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UNIT-1

BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

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BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

Cell injury is any disruption of normal cell structure or function caused by noxious stimuli like physical trauma, toxins, infection, or genetic damage. It occurs when a cell's protective responses are overwhelmed or unable to cope with stress.

Depending on the nature and duration of the damage, the injury may be reversible or evolve into permanent damage, resulting in cell death. Having a thorough understanding of cellular injury is crucial in comprehending the pathophysiology of most diseases.

Types of Cell Injury

1. **Reversible Cell Injury**

Reversible cell injury occurs when cells experience a brief period of ischaemia or hypoxia. In this type of injury, the cells undergo changes in response to various stressors but may recover if the cause is eliminated or properly managed. Reversible cell injury is classified into a few types, which include:

- **Cell Swelling (Hydropic Degeneration):** Dysfunction of ion homeostasis leads to water sequestration and cytoplasmic vacuole formation. This is usually the first sign of reversible cell damage.
- **Lipid Accumulation**: The sequestration of excess lipids in the cytoplasm interferes with cellular metabolism, often in the liver and heart during metabolic distress. If this situation worsens, it can lead to lipotoxicity.
- **Membrane Damage:** Although it is temporary, minor damage to the plasma membrane increases permeability and may lead to leakage, but it can be repaired if detected early.
- **Glycogen Depletion and Enzyme Dysfunction**: Energy deficits caused by mitochondrial dysfunction lead to depleted glycogen stores and compromised enzyme activity, thereby impairing normal functioning.
- **DNA Damage and Reversible Protein Denaturation**: There are minor structural DNA and protein changes, which can be repaired by the cell if the injurious agent is removed.

2. **Irreversible Cell Injury**

Irreversible **cell injury** is a severe type of cell damage in which the cell cannot recover and ultimately dies. This happens when the damage to the cell is greater than its ability to fix itself, resulting in cell death. It is classified into several types:

- **Apoptosis**: Apoptosis is a regulated, energy-requiring process of programmed cell death initiated by stimuli such as DNA damage or cellular stress. It can preserve tissue homeostasis, suppress cancer, and restrict inflammation and is critical in immune defence by removing infected or damaged cells.
- **Necrosis**: It refers to a form of cell death that is not regulated, leading to the swelling of organelles, rupture of the plasma membrane, and ultimately the lysis of the cell.
- **Autophagy**: The cell degrades its own structures in response to starvation or stress. Protective in the short term, but excessive autophagy is fatal.
- **Oxidative Stress**: An overload of reactive oxygen species (ROS) causes damage to proteins, lipids, and nucleic acids, potentially leading to apoptosis or necrosis.
- **Ischaemia and Hypoxia**: Prolonged lack of oxygen and nutrients leads to energy failure, membrane destruction, and irreversible structural damage.

Causes of Cell Injury (Etiology)

Cell injury is caused by a variety of noxious stimuli that interfere with the normal structure or function of cells. Here are some of the reasons:

- **Physical Damage:** Physical trauma, extreme temperatures (burns or frostbite), and exposure to radiation can damage cell membranes and organelles, thereby initiating the pathogenesis of cell injury.
- **Chemical Injury:** Poisonous chemicals, such as drugs and environmental toxins, inhibit cellular metabolism or membrane integrity and result in functional impairment or death.
- **Biological Agents**: Infectious agents like bacteria, viruses, and fungi evoke immune reactions or release toxins, causing direct cell injury pathology. Autoimmune responses may also inadvertently act against normal cells.
- **Oxygen Deficiency (Hypoxia and Ischaemia):** Impaired oxygen supply (hypoxia) or total elimination of blood flow (ischaemia) is a primary reason for reversible and irreversible cellular damage, particularly in organs with high oxygen demands, such as the brain and heart.
- **Nutrient Deficiencies:** Both a lack and an excess of essential nutrients (like vitamins, proteins, and minerals) disrupt cellular functions and cause harm.

