Pathology — Cell injury — LEC. 1

Dr. Methaq Mueen

Learning objectives

- **Define and describe cell injury.**
- **understanding and able to explain:**
  - **Mechanisms of cell injury**
  - **Differences between reversible and irreversible cell injury**
  - **Cellular adaptation to sub-lethal injury including: atrophy ,hypertrophy, hyperplasia and metaplasia.**
  - **Types of cell death**

- Each cell in the body is designed to carry a specific function or functions, which is dependent on its machinery and metabolic pathways.
- Cells are continuously adjusting their structure and function, within a narrow range, to deal with the continually changing extra-cellular environment.
- **This ability to maintain a dynamically stable state is referred to as homeostasis.**
- **Response of the cell to injury depends on:**

Type of injury, Duration, Severity / extent of the injury.

For e.g low dose of toxins or a brief duration of ischemia may lead reversible cell injury While larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death

- **Consequences of an injurious stimulus depend on:**
- **Cell type , status , adaptability and genetic makeup of the injured cell**

1-cell type: **Neurons** are highly susceptible to anoxia (5min)

Cardiac muscle dies after only 20-30 minutes whereas **skeletal muscle** can withstand for a very long time (2-3 hours).

2. Pre-existing state: e.g: nutritional or hormonal state, age of the person etc.

e.g. glycogen rich hepatocyte can tolerate ischemia much better than other cells

- **Types of Response to injury or stress**
- **Recovery to normal status: (**morphologically and functionally): when the injurious agent is removed.
- **Adaptations:** when stressful condition persist but the cell adapt itself to the new stressful condition.

- **Cell injury:** when the cell damage occur which is either **reversible** or **irreversible (cell death) : Apoptosis or Necrosis**

Cellular Adaptation to cell injury:

Adaptation : reversible changes in the **size, number, phenotype, metabolic activity**, or **functions** of cells in response to changes in their environment. It occurs when physiologic or pathologic stressors induce a new state that changes the cell but otherwise preserves its viability in the face of the exogenous stimuli.

Cellular adaptations could be physiological or pathological adaptations.

1- **Physiological Adaptations** usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g. the enlargement of breast)
2- **Pathological Adaptations** usually represent the pathways by which the cells escape the cell injury.

Adaptive changes in cell growth & differentiation are include:

1. **Atrophy** (decrease in cell size).
2. **Hypertrophy** (increase in cell size).
3. **Hyperplasia** (increase in cell number).
4. **Metaplasia** (change in cell type).

Atrophy:

- **Atrophy** means **Shrinkage in the size of the cell** by loss of cell substance, when a sufficient number of cells are involved, the entire tissue or organ diminishes in size, or becomes atrophic.
- Although atrophic cells may have **diminished function**, they are **not dead.**
- Atrophy represents a reduction in the structural components of cell, e.g. reduction of mitochondria, endoplasmic reticulum, & myofilaments of atrophic skeletal muscles to balance the decrease in nutrition supply.
- Atrophy may progress to the point at which cells are injured and die.
- **Underlying mechanism of atrophy**, is thought to be due to loss of balance between protein synthesis and degradation, & Increased protein degradation probably plays a key role in atrophy
- Atrophy can be **physiologic or pathologic**.

  A- Physiologic atrophy

  - Atrophy of **thyroglossal duct** & **notochord** (during embryonic & fetal life)
  - Decreases the size of uterus after labor.

B- Pathologic atrophy. Depends on the underlying cause and can be local or generalized.

The common causes of atrophy are the following:

1) Decreased workload (atrophy of disuse), e.g. immobilized limb in plaster cast, or a patient with complete bed rest, skeletal muscle atrophy which is initially reversible but with more restriction of activity, there are decrease in size .

2) Loss of innervation (denervation atrophy), e.g. atrophy of skeletal muscles due to loss of their nerve supply.

3) Diminished blood supply, e.g. progressive brain atrophy due to ischemia.

4) Inadequate nutrition, e.g. protein calories malnutrition (Marasmus), there is marked muscle wasting due to loss of fat & protein stores in the body.

5) Loss of endocrine stimulation, e.g. loss of estrogen stimulation after menopause results in physiologic atrophy of the endometrium, vaginal epithelium,

Ovaries and breast.

6) Aging (senile atrophy), e.g. atrophy of the brain & heart with aging.

7) Pressure, Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding compressed tissues.

Hypertrophy:

- Hypertrophy refers to an **increase in the size of cells**, resulting in an increase in the size of the organ.
- It is not due to cellular swelling but to the synthesis of more structural components.
- Cells capable of division may respond to stress by undergoing both hyperplasia and hypertrophy, whereas in nondividing cells (e.g.,myocardial fibers), hypertrophy occurs.
- Hypertrophy can be **physiologic or pathologic:**
  1- **Physiological hypertrophy**.e.g. hypertrophy of skeletal muscles of bodybuilders due to increased workload.
  2- **Pathological hypertrophy**: Cardiac muscles hypertrophy in patient with chronic hypertension or cardiac valve diseases.

