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Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Повреждение клетки**

Theme: **Cell damage**

Время 3 ак. часа

Actuality of the theme. Knowledge of the structural and functional reactions of cells and tissues to injurious agents, including genetic defects, is the key for the understanding of disease processes. Currently diseases are defined and interpreted in molecular terms and not just in general descriptions of altered structure. Altered cellular and tissue biology can be the result of adaptation, injury, neoplasia, aging, or death. Adaptation occurs in response to both normal, or physiologic, conditions and adverse, or pathologic, conditions. For example, the uterus adapts to pregnancy – a normal physiologic state – by enlarging. Enlargement occurs because of an increase in the size and number of uterine cells. In an adverse condition, such as high blood pressure, myocardial cells are stimulated to enlarge by the increased work of pumping. Like most of the body's adaptive mechanisms, however, cellular adaptations to adverse conditions are usually only temporarily successful. Severe or long-term stressors overwhelm adaptive processes, and cellular injury or death ensues.

Learning goals of the lesson: to study etiology, pathogenesis, functional manifestations of cell damage, mechanisms of protection and adaptation of cells in damaging effects.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know main causes, mechanisms, main manifestations of cell damage in general, as well as individual subcellular structures and cell components.
2. To know mechanisms of protection and adaptation of cells in damaging effects.
3. To know main differences between necrosis and apoptosis.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Structure of cell (histology, cytology, embryology disciplines).
2. Genetic apparatus of cell (medical biology and genetics discipline).
3. Peroxide oxidation of lipids (biochemistry discipline).

Control questions of the lesson:

1. Cell damage: definition, causes, types.
2. General mechanisms and manifestations of cell damage.
3. Disturbances in structure and functions of single cellular organelles.
4. Manifestations of cell damage: cellular dystrophy and dysplasia.
5. Types of cell death: necrosis and apoptosis.
6. Mechanisms of cell compensation for damage.
7. General reactions of body to damage. Acute phase response.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Types of damage:

1. partial
 2. complete
-
1. reversible
 2. irreversible (death).
-
- I. physical (the extreme temperature, mechanical trauma, ionizing radiation, electric shock)
 - II. chemical (toxins, drugs, environmental factors)
 - III. biological (infection agents, immune reactions, genetic defects, the nutrition disbalance)

By origin:

1. exogenous and endogenous
2. infectious and non-infectious

Reversible cellular injury is characterized with the ability of the cell to return to its normal state after withdrawal of an acute stress. Reversible injury is manifested with hydropic **swelling of the cell** (cellular edema), **dilation of endoplasmic reticulum**, and detachment of ribosomes from the granular endoplasmic reticulum, dissociation of polysomes into monosomes, **mitochondria swelling and enlargement**, blebs of plasma membrane, nucleolar alterations with disaggregation of granular and fibrillar elements.

Irreversible cellular injury or cellular death is necrosis and apoptosis.

The cell pathology is an integrative concept including pathology of cellular ultra structures and components. Mechanisms of structural functional vital ability impairments of the intracellular interactions, and cooperation of cells in the general pathological processes.

MECHANISMS OF CELL INJURY

I. Derangements in the energy supply and utilization.

- 1) Decrease in the rate or efficiency of ATP production.
- 2) Decreased transport of ATP to the sites of utilization.
- 3) Impaired ATP utilization in metabolic processes.

II. Loss of the integrity of cell membranes.

- 1) Increase in free radical production and lipid peroxidation.
- 2) Activation of intracellular hydrolases (lysosomal, membrane-bound, or cytosolic).
- 3) Defects in membrane permeability.
- 4) Detergent effect of amphiphilic compounds.
- 5) Impaired resynthesis of the damaged membrane constituents.
- 6) Abnormal conformation of the membrane-bound enzymes or lipoproteins.
- 7) Overextension and rupture of membranes in the swelled cells or cellular organelles.

III. Ionic and water dysbalance.

- 1) Dysbalance of the particular ions in the cytoplasm.
- 2) Changes in the transmembrane distribution of ions.
- 3) Hyperhydration of a cell.
- 4) Dehydration of a cell.

IV. Changes in the genome or its abnormal realization.

- A. Changes in the genome.
 - 1) Changes in the gene structure.
 - 2) Derepression of pathogenic genes.
 - 3) Repression of the "vital" genes.

4) Insertion of the alien DNA fragment with pathologic information.

B. Disorders of the gene realization program.

1) Abnormalities of mitosis.

a) *damage to chromosomes*

b) *damage to the structures, participating in cell division*

c) *abnormal division*

2) Abnormalities of meiosis.

V. Disorders of intracellular regulatory mechanisms.

1) Abnormal reception of a signal.

2) Disorders of the secondary messenger production.

3) Impaired phosphorylation of protein kinases.

Lysosome Lesions

The lysosome morphological types:

1. Primary

2. Secondary

3. Residual bodies

Primary lysosomes are not surrounded with a one-plan metric lipoprotein membrane, they are filled with the small grain contents. These lysosomes have not participate in the lysis processes yet.

Secondary lysosomes are submitted by phagolysosomes and cytolysosomes – phagolysosomes (digestive vacuoles) are formed at merge of the primary lysosomes with pinocytic visicles and phagosomes. Cytolysosomes (the autophagic vacuoles) are formed at merge of primary lysosomes with the cell destroyed (dead) structures.

Residual bodies are lysosomes with the non-digested wastes of digestive or autophagic vacuoles. The contents of the residual bodies presented by lipopigments

Lysosomes participate in utilizing of the phagocytic material by means of hetero- and autophagy.

Heterophagy is the material capture from outside with the help of endocytosis (absorption of the particles – phagocytosis, absorption of small soluble molecules – pinocytosis).

Heterophagy is characteristics of neutrophils and macophages. There is an absorption of bacteria by neutrophils in the process of heterophagocytosis and removal of the apoptotic bodies by macophages.

Autophagy is the process of removal of the damaged cell destroyed organelles. In this case in-cellular organelles are separated from cytoplasm into autophagic vacuoles, and than merge with primary lisosomes, forming autophagolysosome. The phenomenon of autophagy is expressed in autophagic cells as a result of the insufficient nutrition or the hormonal involution.

Lipopigments.

Cytoplasmic granules and inclusions containing proteins and hard soluble lipids are referred to lipopigments. Lipopigments are presented by lipofuscin and ceroid.

Lipofuscin is a glycoprotein, which structure includes fats (phospholipids, cholesterol, neutral fats, products fat acid oxidation), amino acids, enzymes, carotinoids and flavin compounds. The ultra structural picture is presented by electron-dense granules surrounded by a double membrane containing the myelin-like structures. Lipofuscin is formed by autophagy in parenchymous and measure cells.

There are two stages of the lipofuscin development:

The early unmatre lipofuscin is presented by the perinuclear located light yellow color. The activity of lysosomal enzymes is low. The early lipofuscin give positive iron reactions with copper, fat, SHICK-reaction. It contains redox enzymes. Immature lipofuscin locates close to or inside mitochondria.

Late mature lipofuscin consisits of brown granules, it is located on the cell periphery. The high activity of lysosome enzymes is revealed in the mature pigment, the iron and fat levels are decreased.

The formation and accumulation of lipofuscin in elderly age is a physiological process, therefore lipofuscin is named as the pigment of aging.

Now lipofuscin is referred to as cellular organoid containing granules – cytosomes or carotinosomes. The lipofuscin function is an oxygen deposit. In condition of hypoxia lipofuscin provides oxidation process, and increase in the lipofuscin quantity is an adaptive process.

Processes resulting the lipofuscin accumulation:

1. Increase of the cell functional loading (hypertrophy of myocardium).
2. Poisoning
3. Medical drug affect
4. Lack of vitamin E
5. Cachexy
6. Hypoxia
7. Protein starvation

Selective lipofuscinoses:

Dabin-Jonson's syndrome is a selective lipofuscinosis of hepatocytes.

Ceroid is a neuron lipofuscinosis. Ceroid forms in macrophages by heterophagy. Unlike lipofuscin lipids prevail in ceroid. Ceroid more often forms in case of necrosis.

We refer the following **disease group** to the **lysosome hereditary pathology** associated with the lysosome function frustration

1. diseases associated with cell membrane interaction impairment
2. Lysosomal enzymopathy

TO the first group of lysosome hereditary diseases we refer **Chediak-Higashi syndrome**. In this case there is a **defect of the microtubule polymerization**, that causes a **slowed down merge of lysosomes with phagosomes** in leukocytes and results in the occurrence of large abnormal lysosomes.

