Salahaddin University-Erbil (SUE)

Cellular Changes and Adaptive Responses

Research project

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(In the name of Allah, most Kindness and most Merciful)

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Abstract
The cell is the lowest level of structure capable of performing all the activities of life. Cells are active participants in their environment, constantly adjusting their structure & function to accommodate changing demands & extracellular stress. Cellular adaptation is the ability of cells to respond to various types of stimuli and adverse environmental changes to escape and protect against injury. Cell injury may result as a consequence of a physical, chemical, or biological agents. Such adaptations can take several distinct forms. Severe stresses or injury results, and alters the normal steady state of the cell, consequently, it can survive in a damaged state and adapt to the injury (reversible injury or adaptation). or it can die (irreversible injury or cell death). These adaptations include hypertrophy (enlargement of individual cells), hyperplasia (increase in cell number), atrophy (reduction in size and cell number), metaplasia (transformation from one type of epithelium to another), and dysplasia (disordered growth of cells). When the injury becomes irreversible, at that time the cell cannot recover, thus it dies, this is called (cell death).

Keyword (cell, adaption, injury, cell death, responses, metaplasia).

1. Introduction

Cells are the smallest working unit of all living organism (Nakamura et al., 2011). The first cells were observed and named by Robert Hooke in 1665 from slice of cork. Knowledge of the structural and functional reactions of cells and tissues, is key to understanding disease processes (Hidayat and Catherin, 2023). Cells adapt to the environment to escape and protect against injury. The adaptation of the cell is either normal or injured the condition lies somewhere in between these two conditions. Adaptation is a reversible change in cell size, number, phenotype, metabolic activity, or cell function (Certo et al., 2021).

Cell injury disrupts cellular homeostasis. cellular injury can be caused by any factor that disrupts cellular structure or deprives cells of the need for oxygen and nutrients for survival (Palm and Thompson, 2017). Cells are injured by numerous and diverse causes (etiologic agents) from intrinsic and extrinsic sources; however, all of these causes, and they number in the thousands, activate one or more of four final common biochemical mechanisms leading to cell injury. These fundamental underlying biochemical mechanisms of cell injury are (1) ATP depletion, (2) permeabilization of cell membranes, (3) disruption of biochemical pathways, and (4) damage to DNA (Miller and Zachary, 2017).

Cell injury may be reversible or irreversible. The transition between reversible and irreversible damage, commonly referred to as the "point of no return" is of major importance. Recognition of the point of no return is a key element for devising therapeutic strategies to prevent cell death after injury. Cell death itself is a complex phenomenon that forms the basis for most disease processes (Cobb et al., 1996). Cell death occurs when cells are unable to maintain foundational life functions.

Traditionally, cell death is classified into accidental cell death (ACD) or regulated cell death (RCD) (Tang et al., 2019). Learning about cellular changes and adaptive responses helps us to understanding how cell cope with their environment, and what is cell changes. These cellular adaptations are reversible responses that allow cells to survive and continue to adequately function.

2. Literature and Review

2.1. Cellular injury

Injury to cells and the surrounding environment, called the extracellular matrix, triggers injury to tissues and organs. Although a normal cell is limited by narrow boundaries of structure and function, it is capable of adapting to biological demands or stress to maintain a steady state called homeostasis (Hidayat and Catherine, 2023). Cells have a limited repertoire of responses to injury, depending on the cell type and the nature of the injury. These responses can be categorized as (1) adaptation, (2) degeneration, or (3) death. When a cell undergoes physiological stresses or pathological affect, it encounters the stress by undergoing adaption, it achieves a new steady state preserving viability & function (kumar et al., 2017).

However, cellular adaptation is a central and common part of many disease conditions. In the early stages of a successful adaptive response, the cell may increase its function; thus, it is difficult to distinguish a pathological response from an adaptation extreme with excessive functional demands (Comerford et al., 2014). A cell may adapt to a stimulus or sublethal injury positively, with increased efficiency or productivity, or undergo degeneration with diminished functional capacity (Miller and Zachary, 2017).

