mode of regulation is more important in single-celled organisms than in multicellular organisms such as animals that always maintain an abundance of amino acids in circulation.

A postulated model for mammalian size control situates mass as the driving force of the cell cycle. A cell is unable to grow to an abnormally large size because at a certain cell size or cell mass, the S phase is initiated. The S phase starts the sequence of events leading to mitosis and cytokinesis. A cell is unable to get too small because the later cell cycle events, such as S, G2, and M, are delayed until mass increases sufficiently to begin S phase.

7.6.2 Cell populations

Cell populations go through a particular type of exponential growth called doubling or cell proliferation. Thus, each generation of cells should be twice as numerous as the previous generation. However, the number of generations only gives a maximum figure as not all cells survive in each generation. Cells can reproduce in the stage of Mitosis, where they double and split into two genetically equal cells.

7.6.3 Cell size

Cell size is highly variable among organisms, with some algae such as Caulerpa taxifolia being a single cell several meters in length.[8] Plant cells are much larger than animal cells, and protists such as Paramecium can be 330 µm long, while a typical human cell might be 10 µm. How these cells "decide" how big they should be before dividing is an open question. Chemical gradients are known to be partly responsible, and it is hypothesized that mechanical stress detection by cytoskeletal structures is involved. Work on the topic generally requires an organism whose cell cycle is well-characterized.

7.6.4 Yeast cell size regulation

The relationship between cell size and cell division has been extensively studied in yeast. For some cells, there is a mechanism by which cell division is not initiated until a cell has reached a certain size. If the nutrient supply is restricted (after time t = 2 in the diagram, below), and the rate of increase in cell size is slowed, the time period between cell divisions is increased. Yeast cell-size mutants were isolated that begin cell division before reaching a normal/regular size.

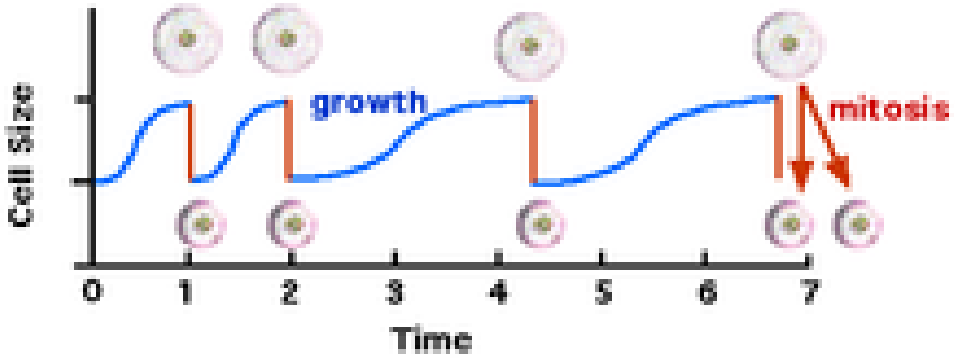


Fig. 5 Cell cycle and growth

Wee1 protein is a tyrosine kinase that normally phosphorylates the Cdc2 cell cycle regulatory protein (the homolog of CDK1 in humans), a cyclin-dependent kinase, on a tyrosine residue. Cdc2 drives entry into mitosis by phosphorylating a wide range of targets. This covalent modification of the molecular structure of Cdc2 inhibits the enzymatic activity of Cdc2 and prevents cell division. Wee1 acts to keep Cdc2 inactive during early G2 when cells are still small. When cells have reached sufficient size during G2, the phosphatase Cdc25 removes the inhibitory phosphorylation, and thus activates Cdc2 to allow mitotic entry. A balance of Wee1 and Cdc25 activity with changes in cell size is coordinated by the mitotic entry control system. It has been shown in Wee1 mutants, cells with weakened Wee1 activity, that Cdc2 becomes active when the cell is smaller. Thus, mitosis occurs before the yeast reach their normal size. This suggests that cell division may be regulated in part by dilution of Wee1 protein in cells as they grow larger.

7.6.5 Linking Cdr2 to Wee1

The protein kinase Cdr2 (which negatively regulates Wee1) and the Cdr2-related kinase Cdr1 (which directly phosphorylates and inhibits Wee1 *in vitro*) are localized to a band of cortical nodes in the middle of interphase cells. After entry into mitosis, cytokinesis factors such as myosin II are recruited to similar nodes; these nodes eventually condense to form the cytokinetic ring. A previously uncharacterized protein, Blt1, was found to colocalize with Cdr2 in the medial interphase nodes. Blt1 knockout cells had increased length at division, which is consistent with a delay in mitotic entry. This finding connects a physical location, a band of cortical nodes, with factors that have been shown to directly regulate mitotic entry, namely Cdr1, Cdr2, and Blt1.

Further experimentation with GFP-tagged proteins and mutant proteins indicates that the medial cortical nodes are formed by the ordered, Cdr2-dependent assembly of multiple interacting proteins during interphase. Cdr2 is at the top of this hierarchy and works upstream of Cdr1 and Blt1. Mitosis is promoted by the negative regulation of Wee1 by Cdr2. It has also been shown that Cdr2 recruits Wee1 to the medial cortical node. The mechanism of this recruitment has yet to be discovered. A Cdr2 kinase mutant, which is able to localize properly despite a loss of function in phosphorylation, disrupts the recruitment of Wee1 to the medial cortex and delays entry into mitosis. Thus, Wee1 localizes with its inhibitory network, which demonstrates that mitosis is controlled through Cdr2-dependent negative regulation of Wee1 at the medial cortical nodes.