The second group of the lysosome hereditary diseases associated with their function impairment, it is presented by lysosomal enzymopathias. These diseases result from the primary genic mutation and they are manifested by the complete lack of the blockage enzyme synthesis, or the decrease in its biocatalytic metabolic production as resulting from the enzyme defects, that is why they were included in the group of the accumulation diseases (thesauristosis).

Lysosomal enzymopathias are presented by various diseases:

1. Glycogenoses: Pompe's disease (type II of glycogenosis) – defect of the sour maltase (lysosomal alpha-1,4-glucosidase).
2. YM2-gangliosidosis:
 - Tay-Sachs disease is the A-hexominidase absence (infantil type of cerebral sphingolipidosis, GM2 gangliosidosis)
 - Sandchor's disease is the absence of A and B hexominidase
 - Uvenile gangliosidosis is an incomplete block of A-hexominidase
3. Hepatoses:
 - Dabin-Jonson disease (constitutional hyperbilirubiemia).

Chediak-Higashi syndrome. Type of inheritance is autosome recessive It is referred to the hereditary impairments of the phagocytic cell functions. It can be found out in the first months and years of life with the clinical features appearance and also incase of the non clear fever relapses, frequent infections of the respiratory ways, and gastro-intestinal tract, skin.

Clinical manifestations are various: infection relapses (acute respiratory diseases, bronchitis, pneumonia, otitis, sinusitis, abscesses). The common infectious complications are caused by microbes (staphylococcus, Gram's negative, less often causes are mycotic infections).

Approximately in 1/3 of the patients hemorrhages are observed, increase in the body temperature in the absence of infection. Partial hair, skin, the eye coloration is marked in patients. The light transparent skin with thin dry light hair of ashy, silvery or leaden color is observed. The iris is light, there is a pigmentation of retina, nistagm is marked. It is characterized by the universal hyperhydrosis and lightfritening.

If the disease proceeds long, the CNS impairments: paresis, the sensitivity impairment, hypo- and areflexia, the cerebellum impairment are noted.

In the majority of children up to 10 the acute torpid phase appears: incase in temperature, adenopathy, hepatosplenomegalia, the hemorrhagic syndrome, that are associated with thrombocytopenia and the neutrophil function impairment. The majority of children in this phase die of hemorrhagic syndrome or sepsis. Other wise this stage is named a stage of acceleration. It can come in any age, from newborn up to the pubertal period.

Morphologically it is characterized by lymphohistiocytic infiltrations of hematophagocytosis. It is necessary to note, that in this syndrome cerebrospinal liquid is primarily investigated erythrophagia is also found out.

Presence of peroxidase positive granules in neutrophils, eosinophils, monocytes of the peripheral blood and bone marrow, in cells – predecessors of granulocytes containing degenerative vacuoles is a characteristic of the syndrome. Granules occur as a result of the primary and secondary lysosome merge. Despite high peroxidase level in them the merge impairment with phagosomes interferes phagocytosis termination, as huge lysosomes are not capable to pass hydrolytical enzymes into phagosomes of neutrophils, containing nonintegrated bacteria. It contributes to bacterial infection development. In this disease phagocytic activity of neutrophils and melanocytes is normal, and chemotaxis and digestive ability are decreased. It can result in neutrophils turning a “refuge” for bacteria from antibiotics and other phagocytic cells.

The reason is unknown. Pathogenesis of the syndrome is supposed to be connected with the presence of cell membrane abnormality. There for there is an uncontrolled erge of lysosomes, impairments of neutrophils, change of thrombocytes function, decrease in natural killer activity of lymphocytes. The majority of clinical manifestations are explained by an abnormal distribution of lysosomal enzymes.

The cell damage is characterized by the change of structural chemical properties, metabolism, structure and function of the cell, which lead to its impairment.

The cell is an open automatically self-operating system. The structure of a normal cell is directed to a certain metabolism realization, differentiation and specialization. Various pathogenic agents affecting a cell can cause the following processes: adaptation, damage, destruction.

Mitochondria Lesions

Signs of impaired mitochondrial function:

1. Decrease in oxygen consumption.
2. Increase in permeability of internal mitochondrial membrane.
3. Decreased ability to accumulate calcium
4. Swelling of mitochondria.

Changes in the structure, size, shape and number of mitochondria

Changes in the structure of mitochondria are manifested in their condensation and swelling, as well as in the appearance of mitochondrial inclusions. Condensation and swelling indicate a functional strain of the cell, but more often about increasing oxygen starvation. Mitochondrial inclusions are attributable to dysfunctional mitochondrial membrane synthesis and/or accumulation of metabolites. The following variants occur: Matrix inclusions are usually amorphous and lie in the mitochondrial matrix. They occur most often in chronic ischemic disorders.

Size of mitochondria varies widely- from **giant** to sharply **reduced forms**. Giant mitochondria, formed due to hypertrophy or fusion, are found only in pathology (for example, in hepatocytes with alcoholism).

Changes in the number of mitochondria:

1. **increase in number** (hyperplasia): reflects the increase in the flow of oxidation phosphorylation in them (with hypertrophy, proliferation and transformation of cells when activating the specialized function of the cell;

2. **decrease in number**: typical for regressive processes (cell aging, cell atrophy).

Changing the mitochondrial crista can touch their structure, size, shape and number.

1. Structure changes:

- lamellar crista (with ↑ mitochondria activity);
- deformation of the crista (with ↓ activity);
- aggregation of crista (with ↓ activity)
- crista inclusions consist of deposits of enzyme-protein complexes and lie in the mitochondrial cristae between the crista membranes. They are primarily typical of mitochondrial myopathy (muscle disorders involving loss of strength).

2. **Changes in the shape of crista** are observed with an increase or decrease in the functional activity of the mitochondria.
3. **Changes in the size of crista**, as a rule, correspond to changes in the size of the mitochondria themselves: **giant** cristae in giant mitochondria, **reduction** of cristae during reduction of mitochondria.
4. **Changes in the number of crista** reflect the activity of mitochondria: an increase in the number of mitochondria is evidence of the growing functional needs of the cell; reduction is evidence of a reduction in these needs.

Structural change in mitochondrial DNA

Physiology: The mitochondria contain their own DNA (mitochondrial DNA) whose base coding differs from that of nuclear DNA. It is sufficient for coding several hydrophobic proteins of the mitochondrial cristae and subunits of the cytochrome oxidase.

Mitochondrial DNA Mutations

Congenital Forms

Pathogenesis: Single-point mutations of mitochondrial DNA with maternal hereditary transmission.

Examples:

- Hereditary types of neuromyopathy.
- Mitochondrial diabetes mellitus.
- Neurologic symptoms such as ataxia and hearing disorders.

Acquired Forms

Occurrence: myocardial ischemia.

Pathogenesis: Following ischemia, toxic oxygen metabolites accumulate in the tissue during the reperfusion phase. This causes damage to mitochondrial DNA.

Nucleus pathology

The following conditions we refer to the nucleus pathology:

1. **Pathology of nucleus** (change of the nucleus size and structure, form, the nucleolus number and the nuclear inclusion appearance)
2. **Pathology of the nuclear membrane**
3. **Pathology of mitosis**

Changes of the nucleus structure:

Polyploidy is an **increase in number of chromosomes** up to the value, **multiple to** their normal **haploid set** (23 chromosomes). Thus, in triploidy the general number of chromosomes equals 69, in tetraploidy – 92 etc. In polyploidy the reproduction process does not achieve the typical endocytosis. Polyploidy develops in DNA reduplication and the spiralization of chromosome absence.

The polyploidy cells are revealed:

1. In aging organism
2. In case of the reparative regeneration
3. In normally functioning human organs, tissues and cells: in liver, kidneys, heart muscle, epidermidis, megakaryocytes, huge cells of trophoblast.
4. In case of the growth.

The polyploidy revealing methods:

1. by nucleus size
2. by the increase in quantity of DNA in the inter-phase nucleus
3. by increase in the number of chromosomes in the mitotic cell

Aneuploidy is an incomplete set of chromosomes.

In case of **aneuploidy there is an increase or decrease in the general number of chromosomes** in organism genotype in relation to its normal value. Thus changes do not grasp every chromosome in the normal haploid set. Aneuploidy is associated with the chromosomal mutation. In Aneuploidy the number of autosomes and the chromosome quantity can vary. Malignant tumors are manifestations of aneuploidy.

Changing the shape of the nucleus

Changes in the shape of the nucleus are observed with tumor growth, inflammation, increase in the synthetic activity of the nucleus. The following changes occur.