- **Ageing**: Cellular damage and lowered repair capacity through time are some of the most common reasons that can lead to **cell injury** or even cell death. Besides, the shortening of telomeres and protein deposition can also cause age-related cell injury.

Mechanisms of Reversible Cell Injury

Here are the mechanisms of reversible cell injury

- **Hydropic Degeneration (Cell Swelling):** Microscopic evaluation shows the presence of vacuoles in the cytoplasm. In extreme cases, the cell fills with fluid and ruptures, leading to cellular death.
- **Damage to the Cell Membrane**: Damage to the plasma membrane leads to the leakage of cell contents and the entry of toxic substances.
- **Glycogen Depletion**: Decreased glycogen is caused by increased energy requirements or decreased production of energy.
- **Reversible Protein Denaturation**: Proteins can undergo alterations due to stress but revert to their normal state upon the removal of the stress factor.
- **Mitochondrial Dysfunction**: Oxidative phosphorylation and ATP production can be impaired, resulting in reduced energy within the cell.

Mechanisms of Irreversible Cell Injury

Discussed below are the mechanisms of irreversible cell injury

- **Severe Cell Membrane Damage**: Severe damage to the plasma membrane can result in loss of cell material and influx of toxic substances.
- **DNA (Deoxyribonucleic Acid) Damage**: Severe and irreversible damage to DNA has the potential to initiate programmed cell death (apoptosis) or necrosis.
- **Mitochondrial Permeability Transition**: Perforation of the mitochondrial membrane has the ability to induce the release of pro-apoptotic factors and additional energy loss.
- **Severe ATP (Energy) Depletion**: Prolonged and extreme depletion of ATP or energy can cause irreparable cell dysfunction and death.
- **Lysosomal Breakdown**: The leakage of lysosomal enzymes into the cytoplasm can induce cell digestion and cell death (necrosis).

Feedback System

A feedback system is a self-regulating mechanism where the output of a process is monitored and fed back into the system to control future performance.

Components of a Feedback System

1. **Stimulus:** A change or perturbation that disrupts the normal internal environment.
2. **Receptor** (Sensor): A specialized cell or organ (such as nerve endings or thermoreceptors) that detects the stimulus and sends information to the control center.
3. **Control Center (Integrator):** Usually the brain, spinal cord, or endocrine gland (like the hypothalamus) that receives the receptor's input, compares it against a normal set point, and determines the appropriate response.
4. **Effector:** A muscle or gland that receives the command from the control center and acts to produce a change.
5. **Response:** The resulting action that either negative feedback (reverses the original stimulus to restore balance, such as sweating to cool down) or positive feedback (enhances or accelerates the stimulus, such as during childbirth) carries out.

