General Pathology

Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

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Correction

Our course in general pathology for this semester will include the following chapters only:

1- Cell injury and adaptation.
2- Inflammation and repair.
3- Hemodynamic disorders.
4- Neoplasia.
Cellular Responses to Stress and Noxious Stimuli

The normal cell is confined to a fairly narrow range of function and structure by its state of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates.

It is nevertheless able to handle physiologic demands, maintaining a steady state called *homeostasis*. 
Adaptations are reversible functional and structural responses to more severe physiologic stresses and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.
The adaptive response may consist of:

1- **Hypertrophy:** Is an increase in the size of cells and functional activity.

2- **Hyperplasia:** Is an increase in their number.

3- **Atrophy:** Is a decrease in the size and metabolic activity of cells.

4- **Metaplasia:** Is a change in the phenotype of cells.
When the stress is eliminated the cell can recover to its original state without having suffered any harmful consequences.

If the limits of adaptive responses are exceeded or if cells are exposed to injurious agents or stress, deprived of essential nutrients, or become compromised by mutations that affect essential cellular constituents, a sequence of events follows that is termed cell injury.
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<td>CELLULAR ADAPTATIONS</td>
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<td>- Increased demand, increased stimulation (e.g., by growth factors, hormones)</td>
<td>- Hyperplasia, hypertrophy</td>
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<td>- Decreased nutrients, decreased stimulation</td>
<td>- Atrophy</td>
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<td>- Acute and transient</td>
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Adaptation, reversible injury, and cell death may be stages of progressive impairment following different types of insults.

Myocardial hypertrophy, caused by increased blood flow requiring greater mechanical effort by myocardial cells. This adaptation leads to thickening of the left ventricular wall to over 2 cm (normal, 1–1.5 cm).

In reversibly injured myocardium there are generally only functional effects, without any readily apparent gross or even microscopic changes.

In the specimen showing necrosis, a form of cell death (lower right), the light area in the posterolateral left ventricle represents an acute myocardial infarction caused by reduced blood flow (ischemia).
Cell death, is the end result of progressive cell injury. It results from diverse causes, including ischemia (reduced blood flow), infection, and toxins.

There are two principal pathways of cell death, necrosis and apoptosis. Nutrient deprivation triggers an adaptive cellular response called autophagy that may also culminate in cell death.
Metabolic derangements in cells and sublethal, chronic injury may be associated with intracellular accumulations of a number of substances, including proteins, lipids, and carbohydrates.

Calcium is often deposited at sites of cell death, resulting in pathologic calcification.

Finally, the normal process of aging itself is accompanied by characteristic morphologic and functional changes in cells.
Adaptations of Cellular Growth and Differentiation

Adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment.

Such adaptations may take several distinct forms.
HYPERTROPHY

Refers to an increase in the size of cells, due to the synthesis of more structural components of the cells, resulting in an increase in the size of the organ.

The hypertrophied organ has no new cells, just larger cells.

Cells capable of division may respond to stress by undergoing both hyperplasia and hypertrophy, whereas in *nondividing cells* (e.g., myocardial fibers) increased tissue mass is due to hypertrophy.
Hypertrophy can be **physiologic** or **pathologic** and is caused by increased functional demand or by stimulation by hormones and growth factors.

**The most common stimulus for hypertrophy of muscle is increased workload.**

In both tissue types (skeletal and cardiac) the muscle cells synthesize more proteins and the number of myofilaments increases.
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 mainly from **hypertrophy** of muscle fibers.

**B-** Small spindle-shaped uterine smooth muscle cells from a normal uterus, compared with **C-** large plump cells from the gravid uterus, at the same magnification.

The cellular enlargement is stimulated by estrogenic hormones acting on smooth muscle estrogen receptors, eventually resulting in increased synthesis of smooth muscle proteins and an increase in cell size.
Mechanisms of Hypertrophy

Hypertrophy is the result of increased production of cellular proteins and can be induced by the linked actions of mechanical sensors (that are triggered by increased work load), growth factors (including TGF-β, insulin-like growth factor-1 [IGF-1], fibroblast growth factor), and vasoactive agents (such as α-adrenergic agonists, endothelin-1, and angiotensin II).
Mechanical sensors themselves induce production of growth factors and agonists. These stimuli work coordinately to increase the synthesis of muscle proteins that are responsible for the hypertrophy.)
The two main biochemical pathways involved in muscle hypertrophy seem to be the phosphoinositide 3-kinase/Akt pathway (PI3k/Akt pathway) (postulated to be most important in physiologic, e.g., exercise-induced, hypertrophy) and signaling downstream of G protein-coupled receptors (induced by many growth factors and vasoactive agents, and thought to be more important in pathologic hypertrophy).
Hypertrophy may also be associated with a switch of contractile proteins from adult to fetal or neonatal forms. For example, during muscle hypertrophy the $\alpha$ isoform of myosin heavy chain is replaced by the $\beta$ isoform, which has a slower, more energetically economical contraction.
Some genes that are expressed only during early development are re-expressed in hypertrophic cells, and the products of these genes participate in the cellular response to stress.