1. Deformation of nuclei by cytoplasmic inclusions

2. Bulge of the nucleus into the cytoplasm

3. The polymorphism of nuclei.

Number of nucleus

1. **Nuclear-free** - occurs as a variant of norm (erythrocytes, platelets), as a pathology (fragments of tumor cells, when cells die).

2. **Multinucleus** - increase in the number of nuclei, possible with the fusion of cells (giant multinuclear cells of foreign bodies and Pirogov-Langhans, formed during the fusion of epithelioid cells), in the pathology of mitosis (fission of the nucleus without subsequent division of the cytoplasm after irradiation or administration of cytostatics, in malignant growth).

3. **"Satellites of the nucleus"** (synonyms: karyomere, small nuclei) are nucleus-like formations with an intrinsic membrane located near an unchanged nucleus in the cytoplasm (kariomeres in malignant tumor cells in the presence of a large number of pathological mitoses).

Nuclear inclusions

1. **Cytoplasmic** - bounded by envelope parts of the cytoplasm and located in the nucleus (in violation of mitotic division).

2. **True** – inclusions located within the nucleus and corresponding to substances found in the cytoplasm (inclusions of glycogen in the liver nuclei in diabetes mellitus - "nuclear glycogen", "holey, empty, nuclei").

3. **Viral-mediated** - (bodies of nuclear inclusions). There are can be:

a) inclusion in the karyoplasm of the crystal lattice of the virus

b) inclusion of protein particles during intranuclear multiplication of the virus

c) "reactive inclusions" in response to cytoplasmic damage by virus.

Cytoplasmic membrane lesions

Physiology: Together with the inner membrane system, the outer cell membrane regulates the exchange of substances between the various compartments of the cell. It separates the individual cells from adjacent cells and contains receptors that enable it to detect signal substances (ligands). The messages borne by these ligands are transmitted via an intracellular communication system to the nucleus, the executing organelle. The cytoskeleton, to which the cytomembrane is attached, aids in this process.

Types of damage to the cytoplasmic membrane:

1. **Damage to the shape of membranes**. Morphologically manifested in the form of deformation or atrophy of specialized structures, the appearance of gaps or ruptures.

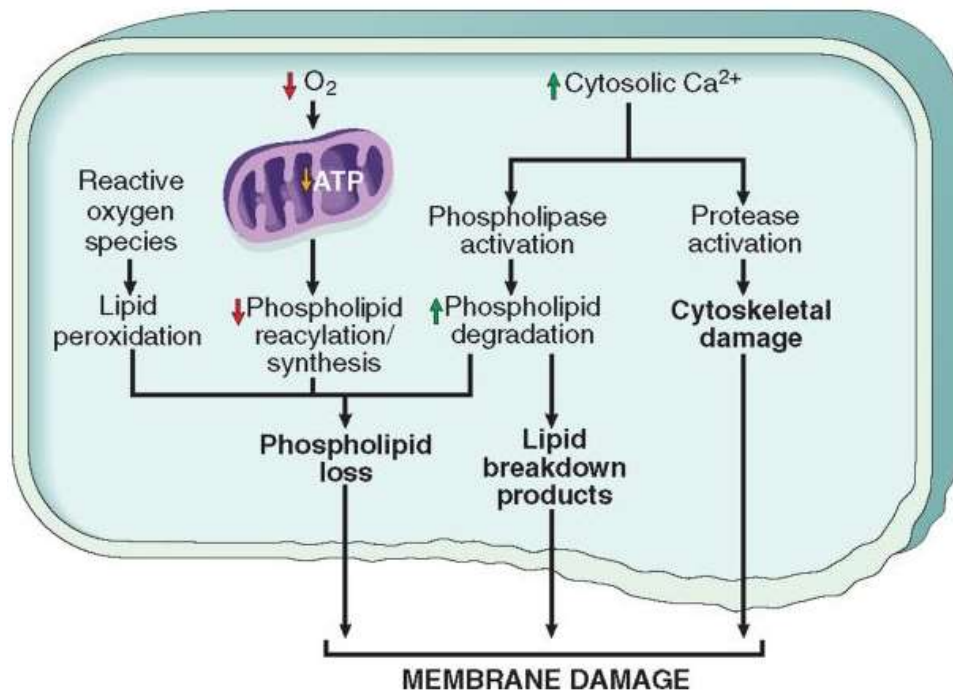
2. **Changes in membrane permeability**. Heavy metals dramatically increase the permeability of the membrane for ions, which leads to rapid swelling of the cells, the disintegration of their cytoskeleton. The increase in the volume of the cell is accompanied by the appearance of gaps and ruptures in the membrane. If the gaps do not increase, the gaps close and disappear. Thickening of the cell membrane can be associated with a decrease in the amount of Ca^{2+} in the extracellular fluid, while the permeability of the membrane changes for Na^{+} and K^{+} , and fluid accumulates in the cell.

3. **Changes in communication of cells and their "recognition"**. Surface antigens can be changed. Changes in cellular "communication" and "recognition" are found in inflammation, regeneration, tumor growth. In tumor cells, the disappearance of the typical arrangement of oligosaccharides in the cell membrane (lectin1 bonding sites), present in normal cells in the form of blood-group antigens and/or adhesion molecules, is indicative of their loss of cell specificity due to the change in their genetic makeup. This disrupts cell-to-cell and cell-to-matrix communication, with the result that tumor cells continue to divide despite contact with adjacent cells due to the loss of contact inhibition (Lectins are glycoproteins, usually from plant seeds or invertebrates, that bond specifically to certain oligosaccharides).

4. **Excessive increase in normal structures**. It manifests itself in the form of an increase in the number, extent and area of membrane structures.

Causes of damage to the cytoplasmic membrane

1. **Formation of free radicals** containing activated oxygen, followed by a reaction between them and lipids of the cell membrane (lipid peroxidation).
2. **Activation of the complement system**. Complement is a system of plasma proteins (C1-C9), which exist in an inactive form and constitute approximately 10% of the blood globulins. When activated, its end products can enzymatically damage to the cytoplasmic membrane.
3. **Lysis with enzymes**. For example, pancreatic lipases (in excess are secreted in acute pancreatitis) and enzymes produced by *Clostridium perfringens* (one of the causative agents of gas gangrene) cause extensive necrosis of cytoplasm.
4. **Lysis by viruses** is carried out both by direct insertion of cytopathic viruses into the cell membrane, and indirectly through the immune response to viral antigens located on the surface of infected cells.
5. **Effects of physical and chemical factors** (high and low temperature, chemicals, etc.)



Reactive oxygen species and free radicals

Reactive oxygen species is a collective term that includes all reactive forms of oxygen, including both radical and non radical species that participate in the initiation and/or propagation of chain reaction. Free radicals represent a class of highly reactive intermediate chemical entities whose reactivity is derived from the presence of unpaired electron in their structure, which are capable of independent existence for very brief interval of time.

Free radicals and other reactive species are derived either from normal essential metabolic processes or from external sources, such as exposure to x-rays, ozone, cigarette smoking, air pollutants, industrial chemicals etc.

Sources of free radical

- Internal sources
- External source
- Physiological Factors

Internal sources: These can be enzymatic reactions, which serve as a source of free radicals. These include those reactions involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis and in the cytochrome P450 system. Some internal sources of generation of free radicals are mitochondria, xanthine oxidase, phagocytes, reactions involving iron and other transition metals, peroxisomes, Arachidonate pathways, exercise, ischaemia / reperfusion, inflammation.

External sources:

These include non-enzymatic reactions of the oxygen with organic compounds. Free radicals also arise in reactions, which are initiated by ionizing radiations. Some external sources of free radicals are

cigarette smoke, environmental pollutant, radiations, ultraviolet light, ozone, certain drugs, pesticides, anesthetics and industrial solvents.

Physiological Factors

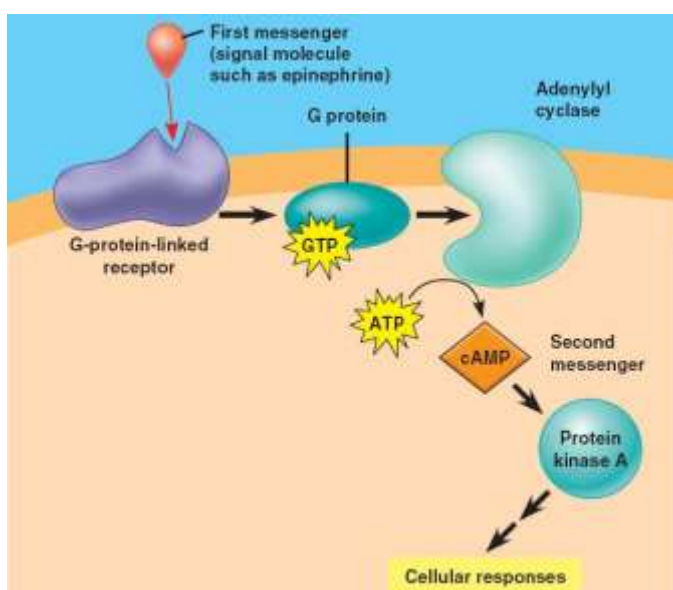
Mental status like stress, emotion etc. and disease conditions are also responsible for the formation of free radicals.