TYPES OF FEEDBACK SYSTEM

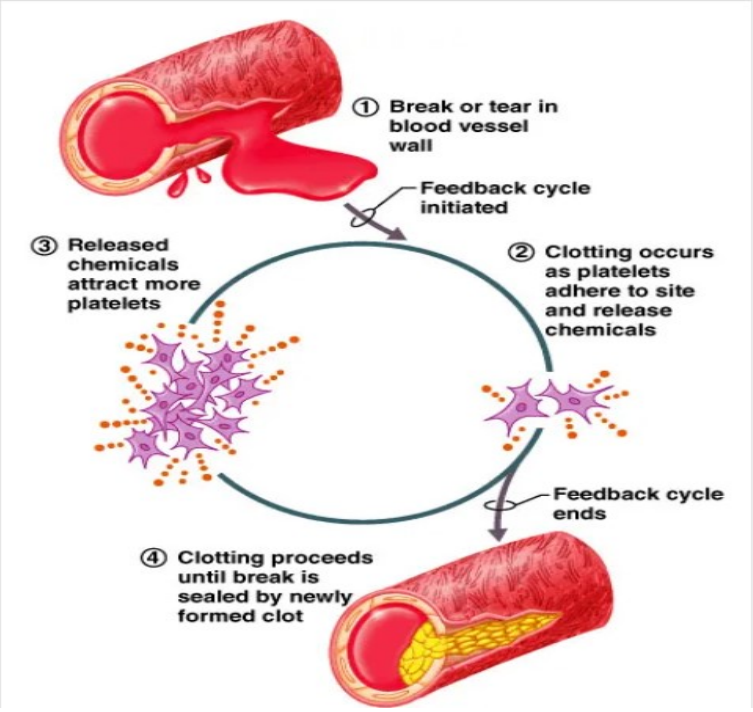
I. Positive feedback mechanism

A positive feedback mechanism involves more stimulation or the acceleration of the process. Let’s find more about it below**.**

Steps / Process / Mechanism of positive feedback mechanism

The process of a positive feedback loop consists of a control system that consists of various components, working in a circular pathway to stimulate or inhibit one another. The overall process can be described in terms of the components of the system.

1. ***Stimulation***. The stimulation that initiates the positive feedback loop in order to complete a process is the initial step. Hormones released by various organs as a result of the start of a process are the most common stimuli in the human body.



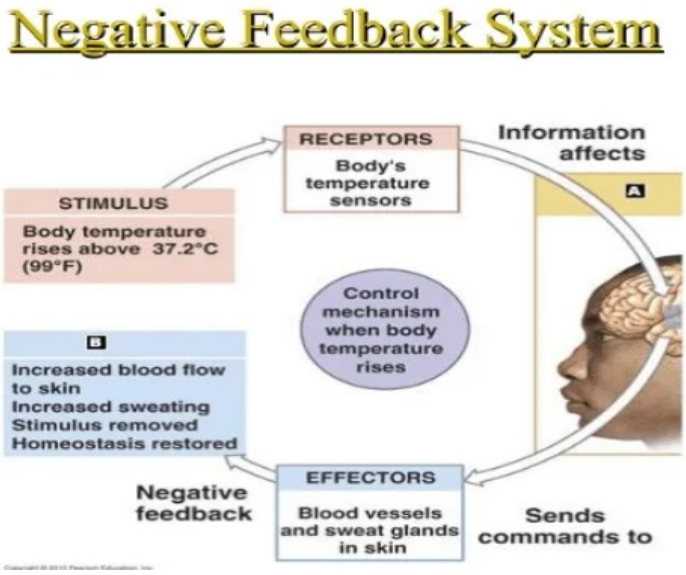
2. ***Reception***. The second step in the loop is the reception of stimuli via various sensors, which provide data to the control unit. These receptors are mostly nerves that transmit signals from the stimulus location to the control unit, which is the brain in humans.
3. ***Processing***. The processing of information supplied to the control unit by the receptors is the next phase in the loop. The control unit tallies the data and displays an output if the stimulus is outside the typical range of the value.
4. ***Stimuli are activated even more***. In order to induce an output in response to the stimulus, information from the brain is conveyed to the location of action via several nerves. The brain's messages tend to activate the stimulus even more in the direction of deviation in the case of a positive feedback loop.