Cell injury may be reversible or irreversible. In early stages or mild forms of injury the functional and morphologic changes are reversible, if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution. Irreversible is unrepairable damage to cell infrastructure. The response to injury can be reversible, with eventual restoration (i.e., healing) of normal or near-normal cellular structure and function, or irreversible with progression from degeneration to death of the cell (Miller and Zachary, 2017). Adaptation of the cell, be it normal or injured, this condition lies somewhere between these two conditions.

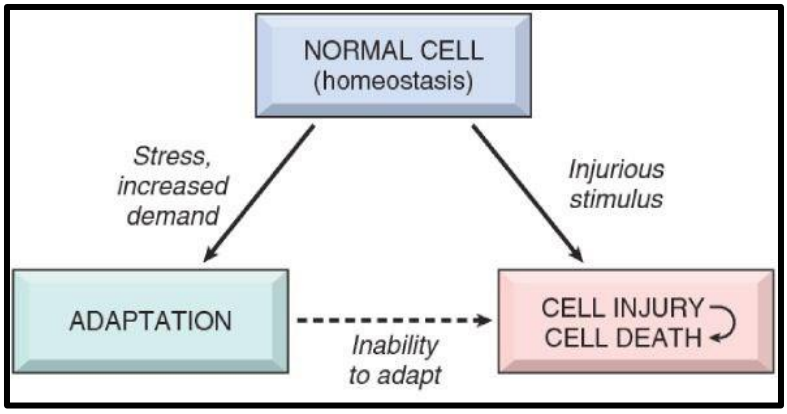

Figure (1): Effect of stress and injurious stimulus on cell

2.2. Causes of Cell Injury

Every disease process is accompanied by some degree of existing of preexisting cellular injury. The general manifestations of cell or tissue injury include metabolic, functional and morphologic alterations. However, all injured cells and tissues share certain common characteristics (Kumar et al., 2017). Cell damage can occur in many ways:

- Hypoxia and ischemia
- Chemical agents
- Physical agents
- Infections
- Immunological reactions
- Genetic defects
- Nutritional defects
- Aging

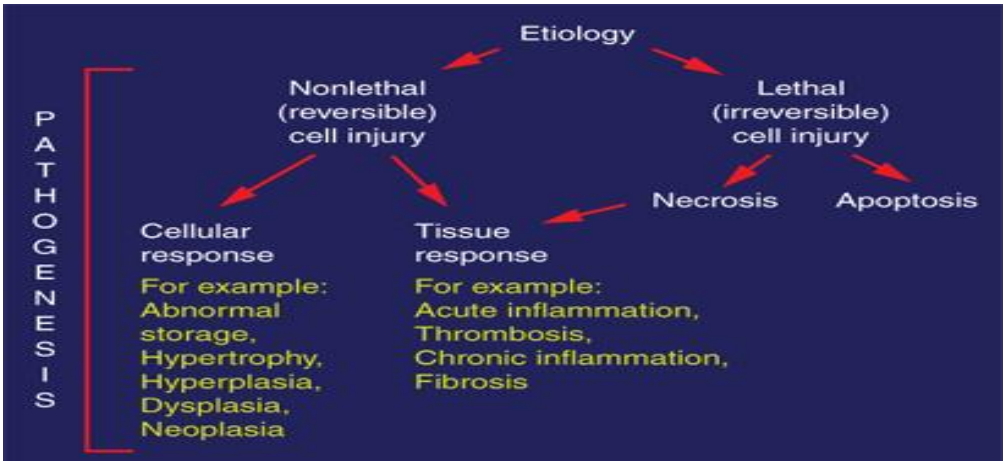

Figure (2): Etiology of Cell Injury

2.3. Mechanism to cell Injury

Cell response to injury is not an all-or-nothing phenomenon. The stronger and the longer the stimulus, the larger the damage. Response to a given stimulus depends on the type, status, and genetic make-up of the injured cell. Cells are complex interconnected systems, and single local injuries can result in multiple secondary and tertiary effects.