Types of free radicals

- Hydroperoxyl radical
- Superoxide radical
- Hydrogen peroxide
- Triplet oxygen
- Active oxygen

Receptor Lesions

The cell's various signal substances (ligands) are detected by specific receptor proteins. The receptors on the surface of the cell consist of extracellular, intramembranous, and intracellular components. The extracellular receptor component has the task of detecting signals. Signal transmission often begins with the bonding of the ligand-receptor complex to G-proteins.



Receptor dysfunction: Is due to one of the following processes:

1. an atypical hormone occupies the receptor but fails to stimulate the effector.
2. an antibody that acts like a hormone occupies the receptor and stimulates the effector.
3. an excess of hormone A can suppress or enhance the receptor bond for hormone B.
4. the number of receptors is no longer kept inversely proportional to the circulating quantity of hormone.
5. the link between ligand bonding and activation of the effector fails.
6. the ligand (hormone or growth factor) is formed by the same cell that expresses the respective receptors.
7. a receptor mutation is present.

Damage to the endoplasmic reticulum

Hyperplasia of EPR is accompanied by the formation of **concentric** structures.

Atrophy of EPR is accompanied by a decrease in the protein-synthetic function of the cell (in fasting, liver disease, aging).

Peroxisomes Lesions

Peroxisomes are the auxiliary system of oxidation in cell. Changes of micro-bodies reflect impairments of the oxidase-catalase activity of cell. The following changes of micro-bodies can be observed in case of the cell damage.

1. Primary – “peroxisome” diseases
2. Secondary – change of the number and structural components of peroxisome.

Peroxisome diseases.

1. Acatalasia. It is characterized by an acute decrease in the catalase activity in the liver and other organs. Clinically it is presented by the oral cavity mucosal ulceration.

2. Cerebro-hepato-renal syndrome (Zellweger's syndrome) is characterized by the absence of peroxisomes in hepatocytes. The synthesis of bilious acids is broken.

3. The systemic insufficiency of carnitine. It is characterized by the expresses deficiency of carnitine in various organs and tissues. Clinically it is manifested by miopathy, the impairment of the liver and brain functions.

The increase in the number of peroxisomes arises in alcoholic intoxication. The decrease in the number of peroxisomes is observed in hypoxia, radiation influence. Destruction of peroxisome matrix occurs in bandaging of hepatic veins, hepatitis, ischemic necrosis, hyperlipidemia, hypercholesterolemia, in case of the tumor growth.

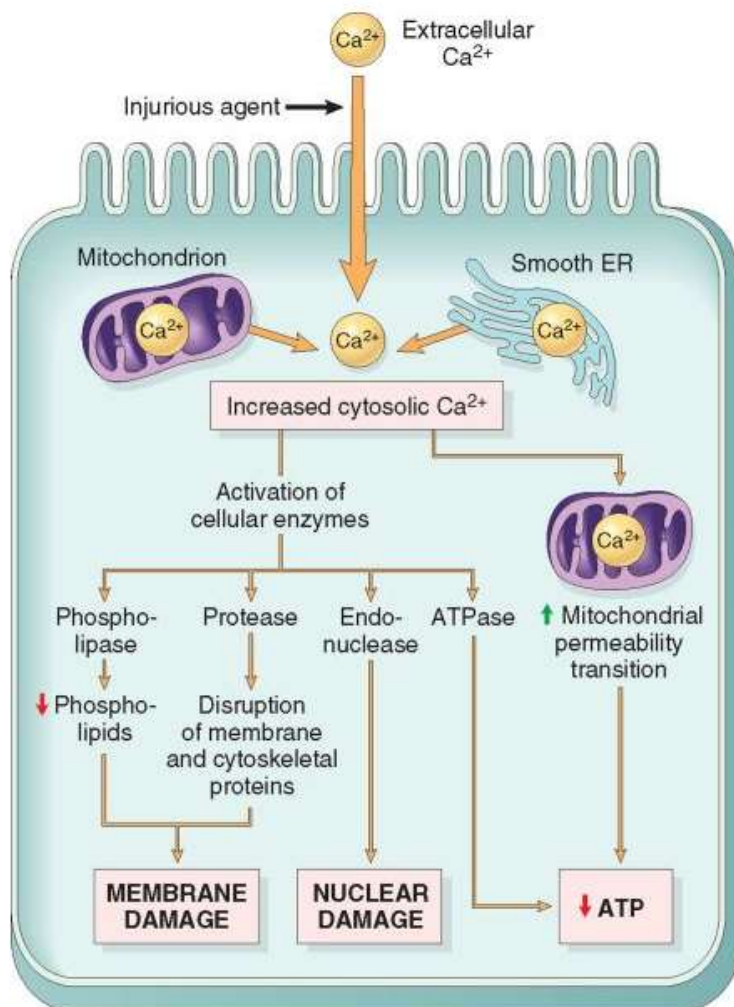
Cytoskeleton Lesions

Physiology of the cytoskeleton:

Microtubules are spiral arrangements of globular proteins (tubulin) that form ultrastructural tubules. These structures aid in transmitting signals, providing structural support, and transporting substances.

Intermediate filaments are present in six different forms:

- Keratin is typically found in epithelial cells and is closely associated with desmosomes. It increases resistance to shear stress.
- Desmin is typically found in muscle cells and is closely associated with the Z bands and intercalated disks in muscle.
- Vimentin is typically found in mesenchymal cells and is closely associated with the cell nucleus, which it holds in place.
- Neurofilaments aid in intracellular fixation and signal transmission.
- Glial filaments aid in intracellular fixation and signal transmission.
- Actin filaments are 6 nm thick and usually lie beneath the cell membrane. They function as a sort of intracellular musculature. They attach to the same membrane molecules as do the fibronectin filaments outside.



Under the action of a variety of altering agents on isolated cells (tissue culture), a distinct change in the shape of their surface is revealed: **cytoplasm protrusions called blebs appear**. This "blebbing" (or bubbling effervescence) of the cell membrane is one of the early and reliable signs of the destruction of the cytoskeleton network. "Effervescence" of the membrane is initiated by substances that disrupt intracellular calcium homeostasis.

Fig. The role of increased cytosolic calcium in cell injury. ER, endoplasmic reticulum.

Mechanisms of Ischemic Cell Injury

The sequence of events following hypoxia or ischemia reflects many of the biochemical alterations in cell injury that have been described above. As the **oxygen tension within the cell decreases**, there is loss of **oxidative phosphorylation** and decreased generation of ATP. The depletion of ATP results in failure of the sodium pump, with loss of potassium, influx of sodium and water, and cell swelling. There is also influx of Ca^{2+} , with its many deleterious effects. There is progressive loss of glycogen and decreased protein synthesis. The functional

consequences may be severe at this stage. For instance, heart muscle ceases to contract within 60 seconds of coronary occlusion. Note, however, that loss of contractility does not mean cell death. If hypoxia continues, worsening ATP depletion causes further deterioration. The cytoskeleton disperses, resulting in the loss of ultrastructural features such as microvilli and the formation of “blebs” at the cell surface. “Myelin figures,” derived from degenerating cellular membranes, may be seen within the cytoplasm (in autophagic vacuoles) or extracellularly. They are thought to result from unmasking of phosphatide groups, promoting the uptake and intercalation of water between the lamellar stacks of membranes. At this time the mitochondria are usually swollen, as a result of loss of volume control in these organelles; the ER remains dilated; and the entire cell is markedly swollen, with increased concentrations of water, sodium, and chloride and a decreased concentration of potassium. If oxygen is restored, all of these disturbances are reversible.

If ischemia persists, irreversible injury and necrosis ensue. Irreversible injury is associated morphologically with severe swelling of mitochondria, extensive damage to plasma membranes (giving rise to myelin figures) and swelling of lysosomes. Large, flocculent, amorphous densities develop in the mitochondrial matrix. In the myocardium, these are indications of irreversible injury and can be seen as early as 30 to 40 minutes after ischemia. Massive influx of calcium into the cell then occurs, particularly if the ischemic zone is reperfused. Death is mainly by necrosis, but apoptosis also contributes; the apoptotic pathway is probably activated by release of pro-apoptotic molecules from leaky mitochondria. The cell's components are progressively degraded, and there is widespread leakage of cellular enzymes into the extracellular space and, conversely, entry of extracellular macromolecules from the interstitial space into the dying cells. Finally, the dead cells may become replaced by large masses composed of phospholipids in the form of myelin figures. These are then either phagocytosed by leukocytes or degraded further into fatty acids. Calcification of such fatty acid residues may occur, with the formation of calcium soaps.

