CHAPTER 5

Cell and Cell Interaction

Q.1. Describe the physiology of nerve conduction.

Or

Define a nerve impulse. How nerve impulse is transmitted ?

Ans. **Transmission of Nerve Impulse**

Conduction of Nerve Impulse

The conduction of nerve impulse is an electrochemical event which involves the passage of measurable electric current along a nerve and a few metabolic activities within it at the synaptic ends.

Like all other cells, the nerve cells exist in a fluid environment in which salts and ions are dissolved. The medium is known as **interstitial fluid.** The neurilemma is impermeable to most of these ions, permitting only potassium (K^+) ions to diffuse freely and keeping sodium (Na^+) and chloride (Cl^-) ions outside.

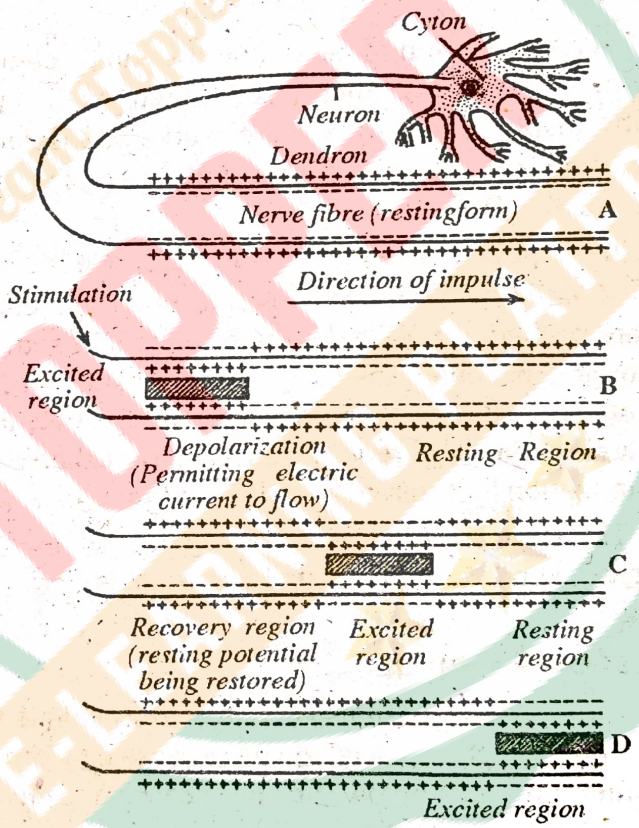


Fig. Propagation of nerve impulse in a nerve fibre.

(1) Resting potential : Under resting condition sodium ions are actively transported from inside to the outside of the nerve fibre. This is known as **sodium pump.** As a result, they are in high concentration outside the membrane in the interstitial fluid and in low concentration in the axoplasm. As a result, the outer surface of the membrane is electrically

positive and the inner surface is negatively charged. The charge on neurilemma is described as **resting potential.** It is about 70-80 mv (millivolt).

(2) Depolarization : When a stimulus of any kind, mechanical, electrical or chemical impinges upon the nerve fibre, momentarily, a local increase occurs in the membrane permeability at the site of stimulus, which permits more sodium ions to rush into the cell. This is just the opposite of the resting state and is called **reverse potential.** It results in **depolarization** of the membrane and a local negatively charged area.

(3) Action potential : This changed electric potential of the neurilema is known as **action potential.** The initial change produces an ionic imbalance in the membrane on either side of the point of stimulus producing local electric current. These areas of negative depolarization, in turn initiate changes in the membrane adjacent to them. A wave of electric change or depolarization along the length of nerve fibre or axon is known as **nerve impulse.**

The propagation of nerve impulse can be compared to the pushing over of a row of dominoes. Energy is required for the intial disturbance, but after that the displacement of domino works to displace the next and once the stimulus has set off a nerve the impulse passes without any change down the length of the fibre.

(4) Repolarization : With the increase of positive charge inside, further entry of Na^+ is prevented and permeability of membrane decreases and Na^+ ions are pushed out. With the establishment of sodium pump the inside of the membrane becomes negative and outside becomes positive and the membrane restores the original resting potential. This is known as **repolarization.** The repolarization starts exactly on the **same spot** where depolarization had started and then continues to advance in both directions.

The entire process of repolarization requires some time during which the nerve cannot be stimulated again. This period is known as **refractory period.**

Threshold Stimulus

A very weak stimulus is unable to propagate a nerve impulse. Intensity of stimulus which is just adequate to cause an impulse is called the **threshold stimulus.** Stimulus below threshold cause a small membrane depolarization but **no action potential.**

☛ Q.2. Write note on cell adhesion.

Ans. A variety of proteins and carbohydrates remain associated with cell membranes. Sometimes these molecules are occur as **glycoproteins** or as **glycolipids.** These molecules form an **extracellular matrix** which

help the membrane in perform a variety of functions like **cell recognition, membrane transport** and **vesicular transoprt.**

The cells in tissue are joined together and remain in contact with the help of extracellular matrix. In verterbrates, these tissues include nerve, blood epithelial and connective tissues. The cell in all these tissues are held together by cell-cell adhesion. In early stages of development only cell-cell adhesions are displayed but in mature adult structures, cell junctions are also associated with cell adhesion.

