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CELL INJURY

(pathophysiological aspects)

Minsk BSMU 2016

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
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КАФЕДРА ПАТОЛОГИЧЕСКОЙ ФИЗИОЛОГИИ

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ПОВРЕЖДЕНИЕ КЛЕТКИ
(патофизиологические аспекты)

CELL INJURY
(pathophysiological aspects)

Учебно-методическое пособие

Минск БГМУ 2016

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MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Methodical recommendations are developed for the purpose of optimization of educational process and are recommended for training of students for practical class in a topic «Cell injury». This subject is considered in the section «Typical pathological processes».

Lesson purpose: to characterize the damage as a typical pathological process; to study the reasons and general mechanisms, features and outcomes of cell injury; to discuss manifestations of cell damage, changing of the structure and function of cellular organelles and consider cellular compensatory mechanisms of cell injury.

Lesson objectives. The student should:

1. Know:

– definitions of cell injury, dystrophy, dysplasia, necrosis, apoptosis;
– the main causes and types of cell damage;
– disorders of energy supply processes;
– mechanisms of the membranes and enzyme systems damage;
– main pathogenetic factors of hyperhydration and dehydration of a cell;
– changes in the genome or its abnormal realization;
– disorders of intracellular regulation mechanisms;
– manifestations of damaged cells;
– types of cell death (necrosis and apoptosis);
– mechanisms of cell adaptation to an injury.

2. Be able:

– to make a conclusion about the presence and type of cell damage and also about the mechanisms of cell damage.

3. Be familiar with:

– the main manifestations of cell damage at the subcellular level and at the level of the whole organism;

– fundamental differences between necrosis and apoptosis, stages and manifestations of them;

– intracellular mechanisms of interaction and adaptation of damaged cells.

Requirements for the initial level of knowledge. For better mastering of the topic student must go over the next notions from:

– histology, cytology and embryology: «cell as the level of structural and functional organization of multicellular organisms».

– biological chemistry: «free radicals», «antioxidants» and «energy metabolism»;

– physiology: «cells exchange with the environment», «chemical signaling».

The control questions of adjacent disciplines:

1. Cell as structural and functional unit of the tissue. Structure of cells.

2. Biological cell membranes, their structure, chemical composition and main features. Plasma membrane. Cell division into compartments and their biological significance.

3. Cell receptors, their classification, structural and functional characteristics.

4. The structural basis of the energy apparatus of cell. Mitochondria, their types and structural organization. Mitochondrial matrix.

5. The reactive properties of the cells and their medical and biological importance.

6. Compensation and decompensation at the cellular and subcellular levels.

Control questions:

1. The definition of the notion «cell injury». Injury as a typical pathological process.

2. Principal causes and types of cell injury. Direct and indirect effect of a damaging agent on a cell.

3. General mechanisms of cell injury.

4. The impairment of energetic supply of processes taking place in cells, as one of master mechanisms of injury.

5. The role of damage of membranes and enzymes in the impairment of cellular vital activity, mechanisms of its development.

6. The role of genetic program impairments and its realization mechanisms in damaging a cell.

7. Perception impairments of regulatory effects on a cell. Regulation impairments of intracellular processes as a major mechanism of damaging a cell.

8. Basic manifestations of cellular injury, their mechanisms. Changes of the structure and functions of some cellular organelles in cell injury.

9. Specific and nonspecific manifestations in cell injury.

10. Intracellular mechanisms of adaptation and compensation in response to damage.

11. Integrated mechanisms of cellular damage and death (mechanisms of hypoxic necrobiosis and apoptosis).

GENERAL CHARACTERISTICS OF CELL INJURY

Impairment of the vital activity of the human body in a variety of extreme conditions and diseases is always based on the changes in the cell function. The cell is the structural and functional unit of tissues and organs. The processes underlying the energy and plastic supply of the tissue structure and its function take place in it. Under the influence of environmental unfavorable factors, impaired functioning of the cells can acquire persistent character and cause damages. Pathology always begins with damage when adaptability becomes impossible. Any pathological process occurs with greater or lesser degree and extent of cell damage, which is expressed in the impairment of their structure and function. Based on this, a damaged cell is a cell with changes in its structure, metabolism, physical and chemical properties and functions, which lead to a damage of its vital activity and which persist after the removal of the damaging agent.

Cell injury *is a typical pathological process which is characterized by such changes in its structure, metabolism, physicochemical properties or function that seriously compromise (endanger) its viability or the ability to adapt to noxious stimuli.*

Cells constantly adapt to physiological demands to maintain a homeostatic steady state. Cells adapt by performing excess work, replicating, decreasing functions, changing its differentiated properties, etc. The main adaptations to a persistent stimulus may involve cellular hypertrophy, hyperplasia and metaplasia. Atrophy occurs whenever certain normal stimuli (workload, blood supply, etc.) are decreased or lost. Depending on the specific condition, adaptive reactions can produce organ damage. Through these adaptations cells maintain their viability.

The term *cell injury* is used to indicate a state in which the capacity for physiological adaptation is exceeded. This may occur when the stimulus is excessive or when the cell is no longer capable to adapt without suffering some form of damage. The capacity for adaptation and the sensitivity to different types of injury varies according to cell type (i.e. myocardial cells and neurons are highly sensitive to ischemic injury; hepatocytes are more sensitive to chemical than ischemic injury). Cell injury may be *reversible* (non-lethal damage which generally can be corrected by removal of the stimulus) or *irreversible* (lethal damage) (fig. 1). 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.

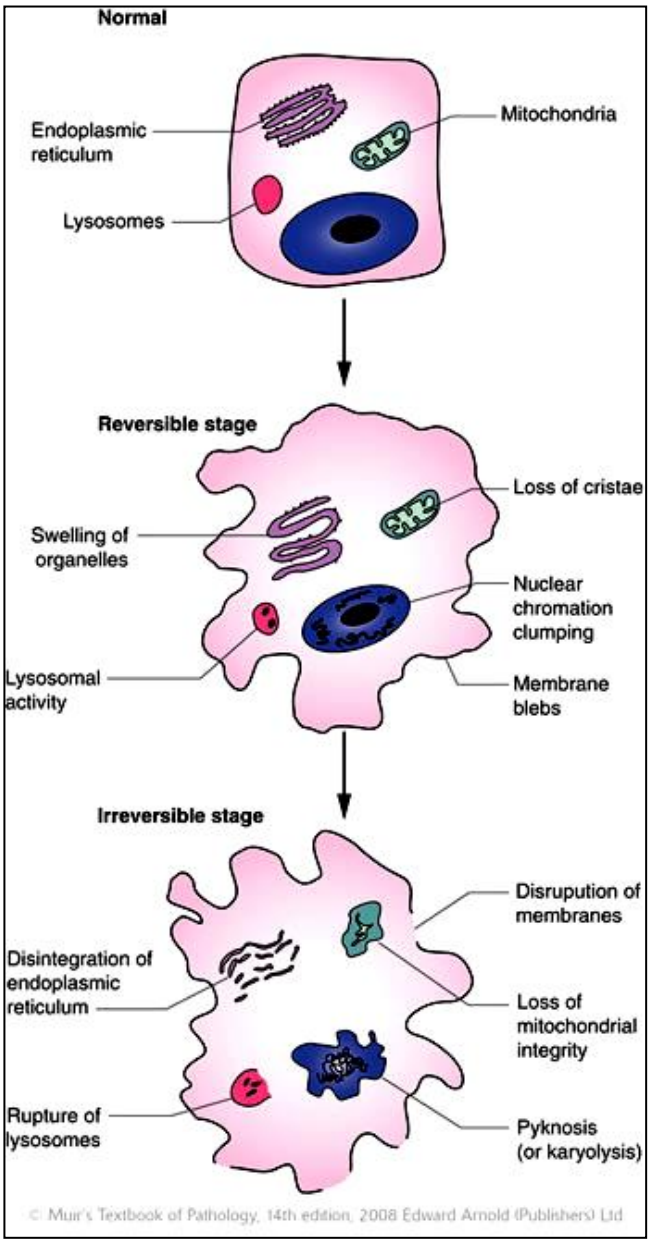

Fig. 1. Reversible and irreversible cell injury

Reversible cell injury occurs in organs rich in mitochondria e. g. renal tubules, cardiac muscles and hepatocytes with alteration of homeostasis. The morphological correlates of reversible cell injury are *cellular swelling (hydropic change or vacuolar degeneration)* and *fatty changes*

(*steatosis*) — it is abnormal accumulation of intracellular neutral fat that occurs in parenchymatous organs most commonly liver and heart.

