CELL INJURY

Cell injury occurs when cells are stressed beyond their ability to adapt, caused by factors like oxygen deprivation (hypoxia), toxins, or physical trauma. It begins as reversible damage (e.g., swelling, fatty change) but can progress to irreversible injury, resulting in cell death via necrosis (pathological) or apoptosis (programmed).

Key Causes of Cell Injury

- **Hypoxia/Ischemia:** Lack of oxygen or reduced blood flow is the most common cause, leading to metabolic failure.
- **Physical/Chemical Agents:** Trauma, extreme temperatures, radiation, toxins, and drugs.
- **Infectious Agents:** Bacteria, viruses, fungi, and parasites.
- **Immunological Reactions:** Immune system malfunction causing tissue damage.
- **Nutritional/Genetic Factors:** Deficiencies, excesses, or DNA abnormalities. **Mechanisms of Cell Injury**

1. **ATP Depletion:** Reduced energy production leads to dysfunction of sodium-potassium pumps (\(Na^{+}-K^{+}\) ATPase), causing cellular swelling and loss of protein synthesis.
2. **Mitochondrial Damage:** Results in ATP depletion and leakage of proteins that trigger apoptosis.
3. **Calcium Influx:** Increased intracellular calcium activates enzymes that damage cellular components.
4. **Free Radicals:** Reactive oxygen species (ROS) damage lipids, proteins, and DNA.

TYPES OF CELL INJURY

- **Reversible Injury:** The cell can return to its original state if the stressor is removed. Characteristics include cellular swelling and fatty changes (steatosis).
- **Irreversible Injury (Cell Death):** The damage is too severe, leading to the breakdown of cell membranes and irreversible nuclear changes.
    - **Necrosis:** Cell death from severe acute injury, characterized by swelling and membrane breakdown (e.g., coagulative, liquefactive, caseous).
    - **Apoptosis:** Programmed cell death where the cell breaks into fragments that are removed without severe inflammation.
    - **Cellular Adaptations**:When faced with stress, cells may adapt to survive, which can manifest as: **Hypertrophy:** Increase in cell size.
- **Hyperplasia:** Increase in cell number.
- **Atrophy:** Decrease in cell size and number.
- **Metaplasia:** Change in cell type

Apoptosis Definition

"The term apoptosis can be defined as a natural biological process of programmed cell death in which the cells destroy themselves for maintaining the smooth functioning of the body."

There are two forms of cell death

1. Programmed death of cells called Apoptosis.
2. An uncontrolled death of cells called Necrosis.

Both apoptosis and necrosis occur under different circumstances and involve different steps.

The term apoptosis is derived from the Greek word meaning dropping or falling off. It was first introduced by Kerr, Wyllie, and Currie. Apoptosis is a biological process which occurs in all multicellular organisms including plants and animals. It removes the cells from the organisms that should no longer be a part of the organism. This process plays a major role in the development of humans and in developing and maintaining a healthy immune system.

On an average, 50 – 80 billion cells die every day in a human adult due to apoptosis. During this biological process, infected cells, pre-cancerous cells and other cancer cells are eliminated successfully and maintain the balance of cells in the human body. Therefore, it is an essential process that is responsible for the normal development of cells, cell cycle maturation and maintaining the regular functions and activities of cells. Apoptosis occurs in all the vertebrates that have fingers and toes like digits. A slight mistake during apoptosis results in fused toes or fingers. The loss of the tail of a tadpole when it develops into a frog is yet another example of apoptosis.

Apoptosis Pathways

The process of apoptosis undergoes two pathways:

- Extrinsic Pathway
- Intrinsic Pathway

Extrinsic Pathway

This pathway triggers apoptosis in response to external stimuli, like, ligand binding at death receptors on the cell surface. These receptors are members of the Tumor Necrosis Factor gene family. The receptor binding initiates caspase activation.

Intrinsic Pathway

This pathway triggers apoptosis in response to internal stimuli such as biochemical stress, DNA damage and lack of growth factors. This pathway is modulated by two groups of molecules- Bax, and Bcl-2. These groups of molecules determine whether a cell will survive or undergo apoptosis in response to the stimuli.

Significance of Apoptosis

Apoptosis is significant for the following reasons:

1. It helps to maintain homeostasis in the multicellular organisms.

2. Proper size of the body is maintained by apoptosis.
3. Apoptosis maintains the constancy of cell number in an organism.
4. The unwanted cells are eliminated from the body by apoptosis.
5. The dangerous T-lymphocytes are eliminated by apoptosis.
6. Programmed cell death is crucial for cell development.

Role Of Apoptosis

Apoptosis plays an important role in the body of an organism. Following are a few such roles performed by the process:

1. The separation of the fingers during the development of the foetus is due to apoptosis.
2. It results in the closure of the neural tube in the dorsal part.
3. Programmed cell death results in the removal of vestigial remnants such as pronephros.
4. During the determination of sex of the foetus, the Wolffian ducts are removed by cell death.
5. In the urachus, apoptosis allows the removal of redundant tissues between the bladder and umbilicus.

Relationship Between Apoptosis and Cancer

Cancer is the uncontrolled division of cells that leads to the development of tumour. If the apoptotic signalling works properly, these unwanted cells can be removed from the body. The main reason for cancer is that they have the ability to prevent apoptosis and therefore multiply uncontrollably.