7.6.6 Cell polarity factors

Cell polarity factors positioned at the cell tips provide spatial cues to limit Cdr2 distribution to the cell middle. In fission yeast Schizosaccharomyces pombe (*S. Pombe*), cells divide at a defined, reproducible size during mitosis because of the regulated activity of Cdk1.The cell polarity protein kinase Pom1, a member of the dual-specificity tyrosine-phosphorylation regulated kinase (DYRK) family of kinases, localizes to cell ends. In Pom1 knockout cells, Cdr2 was no longer restricted to the cell middle, but was seen diffusely through half of the cell. From this data it becomes apparent that Pom1 provides inhibitory signals that confine Cdr2 to the middle of the cell. It has been further shown that Pom1-dependent signals lead to the phosphorylation of Cdr2. Pom1 knockout cells were also shown to divide at a smaller size than wild-type, which indicates a premature entry into mitosis.

Pom1 forms polar gradients that peak at cell ends, which shows a direct link between size control factors and a specific physical location in the cell. As a cell grows in size, a gradient in Pom1 grows. When cells are small, Pom1 is spread diffusely throughout the cell body. As the cell increases in size, Pom1 concentration decreases in the middle and becomes concentrated at cell ends. Small cells in early G2 which contain sufficient levels of Pom1 in the entirety of the cell have inactive Cdr2 and cannot enter mitosis. It is not until the cells grow into late G2, when Pom1 is confined to the cell ends that Cdr2 in the medial cortical nodes is activated and able to start the inhibition of Wee1. This finding shows how cell size plays a direct role in regulating the start of mitosis. In this model, Pom1 acts as a molecular link between cell growth and mitotic entry through a Cdr2-Cdr1-Wee1-Cdk1 pathway. The Pom1 polar gradient successfully relays information about cell size and geometry to the Cdk1 regulatory system. Through this gradient, the cell ensures it has reached a defined, sufficient size to enter mitosis.

7.6.7 Other experimental systems for the study of cell size regulation

One common means to produce very large cells is by cell fusion to form syncytia. For example, very long (several inches) skeletal muscle cells are formed by fusion of thousands of myocytes. Genetic studies of the fruit fly Drosophila have revealed several genes that are required for the formation of multinucleated muscle cells by fusion of myoblasts. Some of the key proteins are important for cell adhesion between myocytes and some are involved in

adhesion-dependent cell-to-cell signal transduction that allows for a cascade of cell fusion events.

Increases in the size of plant cells are complicated by the fact that almost all plant cells are inside of a solid cell wall. Under the influence of certain plant hormones the cell wall can be remodeled, allowing for increases in cell size that are important for the growth of some plant tissues. Most unicellular organisms are microscopic in size, but there are some giant bacteria and protozoa that are visible to the naked eye. (See Table of cell sizes—Dense populations of a giant sulfur bacterium in Namibian shelf sediments—Large protists of the genus Chaos, closely related to the genus Amoeba.)

In the rod-shaped bacteria *E. coli*, *Caulobacter crescentus* and *B. subtilis* cell size is controlled by a simple mechanisms in which cell division occurs after a constant volume has been added since the previous division. By always growing by the same amount, cells born smaller or larger than average naturally converge to an average size equivalent to the amount added during each generation.

7.6.8 Cell division

Cell reproduction is asexual. For most of the constituents of the cell, growth is a steady, continuous process, interrupted only briefly at M phase when the nucleus and then the cell divide in two. The process of cell division, called cell cycle, has four major parts called phases. The first part, called G_1 phase is marked by synthesis of various enzymes that are required for DNA replication. The second part of the cell cycle is the S phase, where DNA replication produces two identical sets of chromosomes. The third part is the G_2 phase in which a significant protein synthesis occurs, mainly involving the production of microtubules that are required during the process of division, called mitosis. The fourth phase, **M phase**, consists of nuclear division (karyokinesis) and cytoplasmic division (cytokinesis), accompanied by the formation of a new cell membrane. This is the physical division of "mother" and "daughter" cells. The M phase has been broken down into several distinct phases, sequentially known as prophase, prometaphase, metaphase, anaphase and telophase leading to cytokinesis.