Irreversible cell injury occurs if the injurious stimulus persists or it is severe enough that the cell passes a «point of no return» and dies. Irreversible cellular injuries can be caused by durable ischemia of myocardium, intoxication, etc. When the disturbance of homeostasis in an injured cell reaches the critical level, the death of the cell occurs, that is characterized by cessation of all living processes in it and death.

There are ***direct*** (primary) and ***indirect*** (secondary) damage that arises as a consequence of primary disorders of the body internal environment.

Primary or secondary cell damage is reflected adversely on the body state and must be eliminated at an early stage of its development. But in order to know how to prevent and protect the cells from the pathogenic effects, it is necessary to know the etiology and mechanisms of cells damage and death in a living organism.

Cell injury may be ***acute or chronic*** depending on the speed and intensity of main manifestations. Acute injury develops quickly, usually as a result of single but intense injurious effects while chronic damage is slow and is the result of multiple, but less intense pathogenic influences.

Depending on the life cycle period, when damaging agent acts, cell damage can be ***mitotic and interphase***.

THE ETIOLOGY OF CELL INJURY

There are different causes of cell injury depending on the nature of the damage factor:

1. ***Physical agents*** — mechanical trauma; very high or very low temperature; changes in osmotic pressure; radiation; electric shock.
2. ***Chemical agents*** — organic and inorganic acids and alkalis; cytotoxic agents; drugs; free radical damage.
3. ***Biologic factors*** — infectious agents; immunologic reactions; genetic disorder; oxygen and nutritional deprivation; hypoxia (ischemia, hypoxemia, loss of oxygen carrying capacity).

Among the ***factors of physical character*** the most frequent causes of cell damage are:

Mechanical effects: for example bruises, stretching of muscle tissue they cause disturbance of plasmalemma and membranes of subcellular structures.

Fluctuations in temperature: the increase of the environmental temperature in which the cell is to the T 45–50 °C and more can cause denaturation of proteins, nucleic acids, decomposition of lipoprotein complexes, increasing the permeability of cell membranes, and other changes. A significant reduction of temperature can cause a considerable slowdown or irreversible cessation of metabolic processes in a cell, the crystallization of intracellular fluid and rupture of the membranes.

Changes of the cell's osmotic pressure can occur as a result of accumulation of incomplete oxidation products of organic substrates, as well as an in it. Excess

of ions as a rule is accompanied by fluid flow in a cell on osmotic pressure gradient, swelling and extension of cell (up to rupture its plasmalemma and membranes of organelles). Decrease in intracellular osmotic pressure or increase in the extracellular surroundings leads to loss of fluid from cell, its shrink (pyknosis), and often to death.

Exposure of ionizing and ultraviolet radiation causes activation of lipid peroxidation processes (PLP) and the formation of free radicals. The products of peroxide free-radical processes activation can damage membranes and cause denaturation of cells enzymes.

Cell damage is often caused by exposure to ***the chemical factors***. These include a variety of substances of exogenous and endogenous origin: *acids, alkalis, salts of heavy metals, poisons of plant and animal products, impaired metabolism, social agents such as alcohol and narcotic drugs and therapeutic administration of drugs*.

Thus, cyanides inhibit cytochrome oxidase. Ethanol and its metabolites inhibit many cell enzymes. Substances containing arsenic salts oppress pyruvate oxidase. Improper use of drugs can also lead to cell damage. For example, an overdose of strophanthin causes significant suppression of K^+-Na^+-ATPhase in the sarcolemma of myocardial cells, which leads to an imbalance of intracellular content of ions and fluid.

It is important that cell damage may be due to an excess or deficiency of one and the same factor. For example, the excess of oxygen in tissues activates the process of lipid peroxidation, which products damage enzymes and cell membranes. On the other hand, the reduction of oxygen causes the disorder of oxidative processes, reduction of ATP and, consequently, cell function disorder.

Frequent reasons of damage are the ***factors of biological origin*** such as *viruses, rickettsia, bacteria, parasites and fungi*. Their metabolic products cause the disorder of cell functions, disturb metabolic reactions, permeability or membrane integrity, and inhibit the activity of cellular enzymes.

Cell damage is often determined by factors of immune and allergic disorders. They may be due, in particular, to the similarity of antigens, such as bacteria and cells.

Damage can also be the result of antibody formation or T-cell effect, acting against the unaltered cells due to a mutation in the genome B or T-cell immune system. Immune system protects the host against various injurious agents but it may also turn lethal and cause cell injury.

So immune reactions may however cause cell injury:

– first — so-called «anaphylactic reaction» — to a foreign protein or drug;

– second — reactions to endogenous «self-antigens» are responsible for a number of so called «autoimmune diseases» hypersensitivity reactions.

Substances that come in a cell from the endings of neurons, in particular, neurotransmitters, trophogens (*neurotrophic factors*), neuropeptides play important role in maintaining metabolic processes in it. Reduction or elimination of their transport is the cause of metabolic disorders in the cells, the disturbance of

their vital activity and the development of pathological conditions, known as *neurodystrophy*.

In addition to these factors, cell damage is often caused by *a significantly increased function of organs and tissues*. For example, prolonged excessive exercise may develop heart failure as a result of disability of cardiomyocytes. Cell damage may be the result not only pathogens but also the result of genetically programmed processes. An example is the death of the epidermis, the intestinal epithelium, red blood cells and other cells by the process of aging. The mechanisms of aging and cell death include progressive irreversible changes in the structure of membranes, enzymes, nucleic acids, depletion of substrates of metabolic reactions, reduced cellular resistance to pathogenic influences.

In origin all causal factors of cell damage are divided into: *exogenous and endogenous; infectious and noninfectious origin.*

MECHANISMS OF CELL INJURY

The mechanisms by which injurious agents cause cell injury and death are complex. Some agents, such as heat, produce direct cell injury; other factors, such as genetic disorders, produce their effects indirectly through metabolic disturbances and altered immune responses. There seem to be at least five major mechanisms whereby most injurious agents exert their effects: 1) *disorder of energy supply processes; 2) damage of cell membranes and enzyme systems; 3) imbalance of ions and fluid in cell; 4) damage of cell genetic program and/or mechanisms for its implementation; 5) disorders of intracellular processes regulation.*

DISORDER OF ENERGY SUPPLY PROCESSES

Disorder of energy supply processes in cells often is an initial and key mechanism of their alteration.