Ex. Blood Clotting

Childbirth

Menstrual cycle

II. Negative feedback mechanism



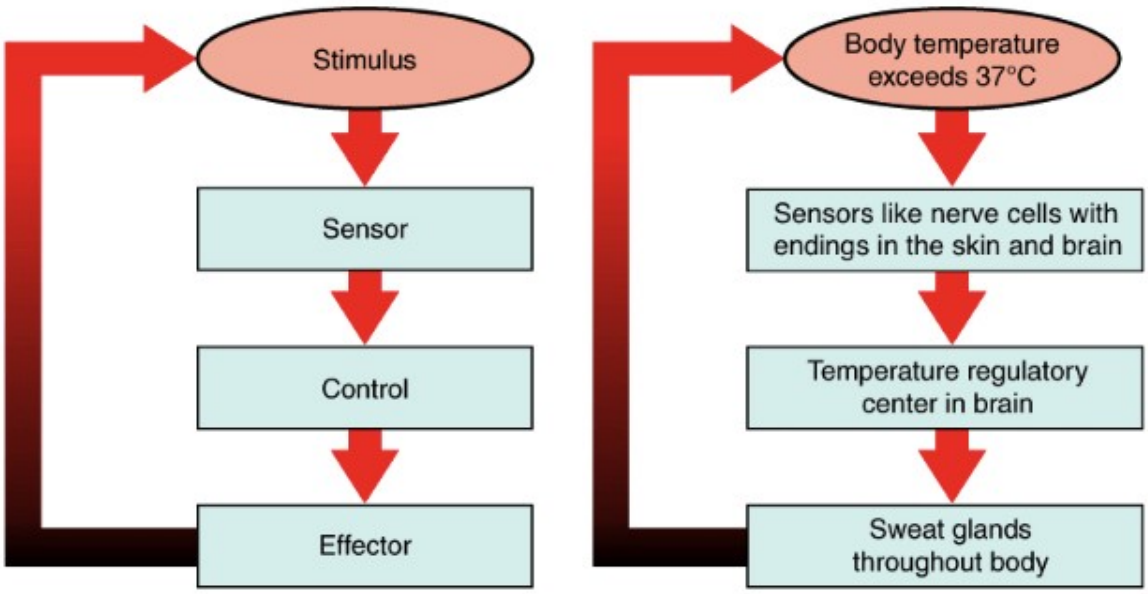
Steps in a negative feedback mechanism

The negative feedback system works in a similar way to the positive feedback loop in that it is activated by stimuli and eventually leads to modifications that tend to cancel out those impulses. The following is a summary of the overall procedure:

1. ***Stimulation***. The development of stimuli as a result of physiological parameter deviations from the normal value is the initial stage in the negative feedback loop. Physiological parameters can deviate from the norm in either direction.
2. ***Reception***. The control unit receives changes in physiological parameters through a variety of receptors located throughout the body. Nerves and other thermoreceptors are examples of common receptors engaged in stimulus transmission.
3. ***Processing***. The brain serves as the loop's control unit, determining whether a change in a physiological parameter necessitates loop activation or inhibition. The brain sends out signals to erase the alterations in different ways depending on the direction of departure.
4. ***Counteract on the stimulus***. The control unit sends out signals at the end of the loop to cancel out the impacts that cause changes in physiological variables. Changes can take several forms and be directed at different sections of the body.

Examples of negative feedback

Regulating Temperature



Negative feedback loop

Body temperature regulation

Ex. Regulating Blood Glucose Level

Causes of Cell Injury (Etiology)

Cell injury is caused by a variety of noxious stimuli that interfere with the normal structure or function of cells. Here are some of the reasons:

- **Physical Damage:** Physical trauma, extreme temperatures (burns or frostbite), and exposure to radiation can damage cell membranes and organelles, thereby initiating the pathogenesis of cell injury.
- **Chemical Injury:** Poisonous chemicals, such as drugs and environmental toxins, inhibit cellular metabolism or membrane integrity and result in functional impairment or death.
- **Biological Agents**: Infectious agents like bacteria, viruses, and fungi evoke immune reactions or release toxins, causing direct cell injury pathology. Autoimmune responses may also inadvertently act against normal cells.

- **Oxygen Deficiency (Hypoxia and Ischaemia):** Impaired oxygen supply (hypoxia) or total elimination of blood flow (ischaemia) is a primary reason for reversible and irreversible cellular damage, particularly in organs with high oxygen demands, such as the brain and heart.
- **Nutrient Deficiencies:** Both a lack and an excess of essential nutrients (like vitamins, proteins, and minerals) disrupt cellular functions and cause harm.
- **Ageing**: Cellular damage and lowered repair capacity through time are some of the most common reasons that can lead to **cell injury** or even cell death. Besides, the shortening of telomeres and protein deposition can also cause age-related cell injury.