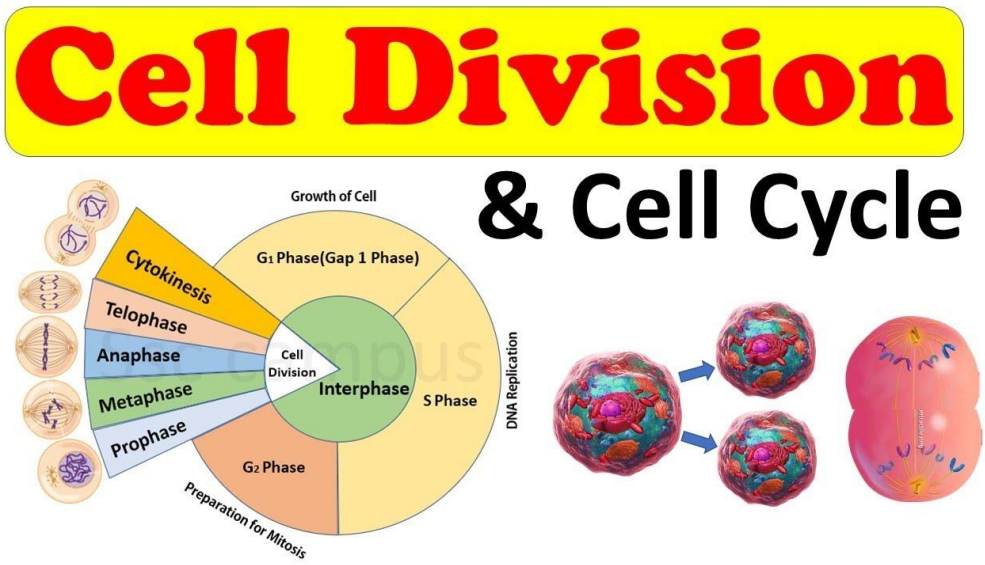


Fig. 6 Phases of the cell cycle

Cell division is more complex in eukaryotes than in other organisms. Prokaryotic cells such as bacterial cells reproduce by binary fission, a process that includes DNA replication, chromosome segregation, and cytokinesis. Eukaryotic cell division either involves mitosis or a more complex process called meiosis. Mitosis and meiosis are sometimes called the two "nuclear division" processes. Binary fission is similar to eukaryote cell reproduction that involves mitosis. Both lead to the production of two daughter cells with the same number of chromosomes as the parental cell. Meiosis is used for a special cell reproduction process of diploid organisms. It produces four special daughter cells (gametes) which have half the normal cellular amount of DNA. A male and a female gamete can then combine to produce a zygote, a cell which again has the normal amount of chromosomes.

7.6.9 Comparison of the three types of cell division

The DNA content of a cell is duplicated at the start of the cell reproduction process. Prior to DNA replication, the DNA content of a cell can be represented as the amount **Z** (the cell has Z chromosomes). After the DNA replication process, the amount of DNA in the cell is **2Z** (multiplication: 2 x Z = 2Z). During Binary fission and mitosis the duplicated DNA content of the reproducing parental cell is separated into two equal halves that are destined to end up in the two daughter cells. The final part of the cell reproduction process is cell division, when daughter cells physically split apart from a parental cell. During meiosis, there are two cell division steps that together produce the four daughter cells.

After the completion of binary fission or cell reproduction involving mitosis, each daughter cell has the same amount of DNA (**Z**) as what the parental cell had before it replicated its DNA. These two types of cell reproduction produced two daughter cells that have the same number of chromosomes as the parental cell. Chromosomes duplicate prior to cell division when forming new skin cells for reproduction. After meiotic cell reproduction the four daughter cells have half the number of chromosomes that the parental cell originally had. This is the haploid amount of DNA, often symbolized as **N**. Meiosis is used by diploid organisms to produce haploid gametes. In a diploid organism such as the human organism, most cells of the body have the diploid amount of DNA, **2N**. Using this notation for counting chromosomes we say that human somatic cells have 46 chromosomes (2N = 46) while human sperm and eggs have 23 chromosomes (N = 23). Humans have 23 distinct types of chromosomes, the 22 autosomes and the special category of sex chromosomes. There are two distinct sex chromosomes, the X chromosome and the Y chromosome. A diploid human cell has 23 chromosomes from that person's father and 23 from the mother. That is, your body has two copies of human chromosome number 2, one from each of your parents.

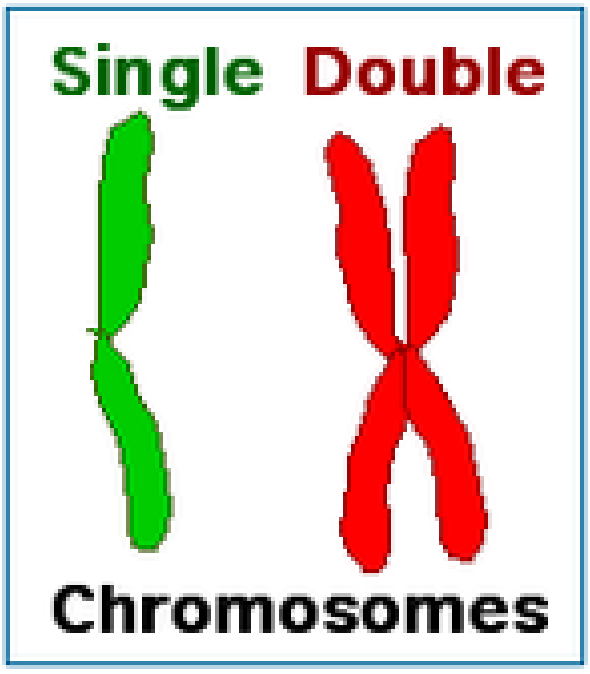


Fig. 7 Chromosomes

Immediately after DNA replication a human cell will have 46 "double chromosomes". In each double chromosome there are two copies of that chromosome's DNA molecule. During mitosis the double chromosomes are split to produce 92 "single chromosomes", half of which go into each daughter cell. During meiosis, there are two chromosome separation steps which

assure that each of the four daughter cells gets one copy of each of the 23 types of chromosome.

7.7.10 Sexual reproduction

Though cell reproduction that uses mitosis can reproduce eukaryotic cells, eukaryotes bother with the more complicated process of meiosis because sexual reproduction such as meiosis confers a selective advantage. Notice that when meiosis starts, the two copies of sister chromatids number 2 are adjacent to each other. During this time, there can be genetic recombination events. Information from the chromosome 2 DNA gained from one parent (red) will transfer over to the chromosome 2 DNA molecule that was received from the other parent (green). Notice that in mitosis the two copies of chromosome number 2 do not interact. Recombination of genetic information between homologous chromosomes during meiosis is a process for repairing DNA damages. This process can also produce new combinations of genes, some of which may be adaptively beneficial and influence the course of evolution. However, in organisms with more than one set of chromosomes at the main life cycle stage, sex may also provide an advantage because, under random mating, it produces homozygotes and heterozygotes according to the Hardy–Weinberg ratio.