ATP depletion. High-energy phosphate in the form of ATP is required for many synthetic and degradative processes within the cell. These include membrane transport, protein synthesis, lipogenesis, and the deacylation-reacylation reactions necessary for phospholipid turnover. ATP is produced in two ways. *The major one* in mammalian cells is oxidative phosphorylation of adenosine diphosphate (ADP), in a reaction that results in reduction of oxygen by the electron transfer system of mitochondria. *The second* is the glycolytic pathway, which can generate ATP in the absence of oxygen using glucose derived either from body fluids or from the hydrolysis of glycogen. Thus, tissues with greater glycolytic capacity (e. g., liver) have an advantage when ATP levels are falling because of inhibition of oxidative metabolism by injury. ATP depletion and decreased ATP synthesis are common consequences of both ischemic and toxic injury.

Derangements in the energy supply processes may occur at the stages of a) *ATP synthesis, b) ATP transport and c) utilization* of its energy.

a) ***Decrease in the rate or efficiency of ATP synthesis.*** ATP synthesis may be impaired as a result of: 1) oxygen deficit; 2) deficit of metabolism substrates (glucose, fatty acids); 3) reduced activity of tissue respiration and oxidative phosphorylation enzymes; 4) reduced activity of glycolysis; 5) mitochondrial damage and destruction.

b) ***Decrease of ATP transport to the sites of utilization.*** It is known that the delivery of the energy of ATP from the locations of its synthesis to the effector structures is realized by using of two enzyme systems: *ADP-ATP-translocase* and c*reatine phosphokinase (CPK)*. *ADP-ATP-translocase* provides transportation energy from mitochondrial matrix through their inner membrane. *Creatine phosphokinase (CPK)* transfers the energy from the inner membrane of mitochondria to creatine with the formation of creatine phosphate which is released in cytosol. These enzyme systems can be damaged by various pathogenic agents, and therefore, even at high total content of ATP in the cell the deficiency in energy consumed by organelles can develop.

c) ***Impairment of ATP utilization in metabolic processes.*** Violation of energy supply processes in cells and their metabolic disorders may develop even during sufficient output and normal transport of ATP. In this case lack of energy in the cell may be due to a violation of enzymes which are responsible for utilization of ATP energy: *ATPase actomyosin; K-Na-dependent ATPase plasmalemma; and* Mg^{2+}*-dependent ATPase «calcium pump» sarcoplasmic reticulum.*

Disorder in energy supply processes of cells, in turn, could become a factor in disorders of the membrane system of cells, their enzyme systems, ions and fluid balance, reducing membrane potential as well as mechanisms of cell regulation.

DAMAGE OF CELL MEMBRANES AND ENZYME SYSTEMS

Damage of membranes and enzymes plays an important role in breakdown of cell activity, as well as the transition of reversible changes into irreversible one. This is due to the fact that the basic properties of cells to a large extent depend on the state of its membranes and associated enzymes.

There are some mechanisms of membranes injury:

1) *intensification of free radical reactions*;
2) *activation of lipid peroxidation*;
3) *activation of intracellular hydrolases*;
4) *introduction of amphiphilic compounds in the lipid phase of membranes*.

1. ***Intensification of free radical reactions*** occurs in cells as a necessary part of the electron transport in the respiratory chain enzymes, in the synthesis of prostaglandins and leukotrienes, maturation and proliferation of cells.

Cells generate energy by reducing molecular oxygen to water. During this process, small amounts of partially reduced reactive oxygen forms are produced as an unavoidable byproduct of mitochondrial respiration. Some of these forms are free radicals. They are referred to as reactive oxygen species. Overproduction of free radicals can cause oxidative damage to biomolecules (lipids, proteins, DNA).

Cells have defense systems to prevent injury caused by these products. An imbalance between free radical-generating and radical-scavenging systems results in oxidative stress, a condition that has been associated with the cell injury seen in many pathologic conditions such as atherosclerosis, cancer, diabetics, rheumatoid arthritis etc., post-ischemic perfusion injury, myocardial infarction, cardiovascular diseases, chronic inflammation, stroke and septic shock, aging and other degenerative diseases in humans.

Mechanisms of Free Radical Injury:

1. Lipid peroxidation → damage to cellular and organelles membranes.

2. Protein cross-linking and fragmentation due to oxidative modification of aminoacids and proteins.

3. DNA damage due to reactions of free radicals with thymine (fig. 2).

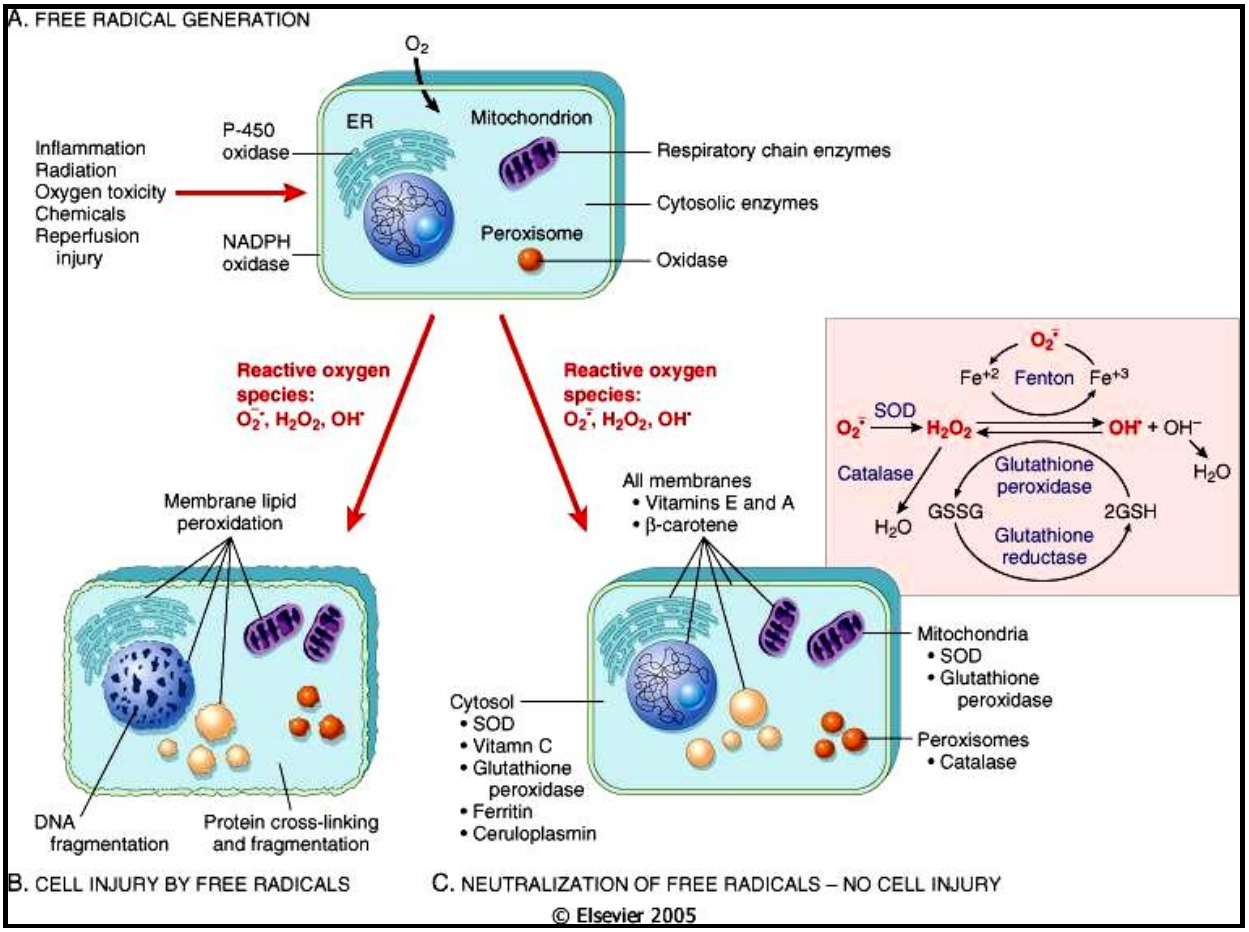

Fig. 2. Mechanisms of Free Radical Injury

2. *Lipid peroxidation of membranes*. Produced in large quantities of free radicals (superoxide and hydroxyl radical ($O_{2^-}^{\cdot}$ ($OH^{\cdot}$),) hydrogen peroxide (H_2O_2), and lipids cause:

1) changes in the physical and chemical properties of membrane lipids, resulting in damaging of the conformation of their lipoprotein complexes, and in connection with this decreasing in activity of proteins and enzyme systems that provide reception of humoral influences, transmembrane transport of ions and molecules, structural integrity of the membranes;

2) changes in the physical and chemical properties of the protein micelles performing structural and enzymatic functions in the cell;

3) formation of structural defects in the membrane — the so-called simple channels (clusters) due to the implantation of lipid peroxidation products in them.