- In hypertrophy of both skeletal & cardiac muscles, there is increased synthesis of proteins & myofilaments per cells to achieve balance between the demands & the cell functional capacity.

Mechanisms of hypertrophy.

1. In hypertrophy of cardiac muscles, **there is re-stimulation of genes (**that are normally present during fetal life), these genes resulting increased synthesis of **growth factors** (Insulin like growth factor, fibroblast growth factor), and these growth factors are responsible for increased production of **cellular proteins** & result in hypertrophy of cardiac muscles.
2. The trigger of these genes are include two groups, Mechanical factors like stretch & trophic factors like Alpha adrenergic agents, vasoactive agents & growth factors**.**

Cardiac hypertrophy eventually reaches a limit beyond which enlargement of muscle mass is no longer able to compensate for the increased burden, and cardiac failure ensues (degenerative changes occur in the myocardial fibers), & myocyte death can occur by either apoptosis or necrosis.

Hyperplasia:

Hyperplasia is an **increase in the number of cells** in an organ or tissue, usually resulting in increased volume of the organ or tissue.

Hyperplasia & hypertrophy are closely related & develop concurrently in tissues, (e.g. gravid uterus)

Hyperplasia could be **Physiological or Pathological**

Physiological hyperplasia: which include

- **Hormonal hyperplasia**, (like proliferation of the glandular epithelium of the female breast at puberty and during pregnancy and the physiologic hyperplasia that occurs in the pregnant uterus).
- **Compensatory hyperplasia**, this hyperplasia occurs when portion of the tissue is removed or diseased e.g. partial hepatectomy, in which the remaining hepatocytes start mitotic activity after 12 hours & eventually restore the normal size of liver.

    - The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced increase in the size of an organ that results from both hypertrophy and hyperplasia (due to estrogen stimulation), similarly, prolactin and estrogen cause hypertrophy of the breasts during lactation.

Mechanism of hyperplasia.

- Hyperplasia is generally caused by **increased** local production of **growth factors,** & increased levels of **growth factor receptors** on the responding cells,
- in some cases, by increased output of new cells from tissue stem cells.
- **Pathological hyperplasia.**

- Pathologic hyperplasias are caused by excessive hormonal stimulation or growth factors acting on target cells.
- **Examples** of pathological hyperplasia
  1. **Endometrial hyperplasia** is an example of abnormal hormone-induced hyperplasia, which is due to disturbance of balance between estrogen and progesterone (absolute or relative increases in the amount of estrogen), This form of hyperplasia is a common cause of abnormal menstrual bleeding.
  2. **Benign prostatic hyperplasia** is another common example of pathologic hyperplasia induced by responses to hormones(androgen),
  3. **Hyperplasia that is associated with certain viral infections, such as papillomaviruses**, which cause skin warts and a number of mucosal lesions composed of masses of hyperplastic epithelium.

❖ **Although these forms of hyperplasia are abnormal, the process remains controlled, because the hyperplasia regresses if the hormonal stimulation is eliminated.**

❖ **Pathologic hyperplasia, however, constitutes a fertile soil in which cancerous proliferation may eventually arise, like hyperplasia of the endometrium are at increased risk for developing endometrial cancer**

Metaplasia:

- Metaplasia is a reversible change **in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.**
- **Metaplasia is cellular adaptation** whereby cells sensitive to a particular stress are replaced by other cell types better able to withstand the adverse environment,
- **Types of metaplasia.**

  A- Epithelial metaplasia: which include
  1. **Epithelial metaplasia from columnar to squamous**, as occurs in the respiratory tract of the cigarette smoker, the normal ciliated columnar

epithelial cells of the trachea and bronchi are often replaced focally or widely by stratified squamous epithelial cells.

These metaplastic squamous cells in the respiratory tract represent an undesirable change **result in** reduced functions. Moreover, the influences that predispose to metaplasia, if persistent, may induce malignant transformation in metaplastic epithelium.

2. **Metaplasia from squamous to columnar type** may also occur, as in Barrett esophagus, in which the esophageal squamous epithelium is replaced by intestinal-like columnar cells under the influence of refluxed gastric acid. Cancers may arise in these areas, and these are typically glandular (adeno) carcinomas.

3**-Metaplasia from transitional epithelium to squamous epithelium:**

This occur in urinary bladder due to stone or schistosomiasis infection (bilharziasis) due to chronic irritation with the spine of Schistosoma hematobium egg. May progress to squamous cell carcinoma.

B-Connective tissue metaplasia is the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements. For example, bone formation in muscle, designated myositis ossificans

Mechanisms of Metaplasia.

Metaplasia does **NOT** result from a change in the phenotype of a differentiated cell type;

Instead it is the result of a **reprogramming of stem cells** that are known to exist in normal tissues, or of undifferentiated mesenchymal cells present in connective tissue.

In a metaplastic change, these precursor cells differentiate along a new pathway. The differentiation of stem cells to a particular lineage is brought about by **signals** generated by **cytokines, growth factors**, and **extracellular matrix components** in the cells' environment.

These external stimuli promote the expression of genes that drive cells toward a specific differentiation pathway.