7.8 Disorders

A series of growth disorders can occur at the cellular level and these consequently underpin much of the subsequent course in cancer, in which a group of cells display uncontrolled growth and division beyond the normal limits, *invasion* (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). Several key determinants of cell growth, like ploidy and the regulation of cellular metabolism, are commonly disrupted in tumors. Therefore, heterogenous cell growth and pleomorphism is one of the earliest hallmarks of cancer progression. Despite the prevalence of pleomorphism in human pathology, its role in disease progression is unclear. In epithelial tissues, pleomorphism in cellular size can induce packing defects and disperse aberrant cells. But the consequence of atypical cell growth in other animal tissues is unknown.

7.9 Measurement methods

The cell growth can be detected by a variety of methods. The **cell size growth** can be visualized by microscopy, using suitable stains. But the **increase of cells number** is usually more significant. It can be measured by manual counting of cells under microscopy observation, using the dye exclusion method (i.e. trypan blue) to count only viable cells. Less fastidious, scalable, methods include the use of cytometers, while flow cytometry allows combining cell counts ('events') with other specific parameters: fluorescent probes for membranes, cytoplasm or nuclei allow distinguishing dead/viable cells, cell types, cell differentiation, expression of a biomarker such as Ki67.

Beside the increasing number of cells, one can be assessed regarding the **metabolic activity growth**, that is, the CFDA and calcein-AM measure (fluorimetrically) not only the membrane functionality (dye retention), but also the functionality of cytoplasmic enzymes (esterases). The MTT assays (colorimetric) and the resazurin assay (fluorimetric) dose the mitochondrial redox potential. All these assays may correlate well, or not, depending on cell growth conditions and desired aspects (activity, proliferation). The task is even more complicated with populations of different cells, furthermore when combining cell growth interferences or toxicity.

7.10 Summary

Under this unit we summarize the concept of growth, development and ageing. Biological developmental, gradual changes in size, shape, and function during an organism's life that translate its genetic potentials (genotype) into functioning mature systems (phenotype). It includes growth but not repetitive chemical changes (metabolism) or changes over more than one lifetime (evolution). DNA directs the development of a fertilized egg so that cells become specialized structures that carry out specific functions. In humans, development progresses through the embryo and fetus stages before birth and continues during childhood. Other mammals follow a similar course. Amphibians and insects go through distinctive stages that are quite different. In plants, the basic pattern is determined by the arrangement of lateral buds around a central growing stem. Different rates of growth of the plant's component elements then determine its shape and that of various parts. In both animals and plants, growth is greatly influenced by hormones; factors within individual cells probably also play a role.

All organisms, including the very simplest, consist of two components, distinguished by a German biologist, August Weismann, at the end of the 19th century, as the "germ plasm" and the "soma." The germ plasm consists of the essential elements, or genes, passed on from one

generation to the next, and the soma consists of the body that may be produced as the organism develops. In more modern terms, Weismann's germ plasm is identified with DNA (deoxyribonucleic acid), which carries, encoded in the complex structure of its molecule, the instructions necessary for the synthesis of the other compounds of the organism and their assembly into the appropriate structures. It is this whole collection of other compounds (proteins, fats, carbohydrates, and others) and their arrangement as a metabolically functioning organism that constitutes the soma.

7.11Terminal questions

Q.1 What do you mean by concept of growth?

Answer:----------

Q. 2 Describe concept of cell death.

Answer:----------

Q. 3 Write a short note on degrowth.

Answer:----------

Q. 4 What do you mean by ageing?

Answer:----------

Q. 5 Describe mechanism of growth.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner

3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.

Unit-8 - Growth curve and its interpretation (types of cell growth, ageing)

Structure

8.1 Introduction

Growth is the irreversible increase of an organism's size over a given period. It may also be defined as one of the characteristics of a living thing. In *biology, "biological growth"* is associated with progressive development. An organism's growth may go on throughout its life, or end when that species is fully mature. An example of biological growth is a plant seed developing into a fully mature tree. At a cellular level, *cell growth* means an increase in size or an increase in number. In *medical science*, growth may be associated with pathology (disease). For example, *pathological growth* may indicate a tumor, which is an abnormal mass of cells or tissue. It can be defined as, An increase in the size of an organism or part of an organism, usually as a result of an increase in the number of cells. Growth of an organism may stop at maturity, as in the case of humans and other mammals, or it may continue throughout life, as in many plants. In humans, certain body parts, like hair and nails, continue to grow throughout life.

Living things tend to grow throughout their lifespan. However, it is a process that happens periodically and in stages. Growth usually commences with the presence of a singular cell. This cell may multiply and grow larger in specific regions like in plants or it may diversify and growth will be located in various parts of the organism, as seen in animals. Many factors including environmental and internal ones determine how quickly or how slowly an organism will grow. Centuries of change in these factors have influenced how living things develop and grow to this day.

Objectives

This is the first unit on developmental biology. Under this unit, we have following objectives. These are as under:

- To know about bacterial growth
- To know about cancer cell growth and exponential growth
- To know about types of cell growth
- To discuss about the factors that regulate growth

Growth curve, in biology, a curve in graph form that shows the change in the number of cells (or single-celled organisms) in an experimental culture at different times. Growth curves are also common tools in ecological studies; they are used to track the rise and fall of populations of plants, animals, and other multicellular organisms over time. The classic

growth curve, as exemplified by a newly established bacterial colony, is divided into four phases, in order of their appearance:

(1) Lag phase;
(2) Log (logarithmic), or exponential, phase;
(3) Stationary phase; and
(4) Death, or decline, phase.

