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Mechanisms of Cellular Adaptation and Change: A Narrative Literature Review

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A B S T R A C T

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. Adaptation is a reversible, structural, or functional response to normal or physiological conditions and adverse or pathological conditions. This review aimed to describe the mechanism of cellular adaptation in the human body. Cells adapt to the environment to escape and protect against injury. Adaptation of the cell, be it normal or injured, this condition lies somewhere between these two conditions. 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. In conclusion, cellular adaptation is a central and common part of many disease conditions.

1. Introduction

Knowledge of the structural and functional reactions of cells and tissues to injury-causing agents, including genetic defects, is key to understanding disease processes. Cellular injury can be caused by any factor that disrupts cellular structure or deprives cells of the need for oxygen and nutrients for survival.[1] The injury may be reversible (sublethal) or irreversible (lethal) and is broadly classified as chemical, hypoxic (deficient in adequate oxygen), free radicals, intentional or accidental, and inflammatory or immunological.[2,3] Cellular injury from a variety of causes own different clinical manifestations and pathophysiology. Stress from metabolic derangements may be related to intracellular accumulation and include carbohydrates, proteins, and lipids. Cell death sites can lead to calcium accumulation leading to pathological calcification. Cell death was confirmed by visible structural changes when cells were stained and observed under a microscope. The most important change is the nucleus. Without a healthy nucleus, the cell cannot survive. The two main types of cell death are necrosis and apoptosis, and nutrient derangements can initiate autophagy leading to cell death.[4,5] This review aimed to describe the mechanism of cellular adaptation in the human body.

Cell adaptation and 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.[1] Adaptation is a reversible, structural, or functional response to normal or physiological conditions and adverse or pathological conditions. For example, the uterus adapts to pregnancy—a normal physiological condition—by enlargement. Enlargement occurs due to an increase in the size and number of uterine cells. Under adverse conditions, such as high blood pressure, myocardial cells are stimulated to enlarge by increasing their pumping action. Like most of the body's adaptation mechanisms, however, cellular adaptation to adverse conditions is usually only temporary. Adverse or long-term stress overwhelms adaptive processes and causes cellular injury or death. Changes in cellular and tissue biology can occur from adaptation, injury, neoplasia, accumulation, aging, or death.[4,5]

Cell aging causes structural and functional changes that eventually lead to cell death or decreased capacity to recover from injury. The mechanisms that explain how and why cells age are unknown, and the distinction between the pathological and physiological changes that occur with aging is often elusive. Aging clearly causes changes in cellular structure and function, but aging or growing old is both inevitable and normal.[6]

Cellular adaptation

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.[7,8] 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. 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).[9] Dysplasia (derangement of cellular growth) is not considered a true cellular adaptation but rather an atypical hyperplasia.[10] This change is shown in Figure 1.

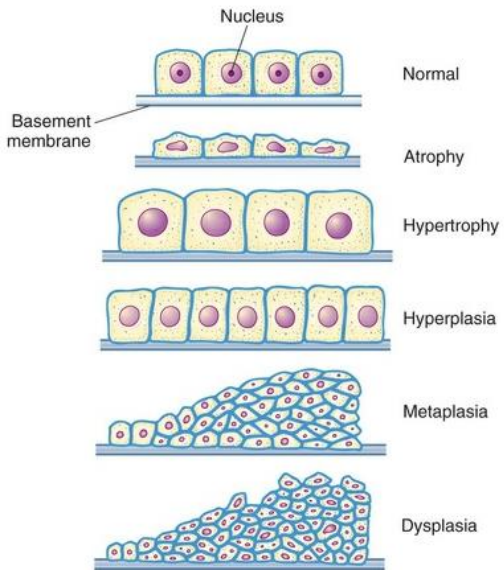

Figure 1. Adaptive changes in simple cuboidal epithelial cells.

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 (Figure 2). Atrophy can be divided into physiological or pathological. 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. Individuals who experience immobilization in bed for a long time show skeletal muscle atrophy which is called disuse atrophy.[11] Aging causes brain cells to become surroundings and endocrine-dependent organs, like gonads, to shrink as hormonal stimulation decreases. Whether atrophy is caused by normal physiological conditions or pathological conditions, atrophic cells show the same basic changes.