Cell adhesion

In the developing embryo different types of cells regregrate and form specific regions through cell sorting. The same type of cells aggregate together through the phenomenon of cell adhesion, occurs due to the presence of specific proteins and carbohydrates in the plasma membrane. These proteins are called adhesive proteins.

Adhesive proteins : ECM (extra cellular matrix) contains a variety of **specialized glycoproteins** and involved in arranging cells into organized structures. These molecules function as substrate adhesive molecules. In the ECM, collagen and proteoglycan function as substrates. Three types of **adhesive glycol proteins** are found on the plasma membrane.

1. Fibronectin : It is a very large **glycoprotein** and is synthesized by cells like **fibroblasts, chondrocytes, endothelial cells, macrophages** and certain **epithelial cells.** It also helps in cell migratin.

2. Laminin : It is a large multi-chain **glycoprotein** and consists of three polypeptide chains. It is a major component of **basal lamina** and provides a link between the cell and the structural components of **basement membrane.** The three chains of laminin are responsible for binding to collagen, heparian sulfate, entactin and laminin receptors.

3. Tenascin : It is also known as **cytotactin** and resembles fibronectin for about half of its length and it is transiently accur in ECM during embryonic development. Different cells react differently to tenascin, so that it does not always promote cell adhesion.

Q.3. Write a short note on various cell functions.

Ans. The cell is the basic unitl of life. There are a lot of differences in size and shape of various types of cells. The main functions of cell are :

1. All cells maintain a that protect the contents of cells from the external environment. This barrier maintains the concentration of the solutes in the cell regulating the transport of materials from in and out of the cells.

2. **Inheritance and transmission of genetic material** from one generation to another are performed in the cell through cell divisions.

3. All cells carry out series of chemical reactions like the synthesis of macromolecules, trapping energy, the degradation of some unused molecules, converting food substances into sugars etc.

4. Cells can show different types of motility starting from locomotion to the movement of components of cells.

☛ **Q.4. Write a short note on exta cellular matrix.**

Ans. Animal tissue is not only composed of cells but also contain many types of extracellular spaces. These spaces are filled up by many types of **macromolecules** consistuting the extracellular matrix. The macromolecules, constitute the extracellular matrix are mainly secreted locally by the cell. In most of the connective tissues these are secreted by **fibroblast,** in some specialized connective tissue like cartilage and bone these are secreted by **chondroblasts** and **osteoblasts.** The extracellular matrix is made of three main types of extracellular macromolecules like glycosaminoglycans, fibrous proteins and specalized extracellular matrix or basal lamina.

☛ **Q.5. Write a short note on neurotransmission and Ion channels.**

Ans. **Membrane Excitability in Animals**

(Neurotransmission and Ion Channels)

All living systems is their ability to respond rapidly to stimuli like sights, sounds, smells, etc. In animals, this will certainly involve movement of muscles and intercellular communications. These communications need to be very fast, certainly faster than the speed with which blood carrying hormones, or lymph flows in the circulatory system. These nerve inpulses are generated and transmitted through a complicated network connecting every part of the body of the brain.

The nervous system contains specialized **receptor proteins** in the membranes of excitable cells. The stimulus causes a conformational change in these receptor proteins or causes a change in permeability of the excitable membranes. These changes in excitable membranes are propagated from one part of the cell to another and from one cell to another in a specific but reversible manner, carrying information from one part of the organism to another. These changes involve regular transport of ions and substances called **neurotransmitters.** Transmission of signals in the nervous system involving transport of ions and neurotransmitters takes place through nerve cells or neurons.

☛ **Q.6. Write a short note on myosin.**

Ans. **Myosin :** Myosin is one of the important protein that is present in the myofibrils and this in conjunction with actin forms a structural

framework of the contractile mechanism in muscles. A myosin molecule has an attachment site for actin molecule and an enzymatic site that breaks down ATP with the liberation of energy.

Q.7. Explain the Neuromuscular Junction.

Ans. Neuromuscular Junction : These are the junctions between the nerve fibre, or the axon reaching the muscle fibre forming an intimate contract with them in the form of an end plate. They receive the nerve impulse on the end plate and result in excitation of muscle fibres.

The area of contact between neuron and muscle fibre is called a **neuromuscular junction.** The important point is that they allow a large area of apposition between axoplasm and sarcoplasm.

Q.8. Write a note on sacromere.

Ans. Sarcomere : A small segment of striated muscle fibril between two successive Z-discs is called as sarcomere. Each sarcomere consists of two types of myofilaments : **(i) Thick :** myosin myofilaments and **(ii) Thin :** actin myofilaments.

Q.9. Distinguish between a cholinergic and adrenergic nerve fibres.

Ans. Difference Between Cholinergic and Adrenergic Fibres : Normally, the transmission of nerve impulses across the synapse in both synmpathetic and parasympathetic system is led by the release at the synpase of acetylcholine or a similar substance.

