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

Hypertrophy refers to an increase in the size of cells, resulting in an increase in the size of the organ. The hypertrophied organ has no new cells, just larger cells. The increased size of the cells is due to the synthesis of more structural components of the cells. Cells capable of division may respond to stress by undergoing both hyperplasia (described below) and hypertrophy, whereas in *nondividing cells* (e.g., myocardial fibers) increased tissue mass is due to hypertrophy. In many organs hypertrophy and hyperplasia may coexist and contribute to increased size.

Hypertrophy can be physiologic or pathologic and is caused by increased functional demand or by stimulation by hormones and growth factors. The striated muscle cells in the heart and skeletal muscles have only a limited capacity for division, and respond to increased metabolic demands mainly by undergoing hypertrophy. *The most common stimulus for hypertrophy of muscle is increased workload*. For example, the bulging muscles of bodybuilders engaged in "pumping iron" result from an increase in size of the individual muscle fibers in response to increased demand. In the heart, the stimulus for hypertrophy is usually chronic hemodynamic overload, resulting from either hypertension or faulty valves. In both tissue types the muscle cells synthesize more proteins and the number of myofilaments increases. This increases the amount of force each myocyte can generate, and thus increases the strength and work capacity of the muscle as a whole.

Mechanisms of Hypertrophy

Hypertrophy is the result of increased production of cellular proteins. Much of our understanding of hypertrophy is based on studies of the heart. Hypertrophy 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). Indeed, 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 (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 α isoform of myosin heavy chain is replaced by the β isoform, which has a slower, more energetically economical contraction. In addition, 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) 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 reinduction of ANF gene expression. ANF is a peptide hormone that causes salt secretion by the kidney, decreases blood volume and pressure, and therefore serves to reduce hemodynamic load.

HYPERPLASIA

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. Hyperplasia can be physiologic or pathologic.

Physiologic Hyperplasia

Physiologic hyperplasia can be divided into: (1) *hormonal hyperplasia*, which increases the functional capacity of a tissue when needed, and (2) *compensatory hyperplasia*, which increases tissue mass after damage or partial resection. Hormonal hyperplasia is well illustrated by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy, usually accompanied by enlargement (hypertrophy) of the glandular epithelial cells. The classical illustration of compensatory hyperplasia comes from the myth of Prometheus, which shows that the ancient Greeks recognized the capacity of the liver to regenerate. As punishment for having stolen the secret of fire from the gods, Prometheus was chained to a mountain, and his liver was devoured daily by an eagle, only to regenerate anew every

night. In individuals who donate one lobe of the liver for transplantation, the remaining cells proliferate so that the organ soon grows back to its original size. Experimental models of partial hepatectomy have been very useful for defining the mechanisms that stimulate regeneration of the liver.

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. Normally, after a menstrual period there is a rapid burst of proliferative activity in the epithelium that is stimulated by pituitary hormones and ovarian estrogen. It is brought to a halt by the rising levels of progesterone, usually about 10 to 14 days before the end of the menstrual period. In some instances, however, the balance between estrogen and progesterone is disturbed. This results in absolute or relative increases in the amount of estrogen, with consequent hyperplasia of the endometrial glands. This form of pathologic hyperplasia is a common cause of abnormal menstrual bleeding. 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. In cancer the growth control mechanisms become dysregulated or ineffective because of genetic aberrations, resulting in unrestrained proliferation. *Thus, hyperplasia is distinct from cancer, but pathologic hyperplasia constitutes a fertile soil in which cancerous proliferation may eventually arise*. For instance, patients with hyperplasia of the endometrium are at increased risk for developing endometrial cancer.

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. But if the proliferative capacity of the liver cells is compromised, as in some forms of hepatitis causing cell injury, hepatocytes can instead regenerate from intrahepatic stem cells.

ATROPHY

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:

1. *Decreased workload (atrophy of disuse)*. When a fractured bone is immobilized in a plaster cast or when a patient is restricted to complete bedrest, skeletal muscle atrophy rapidly ensues. The initial decrease in cell size is reversible once activity is resumed. With more prolonged disuse, skeletal muscle fibers decrease in number (due to apoptosis) as well as in size; this atrophy can be accompanied by increased bone resorption, leading to osteoporosis of disuse.

2. *Loss of innervation (denervation atrophy)*. The normal metabolism and function of skeletal muscle are dependent on its nerve supply. Damage to the nerves leads to atrophy of the muscle fibers supplied by those nerves

3. *Diminished blood supply.* A decrease in blood supply (ischemia) to a tissue as a result of slowly developing arterial occlusive disease results in atrophy of the tissue. In late adult life, the brain may undergo progressive atrophy, mainly because of reduced blood supply as a result of atherosclerosis. This is called *senile atrophy*; it also affects the heart.

4. *Inadequate nutrition*. Profound protein-calorie malnutrition (marasmus) is associated with the use of skeletal muscle as a source of energy after other reserves such as adipose stores have been depleted. This results in marked muscle wasting *(cachexia*). Cachexia is also seen in patients with chronic inflammatory diseases and

cancer. In the former, chronic overproduction of the inflammatory cytokine tumor necrosis factor (TNF) is thought to be responsible for appetite suppression and lipid depletion, culminating in muscle atrophy.

5. *Loss of endocrine stimulation*. Many hormone-responsive tissues, such as the breast and reproductive organs, are dependent on endocrine stimulation for normal metabolism and function. The loss of estrogen stimulation after menopause results in physiologic atrophy of the endometrium, vaginal epithelium, and breast.

6. *Pressure*. Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding uninvolved tissues. Atrophy in this setting is probably the result of ischemic changes caused by compromise of the blood supply by the pressure exerted by the expanding mass.

Mechanisms of Atrophy:

Atrophy results from decreased protein synthesis and increased protein degradation in cells. Protein synthesis decreases because of reduced metabolic activity. The degradation of cellular proteins 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*. This pathway is also thought to be responsible for the accelerated proteolysis seen in a variety of catabolic conditions, including cancer cachexia.

In many situations, atrophy is also accompanied by increased *autophagy*, with resulting increases in the number of *autophagic vacuoles*. Autophagy ("self eating") is the process in which the starved cell eats its own components in an attempt to find nutrients and survive. 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. An example of such residual bodies is the *lipofuscin granules*, discussed later in the chapter. 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

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. In the habitual cigarette smoker, the normal ciliated columnar epithelial cells of the trachea and bronchi are often replaced by stratified squamous epithelial cells. Stones in the excretory ducts of the salivary glands, pancreas, or bile ducts may also cause replacement of the normal secretory columnar epithelium by stratified squamous epithelium. A deficiency of vitamin A (retinoic acid) induces squamous metaplasia in the respiratory epithelium. In all these instances the more rugged stratified squamous epithelium is able to survive under circumstances in which the more fragile specialized columnar epithelium might have succumbed. However, the change to metaplastic squamous cells comes with a price. In the respiratory tract, for example, although the epithelial lining becomes tough, important mechanisms of protection against infection—mucus secretion and the ciliary action of the columnar epithelium—are lost. Thus, 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*. Thus, a common form of cancer in the respiratory tract is composed of squamous cells, which arise in areas of metaplasia of the normal columnar epithelium into squamous epithelium.

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, 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. In the case of vitamin

A deficiency or excess, it is known that retinoic acid regulates gene transcription directly through nuclear retinoid receptors , which can influence the differentiation of progenitors derived from tissue stem cells. How other external stimuli cause metaplasia is unknown, but it is clear that they too somehow alter the activity of transcription factors that regulate differentiation.