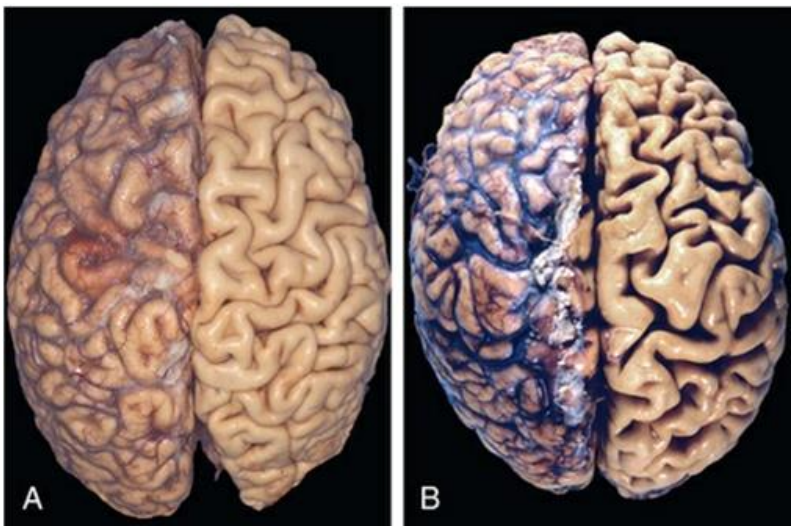

Figure 2. Atrophy. A, The normal brain of a young person. B, Brain atrophy in an 82-year-old man with atherosclerotic disease. Brain atrophy as a result of aging and decreased blood flow. Note that loss of brain substance narrows the gyrus and widens the sulcus. The meninges were stripped from the right half of each specimen to expose the brain surface.

Atrophic muscle cells contain fewer ER and fewer mitochondria and myofilaments (the part of the muscle fiber that controls contraction) than normal cells do. In muscular atrophy caused by nerve loss, oxygen consumption, and amino acid uptake decrease rapidly. The mechanism of atrophy includes decreased synthesis of a protein or increased protein degradation, or both. Protein degradation occurs mainly by the pathway ubiquitin-proteasome.[10,12]

Atrophy as a result of malnutrition can activate ligase ubiquitin which targets proteins for proteasome degradation. Accelerated protein degradation may be the mechanism responsible for catabolic states, including cachexia cancer. Atrophy is often accompanied by a "self-eating" process called autophagy which induces autophagy vacuoles. These vacuoles are membrane-bound vesicles inside cells that contain cellular debris—small fragments of mitochondria and ER—and hydrolytic enzymes, which are isolated in autophagy vacuoles to prevent uncontrolled cell destruction. Sovacuole proliferates as necessary to protect uninjured organelles from injured organelles and is eventually taken up and destroyed by lysosomes. Certain constituents of autophagic vacuoles can resist destruction by lysosomal enzymes and persist in membrane-bound

residual bodies. For example, these granules contain lipofuscin, a yellow-brown aging pigment. Lipofuscin accumulates mainly in hepatic cells, myocardial cells, and atrophic cells.[13]

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 (eg, IGF-1). 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.

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.[14]

Triggers of cardiac hypertrophy include two types of signals: mechanical signals, such as stretch, and trophic signals, such as growth factors and vasoactive agents (Figure 3). The mechanical strain sensor is triggered by an increase in workload. This sensor, by itself, can increase the production of growth factors (eg, IGF-1) and vasoactive factors (eg angiotensin II). Signals from these membrane sensors activate complex signaling pathways, including the phosphoinositide 3-kinase (PI3K)/AKT pathway and G-protein coupled receptor. Transcription factors are activated from signaling pathways to increase muscle protein synthesis. The initial enlargement of the heart is caused by dilatation of the cardiac chambers, temporary life, and is accompanied by an increase in cardiac muscle protein synthesis which enables the muscle fibers to work more. The nucleus is also hypertrophied, and features increased synthesis of DNA. The increase in cell size is related to increased protein accumulation in cellular components (plasma membrane, ER, myofilaments, mitochondria) and not to an increase in the amount of cell fluid. Over time cardiac hypertrophy is characterized by extracellular matrix remodeling and increased growth of mature myocytes. Prolonged cardiac hypertrophy pushes contractile dysfunction, decompensation, and eventually heart failure. Heart failure is a leading cause of death worldwide. One area of investigation is microRNA (miRNAs) that regulate target gene expression after transcription. In mice, miRNA 212-/132 regulates cardiac hypertrophy and cardiomyocyte autophagy. Cardiac tissue remodeling occurs after cardiac stress and can progress to heart failure and death. Researchers are currently studying the formation of cardiac fibrosis caused by increased activity of cardiac fibroblasts that lead to the overproduction of extracellular matrix. Non-coding RNAs (ncRNAs) as gene regulators are a focus for studying cardiac fibrosis and therapeutic targets.[13]