Pathogenesis and mechanisms of cell injury include:

1. ATP depletion or Hypoxia: Hypoxia first causes loss of phosphorylation in mitochondria and decrease the production of ATP which is a source for energy. Loss of ATP (which is energy source) has widespread effects on many systems in the cell. A major component of the injury is the alteration of membrane permeability caused by decreased activity of ATP dependent ionic pumps. Decreased ATP causes decreased action of Na+ / K+ pumps in the cell membranes, leading to increased Na+ and water within the cell (cell swelling).

2. Loss of calcium homeostasis: Cytosolic free calcium is kept at concentrations that are at least 10-fold lower than the extracellular levels. Mitochondria and endoplasmic reticulum keep intracellular calcium under control. It Activate Nitric oxide and Reactive oxygen species which increase the oxidative stress and damage the cell.

3. Oxidative stress (excess Reactive Oxygen Species): Cells generate reactive oxygen forms as byproducts of metabolic reactions that reduce

molecular oxygen to water. These reactive forms, called reactive oxygen species, can damage lipids, proteins and DNA.

4. Damage to mitochondria, and increased permeability of membranes: Mitochondria are important primary or secondary targets for most agents that cause cell injury. Alterations in mitochondrial membrane permeability generally lead to apoptosis Loss of the capacity of the plasma membrane to maintain a proper ionic balance between the intra-and extracellular compartments. Distribution in mitochondrial function produces Reduce ATP Synthesis so it decreases the formation of energy for the cellular activity. Increase the accumulation of intracellular calcium in endoplasmic reticulum. Formation of Reactive oxygen species also enhanced. These all mechanism may lead to damage the cell and produce cellular injury.

2.4. Cellular Adaptation

The most significant adaptive changes in cells include atrophy (decreased cell size), hypertrophy (increased cell size), hyperplasia (increased cell number), and metaplasia (reversible replacement of one mature cell for another less mature cell or change in phenotype). Dysplasia (a disorder of cellular growth) is not considered a true cellular adaptation but rather an atypical hyperplasia (Hidayat and Catherine, 2023).

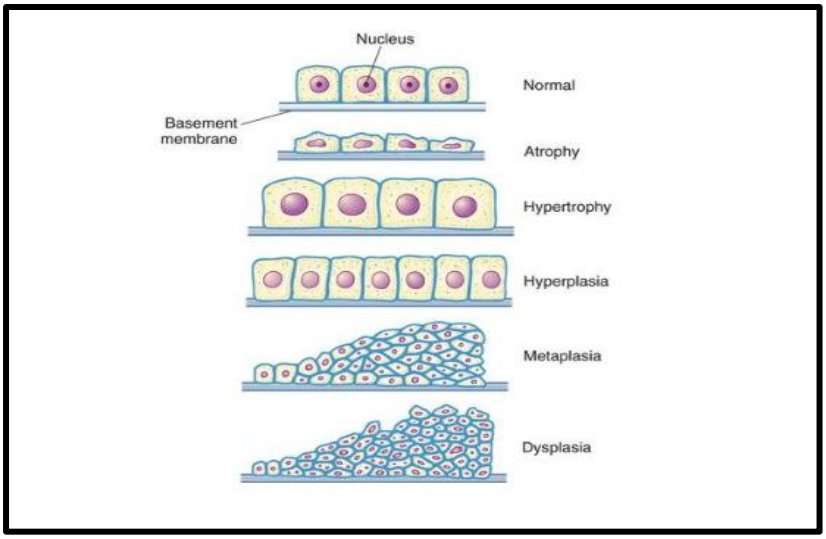

Figure (3): Adaptive changes in simple cuboidal tissue (Hidayat and Catherine, 2023)

2.4.1. Atrophy

Atrophy is a decrease or shrinkage of cellular size. If atrophy occurs in amount enough organ cells, the entire organ will shrink or become atrophic. Atrophy can affect any organ, but mostly skeletal muscle, heart, secondary sex organs, and brain. Atrophy can be divided into physiological or pathological (Hidayat and Catherine, 2023). Physiological atrophy occurs with early development. For example, the thymus gland undergoes physiological atrophy during childhood. Pathological atrophy occurs as a result of decreased workload, usage, pressure, blood flow, nutrition, hormonal stimulation, and nerve stimulation (Méndez-Lucas et al., 2014). Glandular Atrophy, Vaginal Atrophy, Skeletal Muscle Atrophy, Spinal Muscular Atrophy, and Brain atrophy.