These processes, in turn, lead to the damage of vital cell processes — excitability, generation and nerve impulse conduction, metabolism, perception and implementation of regulatory actions, intercellular interactions, etc.

3. ***Activation of intracellular hydrolases (lysosomal, membrane-bound, or cytosolic).*** Acidosis causes the activation of lysosomal hydrolases and increases lysosomes permeability. As a result an intensive hydrolysis of proteins, enzymes and glycerophospholipids of cell membrane develops. This is accompanied by a significant increase in membrane permeability and decrease of the kinetic properties of enzymes.

4. ***Introduction of amphiphilic compounds in the lipid phase of membranes.*** Normally, the composition and state of the membranes is modified not only by free radical processes and lipid pereoxidation, but also by membrane-bound or membrane-free (solubilized) and lysosomal enzymes: lipases, phospholipases, proteases. Under the influence of pathogenic factors their activity or content in hyaloplasm of cell may increase (in particular, due to the development of acidosis, contributing to an increase in output of lysosomal enzymes and their subsequent activation, the penetration of calcium ions into the cell). Therefore glycerophospholipids and membrane proteins as well as enzymes of cells are intensively hydrolised. This is accompanied by a significant increase in membrane permeability and decrease of the kinetic properties of enzymes.

As a result of hydrolases action (mainly lipases and phospholipases) free fatty acids and lysophospholipids, particularly glycerophospholipids: phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine accumulate in the cell. They are called amphiphilic compounds due to the ability to penetrate and settle in both hydrophobic and hydrophilic environments of the cell membrane (AMFI — means «both», «two»). The accumulation of a large number of amphiphiles in membranes as the excess of lipid hydroperoxide leads to the formation of microscopic clusters and microruptures in them. Rupture of membranes and enzymes of cells is one of the main causes of substantial disorder of cell activity, and often leads to death.

IMBALANCE OF IONS AND FLUID IN CELL

As a rule, the disorder of the transmembrane distribution, intracellular content and ratio of different ions develops simultaneously or after disorders of energy supply and is accompanied by signs of cells membrane damages and their enzymes. As a result, membrane permeability changes significantly for many ions. To the greatest extent it relates to potassium, sodium, calcium, magnesium, chlorine, that is to, ions that are involved in vital processes, such as excitement, conduction, etc.

Changes of transmembrane ions ratio (disioniya). As a rule, ion imbalance is manifested by accumulation of sodium and loss of potassium in a cell.

Changes in the resting membrane potential and action potential are the consequence of the imbalance of ions. These changes are important because they often are one of the indicators of existence and character of cell damage. For example, electrocardiogram changes at damaged myocardial cells, deviation of electroencephalogram in case of disorders of neurons structure and function in brain.

Cytosolic free calcium is maintained at extremely low concentrations (less than 0.1 μmol) compared with extracellular levels of 1.3 mmol, and most intracellular calcium is sequestered in mitochondria and endoplasmic reticulum. Such gradients are modulated by membrane-associated, energy-dependent Ca-, Mg-ATPases.

Lack of calcium in the extracellular fluid causes disorder in blood coagulation, changes in the structure of tissues, violation of intercellular interaction.

An excess of calcium in the cell can lead to many negative consequences. Ca^{2+} ions can damage cells if they enter in excessive amounts (for example, in the case of excitotoxicity, or over-excitation of neural circuits, which can occur in neurodegenerative diseases, or after insults such as brain trauma or stroke). Excessive entry of calcium into a cell may damage it or even cause it to undergo apoptosis, or death by necrosis. Calcium also acts as one of the primary regulators of osmotic stress (osmotic shock). Chronically elevated plasma calcium (hypercalcemia) is associated with cardiac arrhythmias and decreased neuromuscular excitability. One cause of hypercalcemia is a condition known as hyperparathyroidism.

Hyperhydration and dehydration. Disorders of intracellular ions cause changes in cell volume due to the fluid imbalance. This may cause the hyperhydration of the cell. For example, elevated levels of sodium and calcium in the damaged cells are accompanied by an increase of osmotic pressure in them. As a result, cells accumulate water. Thus, cells swell, their volume increases, which is often accompanied by increasing of tension, microscopic ruptures of plasmalemma and membranes of organelles. On the contrary, the dehydration of cells (for example, in some infectious diseases and causing the loss of water) is characterized by the release of these fluids and dissolved proteins (including enzymes), as well as other organic and inorganic water-soluble compounds. Intracellular dehydration is often combined with the wrinkling of the nucleus, mitochondrial decay and other organelles destruction.

DAMAGE OF CELL GENETIC PROGRAM AND/OR MECHANISMS FOR ITS REALIZATION

One of the important mechanisms of cell activity disorders is damage of a genetic program and/or mechanisms of its implementation.

The main processes leading to changes in the cell genetic information are: *1) mutations; 2) derepression of pathogenic genes (e. g. oncogenes); 3) suppression of essential genes activity (such as genes regulating the synthesis of enzymes); 4) the introduction in a cell gene of foreign DNA fragment (e. g., DNA of tumor virus, abnormal area DNA of another cell).*

In addition to changes in the cell genetic program, an important mechanism of cell activity disorders is *disturbance of this program realization*, especially in process of cell division during mitosis or meiosis. The causes of violation of a genetic program realization are: *1) damage of chromosomes; 2) damage of the structures participating in cell division; 3) abnormal division and etc.*

DISORDERS OF INTRACELLULAR PROCESSES REGULATION

An important mechanism of cell damage is a disorder of intracellular processes regulation. This may be a result of disturbance one or more levels of cell regulatory mechanisms:

1) at the level of interaction of biologically active substances (hormones, neurotransmitters, etc.) with receptors of cells;

2) at the level of so-called cell «secondary messengers» of nerve influences: cyclic nucleotides-adenosine monophosphate (cAMP) and guanosine monophosphate (cGMP), formed in response to the «first intermediaries» — hormones and neurotransmitters (for example, disorder in the formation of the membrane potential in cardiomyocytes in case of cAMP accumulation in them, which is in particular one of the possible causes of cardiac arrhythmias);

3) at the level of metabolic reactions controlled by cyclic nucleotides or other intracellular factors. Thus, disruption of the activation of cellular enzymes can significantly change the intensity of the metabolic reactions and as a consequence leads to the breakdown of cell activity.

Having examined pathochemical aspects of cell damage, it is necessary not to forget that the problem of cell damage has another very important aspect — the information aspect of cell damage. Communication between cells, the signals that they exchange may also be the sources of the disease.

THE MANIFESTATIONS OF CELL DAMAGE

The next changes are related to main manifestations of cell damage:
1) *dystrophy;*
2) *dysplasia;*
3) *infringement of subcellular structures;*
4) *cell death (necrosis and apoptosis).*

DYSTROPHY

Dystrophy — is a disorder of metabolism in cells and tissues, accompanied by disorders of their functions, plastic manifestations, as well as structural changes, leading to disruption of their vital activity.