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.[10] The main mechanism of hyperplasia is the production of growth factors, which stimulate surviving cells (after cell loss or injury) to synthesize new cell components and, ultimately, to divide. Another mechanism is the increased output of new cells from the stem cell network. For example, if hepatic cells can be compromised, new cells can be regenerated from intrahepatic stem cells. 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. The liver is self-renewing by simple duplication of perfectly differentiated cells. Hepatocytes usually live a year or more; then, through a very slow rate of cell division, they renew themselves. If large numbers of hepatocytes are lost from surgery or injury, an explosion of cell division occurs from the surviving hepatocytes—rapidly replacing the lost tissue. Much is not known about stem cell activation and hepatocyte renewal in severe hepatic injury.[5,6]

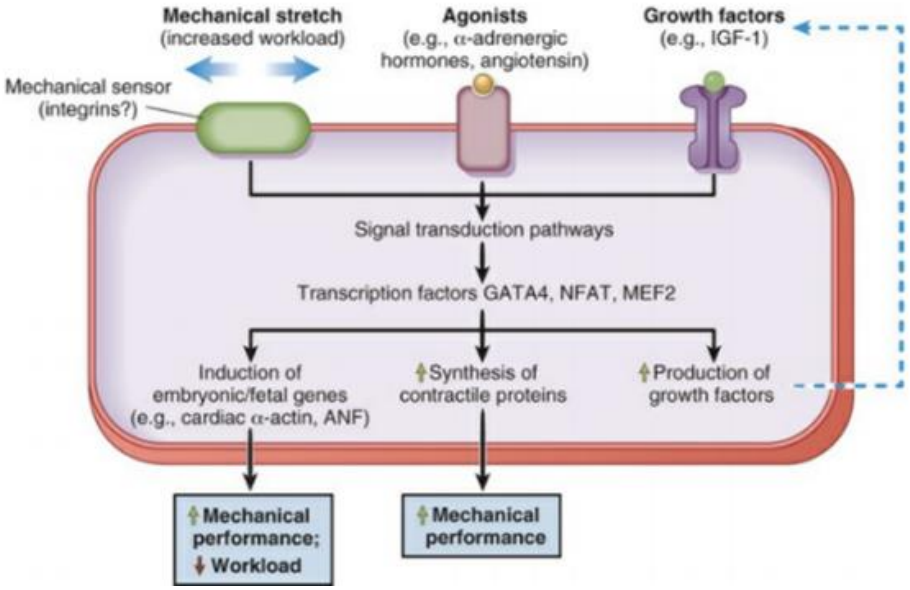

Figure 3. Mechanism of myocardial hypertrophy. Mechanical sensors appear to be the main stimulators for physiological hypertrophy. Other stimuli may be more important to hypertrophy. Pathological factors include agonists (initiators) and growth factors. This factor then becomes a signaling transcription pathway where the transcription factor then binds to the DNA chain, activating muscle proteins responsible for hypertrophy. These pathways include the induction of embryonal/fetal genes, increased contractile protein synthesis, and growth factor production.

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. Another example is the response to wound healing as part of the inflammatory process.

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.