1. In parasympathetic system, the acetylcholine is also released at the nerve ending in the end organs. Such fibres are known as **cholinergic firbres.**

2. In sympathetic system, the chemical substance released at the nerve endings in the end organ is **sympathin** (in place of acetylcholine). The nerve fibres that release sympathin at their endings are known as **adrenergic fibres.**

Q.10. What is cholinesterase and what is its function ?

Ans. Cholinesterase : When a nerve impulse arrives at the motor end plate, the chemical substance acetylcholine is released in the end plate area. This substance transmits the impulse to muscle fibres, which start the process of contraction. Following a brief period of contraction, the nerve releases another substance, **cholinesterase.** The cholinesterae neutralizes acetylcholine and causes the muscle fibres to relax. It, therefore, has an antagonistic effect to the acetylcholine.

Q.11. Describe the function of acetylcholine, adrenamline and serotonin in nerve physiology.

Ans. Acetylcholine : Acetylcholine is a chemical transmitter at the synapses. Depolarization of terminal knobs of axon causes local

movement of ions, including Ca^{++} ions. Entry of Ca^{++} ions releases acetylcholine which diffuses across the synaptic cleft. It combines with specific receptor molecules of postsynaptic membrane and the complex changes the permeability for smaller ions causing depolarization of the postsynaptic cell. Thus it helps in the transmission of nerve impulse at the synapse. It is functional at the cholinergic effector organs (muscles, glands etc.), postganglionic parasympathetic nerve endings, preganglionic sympathetic nerve ending and at neuro-muscular junction.

Adrenaline or **epinephrine** and **serotonin** are also chemical transmitters. Epinephrine is present in preganglionic sympathetic nerve endings.

☛ **Q.12. Write a short note on sodium pump.**

Ans. Sodium Pump : It is a mechanism by which sodium ions are transported out of a neuron across the cell membrane. The process requires energy in the form of ATP since it is a form of active transport. It maintains the different concentration of sodium ions on either side of neuron membrane.

☛ **Q.13. Explain neurosecretion.**

Ans. Neurosecretion : Neurosecrtion plays an important role in the integration of various body activities, viz. growth, reproduction, water balance, pigmentation, moulding etc.

Corpus cardiacum in insects and neurohypophysis in vertebrates, from where they are discharged as and when required. This secretion from these cells can pass along the interganglionic connections in either directions and also outwards along the peripheral nerves.

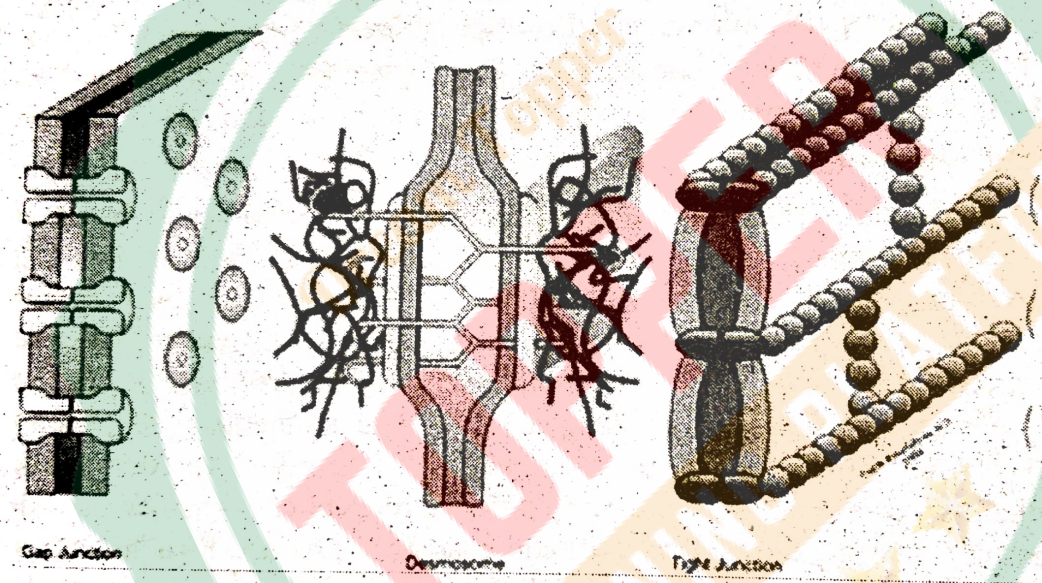
The neurosecretory cells are present in lower animals which possess well defined nervous system except lower coelenterates and tenophores. In higher animals neurosecretory cells aggregate and form well defined neurosecretory system. The major neurosecretory system in vertebrates is located in the supra-optic and paraventricular regions of hypothalamus.

The basal part of the hypothalamus is also neurosecretory in function and secretes **tropic hormones** or releasing factors. The neurosecretory material from this part of hypothalamus is poured into the blood supplying the anterior pituitary. Similarly neurohypophysis located in the caudal region of the spinal cord is another example of neurosecretory system in fishes.