The basic mechanisms of dystrophy are:

1) synthesis of abnormal substances in the cells (protein-polysaccharide complex of amyloid);

2) excessive transformation of some compounds into other (fats and carbohydrates into proteins, carbohydrates into fats);

3) decomposition of membranes (protein-lipid complexes of membranes);

4) infiltration of cells and intracellular substances by organic and inorganic compounds (e.g., infiltration of the arteries by cholesterol at atherosclerosis).

The main dystrophies include *disproteinoses* or protein dystrophies, *lipidoses* or fat dystrophies and *carbohydrate and minerals* dystrophies.

DYSPLASIA

Dysplasia (dys — disorder, frustration, plaseo — generators) is an abnormality of cells development process, manifested by persistent changes of their structure and function, leads to breakdown of their life.

The cause of dysplasia is a damage of genome. The main mechanism of dysplasia is a disorder of differentiation process, which involves a formation of structural and functional specialization of cells. Structural features of dysplasia include changing of cells size and shape, their nuclei and other organelles, the number and structure of chromosomes. Typically, when dysplasia cells are increased in size, are irregular in shape («cell-monsters»), the ratio of different organelles in them is disproportionately. Often there are various inclusions, signs of degenerative processes in these cells. For example, formation of megaloblasts in the bone marrow at pernicious anemia, or sickle cells at pathology of hemoglobin. Cellular dysplasia is one of the manifestations of tumor atypism of cells.

INFRINGEMENT OF SUBCELLULAR STRUCTURES

Cell damage is characterized by varying degrees of disruption of the structure and function of all its components. However, at action of various pathogenic factors the signs of damage of these or other organelles may predominate.

Mitochondria. Under the action of pathogenic factors, a change of the total number of mitochondria, as well as their structure is observed. Reduction in the number of mitochondria in relation to the total weight of the cell is revealed. Reduction or an increase in the size and shape of individual mitochondria is stereotypical change to most of the damaging factors. Many pathogenic effects acting on cells (hypoxia, endogenous and exogenous toxic agents, including drugs at their overdose, ionizing radiation, the change of osmotic pressure) are accompanied by swelling and vacuolization of mitochondria, which may lead to rupture of the membrane, fragmentation and homogenization of cristae (fig 3, 4).

Violation of mitochondrial structure leads to a significant inhibition of respiration in them and the formation of ATP, and an imbalance of ions inside the cell.

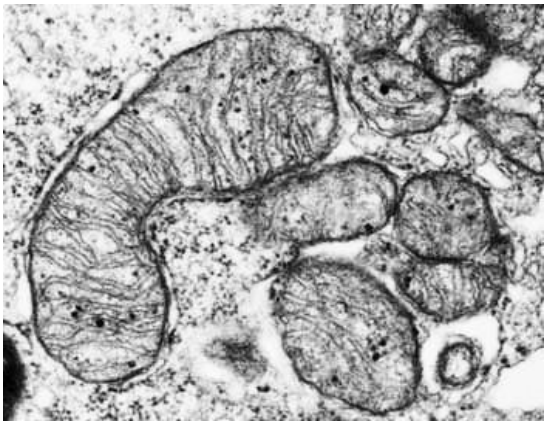

Fig. 3. Mitochondria in norm

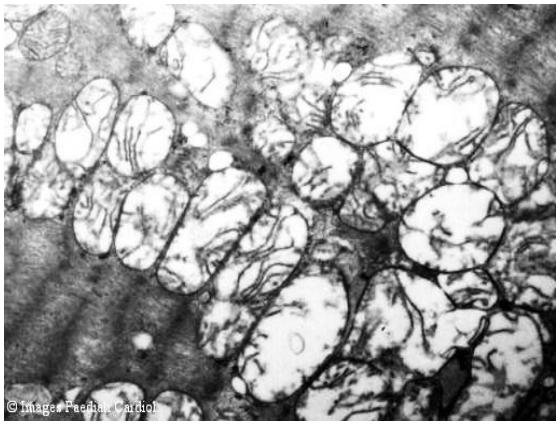

Fig. 4. Mitochondrial swelling and vacuolization

Nucleus. Damage of nucleus is combined with a change of its shape, the condensation of chromatin at the nuclear periphery (margination of chromatin), violation of the nucleus structure or nuclear membrane breaks. The nucleus changes in necrosis and characteristics of this change are determined by the way in which the DNA is broken down, as shown in fig. 5. There are three different ways in which the DNA can be broken down, which are: karyolysis, pyknosis and karyorrhexis.

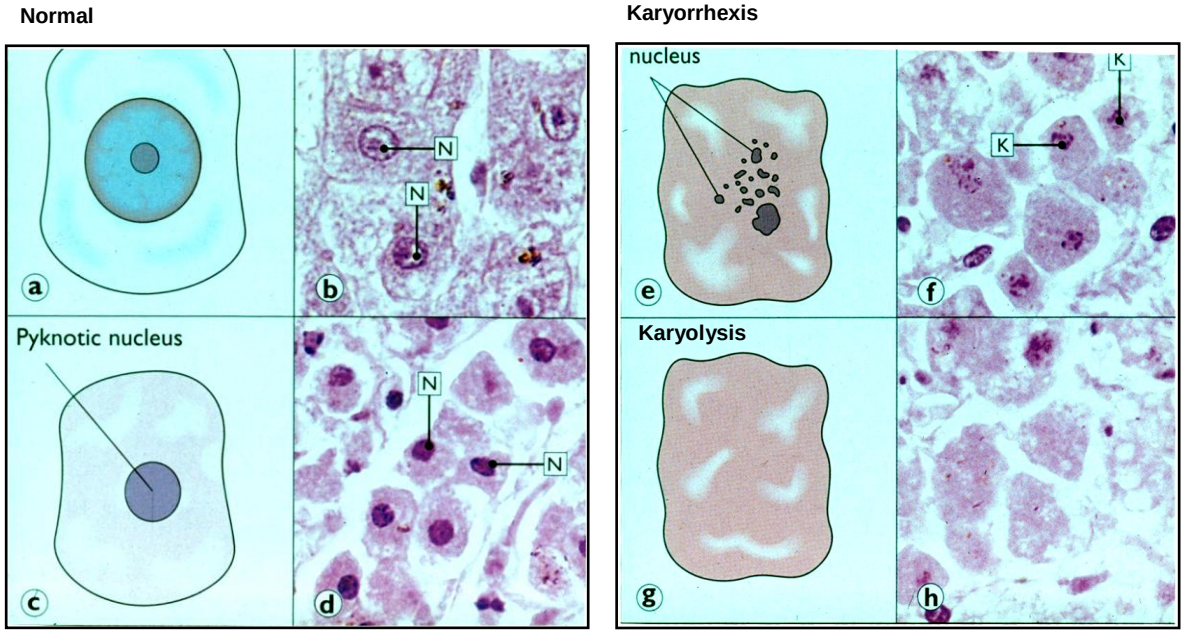

Fig. 5. Morphological characteristics of pyknosis and other forms of nuclear destruction
https://en.wikipedia.org/wiki/Pyknosis

Karyolysis is a process where the chromatin of the nucleus fades due to the loss of the DNA by degradation. Pkynosis is where the nucleus shrinks and the chromatin in the nucleus condenses. Karyorrhexis follows on from the process of pyknosis, and involves the shrunken nucleus proceeding to fragmentation until the nucleus completely disappears. Plasma alterations are also seen in necrosis.