As mentioned before, leakage of intracellular enzymes and other proteins across the abnormally permeable plasma membrane and into the blood provides important clinical indicators of cell death. For example, elevated serum levels of cardiac muscle creatine kinase MB and troponin are early signs of myocardial infarction, and may be seen before the infarct is detectable morphologically.

Mammalian cells have developed protective responses to hypoxic stress. The best-defined of these is induction of a transcription factor called hypoxia-inducible factor-1, which promotes new blood vessel formation, stimulates cell survival pathways, and enhances anaerobic glycolysis. It remains to be seen if understanding of such oxygen-sensing mechanisms will lead to new strategies for preventing or treating ischemic and hypoxic cell injury.

Reperfusion cells injury

Reperfusion injury is characterized by the phenomenon of “NO reflow» (renewed blood flow). It means maintenance of blood supply deficiency after the resumption of coronary perfusion, feeding the ischemic myocardial areas.

Factors affecting the coronary reperfusion injury microcirculation after reperfusion:

- swelling of endothelial cells;
- aggregation of the blood particles and increased blood viscosity;
- the formation of blood clots;
- margination of leukocytes

There are two modern hypotheses of reperfusion mechanisms:

1. «Calcium» hypothesis — an overload of cardiomyocytes with calcium ions results in reperfusion contracture, a decrease in diastolic volume and cardiac output.
2. «Free radical» hypothesis — the toxic effect of oxygen on the myocardium in reoxygenation after ischemia.

MECHANISMS OF CELL ADAPTATION TO INJURY:

I. Compensation for derangements in the energy supply.

- 1) activation of anaerobic ATP resynthesis in the glycolytic process in the cytosol, and aerobic respiration in the intact mitochondria;
- 2) stimulation of the energy transport from the sites of production to the sites of utilization.

II. Protection of the membranes and cellular enzymes.

- 1) activation of the antioxidative systems;
- 2) activation of the buffer systems;
- 3) increased synthesis of the microsomal cytochrome P-450 or other enzymes involved in detoxification;
- 4) increased resynthesis of the damaged molecules of enzymes and components of membranes.

III. Alleviation or removal of water and ionic dysbalance.

- 1) activation of ionic pumps;
- 2) repair of membrane and removal of the "high-conductance channels".

IV. Repair of damage to the cellular genetic program.

- 1) removal of breaks in the DNA strands;
- 2) excision of the altered sites in the DNA molecule;
- 3) restoration of the native DNA fragment in place of the damaged one.

V. Compensation for disturbance of the intracellular regulatory processes.

- 1) changes in the density of the cell receptors;
- 2) "up-" or "down-regulation" of the receptors affinity toward ligand;
- 3) changes in the activity of adenylate cyclase, guanylate cyclases, phospholipase C, protein kinases or other factors involved in signal transduction;

VI. Decrease of the cell's functional activity.

VII. Regeneration.

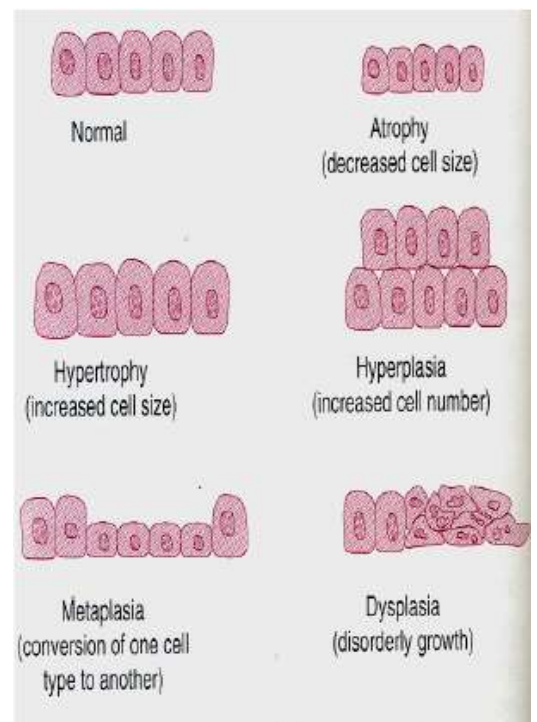
VIII. Hypertrophy.

IX. Hyperplasia.

1. Cellular atrophy decreases the cell substance and results in cell shrinkage. The size of all the structural components of the cell usually decreases as the cell atrophies. Causes of atrophy include disuse, denervation, lack of endocrine stimulation, decreased nutrition, or ischemia. Disuse atrophy is seen in muscles that are not used. Denervation atrophy occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation causes changes that may occur in reproductive structures during menopause. During prolonged periods of malnutrition, the body may undergo a generalized wasting of tissue mass. Ischemia reduces blood flow and delivery of oxygen and nutrients to tissues.

2. Hypertrophy increases the amount of functioning mass by increasing cell size. This allows the cell to achieve an equilibrium between demand and function. Hypertrophy usually is seen in cardiac and skeletal muscle tissue. These tissues cannot adapt to increased workload by mitosis to form more cells. The increase in cell components is related to limitations in blood flow. Hypertrophy may be either physiologic or pathologic. In myocardial hypertrophy, initial enlargement is caused by dilation of the cardiac chambers in response to valvular disease or hypertension. This adaptation is short-lived and is followed by increased synthesis of cardiac muscle proteins that allows cardiac muscle fibers to do more work. Ultimately, advanced hypertrophy becomes pathologic and can lead to heart failure.

3. Hyperplasia is an increase in the number of cells of a tissue or organ. It occurs in tissues where cells are capable of mitotic division. Hyperplasia is a controlled response to an appropriate stimulus and ceases once the stimulus has been removed. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that is hormonally regulated. A pathologic hyperplasia occurs when the endometrium enlarges because of excessive estrogen production. Then, the abnormally thickened uterine layer may bleed excessively and frequently. Compensatory hyperplasia enables certain organs, like the liver, to regenerate after loss of substance.



4. Dysplasia is deranged cell growth that results in cells that vary in size, shape, and appearance of mature cells and is related to hyperplasia. Minor degrees of dysplasia occur in association with chronic irritation or inflammation in the uterine cervix, oral cavity, gallbladder, and respiratory passages. Dysplasia is potentially reversible once the irritating cause has been removed. Dysplastic changes may progress to neoplastic disease. This makes dysplasia a phenomenon of importance.

5. Metaplasia is a reversible conversion from one adult cell type to another adult cell type. It allows for replacement with cells that are better able to tolerate environmental stresses. In metaplasia, one type of cell may be converted to another type of cell within its tissue class (i. e., an epithelial cell cannot change to a connective tissue cell). An example of metaplasia is the substitution of stratified squamous epithelial cells for ciliated columnar epithelial cells in the airways of the person who is a habitual cigarette smoker.

ANTIOXIDANTS

Antioxidants are an inhibitor of the process of oxidation, even at relatively small concentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and helps in converting the radicals to less reactive species. A variety of free radical scavenging antioxidants is found in dietary sources like fruits, vegetables and tea, etc.

Antioxidants defense both enzymatic and non enzymatic reactions protect the body against oxidative damage.

Classification of antioxidants

- A) Natural antioxidants
- B) Synthetic antioxidants

Natural antioxidants: Naturally occurring antioxidants of high or low molecular weight can differ in their composition, in their physical and chemical properties, in their mechanism and in their site of action. They can be divided into following categories:

- **Enzymes:** Enzyme such as **superoxide dismutase** (SOD), catalase and glutathione peroxidase attenuate the generation of reactive oxygen species by removing potential oxidants or by transferring ROS/RNS (reactive nitrogen species) into relatively stable compounds. SOD which was discovered in late 60s, catalyses the transformation of the superoxide radical into hydrogen peroxide, which can than be transformed by enzyme catalase into water and molecular oxygen. While superoxide anion in itself is not particularly reactive, it can reduce transition metal ions, such as iron and gets converted to most reactive radicals - the hydroxyl radical. Thus, elimination of superoxide radical can attenuate the formation of hydroxyl radical. **Glutathione peroxidase** (GPx) reduces lipid peroxides (ROOH), formed by the oxidation of polyunsaturated fatty acids (PUFA), to a stable, non toxic molecule - hydroxyl fatty acid (ROH). Together with phospholipase, GPx can also convert phospholipids hydro peroxide (PL-OOH) into phospholipids hydroxide (PL-OH) [Ursini et al., 1982].