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 (Figure 4). Hyperplastic cells are recognized by nuclear enlargement, clumping of

chromatin, and the presence of one or more enlarged nucleoli. The most common example is pathological hyperplasia of the endometrium, which causes an imbalance between estrogen and progesterone with a relative increase in estrogen. Hyperplasia pathological endometriosis, which causes excessive menstrual bleeding, is under the control of regular growth restriction. If this control fails, endometrial hyperplastic cells may undergo malignant transformation. Benign prostatic hyperplasia is another example of pathological hyperplasia and results from changes in hormonal balance. In both of these examples, if the hormonal imbalance is corrected, the hyperplasia decreases.[6,7]

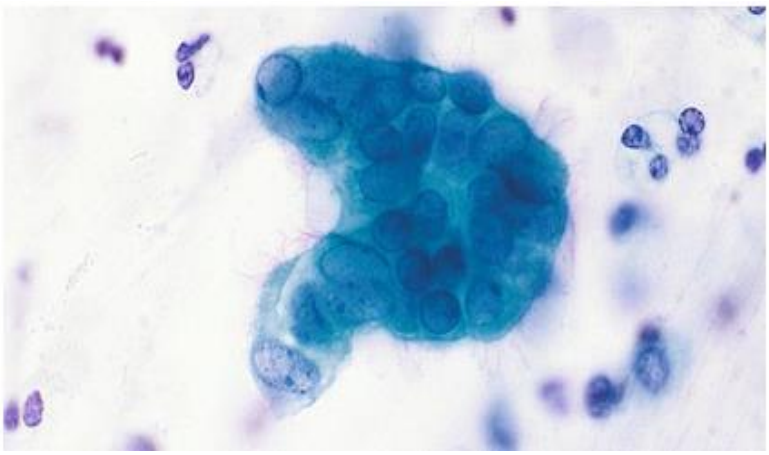

Figure 4. Bronchial epithelial hyperplasia.

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. The architecture of dysplastic tissue can be untidy. It is also important that the term dysplasia is not cancer and may not develop into cancer.[8] Dysplasia that does not involve the full thickness of the epithelium may improve completely. Removal of a stimulating stimulus, for example, certain hormonal stimuli, in mild to moderate dysplasia that does not involve the entire epithelium may be improved. When the dysplastic change penetrates the basement membrane, it is considered a preinvasive neoplasm and is known as carcinoma in situ.

Metaplasia

Metaplasia is the reversible replacement of one mature (epithelial or mesenchymal) cell by another, sometimes less differentiated. Found related to tissue damage, repair, and regeneration. 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. 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 (Figure 5). The squamous epithelial cells newly formed do not secrete mucus or have cilia, causing loss of vital protective mechanisms. Bronchial metaplasia may be reversible if the inducing stimulus, usually smoking, is removed.[9] If the induction stimulus persists, it can initiate the malignant transformation of the metaplastic epithelium.

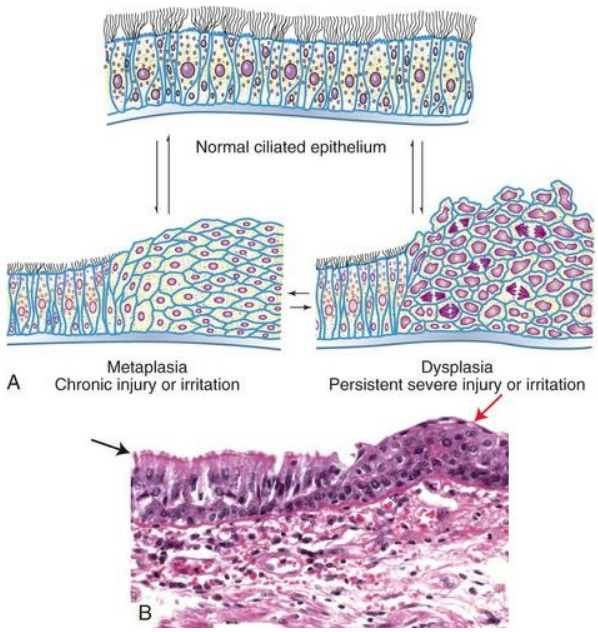

Figure 5. Reversible changes of cell boundaries in bronchi. A, Normal ciliated epithelium, metaplasia, and dysplasia. B, Histological view with top left (black arrow) normal columnar epithelium and basement membrane, and top right (red arrow) squamous metaplasia.

Metaplasia develops from reprogrammed stem cells and persists in most epithelial or mesenchymal cells undifferentiated (tissue from the embryonic mesoderm) present in the connective tissue.[8,12] These precursor cells mature along new pathways due to signals generated by cytokines and growth factors in the cell environment. The mechanism of metaplasia does not result from a change in the phenotype of a differentiated cell type.

2. Conclusion

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.

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