☛ **Q. 14. Discuss cell–cell interaction?**

Ans. Cell–cell interaction refers to the direct interactions between cell surfaces that play a crucial role in the development and function of multicellular organisms. These interactions allow cells to

communicate with each other in response to changes in their microenvironment. This ability to send and receive signals is essential for the survival of the cell. Interactions between cells can be stable such as those made through cell junctions. These junctions are involved in the communication and organization of cells within a particular tissue. Others are transient or temporary such as those between cells of the immune system or the interactions involved in tissue inflammation. These types of intercellular interactions are distinguished from other types such as those between cells and the extracellular matrix. The loss of communication between cells can result in uncontrollable cell growth and cancer.



Various types of cell junctions In this diagram, the interface between neighboring cells or the basolateral membrane is depicted as "sheets"; the space between these sheets being the extracellular environment and the location of adhesion protein interaction.

Stable cell-cell interactions are required for cell adhesion within a tissue and controlling the shape and function of cells. These stable interactions involve cell junctions which are multiprotein complexes that provide contact between neighboring cells. Cell junctions allow for the preservation and proper functioning of epithelial cell sheets. These junctions are also important in the organization of tissues where cells of one type can only adhere to cells of the same tissue rather than to a different tissue.

Tight Junctions

Tight junctions are multi-protein complexes that hold cells of a same tissue together and prevent movement of water and water-soluble molecules between cells. In epithelial cells, they function also to separate the extracellular fluid surrounding their apical and basolateral membranes. These

junctions exist as a continuous band located just below the apical surface between the membranes of neighboring epithelial cells. The tight junctions on adjacent cells line up so as to produce a seal between different tissues and body cavities. For example, the apical surface of gastrointestinal epithelial cells serves as a selective permeable barrier that separates the external environment from the body. The permeability of these junctions is dependent on a variety of factors including protein makeup of that junction, tissue type and signaling from the cells.

Tight junctions are made up of many different proteins. The four main transmembrane proteins are occludin, claudin, junctional adhesion molecules (JAMs) and tricellulins. The extracellular domains of these proteins form the tight junction barrier by making homophilic (between proteins of the same kind) and heterophilic interactions (between different types of proteins) with the protein domains on adjacent cells. Their cytoplasmic domains interact with the cell cytoskeleton to anchor them.

Anchoring Junctions

Of the three types of anchoring junctions, only two are involved in cell-cell interactions: adherens junctions and desmosomes. Both are found in many types of cells. Adjacent epithelial cells are connected by adherens junctions on their lateral membranes. They are located just below tight junctions. Their function is to give shape and tension to cells and tissues and they are also the site of cell-cell signaling. Adherens junctions are made of cell adhesion molecules from the cadherin family. There are over 100 types of cadherins, corresponding to the many different types of cells and tissues with varying anchoring needs. The most common are E-, N- and P-cadherins. In the adherens junctions of epithelial cells, E-cadherin is the most abundant.

Desmosomes also provide strength and durability to cells and tissues and are located just below adherens junctions. They are sites of adhesion and do not encircle the cell. They are made of two specialized cadherins, desmoglein and desmocollin. These proteins have extracellular domains that interact with each other on adjacent cells. On the cytoplasmic side, plakins form plaques which anchor the desmosomes to intermediate filaments composed of keratin proteins. Desmosomes also play a role in cell-cell signaling.

Gap Junctions

Gap junctions are the main site of cell-cell signaling or communication that allows small molecules to diffuse between adjacent cells. In vertebrates, gap junctions are composed of transmembrane proteins called connexins. They form hexagonal pores or channels through which ions, sugars, and other small molecules can pass. Each pore is made of 12 connexin molecules; 6 form a hemichannel on one cell membrane and interact with a hemichannel

on an adjacent cell membrane. The permeability of these junctions is regulated by many factors including pH and Ca2+ concentration.

Receptor Proteins in Direct-contact Signaling

Receptor proteins on the cell surface have the ability to bind specific signaling molecules secreted by other cells. Cell signaling allows cells to communicate with adjacent cells, nearby cells (paracrine) and even distant cells (endocrine). This binding induces a conformational change in the receptor which, in turn, elicits a response in the corresponding cell. These responses include changes in gene expression and alterations in cytoskeleton structure. The extracellular face of the plasma membrane has a variety of proteins, carbohydrates, and lipids which project outward and act as signals. Direct contact between cells allows the receptors on one cell to bind the small molecules attached to the plasma membrane of different cell. In eukaryotes, many of the cells during early development communicate through direct contact.