- **Low molecular weight antioxidants:** These are subdivided into lipid-soluble antioxidants (tocopherol, carotenoids, quinones, bilirubin and some polyphenols) and water soluble antioxidants (ascorbic acid, uric acid and polyphenols). These delay or inhibit cellular damage mainly through free radical scavenging property.

- ✓ **Lipids soluble antioxidants:** These antioxidants tend to accumulate in lipid plasma lipoprotein (eg. LDL); upon supplementation. This group of antioxidants are supposed to act as highly efficient scavengers, such as against lipid peroxy radical, which are formed within the lipoprotein as a consequence of free radical chain reaction of lipid peroxidation.

- ✓ **Water soluble antioxidants:** These antioxidants cannot enter the lipid moiety of low density lipoprotein (LDL); these will be less efficient as these are principally unable to encounter most of these lyophilic radicals; however, such a compound may act in a synergistic manner with lipophilic antioxidants by regenerating them.

Synthetic antioxidants These are most effective antioxidants and are synthetic chemicals, approved by food and drug administration for addition to foods, ego BHA (Butylated hydroxy anisole), BHT (butylated hydroxy toluene), TVHQ (tertiary butylated hydroxy quinone) etc .

Depending on their function, there are:

- Primary antioxidants (antioxidants proper): ascorbic acid and its derivatives, tocopherols, the esters of gallic acid, erythorbic acid and its sodium salt.
- Secondary antioxidants (substances with antioxidant action but that have other functions as well). Sulphur dioxide and sulphites as well as lecithin are secondary antioxidants.

Antioxidants can be grouped into three categories:

- Preventive antioxidants, that reduce the formation of radicals and of ROS by decomposing hydrogen peroxide and hydroperoxide without generating FR (GPx, GST, HRP, CAT) by capturing metal ions (apoferritin, transferrin, lactoferrin, ceruloplasmin) and by deactivating active oxygen (carotenoids, SOD).
- Radical-deactivating antioxidants, that inhibit the initiation stage and interrupt the propagation stage by capturing radicals before they reach target-cells (vitamin C, uric acid, albumin, bilirubin, vitamin E, carotenoids).
- Molecules involved in recovery and in de novo mechanisms (phospholipases, proteases, transferases).

Mode of action of antioxidants:

- Chain breaking reaction eg. α -tocopherol, which act in lipid phase to trap free radical.
- By reducing concentration of reactive oxygen species eg. Glutathione.
- By scavenging initiating radicals eg. superoxide dismutase which act in the lipid phase to trap superoxide free radicals.
- By chelating transition metal catalyst: a group of compound which act by sequestration of transition metals that are well established prooxidants. In this way transferrin, lactoferrin and ferritin function to keep iron induced oxidant stress in check and ceruloplasmin and albumin as copper sequestrants.

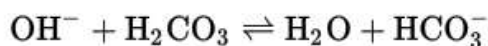
The Buffer Systems

Buffers in the human body			
Buffer	Acid	Conjugate base	Main buffering action
Hemoglobin	HHb	Hb ⁻	erythrocytes
Proteins	HProt	Prot ⁻	intracellular
Phosphate buffer	H ₂ PO ₄ ⁻	HPO ₄ ²⁻	intracellular
Bicarbonate	CO ₂ → H ₂ CO ₃	HCO ₃ ⁻	extracellular

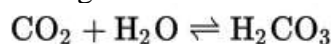
The bicarbonate buffer minimizes changes in hydrogen ion concentration when either acid or alkali is added to blood. When an acid (H⁺) is added, it reacts with bicarbonate; this forms carbonic acid which on dissociation releases CO₂. The blood pCO₂ increases slightly and the CO₂ is eliminated through the lungs. The excess hydrogen ion has been neutralized.



When alkali (OH⁻) is added, it reacts with the carbonic acid, yielding water. The bicarbonate concentration increases slightly.



as a consequence of a decrease in the H₂CO₃ concentration; the reaction proceeds to the right, supplementing the used H₂CO₃.



The excess of OH⁻ has been neutralized. Depletion of CO₂ is subsequently compensated by a decreased ventilation rate.

Erythrocytes and renal tubular cells contain a zinc-containing enzyme, carbonic anhydrase (CA), which converts dissolved CO₂ into carbonic acid. Carbonic acid dissociates, yielding the hydrogen and bicarbonate ions:



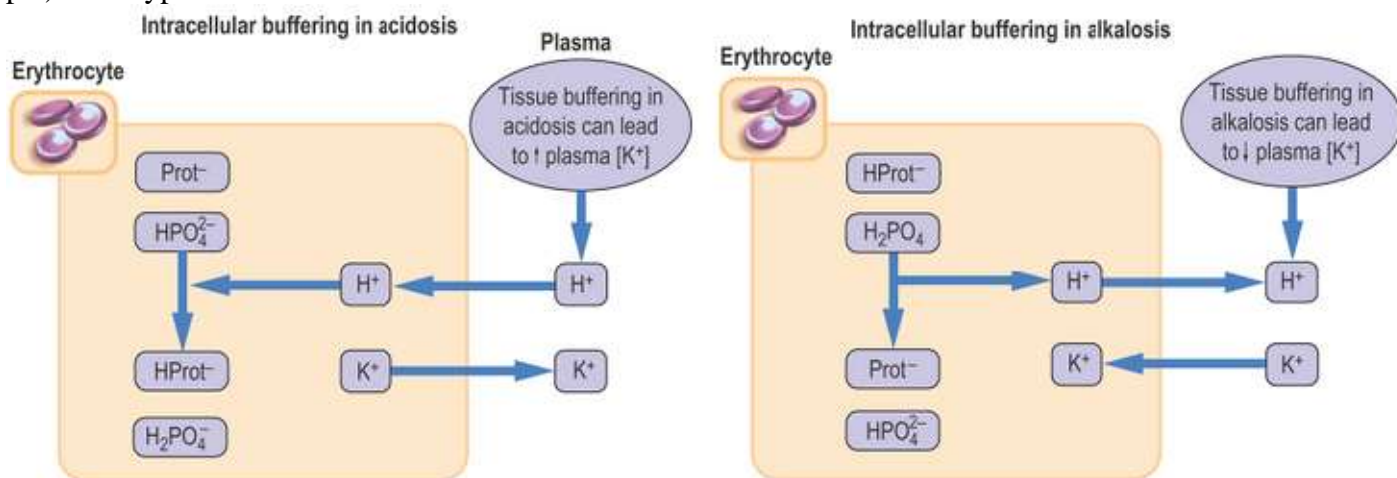
This is how renal tubular cells and erythrocytes produce bicarbonate. The kidneys regulate bicarbonate reabsorption and synthesis, and the erythrocytes adjust its concentration in response to changes in pCO₂.

Intracellular Buffering

Intracellular buffers are proteins and phosphates

Hydrogen ion enters cells in exchange for potassium (this may result in an increase in plasma potassium concentration). Conversely, decrease in plasma hydrogen ion, or bicarbonate excess, would be buffered by cell-derived hydrogen ion. Hydrogen ion would enter plasma in exchange for potassium, decreasing plasma potassium.

Thus acidemia (low plasma pH) may be associated with hyperkalemia and alkalemia (high blood pH) with hypokalemia



APOPTOSIS.

In the organism of a healthy man cellular homeostasis is defined by the balance between destruction and proliferation of cells. Daily, approximately about 5% of cells of organism are exposed to apoptosis, and they are replaced by new cells. In the process of apoptosis cell disappears without leaving a trace within 15 to 120 minutes.

Apoptosis (in Greek apo-removal, termination; ptosis-fall) is programmed cell destruction. It is an energetically dependent; genetically controllable process started by specific signals, which relieves the organism from weakened unnecessary or damaged cells and their effective removal from the tissue.

Apoptosis is a biochemical specific type of the cell destruction; it is characterized by activation of the non-lysosomal endogenous endonucleases, splitting nuclear DNA into small fragments. Morphologically apoptosis is shown by the destruction of the single cells, that is accompanied by the formation of round and membrane surrounded bodies ("apoptotic bodies"), phagocytes by the surrounding cells.

It plays a great role in morphogenesis and it is a mechanism of the constant control of the organ sizes. In case of apoptosis inhibition there a cell accumulation occurs. In case of apoptosis activation the decrease of the cell quantity in tissues (atrophy) is observed.

The apoptosis morphological manifestations.