A growth curve is an empirical model of the evolution of a quantity over time. Growth curves are widely used in biology for quantities such as population size or biomass (in population ecology and demography, for population growth analysis), individual body height or biomass (in physiology, for growth analysis of individuals). Values for the measured property can be plotted on a graph as a function of time; as in given figure for an example.

8.2 Bacterial growth

In the given example, the number of bacteria present in a nutrient-containing broth was measured during the course of an 8-hour cell growth experiment. The observed pattern of bacterial growth is bi-phasic because two different sugars were present, glucose and lactose. The bacteria prefer to consume glucose (Phase I) and only use the lactose (Phase II) after the glucose has been depleted. Analysis of the molecular basis for this bi-phasic growth curve led to the discovery of the basic mechanisms that control gene expression.

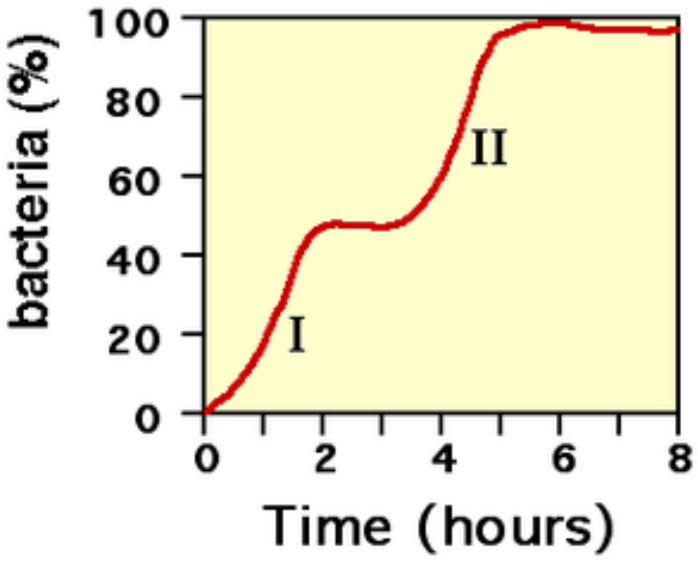


Fig. 1 A bi-phasic bacterial growth curve.

8.3 Cancer cell growth

Cancer research is an area of biology where growth curve analysis plays an important role. In many types of cancer, the rate at which tumors shrink following chemotherapy is related to the rate of tumor growth before treatment. Tumors that grow rapidly are generally more sensitive to the toxic effects that conventional anticancer drugs have on the cancer cells. Many conventional anticancer drugs (for example, 5-Fluorouracil) interfere with DNA replication and can cause the death of cells that attempt to replicate their DNA and divide. A rapidly growing tumor will have more actively dividing cells and more cell death upon exposure to such anticancer drugs.

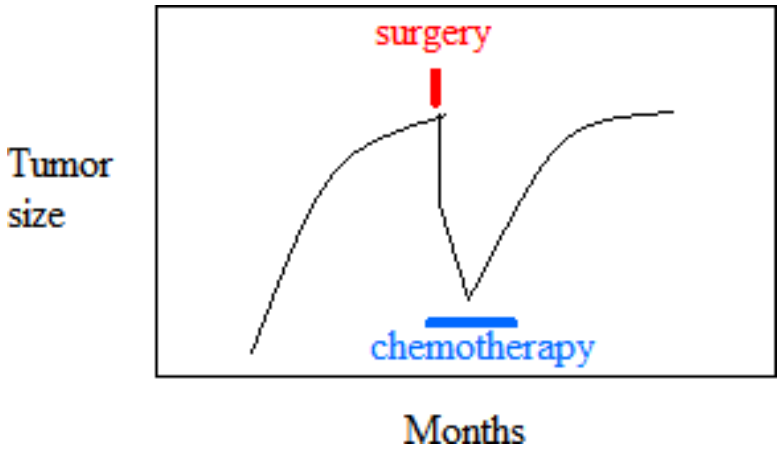


Fig. 2 Tumor growth curve

In the example shown in above Fig. a tumor is found after the cell growth rate has slowed. Most of the cancer cells are removed by surgery. The remaining cancer cells begin to proliferate rapidly and cancer chemotherapy is started. Many tumor cells are killed by the chemotherapy, but eventually some cancer cells that are resistant to the chemotherapy drug begin to grow rapidly. The chemotherapy is no longer useful and is discontinued.

8.4 Exponential growth

Exponential growth is a process that increases quantity over time. It occurs when the instantaneous rate of change (that is, the derivative) of a quantity with respect to time is proportional to the quantity itself. Described as a function, a quantity undergoing exponential growth is an exponential function of time, that is, the variable representing time is the exponent (in contrast to other types of growth, such as quadratic growth). If the constant of proportionality is negative, then the quantity decreases over time, and is said to be undergoing exponential decay instead. In the case of a discrete domain of definition with equal intervals, it is also called geometric growth or geometric decay since the function values form a geometric progression.