Synaptic signaling, an integral part of nervous system activity, occurs between neurons and target cells. These target cells can also be neurons or other cell types (i.e. muscle or gland cells). Protocadherins, a member of the cadherin family, mediate the adhesion of neurons to their target cells at synapses otherwise known as synaptic junctions. In order to for communication to occur between a neuron and its target cell, a wave of depolarization travels the length of the neuron and causes neurotransmitters to be released into the synaptic junction. These neurotransmitters bind and activate receptors on the post-synaptic neuron thereby transmitting the signal to the target cell. Thus, a post-synaptic membrane belongs to the membrane receiving the signal, while a pre-synaptic membrane is the source of the neurotransmitter. In a neuromuscular junction, a synapse is formed between a motor neuron and muscle fibers. In vertebrates, acetylcholine released from the motor neuron acts as a neurotransmitter which depolarizes the muscle fiber and causes muscle contraction. A neuron's ability to receive and integrate simultaneous signals from the environment and other neurons allows for complex animal behavior.

Plant cell-cell Interactions

Plant cells are surrounded by cell walls which are barriers for cell-cell communication. This barrier is overcome by specialized junctions called plasmodesmata. They are similar to gap junctions, connecting the cytosol of adjacent cells. Small molecules (<1000 Da), such as ions, amino acids and sugars, can diffuse freely though plasmodesmata. These small molecules include signaling molecule and transcription factors. The size of the channel is also regulated to allow molecules up to 10,000 Da in size. The permeability of these channels is dependent on many factors, including Ca2+

concentration. An increase in cytosolic Ca^{2+} concentration will reversibly limit passage through the plasmodesmata. Unlike gap junctions, the cell membranes of adjacent cells merge to form a continuous channel called an annulus. Additionally, within the channel, there is an extension of the endoplasmic reticulum, called a desmotubule, which spans between the cells. The cell-cell interactions facilitated by plasmodesmata play an important role in development of plant cells and tissues and defense against viral infection.

Transient Interactions

Immune System

Leukocytes or white blood cells destroy abnormal cells and also provide protection against bacteria and other foreign matter. These interactions are transitory in nature but are crucial as an immediate immune response. To fight infection, leukocytes must move from the blood into the affected tissues. This movement into tissues is called extravasation. It requires successive forming and breaking of cell-cell interactions between the leukocytes and the endothelial cells that line blood vessels. These cell-cell interactions are mediated mainly by a group of Cell Adhesion Molecules (CAMs) called selectins.

T helper cells, central to the immune system, interact with other leukocytes by releasing signals known as cytokines which activate and stimulate the proliferation of B cells and killer T cells.T helper cells also directly interact with macrophages, cells that engulf foreign matter and display antigens on its surface. T-helper cells that possess the appropriate receptors can bind to these antigens and proliferate resulting in T-helper cells that have the ability to identify the same antigens.

Coagulation

Coagulation or blood clotting relies on, in addition to the production of fibrin, interactions between platelets. When the endothelium or the lining of a blood vessel is damaged, connective tissue including collagen fibers is locally exposed. Initially, platelets stick to the exposed connective tissue through specific cell-surface receptors. This is followed by platelet activation and aggregation in which platelets become firmly attached and release chemicals that recruit neighboring platelets to the site of vascular injury. A meshwork of fibrin then forms around this aggregation of platelets to increase the strength of the clot.

Cell interactions between bacteria

Bacterial populations interact in a similar manner to cells in tissue. They communicate through physical interactions and signaling molecules such as homoserine lactones and peptides as a means to control metabolism and regulate growth. A common example and one of the most studied forms of

bacterial cell interactions is biofilm. Biofilm is a cell aggregate that can be attached to biological or abiotic surfaces. Bacteria form biofilms to adapt to various environments such as changes in substrate availability. For example, the formation of biofilm increases a bacterial cell's resistance to antibiotics compared to cells which are not part of the aggregate.

Pathological Implications

Cancer

Cancer can result from the loss of cell-cell interaction. In normal cells, growth is controlled by contact inhibition in which contact with neighboring cells causes a stunt in cell growth. Contact inhibition is thought to be mediated by cadherins, proteins that play an important role in cell adhesion. This inhibition prevents cells from piling up on top of one another and forming mounds. However, in cancerous cells where expression of E-cadherin is lost, contact inhibition is lost and results in uncontrolled growth or proliferation, tumor formation, and metastasis.

Bacterial Pathogens

In order for pathogenic bacteria to invade a cell, communication with the host cell is required. The first step for invading bacteria is usually adhesion to host cells. Strong anchoring, a characteristic that determines virulence, prevents the bacteria from being washed away before infection occurs. Bacterial cells can bind to many host cell surface structures such as glycolipids and glycoproteins which serve as attachment receptors. Once attached, the bacteria begin to interact with the host to disrupt its normal functioning and disrupt or rearrange its cytoskeleton. Proteins on the bacteria surface can interact with protein receptors on the host thereby affecting signal transduction within the cell. Alterations to signaling are favorable to bacteria because these alterations provide conditions under which the pathogen can invade. Many pathogens have Type III secretion systems which can directly inject protein toxins into the host cells. These toxins ultimately lead to rearrangement of the cytoskeleton and entry of the bacteria.

Disease

Cell–cell interactions are highly specific and are tightly regulated. Genetic defects and dysregulation of these interactions can cause much different disease. Dysregulation that leads to leukocyte migration into healthy tissues can cause conditions such as acute respiratory distress syndrome and some types of arthritis. The autoimmune disease pemphigus vulgaris results from autoantibodies to desmoglein and other normal body proteins. The autoantibodies disrupt the adhesion between epithelial cells. This causes blisters of the skin and mucous membranes. Mutations in the connexin genes cause 8 human diseases including heart malformations and neurosensory deafness.