For example, the gene for atrial natriuretic factor (ANF - a peptide hormone that causes salt secretion by the kidney, decreases blood volume and pressure, and therefore serves to reduce hemodynamic load.) is expressed in both the atrium and the ventricle in the embryonic heart, but it is down-regulated after birth.

Cardiac hypertrophy, however, is associated with re-induction of ANF gene expression.
Although **hypertrophy** usually refers to increase in size of cells or tissues, sometimes a **subcellular organelle** may undergo selective hypertrophy.

For instance, individuals treated with **drugs such as barbiturates** show **hypertrophy** of the smooth endoplasmic reticulum (ER) in hepatocytes, which is an adaptive response that increases the amount of enzymes (cytochrome P-450 mixed function oxidases) available to detoxify the drugs. **Over time, the patients respond less to the drug because of this adaptation.**
HYPERPLASIA

is an increase in the number of cells in an organ or tissue, usually resulting in increased mass of the organ or tissue. Although hyperplasia and hypertrophy are distinct processes, frequently they occur together, and they may be triggered by the same external stimulus. Hyperplasia takes place if the cell population is capable of dividing, and thus increasing the number of cells.
Physiologic Hyperplasia can be divided into:

(1) **Hormonal** hyperplasia, which increases the functional capacity of a tissue when needed.

(2) **Compensatory** hyperplasia, which increases tissue mass after damage or partial resection.
Pathologic Hyperplasia

Most forms of pathologic hyperplasia are caused by excesses of hormones or growth factors acting on target cells.

(Endometrial hyperplasia is an example of abnormal hormone-induced hyperplasia, when in some instances, however, the balance between estrogen and progesterone is disturbed With increase in the amount of estrogen)

(Benign prostatic hyperplasia is another common example of pathologic hyperplasia induced by responses to hormones, in this case, androgens)
Although these forms of hyperplasia are abnormal, the process remains controlled because there are no mutations in genes that regulate cell division, and the hyperplasia regresses if the hormonal stimulation is eliminated.
Hyperplasia is a characteristic response to certain viral infections, such as papillomaviruses, which cause skin warts and several mucosal lesions composed of masses of hyperplastic epithelium.

Here, growth factors produced by viral genes or by infected cells may stimulate cellular proliferation
Mechanisms of Hyperplasia

Hyperplasia is the result of growth factor–driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells.

For instance, after partial hepatectomy growth factors are produced in the liver that engage receptors on the surviving cells and activate signaling pathways that stimulate cell proliferation.
ATROPHY

Is reduced size of an organ or tissue resulting from a decrease in cell size and number.

Atrophy can be physiologic or pathologic.

Physiologic atrophy is common during normal development. Some embryonic structures, such as the notochord and thyroglossal duct, undergo atrophy during fetal development. The uterus decreases in size shortly after parturition, and this is a form of physiologic atrophy.
Pathologic atrophy depends on the underlying cause and can be local or generalized. The common causes of atrophy are the following:

- Decreased workload (atrophy of disuse).
- Loss of innervation (denervation atrophy).
- Diminished blood supply.
- Inadequate nutrition.
- Loss of endocrine stimulation.
- Pressure.
The fundamental cellular changes associated with atrophy are identical in all of these settings. The initial response is a decrease in cell size and organelles, which may reduce the metabolic needs of the cell sufficiently to permit its survival. In atrophic muscle, the cells contain fewer mitochondria and myofilaments and a reduced amount of rough ER.
Mechanisms of Atrophy

Atrophy results from decreased protein synthesis because of reduced metabolic activity and increased protein degradation in cells, occurs mainly by the ubiquitin-proteasome pathway. Nutrient deficiency and disuse may activate ubiquitin ligases, which attach the small peptide ubiquitin to cellular proteins and target these proteins for degradation in proteasomes.
In many situations, atrophy is also accompanied by increased autophagy, with resulting increases in the number of autophagic vacuoles.

(Autophagic vacuoles are membrane-bound vacuoles that contain fragments of cell components. The vacuoles ultimately fuse with lysosomes, and their contents are digested by lysosomal enzymes.)
Some of the cell debris within the autophagic vacuoles may resist digestion and persist as membrane-bound *residual bodies* that may remain as a sarcophagus in the cytoplasm. When present in sufficient amounts, they impart a brown discoloration to the tissue (*brown atrophy*). Autophagy is associated with various types of cell injury, and we will discuss it in more detail later.
METAPLASIA

Is a reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. It may represent an adaptive substitution of cells that are sensitive to stress by cell types better able to withstand the adverse environment.
The most common epithelial metaplasia is **columnar** to **squamous**, as occurs in the respiratory tract in response to chronic irritation.

Epithelial metaplasia is a double-edged sword and, in most circumstances, represents an undesirable change. Moreover, the influences that predispose to metaplasia, if persistent, may initiate malignant transformation in metaplastic epithelium.
Metaplasia from squamous to columnar type may also occur, as in Barrett esophagus.

Connective tissue metaplasia is the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements.

This type of metaplasia is less clearly seen as an adaptive response, and may be a result of cell or tissue injury.
Mechanisms of Metaplasia

Metaplasia does not result from a change in the phenotype of an already 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, GF, and ECM components in the cells' environment.
Next lecture

Overview of Cell Injury and Cell Death