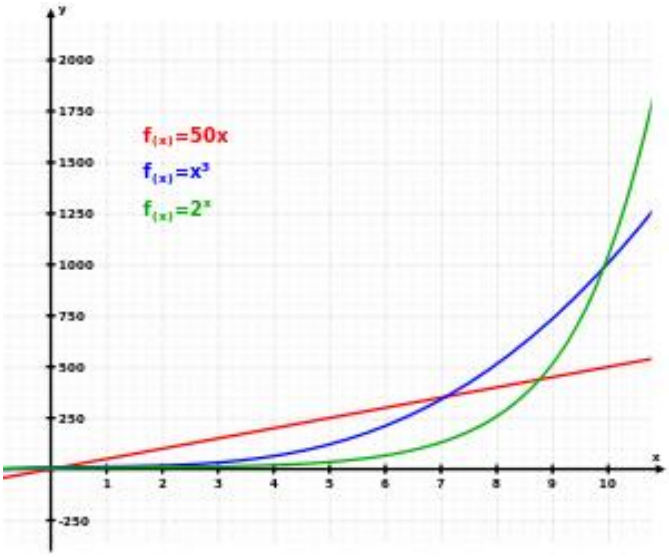


Fig. 3 The graph illustrates how exponential growth (green) surpasses both linear (red) and cubic (blue) growth.

The formula for exponential growth of a variable x at the growth rate r, as time t goes on in discrete intervals (that is, at integer times 0, 1, 2, 3,. ..), Where x_0 is the value of x at time 0. The growth of a bacterial colony is often used to illustrate it. One bacterium splits itself into two, each of which splits itself resulting in four, then eight, 16, 32, and so on. The rate of increase keeps increasing because it is proportional to the ever-increasing number of bacteria. Growth like this is observed in real-life activity or phenomena, such as the spread of virus infection, the growth of debt due to compound interest, and the spread of viral videos. In real cases, initial exponential growth often does not last forever, instead slowing down eventually due to upper limits caused by external factors and turning into logistic growth. Terms like "exponential growth" are sometimes incorrectly interpreted as "rapid growth". Indeed, something that grows exponentially can in fact be growing slowly at first.

8.4.1 Examples

8.4.1.1 In biology

- The number of microorganisms in a culture will increase exponentially until an essential nutrient is exhausted. Typically the first organism splits into two daughter organisms, who then each split to form four, who split to form eight, and so on. Because exponential growth indicates constant growth rate, it is frequently assumed that exponentially growing cells are at a steady-state. However, cells can grow exponentially at a constant rate while remodeling their metabolism and gene expression.

- A virus (for example COVID-19, or smallpox) typically will spread exponentially at first, if no artificial immunization is available. Each infected person can infect multiple new people.

8.4.1.2 In physics

- Avalanche breakdown within a dielectric material. A free electron becomes sufficiently accelerated by an externally applied electrical field that it frees up additional electrons as it collides with atoms or molecules of the dielectric media. These *secondary* electrons also are accelerated, creating larger numbers of free electrons. The resulting exponential growth of electrons and ions may rapidly lead to complete dielectric breakdown of the material.
- Nuclear chain reaction (the concept behind nuclear reactors and nuclear weapons). Each uranium nucleus that undergoes fission produces multiple neutrons, each of which can be absorbed by adjacent uranium atoms, causing them to fission in turn. If the probability of neutron absorption exceeds the probability of neutron escape (a function of the shape and mass of the uranium), the production rate of neutrons and induced uranium fissions increases exponentially, in an uncontrolled reaction. "Due to the exponential rate of increase, at any point in the chain reaction 99% of the energy will have been released in the last 4.6 generations. It is a reasonable approximation to think of the first 53 generations as a latency period leading up to the actual explosion, which only takes 3–4 generations.
- Positive feedback within the linear range of electrical or electroacoustic amplification can result in the exponential growth of the amplified signal, although resonance effects may favor some component frequencies of the signal over others.

8.4.1.3 In economics

- Economic growth is expressed in percentage terms, implying exponential growth.

8.4.1.4 In finance

- Compound interest at a constant interest rate provides exponential growth of the capital.
- Pyramid schemes or Ponzi schemes also show this type of growth resulting in high profits for a few initial investors and losses among great numbers of investors.

8.4.1.5 In computer science

- Processing power of computers. See also Moore's law and technological singularity. (Under exponential growth, there are no singularities. The singularity here is a metaphor, meant to convey an unimaginable future. The link of this hypothetical concept with exponential growth is most vocally made by futurist Ray Kurzweil.
- In computational complexity theory, computer algorithms of exponential complexity require an exponentially increasing amount of resources (e.g. time, computer memory) for only a constant increase in problem size. So for an algorithm of time complexity 2^x, if a problem of size $x = 10$ requires 10 seconds to complete, and a problem of size $x = 11$ requires 20 seconds, then a problem of size $x = 12$ will require 40 seconds. This kind of algorithm typically becomes unusable at very small problem sizes, often between 30 and 100 items (most computer algorithms need to be able to solve much larger problems, up to tens of thousands or even millions of items in reasonable times, something that would be physically impossible with an exponential algorithm). Also, the effects of Moore's Law do not help the situation much because doubling processor speed merely allows you to increase the problem size by a constant. **e.g.** if a slow processor can solve problems of size x in time t, then a processor twice as fast could only solve problems of size x + constant in the same time t. So exponentially complex algorithms are most often impractical, and the search for more efficient algorithms is one of the central goals of computer science today.

8.5 Cell growth

Cell growth refers to an increase in the total mass of a cell, including both cytoplasmic, nuclear and organelle volume. Cell growth occurs when the overall rate of cellular biosynthesis (production of biomolecules or anabolism) is greater than the overall rate of cellular degradation (the destruction of biomolecules via the proteasome, lysosome or autophagy, or catabolism). Cell growth is not to be confused with cell division or the cell cycle, which are distinct processes that can occur alongside cell growth during the process of cell proliferation, where a cell, known as the "mother cell", grows and divides to produce two daughter cells. Importantly, cell growth and cell division can also occur independently of one another. During early embryonic development (cleavage of the zygote to form a morula and blastoderm), cell divisions occur repeatedly without cell growth. Conversely, some cells can grow without cell division or

without any progression of the cell cycle, such as growth of neurons during axonal path finding in nervous system development.