Q.15. What is programmed cell death? What are the types of programmed cell death?

Ans. Programmed cell-death (or PCD) is death of a cell in any form, 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 are separate. PCD serves fundamental functions during both plant and metazoa (multicellular animals) tissue development. Apoptosis and autophagy are both forms of programmed cell death, but necrosis is a non-physiological process that occurs as a result of infection or injury.

Necrosis is the death of a cell caused by external factors such as trauma or infection and occurs in several different forms. Recently a form of programmed necrosis, called necroptosis, has been recognized as an alternate 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.

Types

1. Apoptosis or Type I cell-death.
2. Autophagic or Type II cell-death. (Cytoplasmic: characterized by the formation of large vacuoles that eats away organelles in a specific sequence prior to the destruction of the nucleus.)

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, nuclearfragmentation, 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.

Autophagy

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.

Mechanism

A critical regulator of autophagy induction is the kinase mTOR, which when activated, suppresses autophagy and when not activated promotes it. Three relatedserine/threonine kinases, UNC-51-like kinase-1, -2, and -3 (ULK1, ULK2, UKL3), which play a similar role as the yeast Atg1, act downstream of the mTOR complex.ULK1 and ULK2 form a large complex with the mammalian homolog of an autophagy-related (Atg) gene product (mAtg13) and the scaffold protein FIP200. Class III PI3K complex, containing hVps34, Beclin-1, p150 and Atg14-like protein or ultraviolet irradiation resistance-associated gene (UVRAG), is required for the induction of autophagy.

The ATG genes control the autophagosome formation through ATG12-ATG5 and LC3-II (ATG8-II) complexes. ATG12 is conjugated to ATG5 in a ubiquitin-like reaction that requires ATG7 and ATG10. The Atg12–Atg5 conjugate then interacts non-covalently with ATG16 to form a large complex. LC3/ATG8 is cleaved at its C terminus by ATG4 protease to generate the cytosolic LC3-I. LC3-I is conjugated to phosphatidylethanolamine (PE) also in a ubiquitin-like reaction that requires Atg7 and Atg3. The lipidated form of LC3, known as LC3-II, is attached to the autophagosome membrane.

Autophagy and apoptosis are connected both positively and negatively, and extensive crosstalk exists between the two. During nutrient deficiency, autophagyfunctions as a pro-survival mechanism, however, excessive autophagy may lead to cell death, a process morphologically distinct from apoptosis. Several pro-apoptotic signals, such as TNF, TRAIL, and FADD, also induce autophagy. Additionally, Bcl-2 inhibits Beclin-1-dependent autophagy, thereby functioning both as a pro-survival and as an anti-autophagic regulator.

Other Types

Besides the above two types of PCD, other pathways have been discovered. Called "non-apoptotic programmed cell-death" (or

"caspase-independent programmed cell-death" or "necroptosis"), these alternative routes to death are as efficient as apoptosis and can function as either backup mechanisms or the main type of PCD.

Other forms of programmed cell death include 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.

Atrophic Factor

An atrophic factor is a force that causes a cell to die. Only natural forces on the cell are considered to be atrophic factors, whereas, for example, agents of mechanical or chemical abuse or lysis of the cell are considered not to be atrophic factors. Common types of atrophic factors are:

1. Decreased workload
2. Loss of innervation
3. Diminished blood supply
4. Inadequate nutrition
5. Loss of endocrine stimulation
6. Senility
7. Compression

Role of PCD in Neural Development

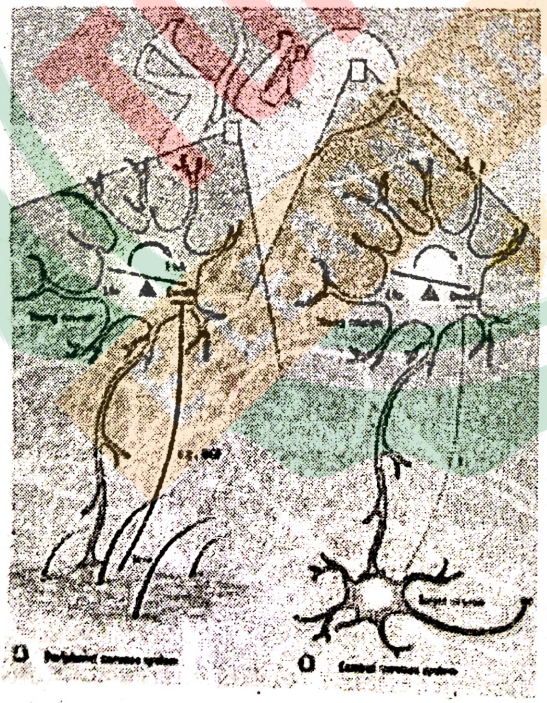
PCD in the developing nervous system has been observed in proliferating as well as post-mitotic cells. One theory suggests that PCD is an adaptive mechanism to regulate the number of progenitor cells. In humans, PCD in progenitor cells starts at gestational week 7 and remains until the first trimester. This process of cell death has been identified in the germinal areas of the cerebral cortex, cerebellum, thalamus, brainstem, and spinal cord among other regions. At gestational weeks 19-23, PCD is observed in post-mitotic cells. The prevailing theory explaining this observation is the neurotrophic theory which states that PCD is required to optimize the connection between neurons and their afferent inputs and efferent targets. Another theory proposes that developmental PCD in the nervous system occurs in order to correct for errors in neurons that have migrated ectopically, innervated incorrect targets, or have axons that have gone awry during path finding. It is possible that PCD during the development of the nervous system serves different functions determined by the developmental stage, cell type, and even species.