PATHOGENESIS

a) Cell Membrane Damage

Loss of selective permeability: Ion pumps (such as the Na^+/K^+-ATPase) fail due to ATP depletion or direct injury, leading to an uncontrolled influx of Na^+ and water, causing cellular (hydropic) swelling.

Enzyme and content leakage: Damage to the plasma membrane allows intracellular enzymes (like troponins or transaminases) to leak out into the extracellular space/bloodstream.

Ca^{2+} influx: Extracellular calcium floods into the cytosol, activating harmful calcium-dependent enzymes including phospholipases (which degrade membrane phospholipids further), proteases, and endonucleases.

b) Mitochondrial Damage

ATP depletion: Hypoxia, toxins, or direct mitochondrial injury halt oxidative phosphorylation, dropping energy levels and crippling energy-dependent cellular functions.

Mitochondrial Permeability Transition (MPT) Pore: Opening of this pore causes a loss of mitochondrial membrane potential and matrix swelling.

Release of pro-apoptotic factors: Damaged mitochondria leak cytochrome c and other apoptosis-inducing proteins into the cytosol, activating caspases and triggering programmed cell death.

Amorphous densities: Severe structural breakdown manifests as large amorphous calcium-rich densities inside the mitochondrial matrix, signaling irreversible injury.

c) Ribosome Damage

Detachment from the Rough Endoplasmic Reticulum (RER): Energy deprivation and RER swelling cause ribosomes and polyribosomes to detach and disperse into the cytoplasm.

Halted protein synthesis: Disaggregation of polysomes into single monosomes impairs translation, decreasing overall protein production necessary for cell repair and survival.

d) Nuclear Damage

Chromatin clumping: Early or mild/reversible injury (often aided by intracellular acidosis from lactic acid accumulation) causes clumping and condensation of nuclear chromatin.

DNA fragmentation: Endonucleases activated by excess cytosolic Ca^{2+} or oxidative stress cleave nuclear DNA into random fragments.

Progression to cell death: Irreversible nuclear damage proceeds through three characteristic morphological stages: **pyknosis** (shrinkage/condensation), **karyorrhexis** (fragmentation), and **karyolysis** (dissolution).

Morphology of Cell Injury: The morphology of cell injury refers to the structural and functional changes that occur in cells when they are exposed to physiological stress or harmful stimuli. Cells are constantly subjected to changes in their internal and external environment. Under normal conditions, they adapt to these changes to maintain their normal function and ensure survival. However, when the stress exceeds the adaptive capacity of the cell or the injurious stimulus is severe or prolonged, cellular injury develops.

Adaptive Changes of Cells

Cellular adaptation is the process by which cells adjust their structure, function, or number in response to physiological demands or pathological stress. These adaptations enable cells to survive in altered environments while maintaining their essential functions. The major adaptive changes include atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia.

1. Atrophy

Atrophy is the decrease in the size of a cell, tissue, or organ due to a reduction in the size and number of cellular components. As a result, the affected organ becomes smaller and its functional capacity is reduced. Atrophy is generally an adaptive response that allows the cell to survive under conditions of reduced workload or limited nutrient supply.

Atrophy may occur under both physiological and pathological conditions. Physiological atrophy is a normal part of development and ageing, such as the shrinkage of the thymus after puberty or the involution of the uterus after childbirth. Pathological atrophy occurs as a result of disuse, denervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, pressure, or ageing.

The mechanisms responsible for atrophy include decreased protein synthesis, increased protein degradation through the ubiquitin-proteasome pathway, and activation of autophagy, in which damaged cellular organelles are digested within lysosomes to provide nutrients for cell survival.