Plasma membranes appear discontinuous when viewed with an electron microscope. This discontinuing membrane is caused by cell blebbing and the loss of microvilli.

Lysosomes. When pathogenic influences the release and activation of lysosomal enzymes can lead to «self-digestion» (autolysis) of cells. Release of lysosomal hydrolases in the cytoplasm can be caused by mechanical ruptures of their membranes or a significant increase in their permeability (fig. 6, 7). This is due to the accumulation of hydrogen ions (intracellular acidosis), lipid peroxidation products, toxins and other agents in the cells.

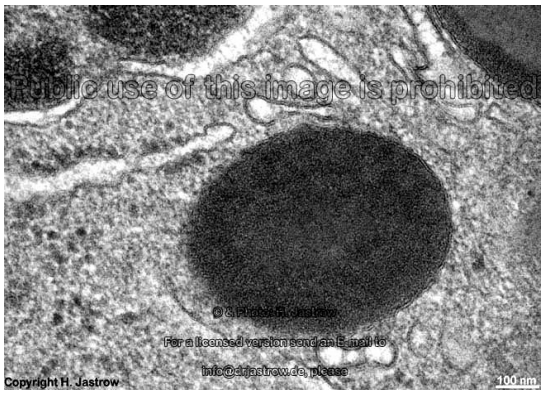
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Fig. 6. Lysosome in norm

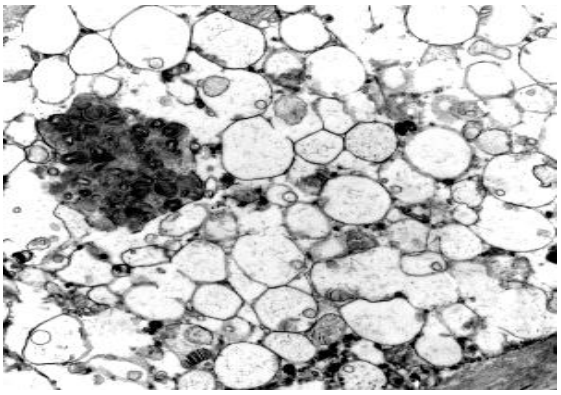

Fig. 7. Increase of lysosome permeability

Ribosomes. Under the influence of damaging factors destruction of polysomes usually consisting of several ribosomes («monomers»), reducing of ribosomes number and separation of the organelles from intracellular membranes are observed. These changes are accompanied by a decrease in the intensity of protein synthesis process in the cell.

Endoplasmic reticulum. At damage extension tubular network, up to the formation of large vacuoles and cisterns as a result of accumulation of fluid in it, focal destruction of tubules network membrane and their fragmentation are revealed (fig. 8, 9).

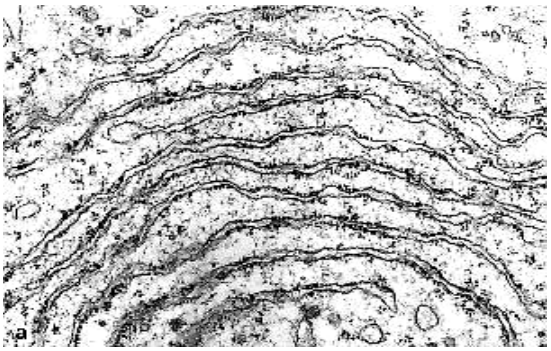

Fig. 8. Endoplasmic reticulum in norm

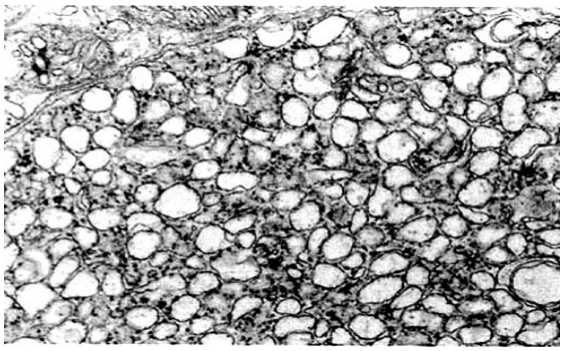

Fig. 9. Vacuolization of endoplasmic reticulum

Golgi apparatus. Damage to the Golgi apparatus is accompanied by structural changes similar to those in the endoplasmic reticulum (fig. 10, 11). Thus removing waste products from the cells is disturbed. This leads to the breakdown of its function as a whole.

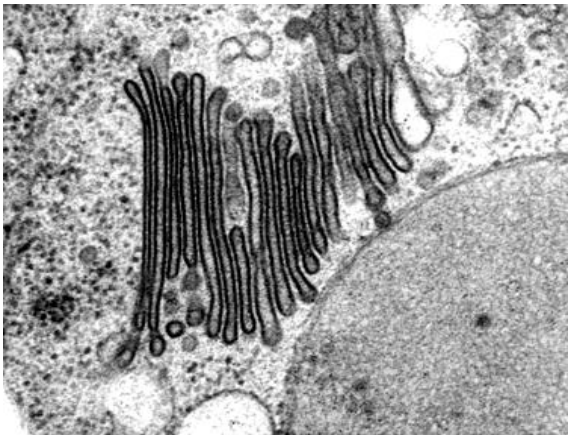

Fig. 10. Golgi apparatus in norm

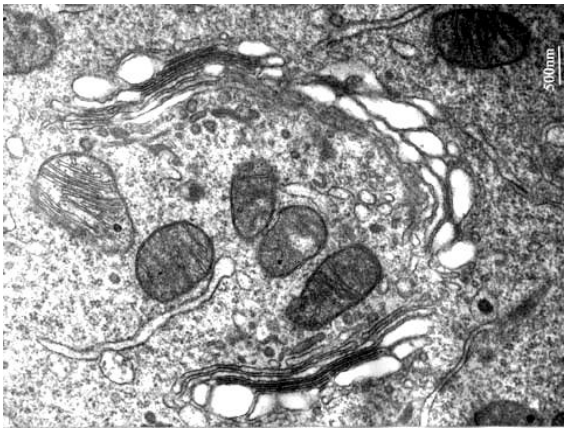

Fig. 11. Vacuolization of Golgi apparatus

The cytoplasm is a liquid, low-viscosity medium that contains organelles and inclusions of cell. Damaging factors may contribute to a decrease or increase in fluid in the cytoplasm, proteolysis or a protein coagulation, violation of inclusions formation. The change in state of the cytoplasm, in turn, affects significantly the metabolism, the function of the organelles and the processes of perception of regulating effects on the cell. This is due to the fact that many enzymes (e. g., those which participate in glycolysis) are located in the cell matrix.

CELL DEATH

NECROSIS

Necrosis is a form of cell injury that results in the premature death of cells in living tissue by autolysis. Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma that result in the unregulated digestion of cell components. In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death. While apoptosis often provides beneficial effects to the organism, necrosis is almost always detrimental and can be fatal.

Cells that die due to necrosis do not follow the apoptotic signal transduction pathway but rather various receptors are activated that result in the loss of cell membrane integrity and an uncontrolled release of products of cell death into the extracellular space. This initiates in the surrounding tissue an inflammatory response which prevents nearby phagocytes from locating and eliminating the dead cells by phagocytosis. For this reason, it is often necessary to remove necrotic tissue surgically, a procedure known as debridement. Untreated necrosis results in a build-up of decomposing dead tissue and cell debris at or near the site of the cell death. A classic example is gangrene.

Morphological changes in necrosis

Morphological changes in necrosis are the next: 1) the cell does not change its volume; 2) first, a cytoplasm and specialized elements of cells breaks, and later — the cell nucleus; 3) cell surrounding connective tissue fibers become basophilic color and fragmented (fig. 12).