The Neurotrophic Theory

The neurotrophic theory is the leading hypothesis used to explain the role of programmed cell death in the developing nervous system. It postulates that in order to ensure optimal innervation of targets, a surplus of neurons is first produced which then compete for limited quantities of protective neurotrophic factors and only a fraction survive while others die by programmed cell death. Furthermore, the theory states that predetermined factors regulate the amount of neurons that survive and the size of the innervating neuronal population directly correlates to the influence of their target field.

The underlying idea that target cells secrete attractive or inducing factors and that their growth cones have a chemotactic sensitivity was first put forth by Santiago Ramon y Cajal in 1892. Cajal presented the idea as an explanation for the "intelligent force" axons appear to take when finding their target but admitted that he had no empirical data. The theory gained more attraction when experimental manipulation of axon targets yielded death of all innervating neurons. This developed the concept of target derived regulation which became the main tenet in the neurotrophic theory. Experiments that further supported this theory led to the identification of the first neurotrophic factor, nerve growth factor (NGF).

Peripheral Versus Central Nervous System



Cell death in the peripheral vs central nervous system

Different mechanisms regulate PCD in the peripheral nervous system (PNS) versus the central nervous system (CNS). In the PNS, innervation of

the target is proportional to the amount of the target-released neurotrophic factors NGF and NT3.Expression of neurotrophin receptors, TrkA and TrkC, is sufficient to induce apoptosis in the absence of their ligands. Therefore it is speculated that PCD in the PNS is dependent on the release of neurotrophic factors and thus follows the concept of the neurotrophic theory.

Programmed cell death in the CNS is not dependent on external growth factors but instead relies on intrinsically derived cues. In the neocortex, a 4:1 ratio of excitatory to inhibitory interneurons is maintained by apoptotic machinery that appears to be independent of the environment. Supporting evidence came from an experiment where interneuron progenitors were either transplanted into the mouse neocortex or cultured in vitro. Transplanted cells died at the age of two weeks, the same age at which endogenous interneurons undergo apoptosis. Regardless of the size of the transplant, the fraction of cells undergoing apoptosis remained constant. Furthermore, disruption of TrkB, a receptor for brain derived neurotrophic factor (Bdnf), did not affect cell death. It has also been shown that in mice null for the proapoptotic factor Bax (Bcl-2-associated X protein) a larger percentage of interneurons survived compared to wild type mice. Together these findings indicate that programmed cell death in the CNS partly exploits Bax-mediated signaling and is independent of BDNF and the environment. Apoptotic mechanisms in the CNS are still not well understood, yet it is thought that apoptosis of interneurons is a self-autonomous process.

Nervous System Development in the Absence of Programmed cell Death

Programmed cell death can be reduced or eliminated in the developing nervous system by the targeted deletion of pro-apoptotic genes or by the overexpression of anti-apoptotic genes. The absence or reduction of PCD can cause serious anatomical malformations but can also result in minimal consequences depending on the gene targeted, neuronal population, and stage of development. Excess progenitor cell proliferation that leads to gross brain abnormalities is often lethal, as seen in caspase-3 or caspase-9 knockout mice which develop exencephaly in the forebrain. The brainstem, spinal cord, and peripheral ganglia of these mice develop normally, however, suggesting that the involvement of caspases in PCD during development depends on the brain region and cell type. Knockout or inhibition of apoptotic protease activating factor 1 (APAF1), also results in malformations and increased embryonic lethality. Manipulation of apoptosis regulator proteins Bcl-2 and Bax (overexpression of Bcl-2 or deletion of Bax) produces an increase in the number of neurons in certain regions of the nervous system such as the retina, trigeminal nucleus, cerebellum, and spinal cord. However, PCD of neurons

due to Bax deletion or Bcl-2 overexpression does not result in prominent morphological or behavioral abnormalities in mice. For example, mice overexpressing Bcl-2 have generally normal motor skills and vision and only show impairment in complex behaviors such as learning and anxiety. The normal behavioral phenotypes of these mice suggest that an adaptive mechanism may be involved to compensate for the excess neurons.