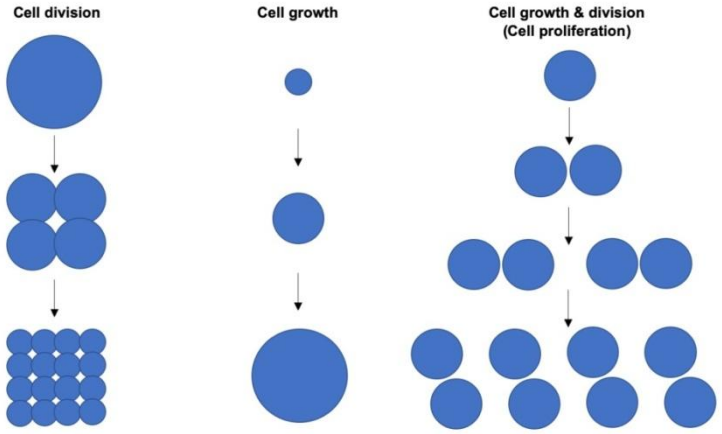


Fig. 4 Cell division, growth & proliferation

In multicellular organisms, tissue growth rarely occurs solely through cell growth without cell division, but most often occurs through cell proliferation. This is because a single cell with only one copy of the genome in the cell nucleus can perform biosynthesis and thus undergo cell growth at only half the rate of two cells. Hence, two cells grow (accumulate mass) at twice the rate of a single cell, and four cells grow at 4-times the rate of a single cell. This principle leads to an exponential increase of tissue growth rate (mass accumulation) during cell proliferation, owing to the exponential increase in cell number.

Cell size depends on both cell growth and cell division, with a disproportionate increase in the rate of cell growth leading to production of larger cells and a disproportionate increase in the rate of cell division leading to production of many smaller cells. Cell proliferation typically involves balanced cell growth and cell division rates that maintain a roughly constant cell size in the exponentially proliferating population of cells.

Some special cells can grow to very large sizes via an unusual endoreplication cell cycle in which the genome is replicated during S-phase but there is no subsequent mitosis (M-phase) or cell division (cytokinesis). These large endoreplicating cells have many copies of the genome, so are highly polyploid.

Oocytes can be unusually large cells in species for which embryonic development takes place away from the mother's body within an egg that is laid externally. The large size of some eggs can be achieved either by pumping in cytosolic components from adjacent cells through cytoplasmic bridges named ring canals (Drosophila) or by internalisation of nutrient storage granules (yolk granules) by endocytosis (frogs).

8.6 Factors that regulate growth

Growth, like all the characteristics of living things, requires regulation to occur. Numerous different factors permit the process of growth to occur. For instance, if anything in the environment is not at its optimum this will either hinder or excessively speed up the growth of an organism. These physical factors can also give rise to different forms of certain structures. Plants that undergo extreme physical stress such as drought will eventually wither from lack of water. On the other hand, leaves grown in the air have a different physical shape from those grown in water for the buttercup plant. The ideal temperature is also necessary for all living things as most mammals would suffer from hypothermia in conditions that are too cold.

Within organisms, there are also internal factors that can promote or inhibit their growth. This is often what the organism possesses in its gene pool and it can result in either regular or abnormal growth in a living thing. Hormones – *those regulatory stimulants which activate the body into performing certain actions* – determine the speed, size, and physical trait the organism will develop in its system. These can even determine the likelihood of the organism to survive and its lifespan. For instance, the pituitary growth hormone has a massive effect on the speed at which mammals grow. A pig that is injected with the growth hormone will not only grow quicker than the ordinary pig but will also be leaner and require less food.

8.7 Types of cell growth

Three types of cell reproduction are compared: the relatively simple Binary fission and two more complicated types that either involve mitosis or meiosis.

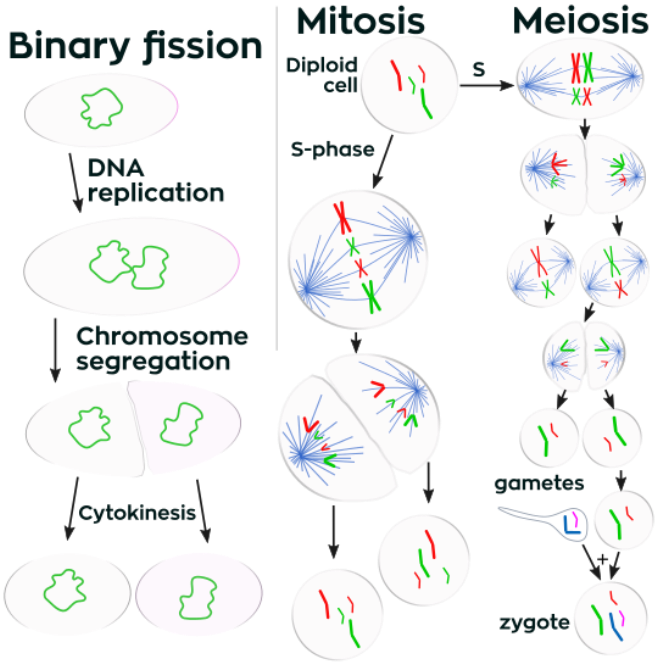


Fig. 5 Types of cell growth

8.7.1 Binary fission

Organisms such as bacteria typically have a single chromosome (green). At the start of the binary fission process, the DNA molecule of the cell's chromosome is replicated, producing two copies of the chromosome. A key aspect of bacterial cell reproduction is making sure that each daughter cell gets a copy of the chromosome. Cytokinesis is the actual physical separation of the two new daughter cells.