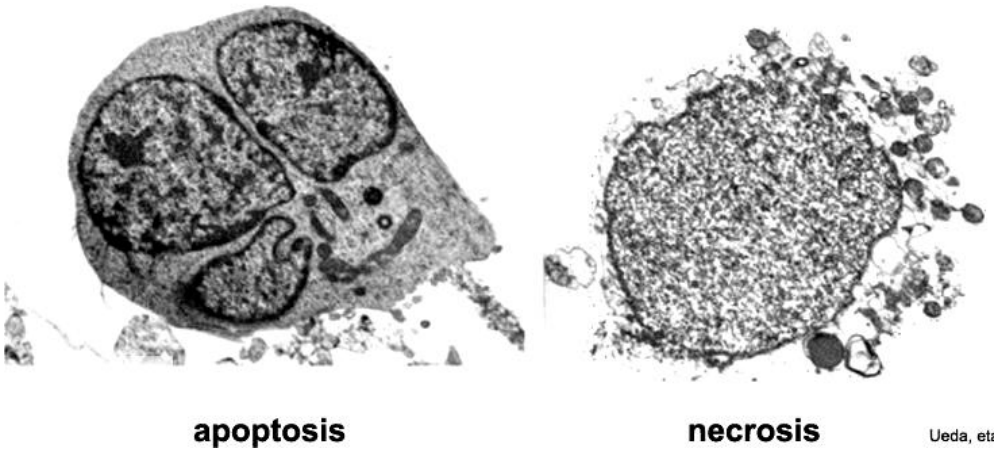

Fig. 12. Morphological changes at necrosis and apoptosis

APOPTOSIS

Apoptosis is a genetically directed process of cell self-destruction that is marked by the fragmentation of nuclear DNA, is activated either by the presence of a stimulus or removal of a suppressing agent or stimulus, and is a normal physiological process eliminating DNA-damaged, superfluous, or unwanted cells — called also programmed cell death.

Mechanisms of Apoptosis

Apoptosis is the endpoint of an energy-dependent cascade of molecular events, initiated by certain stimuli, and consisting of 4 separable but overlapping components: 1) signaling pathways that initiate apoptosis; 2) control and integration processes, in which intracellular positive and negative regulatory molecules inhibit, stimulate, or forestall apoptosis and thus determine the outcome; 3) a common execution phase including realization of the death program; 4) removal of dead cells by phagocytosis.

Apoptosis is involved in many processes, some physiological, some pathological: programmed cell death during embryogenesis; hormone-dependent involution of organs in the adult (e. g., thymus); cell deletion in proliferating cell populations; cell death in tumors; cell injury in some viral diseases (e. g., hepatitis).

Morphologic Features of Apoptosis

Morphological changes in apoptosis are the next: *1) cell shrinkage with increased cytoplasmic density; 2) chromatin condensation; 3) formation of cytoplasmic blebs and apoptotic bodies; 4) phagocytosis of apoptotic cells by adjacent healthy cells* (fig. 13).

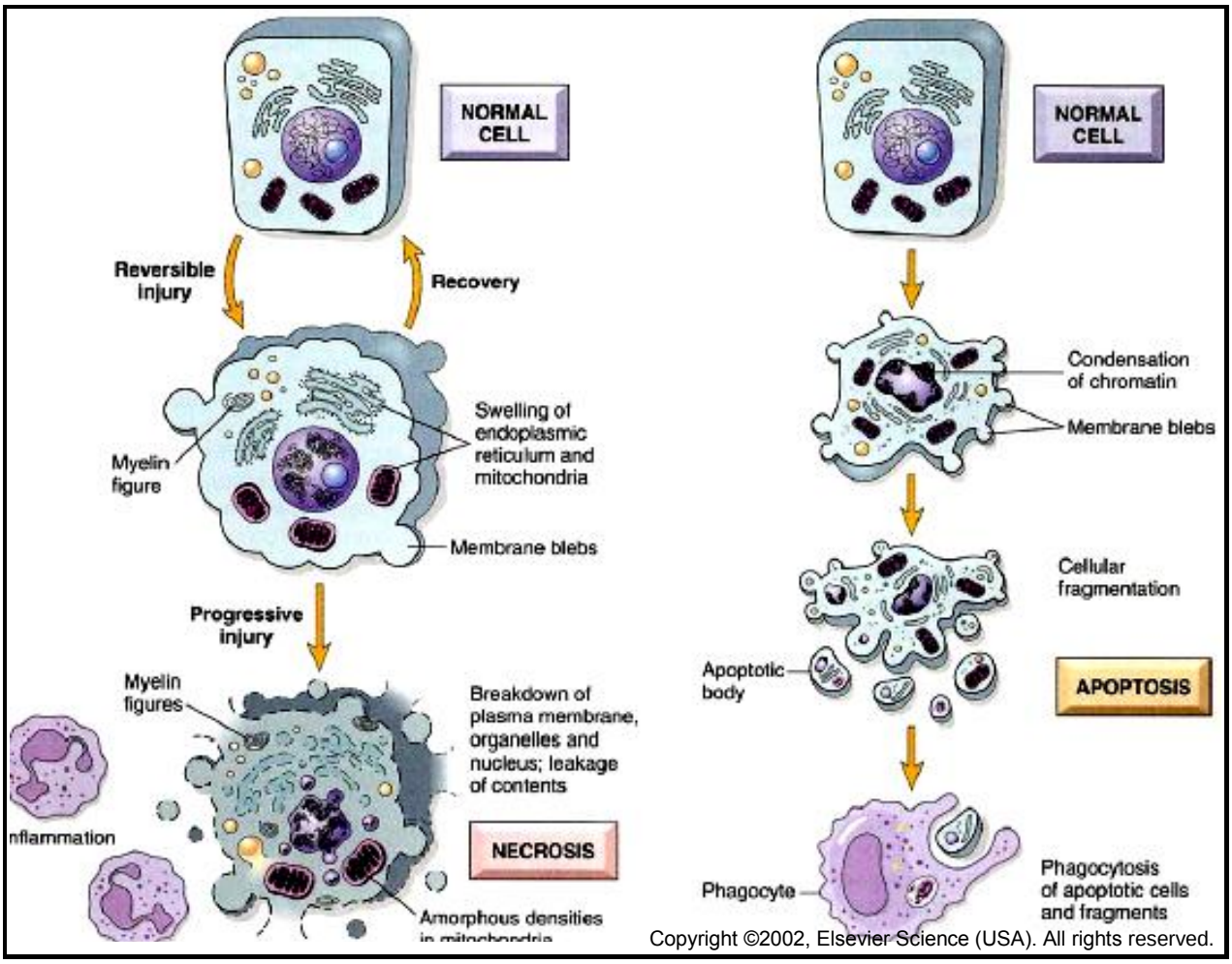

Fig. 13. Diagram illustrating the morphological stages of necrosis and apoptosis

The comparative characteristics of necrosis and apoptosis are in table 1.

Table 1

Differences between necrosis and apoptosis

Necrosis	Apoptosis
is the result of casual degradation	in a series of physiologic events it is not casual, but programmed
is accompanied by destruction of membranes	is not accompanied by destruction; the cell shrinks
is executed by lysosomal hydrolases	is executed by cytosolic caspases
is accompanied by release of inflammation-inducing intracellular constituents	is not accompanied by a release of inflammation-inducing substances
causes damage to adjacent cells by intracellular hydrolases and indirectly by attracting neutrophils	does not cause inflammation: cells disappear without trace

SPECIFIC AND NONSPECIFIC CHANGES AT CELL INJURY

Any damaging factor can cause a complex of *specific and nonspecific changes* in the cell.