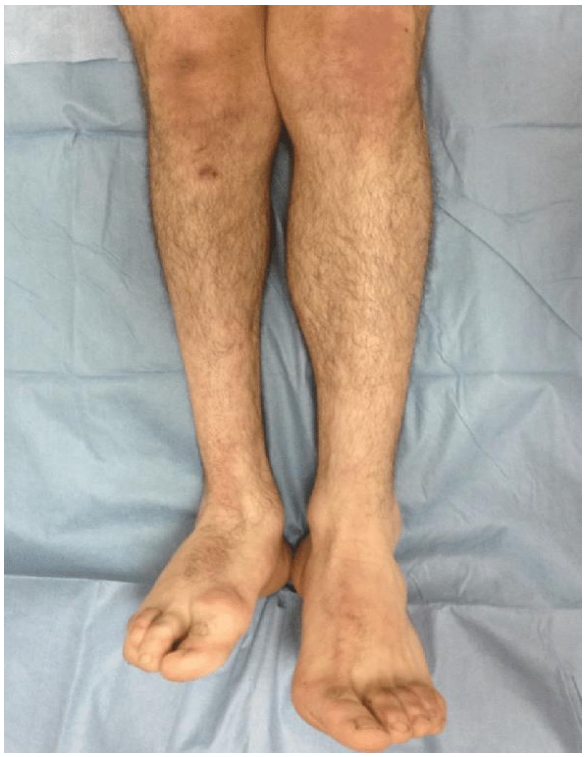

Figure (4): clinical significance of atrophy

2.4.2. Hypertrophy

Hypertrophy is an increase in cell size, thereby increasing the size of the affected organ. Much of the knowledge about hypertrophy comes from research on the heart. Cells from the heart and kidneys are particularly responsive to enlargement. Hypertrophy can be physiological or pathological. Physiological hypertrophy is the result caused by increased demand, stimulation by hormones (for example, hormone atrial natriuretic peptide), and growth factors. Physiological hypertrophy of skeletal cells occurs in response to strenuous exercise. Muscular hypertrophy tends to decrease if the excessive workload is also reduced. Pregnancy is an example of physiological hypertrophy and hormone-induced enlargement of the uterus (Hidayat and Catherine, 2023). Pathological hypertrophy results from chronic hemodynamic overload, for example, from hypertension or valvular dysfunction. A focus of much research is basic molecular from cardiac hypertrophy because it can progress to maladaptive conditions, including dysrhythmias, heart failure, and sudden death (Pakos-Zebrucka et al., 2016).

Figure (5): Muscle hypertrophy; Muscle Growth

2.4.3. Hyperplasia

Hyperplasia is an increase in the number of cells in an organ or tissue resulting from an increase in the defender ratio of just cells. Hyperplasia occurs in response to injury that occurs when the wound or injury is severe and lasts a long time (Hanson and Reshef, 2003). Although hyperplasia and