8.7.2 Cell reproduction that involves mitosis

Most eukaryotic organisms like humans have more than one chromosome. In order to make sure that a copy of each chromosome gets segregated into each daughter cell, the spindle apparatus is used (blue threads). The chromosomes are moved along the long thin microtubules like trains moving along train tracks. Humans are diploid; we have two copies of each type of chromosome, one from the father (red) and one from the mother (green).

8.7.3 Cell reproduction that involves meiosis

The human sex cells (gametes) are produced by meiosis. For sperm production there are two cytokinesis steps that produce a total of four cells, each with half the normal number of chromosomes. The situation is different in the ovaries for egg production where one of the four sets of chromosomes that is segregated is placed in a large egg cell, ready to be combined with the DNA from a sperm cell

8.8 Ageing

Ageing or aging is the process of becoming older. The term refers mainly to humans, many other animals, and fungi, whereas for example, bacteria, perennial plants and some simple animals are potentially biologically immortal. Furthermore, ageing connotes a biological and social construct. It is usually associated with dynamic changes in the biological, psychological, physiological, environmental, behavioral and social processes. In the broader sense, ageing can refer to single cells within an organism which have ceased dividing or to the population of a species.

In humans, ageing represents the accumulation of changes in a human being over time and can encompass physical, psychological, and social changes. Reaction time, for example, may slow with age, while memories and general knowledge typically increase. Ageing increases the risk of human diseases such as cancer, Alzheimer's disease, diabetes, Cardiovascular disease, stroke and many more. Of the roughly 150,000 people who die each day across the globe, about two-thirds die from age-related causes.

Current ageing theories are assigned to the damage concept, whereby the accumulation of damage (such as DNA oxidation) may cause biological systems to fail, or to the programmed ageing concept, whereby problems with the internal processes (epigenetic maintenance such as DNA methylation) may cause ageing. Programmed ageing should not be confused with programmed cell death (apoptosis). Additionally, there can be other reasons, which can speed up the rate of ageing in organisms including human beings like obesity and compromised immune system.

Scientists have long known that dietary calorie restriction in non-primate animals slows ageing while maintaining good health and body functions. Rats and mice fed 30 to 50% fewer calories than they would freely eat beginning in early life shows various physiological health benefits, lower incidence of chronic diseases, and up to 50% increase in length of life . Though life-extending effects remain uncertain in primates (including humans), the diverse health benefits of limiting calorie intake are now well-established. They seem to result from a physiological response to food scarcity that evolved to enhance the body's capacity to survive adversity.

Nevertheless, few people would be willing to maintain a substantially reduced diet for most of their lifespan. As a result, scientists have begun to explore calorie-restriction mimetics-

natural and synthetic drug compounds that might yield the same health effects as calorie restriction, without dieting. These investigations are still in their early stages.

Biologically, ageing results from the impact of the accumulation of a wide range of molecular and cellular damage over time. Thus, this leads to a gradual decline in physical and mental capacity, a growing risk of diseases, and ultimately, death. These changes are usually consistent, and they are associated with a person's age in years. While some people aged 70 years may be strong and enjoy good health, others who are 70 years may be weak and require others to help them.

8.9 Summary

Under this unit we have summarized growth, growth curve and ageing. Growth in biology is the increase in size and mass of a living organism over time. Most importantly, it is an irreversible change that occurs in the body of the organism. Generally, growth is a result of two processes: cell division and cell enlargement. Here, the main form of cell division occurs during growth is mitosis, which is responsible for the production of cell offspring with the same genetic makeup. On the other hand, enlargement is the increase in the size of the divided cells by increasing the content inside the cell, mainly the water content in vacuoles. Furthermore, the growth of an organism can occur in two types: determinate growth and indeterminate growth. In determinate growth, the size of a part of the organism or the whole organism increases only up to a certain size. Thereafter, growth stops. In contrast, in indeterminate growth, the size of the organism continuously increases throughout its life. For example, plants show indeterminate growth while organs of the animal body undergo determinate growth. In addition, some may describe growth as the increase in the number of organisms in the population, mainly during ecological studies.

Development in biology is the increase in complexity of an organism. The three main processes that occur during development are growth, morphogenesis, and differentiation. As mentioned before, growth is the increase in size and number. However, morphogenesis is the acquisition of form and structure. It is responsible for developing the shape of the organism. Growth refers to the increases in cell size and number, which takes place during the life history of an organism while development refers to the progressive changes in size, shape, and function during the life of an organism by which its genetic potentials (genotype) are translated into functioning mature systems (phenotype). Thus, this explains the fundamental difference between growth and development in biology. That is; growth is the increase in size and mass over a period of time while development is the transformation of an organism into a

more complex form in terms of function and organization. Hence, this is the main difference between growth and development in biology.

8.10 Terminal questions

Q.1 What do you mean by ageing?

Answer:----------

Q. 2Describe growth curve with its interpretation.

Answer:----------

Q.3 Write a short note on cell growth.

Answer:----------

Q.4 Describe type of cell growth.

Answer:----------

Q.5 Draw growth curve.

Answer:----------

Further readings

1. Vertebrate Endocrinology- David O. Norris
2. Invertebrate Zoology –Robert W. Hegner
3. Textbook of Biotechnology –B. D. Singh
4. Textbook of Biochemistry for Undergraduates - Rafi, M.D.
5. Biochemistry and molecular biology- Wilson Walker.