Specific changes are typical *for only one certain pathogenic agent*. Thus, the action of mechanical factors on any cell accompanied by a violation of the integrity of it membrane. Synthesis in the organism of anti-RBC antibodies leads to immune hemolysis of erythrocytes.

At the same time, damage is always accompanied by a complex of **nonspecific changes** in cells. They are observed in various cell types under the action of various agents. For example, the development of acidosis, excessive activation of free radical and peroxide reactions, denaturation of protein molecules, increase in the permeability of a cell membrane, increase of the sorption properties of cells at injury.

Revealing of the complex of specific and nonspecific changes in the cells of organs and tissues allows to judge about the nature and force of pathogenic factors action, about of damage degree, as well as the efficiency of the applied for the treatment medicines.

CELL ADAPTATION TO INJURY

MECHANISMS OF CELL ADAPTATION TO INJURY

Effect on the cells of pathogenic factors and the development of injury is associated with activation of reactions aimed at the eliminating or reducing the amount of damage and its consequences. The complex of these reactions provides the adaptation of the cell to the changed conditions of its functioning. The main adaptive mechanisms include *the reaction of compensation, rehabilitation and replacement of lost or damaged structures and functions, protecting of cells from the action of pathogenic agents, and regulatory reduction of their functional activity*.

The whole complex of these reactions can be divided into two groups: *the intracellular and extracellular* (intercellular mechanisms). The main intracellular mechanisms of compensation in case of damage are the following:

1. *Compensation of cell energy supply disturbance.* One way to compensate disturbance of energy metabolism due to mitochondrial damage is *intensification of glycolysis*. Some contribution to the compensation of energy supply disturbance of intracellular processes at damage brings *the activation of transport and utilization enzymes of ATP energy* (adenine nucleotide transferase, creatine phosphokinase, ATP-ase), and *decreased functional activity of the cells*. The latter reduces the consumption of ATP.

2. *Protection of membranes and enzymes of cells*. One of the mechanisms for the protection of membranes and enzymes of cells is to *limit free radical reactions and lipid peroxidation by enzymes of antioxidant defenses* (superoxide dismutase, catalase, glutathione peroxidase). Another mechanism to protect

the membranes and enzymes from the damaging effect, in particular, lysosomal enzymes can be *activation of buffer systems of cells*. This causes a decrease in the intracellular acidosis and, as a result, excessive hydrolytic activity of lysosomal enzymes. Important role in the protection of membranes and enzymes of cells from damage belongs to microsomal enzymes, providing physical and chemical transformation of pathogenic agents by their oxidation, reduction, demethylation, etc.

3. *Compensation of ions and fluid imbalance.* Compensation of ion imbalance in the cell can be achieved by *activating the mechanisms of ion "pumps" energy supply*, and *the protection of membranes and enzymes involved in transport of ions*. A definite role in reducing a degree of ionic imbalance belongs to the effect of buffer systems. *Activation of intracellular buffer systems* (carbonate, phosphate, protein) can help to restore optimum ratio of K^+, Na^+ and Ca^{2+}. Reducing the imbalance of ions, in turn, may result in normalization of the intracellular fluid.

4. *Elimination of cells genetic program disturbances.* Damages in DNA can be detected and eliminated by enzymes of *DNA repair synthesis*. These enzymes 1) detect and remove the part of damaged DNA (*endonuclease and restriction enzyme*); 2) synthesize normal nucleic acid fragment to replace the remote (*DNA polymerase*) and 3) insert this newly synthesized fragment instead of deleted (*ligase*). In addition to these complex enzyme systems of DNA reparation there are enzymes that remove the «small» biochemical changes in cell genome. These include *demethylase* that remove methyl groups and *ligases* which eliminate gaps in the DNA chains appearing under the effect of ionizing radiation and free radicals action.

5. *Compensation of intracellular metabolic disorders caused by disturbances of cell functions regulation.* These include *changes of hormone receptors number*, *content of neurotransmitters and other physiologically active substances on the surface of cells and variation of receptor sensitivity to these substances*. The number of receptors may vary due to the fact that their molecules are able to dive into the membrane or the cytoplasm of the cell and raise to the surface. The number and sensitivity of receptors, which receive regulatory incentives, largely determines the character and extent of response to them.

Excess or deficiency of hormones and neurotransmitters or their effects can be compensated at the level of second messengers - cyclic nucleotides. It is known that the ratio of cAMP and cGMP changes not only by the action of extracellular regulatory incentives, but by *intracellular factors*, such as *phosphodiesterase and calcium ions.*

6. *Decrease in the functional activity of cells.* As a result of decrease of functional activity of the cells the reduction of the energy and substrates consumption necessary to implement the functions of plastic processes is achieved. Consequently, the degree and extent of cells damage under the influence of pathogenic factor is significantly reduced. After termination of pathogenic factor action the recovery of cells structures and their functions becomes more intense and full. The major mechanisms for the temporary reduction of cell

function include: 1) reduction of efferent impulses from the nerve centers; 2) reducing of number or sensitivity of cell surface receptors; 3) intracellular regulatory suppression of metabolic reactions.

Cells adaptation to damage occurs not only at metabolic or functional levels. Prolonged or repeated serious damage causes significant structural changes in the cell that have adaptive value. They are achieved by *regeneration, hypertrophy, hyperplasia, malnutrition.*

7. *Regeneration* (regeneratio - revival, restoration) means revitalization of cells and/or some of its structural elements to replace lost, damaged or have completed their life cycle. There are so-called cellular and intracellular forms of regeneration. The first one is characterized by proliferation of cells by means of mitosis or amitosis. Intracellular regeneration is manifested in restoration of organelles — mitochondria, nucleus, endoplasmic reticulum and others instead of damaged or dead.

8. *Hypertrophy* (hyper — excessive, augmentation; trophe — feed) is an increase of the volume and amount of the structural elements, in particular, cells (fig. 14, 15). Hypertrophy of intact cell organelles compensates impaired functions of damaged cells.

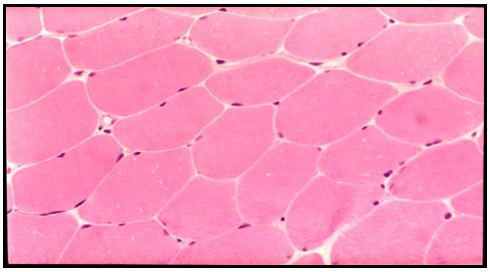

Fig.14. Normal muscle

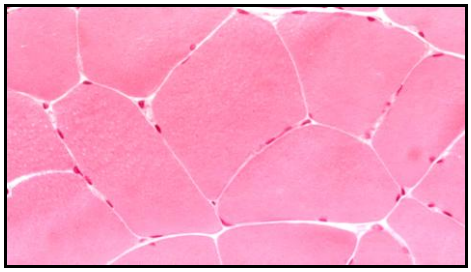

Fig.15. Physiologic hypertrophy of skeletal muscle from exercise

9. *Hyperplasia* (hyper — excessive; plaseo — form) is characterized by an increase in the number of structural elements, in particular, the organelles in the cell. Often in the same cell, there are signs of hyperplasia and hypertrophy. Both processes provide not only compensation of structural defect, but also the possibility to increase cell function.

CONCLUSION

Any pathological process is accompanied by damage of cells. Despite the variety of pathogenic factors, cells respond similar reactions of alteration. In turn, damage of cells, usually accompanied by the activation of factors of protection, compensation, refunds and adaptation aimed at stopping or limiting the damaging factor, and elimination of the consequences of its impact.

Knowledge of these mechanisms is the basis for development of principles and methods for identifying of pathological processes, predicting its course, as well as ways of pathogenetic therapy and prevention of damage of cells.

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