Repair

When a cell is damaged, the body will try to repair or replace the cell to continue normal functions. If a cell dies, the body will remove it and replace it with another functioning cell, or fill the gap with connective tissue to provide structural support for the remaining cells. The motto of the repair process is to fill a gap caused by the damaged cells to regain structural continuity. Normal cells try to regenerate the damaged cells but this cannot always happen.

Regeneration

Regeneration of parenchyma cells, or the functional cells, of an organism. The body can make more cells to replace the damaged cells keeping the organ or tissue intact and fully functional.

Replacement

When a cell cannot be regenerated, the body will replace it with stromal connective tissue to maintain tissue or organ function. Stromal cells are the cells that support the parenchymal cells in any organ. Fibroblasts, immune cells, pericytes, and inflammatory cells are the most common types of stromal cells.[16]

Biochemical changes in cellular injury

ATP (adenosine triphosphate) depletion is a common biological alteration that occurs with cellular injury. This change can happen despite the inciting agent of the cell damage. A reduction in intracellular ATP can have a number of functional and morphologic consequences during cell injury. These effects include:

- ATP-depleted cells begin to undertake anaerobic metabolism to derive energy from glycogen which is known as glycogenolysis.
- A consequent decrease in the intracellular pH of the cell arises, which mediates harmful enzymatic processes.
- Early clumping of nuclear chromatin then occurs, known as pyknosis, and leads to eventual cell death.

DNA damage and repair

DNA damage

DNA damage (or RNA damage in the case of some virus genomes) appears to be a fundamental problem for life. As noted by Haynes,[18] the subunits of DNA are not endowed with any peculiar kind of quantum mechanical stability, and thus DNA is vulnerable to all the "chemical horrors" that might befall any such molecule in a warm aqueous medium. These chemical horrors are DNA damages that include various types of modification of the DNA bases, single- and double-strand breaks, and inter-strand cross-links (see DNA damage (naturally occurring). DNA damages are distinct from mutations although both are errors in the DNA. Whereas DNA damages are abnormal chemical and structural alterations, mutations ordinarily involve the normal four bases in new arrangements. Mutations can be replicated, and thus inherited when the DNA replicates. In contrast, DNA damages are altered structures that cannot, themselves, be replicated.

Several different repair processes can remove DNA damages (see chart in DNA repair). However, those DNA damages that remain un-repaired can have detrimental consequences. DNA damages may block replication or gene transcription. These blockages can lead to cell death. In multicellular organisms, cell death in response to DNA damage may occur by a programmed process, apoptosis. Alternatively, when DNA polymerase replicates a template strand containing a damaged site, it may inaccurately bypass the damage and, as a consequence, introduce an incorrect base leading to a mutation. Experimentally, mutation rates increase substantially in cells defective in DNA mismatch repair or in Homologous recombinational repair (HRR).

In both prokaryotes and eukaryotes, DNA genomes are vulnerable to attack by reactive chemicals naturally produced in the intracellular environment and by agents from external sources. An important internal source of DNA damage in both prokaryotes and eukaryotes is reactive oxygen species (ROS) formed as byproducts of normal aerobic metabolism. For eukaryotes, oxidative reactions are a major source of DNA damage (see DNA damage (naturally occurring) and Sedelnikova et al.). In humans, about 10,000 oxidative DNA damages occur per cell per day. In the rat, which has a higher metabolic rate than humans, about 100,000 oxidative DNA damages occur per cell per day. In aerobically growing bacteria, ROS appear to be a major source of DNA damage, as indicated by the observation that 89% of spontaneously occurring base substitution mutations are caused by introduction of ROS-

induced single-strand damages followed by error-prone replication past these damages. Oxidative DNA damages usually involve only one of the DNA strands at any damaged site, but about 1–2% of damages involve both strands. The double-strand damages include double-strand breaks (DSBs) and inter-strand crosslinks. For humans, the estimated average number of endogenous DNA DSBs per cell occurring at each cell generation is about 50. This level of formation of DSBs likely reflects the natural level of damages caused, in large part, by ROS produced by active metabolism.

Repair of DNA damages

Five major pathways are employed in repairing different types of DNA damages. These five pathways are nucleotide excision repair, base excision repair, mismatch repair, non-homologous end-joining and homologous recombinational repair (HRR) (see chart in DNA repair) and reference. Only HRR can accurately repair double-strand damages, such as DSBs. The HRR pathway requires that a second homologous chromosome be available to allow recovery of the information lost by the first chromosome due to the double-strand damage.

DNA damage appears to play a key role in mammalian aging, and an adequate level of DNA repair promotes longevity (see DNA damage theory of aging and reference.). In addition, an increased incidence of DNA damage and/or reduced DNA repair cause an increased risk of cancer (see Cancer, Carcinogenesis and Neoplasm) and reference). Furthermore, the ability of HRR to accurately and efficiently repair double-strand DNA damages likely played a key role in the evolution of sexual reproduction (see Evolution of sexual reproduction and reference). In extant eukaryotes, HRR during meiosis provides the major benefit of maintaining fertility.