Apoptosis has its distinctive morphological signs. Apoptosis is found in single cells or small group of cells. Apoptotic cells look like rounded or oval accumulation of intensively eosinophilic cytoplasm with dense fragments of nuclear chromatin.

The cell shrinkage is observed. The cell decreases in size; cytoplasm is condensed; organelles, which look rather normal are settle down more compactly.

It is supposed that the form and volume of the cell impairment occurs as a result of the transglutaminase activation in the apoptotic cells. This enzyme causes progressive formation of cross connections in Cytoplasmic proteins, that cause the formation of the specific membrane under the cellular membrane, that looks like germinal cells of epithelium. Chromatin is condensed on the periphery, under the nucleus membrane, thus a precisely outlined dense mass of various form and size is formed. The nucleus can be broken into two or several fragments.

The chromatin condensation mechanism is investigated well enough. It is caused by the splitting of the nuclear DNA in places connecting single nucleosomes, that results in the formation of numerous fragments, in which the number of bases of the pairs is divided into 180-200. During electrophoresis fragments give the characteristic picture of the ladder. This picture differs from that in necrosis, where the length of the DNA fragments varies. Fragmentation of DNA in nucleosomes occurs under the action of the Calcium dependent endonucleases. Endonuclease in some cells presents constantly (for example in

thymocytes), where it is activated by the free cytoplasm Calcium occurrence, and in other cells is synthesized before the beginning of apoptosis. But, how chromatin condensation after the DNA splitting by endonucleases takes place hasn't been found out yet?

The deep protrusion of the surface with the cavity formation is primary formed in apoptotic cell, that leads to the cell fragmentation and formation of the surrounded by membrane apoptotic bodies consisting of cytoplasm and the densely located organelles, with or without nucleus fragments.

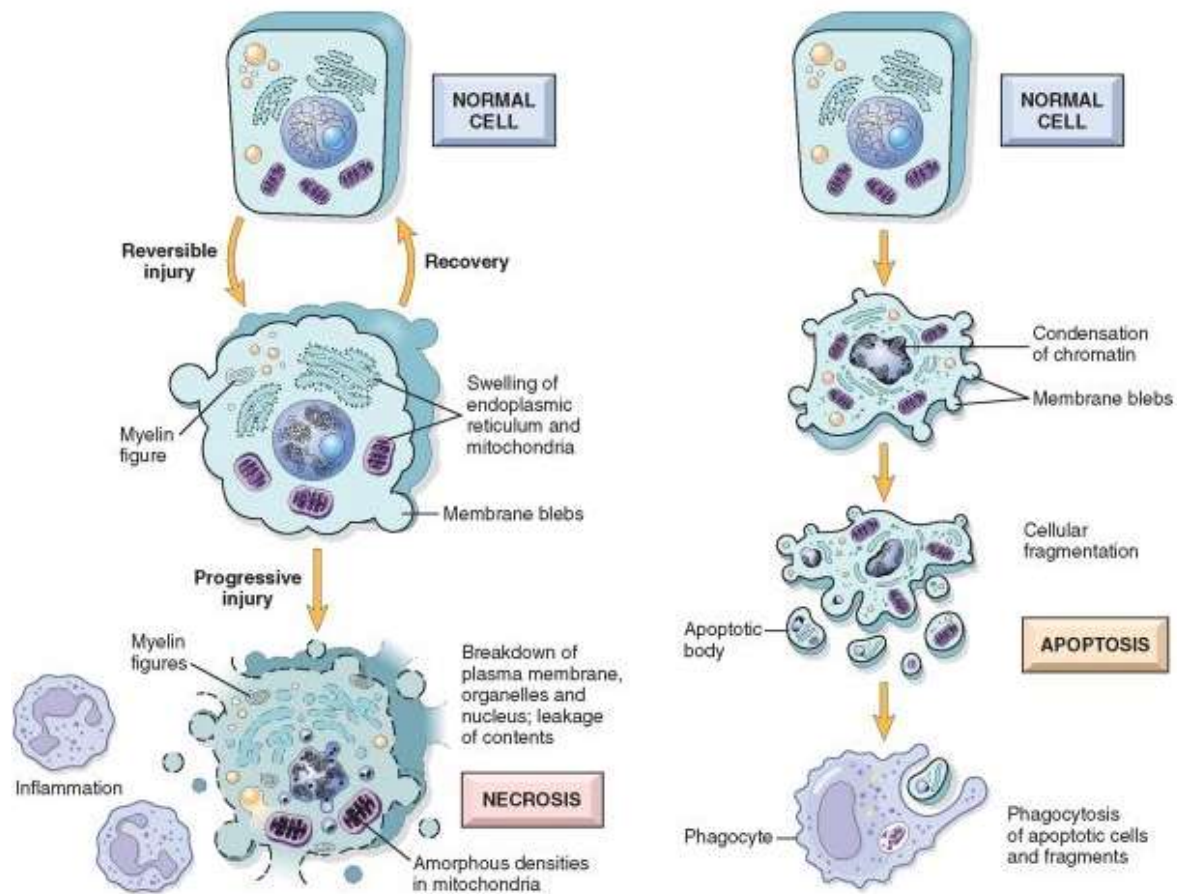


Fig 2 Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.

Phagocytosis of apoptotic cells or bodies is carried out by the surrounding healthy cells, either parenchymatous cells, or macrophages. Apoptotic bodies are quickly destroyed in lysosomes, and the surrounding cells migrate or proliferate to fill the released space of apoptotic bodies. Phagocytosis of the apoptotic bodies is activated by cell receptors on macrophages or other cells: they grasp and absorb apoptotic cells. One of such macrophage receptors is the receptor of vitronectin, which is a beta-3-integrin and it is activated by phagocytosis of the apoptotic neutrophils.

Table 1. Difference necrosis from apoptosis

Sign	Apoptosis	Necrosis
induction	is activated by physiological or pathological stimuli	induction is depending on the damaging factor
distribution	a single cell	group of cells
biochemical changes	Energy dependent fragmentation of DNA by endogenous endonucleases. Intact lysosomes.	impairment or termination of the ionic exchange. Enzymes are released from lysosomes.
disintegration of DNA	internuclear condensation with splitting into phragments	diffuse localization in the necrotic cell
the integrity of the cellular membrane	is saved	is broken
morphology	shrinking and fragmentation with the formation of apoptotic bodies with condensed chromatin	Swelling and lysis cells

the inflammation response	no response	usually it is present
The removal of the dead cells	absorption (phagocytosis) by the neighboring cells	absorption (phagocytosis) by neutrophils and macrophages

Apoptosis takes part in the following physiological and pathological processes:

1. Programmed destruction of cells during embryogenesis (including implantation, organogenesis).
2. Hormon-dependent involution of the organs in adult (the endometrium seizures during mens cycle, the follicular atresia in menopause and the mammary gland regress at the end of lactation).
3. Age –specific and physiological involution of organs (thymus, atrophy of muscles in case of the absence of physical exercise).
4. The removal of some cells in proliferation of the cell population.
5. Destruction of single cells in tumors (basically in its regress, but also in the actively growing tumor).
6. Destruction of the immune system cells (B- and T-lymphocytes, after cytokine stock exhaustion, the destruction of auto-reactive T-cells in thymus development).
7. Pathological atrophy of hormone –dependent organs (prostate atrophy, after castration, exhaustion of lymphocytes in thymus, in glucocorticoids therapy).
8. Cell destruction inhibition caused by cytotoxic T-cell action in case of transplantant rejection, “transplantant-host” disease.
9. Damage of cells in some virus diseases (in virus hepatitis, when the fragments of apoptotic cells are found out in the liver – Caunsilman’s bodies).