Invertebrates and Vertebrates

Learning about PCD in various species is essential in understanding the evolutionary basis and reason for apoptosis in development of the nervous system. During the development of the invertebrate nervous system, PCD plays different roles in different species. The similarity of the asymmetric cell death mechanism in the nematode and the leech indicates that PCD may have an evolutionary significance in the development of the nervous system. In the nematode, PCD occurs in the first hour of development leading to the elimination of 12% of non-gonadal cells including neuronal lineages. Cell death inarthropods occurs first in the nervous system when ectoderm cells differentiate and one daughter cell becomes a neuroblastand the other undergoes apoptosis. Furthermore, sex targeted cell death leads to different neuronal innervation of specific organs in males and females. In Drosophila, PCD is essential in segmentation and specification during development.

In contrast to invertebrates, the mechanism of programmed cell death is found to be more conserved in vertebrates. Extensive studies performed on various vertebrates show that PCD of neurons and glia occurs in most parts of the nervous system during development. It has been observed before and during synaptogenesis in the central nervous system as well as the peripheral nervous system. However, there are a few differences between vertebrate species. For example, mammals exhibit extensive arborization followed by PCD in the retina while birds do not. Although synaptic refinement in vertebrate systems is largely dependent on PCD, other evolutionary mechanisms also play a role.

Programmed cell death in plants has a number of molecular similarities to animal apoptosis, but it also has differences, the most obvious being the presence of acell wall and the lack of an immune system that removes the pieces of the dead cell. Instead of an immune response, the dying cell synthesizes substances to break itself down and places them in a vacuole that ruptures as the cell dies.

Basic morphological and biochemical features of PCD have been conserved in both plant and animal kingdoms. It should be noted, however, that specific types of plant cells carry out unique cell-death programs. These have common features with animal apoptosis—for instance, nuclear DNA

degradation—but they also have their own peculiarities, such as nuclear degradation triggered by the collapse of the vacuole in tracheary elements of the xylem.

Janneke Balk and Christopher J. Leaver, of the Department of Plant Sciences, University of Oxford, carried out research on mutations in the mitochondrial genomeof sun-flower cells. Results of this research suggest that mitochondria play the same key role in vascular plant PCD as in other eukaryotic cells.

PCD in Pollen Prevents Inbreeding

During pollination, plants enforce self-incompatibility (SI) as an important means to prevent self-fertilization. Research on the corn poppy (Papaver rhoeas) has revealed that proteins in the pistil on which the pollen lands, interact with pollen and trigger PCD in incompatible (i.e., self) pollen. The researchers, Steven G. Thomas and Veronica E. Franklin-Tong, also found that the response involves rapid inhibition of pollen-tube growth, followed by PCD.

In Slime Molds

The social slime mold Dictyostelium discoideum has the peculiarity of either adopting a predatory amoeba-like behavior in its unicellular form or coalescing into a mobile slug-like form when dispersing the spores that will give birth to the next generation.

The stalk is composed of dead cells that have undergone a type of PCD that shares many features of an autophagic cell-death: massive vacuoles forming inside cells, a degree of chromatin condensation, but no DNA fragmentation. The structural role of the residues left by the dead cells is reminiscent of the products of PCD in plant tissue.

D. discoideum is a slime mold, part of a branch that might have emerged from eukaryotic ancestors about a billion years before the present. It seems that they emerged after the ancestors of green plants and the ancestors of fungi and animals had differentiated. But, in addition to their place in the evolutionary tree, the fact that PCD has been observed in the humble, simple, six-chromosome D. discoideum has additional significance: It permits the study of a developmental PCD path that does not depend on caspases characteristic of apoptosis.

Evolutionary origin

The occurrence of programmed cell death in protists is possible, but it remains controversial. Some categorize death in those organisms as unregulated, by necrosis or incidental death.

Biologists had long suspected that mitochondria originated from bacteria that had been incorporated as endosymbionts ("living together

inside") of larger eukaryotic cells. It was Lynn Margulis who from 1967 on championed this theory, which has since become widely accepted. The most convincing evidence for this theory is the fact that mitochondria possess their own DNA and are equipped with genes and replication apparatus.

This evolutionary step would have been risky for the primitive eukaryotic cells, which began to engulf the energy-producing bacteria, as well as a perilous step for the ancestors of mitochondria, which began to invade their proto-eukaryotic hosts. This process is still evident today, between human white blood cells and bacteria. Most of the times, invading bacteria are destroyed by the white blood cells; however, it is not uncommon for the chemical warfare waged by prokaryotes to succeed, with the consequence known as infection by its resulting damage.

One of these rare evolutionary events, about two billion years before the present, made it possible for certain eukaryotes and energy-producing prokaryotes to coexist and mutually benefit from their symbiosis.

Mitochondriate eukaryotic cells live poised between life and death, because mitochondria still retain their repertoire of molecules that can trigger cell suicide. This process has now been evolved to happen only when programmed. Given certain signals to cells (such as feedback from neighbors, stress or DNA damage), mitochondria release caspase activators that trigger the cell-death-inducing biochemical cascade. As such, the cell suicide mechanism is now crucial to all of our lives.