Common examples include skeletal muscle atrophy after prolonged immobilization, cerebral atrophy in Alzheimer's disease, renal atrophy due to chronic ischemia, and testicular atrophy following hormonal deficiency.

Although atrophy is generally reversible if the underlying cause is corrected early, prolonged atrophy may become irreversible because of permanent loss of cells and tissue function.

2. Hypertrophy

Hypertrophy is an increase in the size of individual cells, resulting in enlargement of the affected organ or tissue without an increase in the number of cells. This adaptation occurs when cells are unable to divide or when increased functional demand requires greater cellular activity.

Hypertrophy develops through increased synthesis of structural proteins and intracellular organelles, leading to enlargement of the cytoplasm and increased functional capacity of the cell. The process is regulated by mechanical stress, growth factors, and hormones.

Physiological hypertrophy occurs during normal body development or increased physical activity. For example, enlargement of skeletal muscles in athletes occurs due to regular exercise, while enlargement of the uterus during pregnancy results from hormonal stimulation.

Pathological hypertrophy commonly occurs in the heart. In patients with hypertension or valvular heart disease, cardiac muscle cells enlarge because they must generate greater force to pump blood against increased resistance. Initially, this adaptation improves cardiac function;

however, prolonged hypertrophy eventually leads to heart failure due to increased oxygen demand and reduced efficiency.

Hypertrophy is therefore considered a beneficial adaptive response in its early stages but may become harmful if excessive or prolonged.

3. Hyperplasia

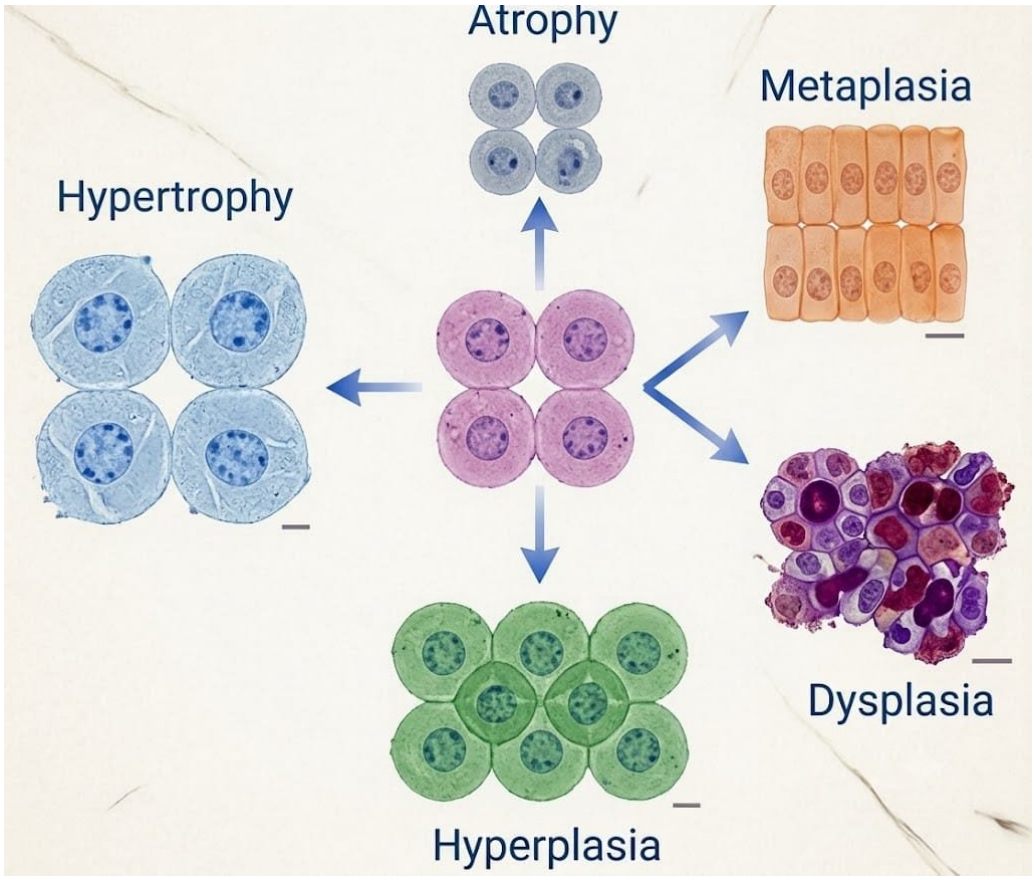
Hyperplasia is an increase in the number of cells within a tissue or organ due to increased cellular proliferation. Unlike hypertrophy, where individual cells become larger, hyperplasia results from cell division, leading to enlargement of the affected tissue.