hypertrophy have distinct processes, they may occur together, and the specific mechanism is unknown. Hyperplasia can be physiological or pathological. Two types of normal or physiological hyperplasia are compensatory hyperplasia and hormonal hyperplasia. Compensatory hyperplasia is an adaptive mechanism that enables certain organs to regenerate. For example, the removal of part of the liver triggers hyperplasia of the surviving liver cells (hepatocytes) to compensate for the loss. Even with 70% hepatic removal, complete regeneration can occur in about 2 weeks (Friedl and Alexander, 2011). Significant compensatory hyperplasia occurs in the intestinal and epidermal epithelium, hepatocytes, bone marrow cells, and fibroblasts. An example of compensatory hyperplasia is a callus, or thickening, of the skin as a result of epidermal cell hyperplasia in response to stimulus mechanics (Hidayat and Catherine, 2023). Hormonal hyperplasia occurs mainly in estrogen dependent organs, such as the uterus and breasts. After ovulation, for example, estrogen stimulates the endometrium to grow and thicken for the reception of a fertilized ovum. If pregnancy occurs, hormonal hyperplasia, like hypertrophy, enables the uterus to enlarge (Hagenfeldt et al., 2008). Pathological hyperplasia is an abnormal proliferation of normal cells and can occur in response to excess external stimuli or the effects of growth factors on target cells. The most common example is pathological hyperplasia of the endometrium, which causes an imbalance between estrogen and progesterone with a relative increase in estrogen (Hidayat and Catherine, 2023).

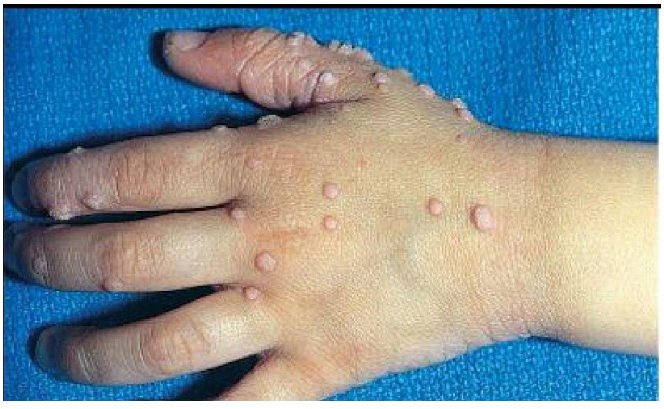

Figure (6): hyperplasia that is associated with certain viral infection

2.4.4. Metaplasia

Metaplasia is a change in which an adult cell type is replaced by another type. The cell is replaced by another cell more capable to withstand the adverse environment. Over time, the adaptive turnover of cells can better match their changing environment. For example, gastroesophageal reflux damages the squamous epithelium of the esophagus, and adaptive changes or replacement by the glandular epithelium may be better tolerated by an acidic environment (Fausto, 2006). Usually, however, change is not always beneficial. In long-term smokers, chronic irritation from smoking causes ciliated columnar epithelial cells of the trachea and bronchi to be replaced by pseudo-squamous epithelial cells (kumar et al., 2017). Bronchial metaplasia may be reversible if the inducing stimulus, usually smoking, is removed. The mechanism of metaplasia does not result from a change in the phenotype of a differentiated cell type (Hidayat and Catherine, 2023).

2.4.5. Dysplasia

Dysplasia refers to abnormal changes in the size, shape, and arrangement of mature cells. Dysplasia is not considered a true adaptive process but is associated with hyperplasia and is often called atypical hyperplasia. Dysplastic changes are mostly found in the epithelium. It is also important that the term dysplasia is not cancer and may not develop into cancer. Dysplasia that does not involve the full thickness of the epithelium may improve completely (Certo et al., 2021).

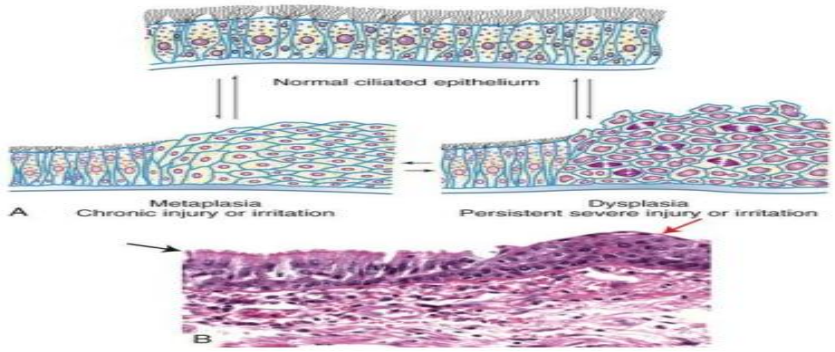

Figure (7): Reversible changes of cell boundaries in bronchi. A, Normal ciliated epithelium, metaplasia, and dysplasia (Hidayat and Catherine, 2023).