The mechanism of apoptosis

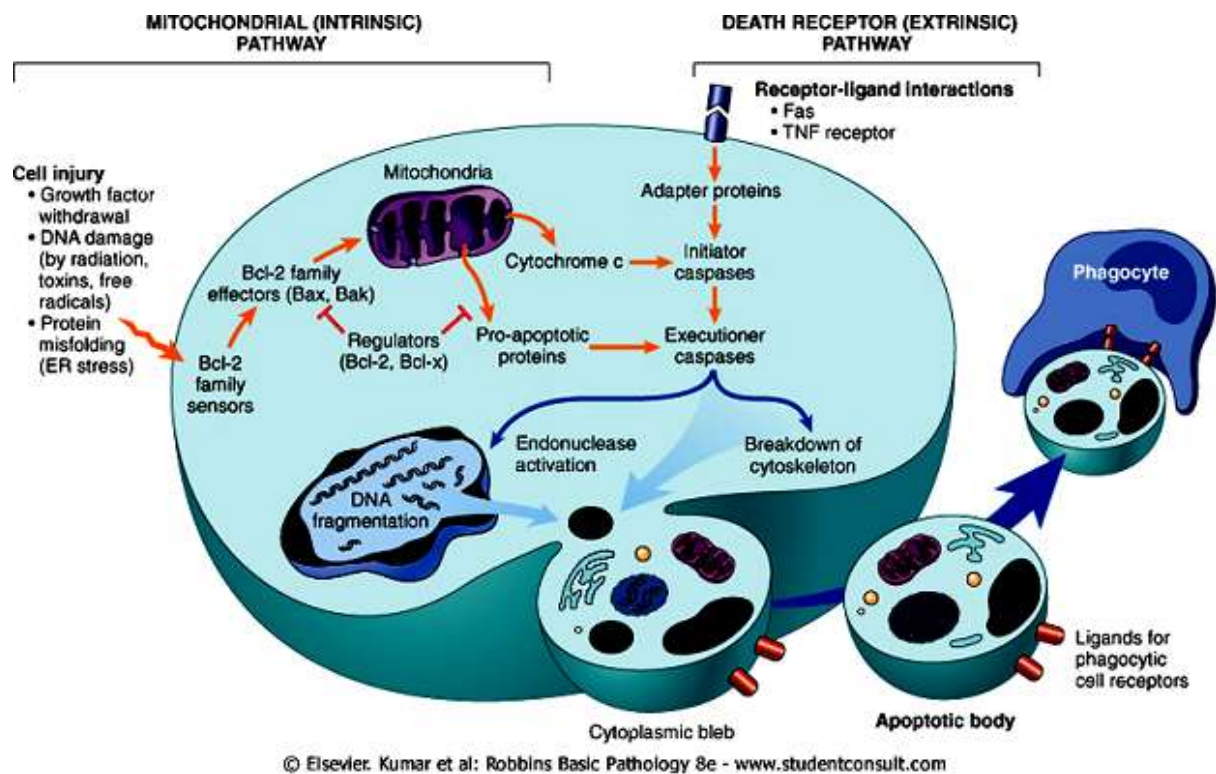
At present several major mechanisms of implementation of apoptosis:

- 1) **Receptor.** Implemented using the "death receptors" by reacting with the appropriate ligands most of which belongs to the tumor necrosis factor superfamily. Receptor-ligand interaction leads to the activation of adapter proteins associated with «death domain» (FADD - Fas-associated death domain, TRADD - TNF-R-associated death domain), and procaspase 8 whose product - caspase 8 (initiator) activates caspase 3 (effector), which in turn leads to the activation of endonucleases, fragmenting DNA.
- 2) **Mitochondrial.** Involvement of mitochondria in apoptosis provided by the presence in their matrix and intermembrane space large number of biologically active substances (cytochrome C (Cyt C), procaspases 2, 3, 9, apoptosis-inducing factor (AIF), possessing a pronounced apoptotic effect. Factor is activation of apoptosis output of these substances into the cytoplasm while reducing mitochondrial transmembrane potential due to the opening of giant mitochondrial pores (play the role Ca^{2+} -, pH, voltage-, NADPH / NADP + - and redox-dependent channels) and increasing the permeability of the mitochondrial membranes. To open the pores is a result in the depletion of glutathione in the cells, NADPH, ATP and ADP, the formation of reactive oxygen species, uncoupling of oxidative phosphorylation, an increase in the content of Ca^{2+} in the cytoplasm. Entering of intermembrane proteins and activation of apoptosis may also at break of the outer mitochondrial membrane as a result of hyperpolarization of the inner membrane.
- 3) **p53-mediated.** p53 - a multifunctional protein that plays an important role in monitoring the signals on the state of the cells, the integrity of its genome, the activity of DNA repair systems. DNA damage leads to accumulation of p53 protein in a cell. This defines a cell cycle arrest in the G1 and G2 phases, prevents replication activates the synthesis and repair of DNA, and thus creates conditions for recovery of the native DNA structure, and prevent occurrence of mutant aneuploid cells in the body. If there is failure of systems of DNA repair and DNA damage are saved, the cell undergoes apoptosis. In particular, the p53 protein is able to induce transcription of apoptogenic factors such as Bax, Fas-receptor, DR-5, and others.
- 4) **Perforin-granzymes.** Cytotoxic T lymphocytes (T killer) induce apoptosis in target cells (e.g., infected cells) using protein perforin. Polymerizing, perforin forms in the cytoplasmic membrane of the target cell transmembrane channels through which secreted into the cell receives a T-killer granzymes

(fragmentiny) - a mixture of serine proteases. The main component of this mixture is granzyme B - proteolytic enzyme that activates caspase 3.

Apoptosis is the endpoint of an energy-dependent cascade of molecular events, initiated by certain stimuli, and consisting of four separable but overlapping components.

1. **Signaling pathways** that initiate apoptosis
2. **Control and integration**, in which intracellular positive and negative regulatory molecules inhibit, stimulate, or forestall apoptosis and thus determine the outcome
3. **A common-execution phase** consisting of the actual death program and accomplished largely by the caspase family of proteases
4. **Removal of dead cells** by phagocytosis



Autophagy

Autophagy is a process in which a cell eats its own contents. It is a survival mechanism in times of nutrient deprivation, when the starved cell lives by cannibalizing itself and recycling the digested contents. In this process intracellular organelles and portions of cytosol are first sequestered from the cytoplasm in an autophagic vacuole, which subsequently fuses with lysosomes to form an autophagolysosome, and the cellular components are digested by lysosomal enzymes.

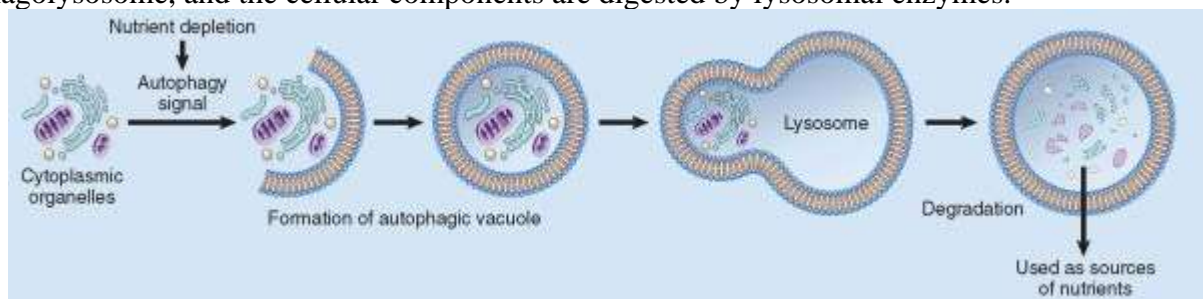


FIGURE Autophagy. Cellular stresses, such as nutrient deprivation, activate autophagy genes that create vacuoles in which cellular organelles are sequestered and then degraded following fusion of the vesicles with lysosomes.

Interest in autophagy has been spurred by the finding that it is regulated by a defined set of “autophagy genes” (called Atgs) in single-celled organisms and mammalian cells. The products of many of these genes function in the creation of the autophagic vacuole, but how they do so is unknown. It has also been suggested that autophagy triggers cell death that is distinct from necrosis and apoptosis.

However, the mechanism of this type of cell death is not known, nor is it clear that the cell death is caused by autophagy rather than by the stress that triggers autophagy. Nevertheless, autophagy has been invoked as a mechanism of cell loss in various diseases, including degenerative diseases of the nervous system and muscle; in many of these disorders, the damaged cells contain abundant autophagic vacuoles.

Questions for self-control of knowledge:

1. What is the role of immune processes in self-harm cells when they are prolonged inactivity, aging, disorders of trophic functions of nervous system?
2. What are the levels of cell damage?
3. What are the mechanisms for violations of genetic apparatus and realization of genetic program?
4. What is the role of free radicals in development of pathological processes?
5. What are the changes in balance of pro-and antioxidant systems of cells?
6. Give a description of peroxisome diseases.
7. What are the abnormal shapes of mitochondria?
8. Describe the concepts of "substitution" and "restitution."
9. What is the biological role of apoptosis?
10. Specify the role of genes bcl and p53 in process of apoptosis.
11. What are the differences of apoptosis from necrosis?
12. What are the ways to increase cell resistance to action of pathogenic factors?
13. What are the mechanisms of compensation for damage.

Tasks for self-managed student work:

1. Ways of increasing a resistance of cells to the action of pathogenic factors.
2. Stimulation of regenerative processes in damaged cells.
3. Peroxisome diseases.

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