Hyperplasia occurs only in tissues whose cells retain the ability to divide. It is regulated by growth factors, hormones, and cytokines that stimulate DNA synthesis and cell proliferation.

Physiological hyperplasia occurs as a normal response to hormonal stimulation or increased functional demand. During pregnancy, the glandular tissue of the breast undergoes hyperplasia to prepare for milk production. Similarly, regeneration of the liver following partial surgical removal occurs through compensatory hyperplasia.

Pathological hyperplasia develops because of excessive hormonal stimulation or abnormal growth factor activity. Examples include endometrial hyperplasia caused by excessive estrogen stimulation and benign prostatic hyperplasia (BPH), in which the prostate gland enlarges due to hormonal influences in elderly men.

Hyperplasia is usually reversible after removal of the stimulating factor. However, persistent pathological hyperplasia may increase the risk of developing certain cancers, particularly in tissues such as the endometrium.



4. Metaplasia

Metaplasia is a reversible adaptive process in which one mature differentiated cell type is replaced by another mature cell type better able to withstand adverse environmental conditions. This transformation occurs through the reprogramming of stem cells rather than direct conversion of one mature cell into another.

Metaplasia develops as a protective mechanism against chronic irritation or inflammation. Although the new cell type is more resistant to injury, it often loses the specialized functions of the original cells, thereby reducing normal tissue function.

One of the most common examples is squamous metaplasia in the respiratory tract of chronic smokers. Normally, the bronchi are lined by ciliated columnar epithelial cells that remove mucus and inhaled particles. Continuous exposure to cigarette smoke causes these cells to be replaced by stratified squamous epithelium, which is more resistant to irritation but lacks cilia, reducing the efficiency of mucociliary clearance.

Another example is Barrett's esophagus, in which the normal stratified squamous epithelium of the lower esophagus is replaced by columnar epithelium because of chronic gastroesophageal reflux disease (GERD).

Metaplasia is generally reversible if the injurious stimulus is removed. However, persistent metaplasia may progress to dysplasia and eventually carcinoma.

5. Dysplasia

Dysplasia refers to abnormal growth, maturation, and organization of cells within a tissue. It is characterized by variations in cell size and shape, enlarged hyperchromatic nuclei, increased mitotic activity, and loss of normal cellular architecture.

Unlike metaplasia, dysplasia is not considered a true adaptive response but rather a premalignant change that may precede the development of cancer. Dysplasia most commonly occurs in epithelial tissues exposed to chronic irritation or persistent inflammation.

Examples include cervical dysplasia associated with persistent human papillomavirus (HPV) infection, bronchial dysplasia in chronic smokers, and dysplastic changes in the oral mucosa of tobacco users.

Mild dysplasia may regress if the underlying cause is eliminated. However, severe dysplasia has a high risk of progressing to carcinoma if left untreated. Therefore, early detection through screening programs such as the Pap smear is essential.

Cell Swelling

Cell swelling, also known as hydropic change or cloudy swelling, is the earliest and most common morphological manifestation of reversible cell injury. It occurs when the cell loses its ability to regulate the movement of sodium and water across the plasma membrane.