2.4.6. Cell death

If the genetic and metabolic adaptive responses are inadequate for a given injury, the cell will die (Cobb et al., 1996). The death of cells is an essential "value-added" part of embryonic development and maturation of the fetus and of homeostasis within populations of adult somatic cells. In these physiologic examples of cell death, cells that are no longer needed are removed during development or remodeling of tissues. However, cell death is also a point-of-no-return response to severe injury, and it is this pathologic form of cell death that is the topic of this section. Cell death typically assumes one of two morphologic forms: necrosis or apoptosis. (Miller and Zachary., 2017). Although necrosis is only recognized by morphologic changes occurring during and after cell death (i.e., enzymatic digestion, "coagulation", etc.), apoptosis is an active (programmed) form of cell death that can be detected both by morphology and gene expression changes. Necrosis is always pathologic (the end point of irreversible injury). Apoptosis may be physiologic or pathologic (Fausto, 2006).

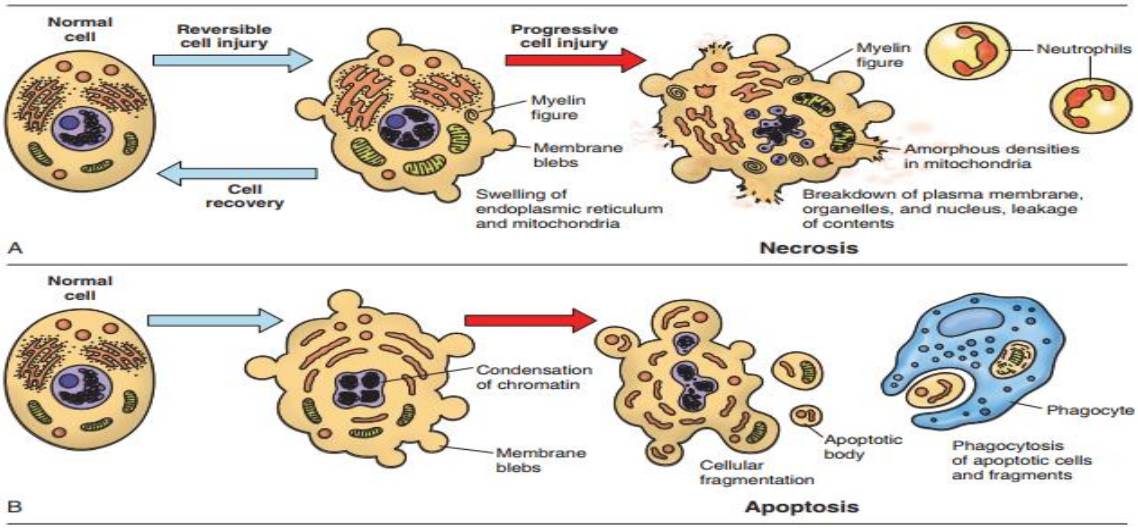

Figure (8): The Sequential Ultrastructural Changes of Necrosis and Apoptosis. A, In necrosis, leakage of cell contents through the ruptured plasma membrane into the extracellular matrix elicits inflammation. B, In apoptosis, cellular fragments are extruded as plasma membrane-bound apoptotic bodies that are recognized by phagocytes but do not cause inflammation (Miller and Zachary., 2017).

3. Conclusion

Cells are the smallest working unit of all living things. Adaptation is a reversible change in cell size, number, phenotype, metabolic activity, or cell function. However, cellular adaptation is a central and common part of many disease conditions Cells adapt to the environment to escape and protect against injury. Cell injury may be reversible or irreversible. If the genetic and metabolic adaptive responses are inadequate for a given injury, the cell will die.

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