Normally, the sodium-potassium ATPase pump maintains ionic balance by actively transporting sodium out of the cell and potassium into the cell. During hypoxia, ischemia, or ATP depletion, this pump fails, causing sodium and water to accumulate within the cytoplasm. As a result, the cell enlarges, and intracellular organelles such as the endoplasmic reticulum and mitochondria become swollen.

Microscopically, swollen cells appear enlarged with pale, vacuolated cytoplasm. Electron microscopy reveals distended endoplasmic reticulum, mitochondrial swelling, and membrane blebbing.

Cell swelling is generally reversible if oxygen supply and ATP production are restored. However, persistent swelling eventually progresses to irreversible cellular injury and cell death.

Intracellular Accumulation

Intracellular accumulation refers to the abnormal build-up of substances within the cytoplasm, nucleus, or lysosomes of cells. These substances may be produced normally but accumulate because of defective metabolism, impaired transport, excessive production, or inability of the cell to degrade them.

The most common intracellular accumulations include lipids (fat), proteins, glycogen, pigments, and minerals.

Fat accumulation, also known as fatty change (steatosis), occurs mainly in the liver and heart. It is commonly associated with alcohol abuse, obesity, diabetes mellitus, malnutrition, and hypoxia. Excess triglycerides accumulate within hepatocytes, causing enlargement of the liver and impaired liver function.

Protein accumulation may occur in kidney diseases, plasma cell disorders, and chronic inflammation. Glycogen accumulation is observed in uncontrolled diabetes mellitus and inherited glycogen storage diseases.

Pigments may be either endogenous or exogenous. Endogenous pigments include melanin, lipofuscin, and hemosiderin, whereas exogenous pigments include carbon particles deposited in the lungs of smokers or individuals exposed to air pollution.

Excessive intracellular accumulation interferes with normal cellular metabolism and may eventually lead to cellular dysfunction and injury.

Cell Death

When cellular injury becomes severe and irreversible, the cell undergoes cell death. Cell death is the final outcome of irreversible cellular injury and occurs primarily through necrosis or apoptosis.

Necrosis

Necrosis is an uncontrolled form of cell death resulting from severe injury such as ischemia, infections, toxins, trauma, or chemical exposure. During necrosis, the plasma membrane ruptures, intracellular enzymes leak into the surrounding tissues, and an inflammatory response develops.

Morphologically, necrotic cells exhibit increased cytoplasmic eosinophilia, disruption of cellular architecture, and characteristic nuclear changes such as pyknosis (nuclear shrinkage), karyorrhexis (fragmentation of the nucleus), and karyolysis (dissolution of the nucleus).

Common examples include myocardial infarction, gangrene, burns, and cerebral infarction.

Apoptosis

Apoptosis is a programmed and highly regulated form of cell death that removes unwanted, damaged, or aged cells without causing inflammation. It plays an essential role in embryonic development, maintenance of tissue homeostasis, immune regulation, and elimination of genetically damaged cells.

During apoptosis, the cell shrinks, chromatin condenses, DNA fragments, and membrane-bound apoptotic bodies are formed. These apoptotic bodies are rapidly engulfed by macrophages without releasing intracellular contents, thereby preventing inflammation.

Apoptosis occurs during normal physiological processes such as embryogenesis and tissue remodeling, as well as in pathological conditions including DNA damage, viral infections, and certain neurodegenerative diseases.

Clinical Significance

The study of the morphology of cell injury is essential for understanding the development and progression of many diseases. Adaptive changes such as atrophy, hypertrophy, hyperplasia, and metaplasia initially help cells survive adverse conditions, but persistent stress may lead to dysplasia, irreversible injury, and cancer. Similarly, cell swelling and intracellular accumulation are important indicators of reversible injury, whereas necrosis and apoptosis represent the final outcomes of severe cellular damage. Recognition of these morphological changes assists clinicians and pathologists in diagnosing diseases, assessing disease severity, and planning appropriate treatment strategies.