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General Mechanisms of Cell Damage

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Abstract: This study examines pathogenetic factors such as disruption of cellular energy supply processes; damage to membranes and enzymatic systems; ion and fluid imbalance; disruption of the genetic program and/or its implementation; and disruption of cell function regulation mechanisms. It is demonstrated that enzymatic and non-enzymatic mechanisms play a leading role in the cellular antioxidant defense system.

Key words: pathogenetics, cell support, membrane damage, enzyme system, ion imbalance, creatine phosphokinase.

The fundamental mechanisms of cell damage have evolved, including typical mechanisms of cell membrane damage, the characteristics of which are independent of the nature of the pathogen and cell type. These mechanisms determine nonspecific indicators of cell damage used for diagnostic purposes and for assessing the functional state of damaged tissues and organs. Cellular mechanisms of damage are central to the development and progression of diseases. Understanding the specifics of these mechanisms, the interactions between them, and their consequences for the body is essential for developing treatment strategies and shaping the clinical judgment of future physicians.

At the cellular level, damaging factors "turn on" several pathogenetic links.

These include:

- disorder of the processes of energy supply of cells;
- damage to membranes and enzyme systems;
- imbalance of ions and fluid;
- violation of the genetic program and/or its implementation;
- disorder of the mechanisms regulating cell function.

Disruption of the energy supply for cellular processes is often the initial and leading mechanism for their alteration. Energy supply can be disrupted at the stages of ATP synthesis, transport, and utilization [1-3].

ATP synthesis can be disrupted as a result of a deficiency of oxygen and/or metabolic substrates, a decrease in the activity of tissue respiration and glycolysis enzymes, damage and destruction of mitochondria, in which the reactions of the Krebs cycle and the transfer of electrons to molecular oxygen, coupled with the phosphorylation of ADP, are carried out.

It is known that the delivery of ATP energy from the sites of its synthesis – from mitochondria and hyaloplasm – to effector structures (myofibrils, membrane ion "pumps", etc.) is carried out with the help of enzyme systems: ADP -ATP- translocase (adenine nucleotide transferase) and creatine phosphokinase (CPK).

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Adenine nucleotide transferase ensures the transport of energy from the macroergic phosphate bond of ATP from the mitochondrial matrix through their inner membrane, and CPK transfers it further to creatine with the formation of creatine phosphate , which enters the cytosol .

Creatine phosphokinase Effector cellular structures transport the phosphate group of creatine phosphate to ADP, forming ATP, which is used in cellular life processes. Enzymatic energy transport systems can be damaged by various pathogens, which is why , even with a high overall ATP content in the cell, ATP deficiency can develop in energy-consuming structures.

Disruption of cellular energy supply and disruption of their vital functions can develop even under conditions of sufficient production and normal transport of ATP. This may result from damage to the enzymatic mechanisms of energy utilization, primarily due to decreased ATPase activity (actomyosin ATPase , K^+ -Na^+-dependent ATPase of the plasma membrane, Mg^{2+}-dependent ATPase of the sarcoplasmic reticulum "calcium pump," etc.).

Disruption of energy supply processes, in turn, can become one of the factors in the dysfunction of the membrane apparatus of cells, their enzyme systems, the balance of ions and fluid, as well as the mechanisms of cell regulation.

Damage to membranes and enzymes plays a significant role in disrupting cellular function, as well as transforming reversible changes into irreversible ones. This is because the cell's fundamental properties depend significantly on the condition of its membranes and the enzymes bound or free to them .

A) One of the most important mechanisms of membrane and enzyme damage is the intensification of free radical reactions (FRR) and phospholipidase (PSOL). These reactions occur in cells normally, serving as a necessary link in such vital processes as electron transport in the respiratory enzyme chain, prostaglandin and leukotriene synthesis , cell proliferation and maturation, phagocytosis, catecholamine metabolism, and others. Phospholipidase (PSOL) is involved in regulating the lipid composition of biomembranes and enzyme activity.

The latter is the result of both the direct action of lipid peroxide reaction products on enzymes and the indirect action through changes in the state of the membranes with which many enzymes are associated.

The intensity of the PSOI is regulated by the ratio of factors that activate (prooxidants) and suppress (antioxidants) this process. The most active prooxidants include easily oxidizable compounds that induce free radicals, particularly naphthoquinones, vitamins A and D, reducing agents such as $NADPH_2$, $NADH_2$, lipoic acid, and the metabolic products of prostaglandins and catecholamines.

The PSOL process can be divided into three stages:

1) oxygen initiation (“oxygen” stage),

2) the formation of free radicals of organic and inorganic agents (“ free radical ” stage),

3) production of lipid peroxides (“peroxide” stage).

The initial step in free-radical peroxide reactions during cellular damage is typically the formation of so-called reactive oxygen species (ROS) during oxygenase reactions: superoxide radicals (O_2^-) , hydroxyl radicals (OH), and hydrogen peroxide (H_2O_2). These react with cellular structural components, primarily lipids, proteins, and nucleic acids. This results in the formation of reactive radicals, particularly lipid radicals and their peroxides. This can lead to a chain reaction, known as an avalanche.

However, this doesn't always happen. Cells undergo processes and are affected by factors that limit or even stop free radical and peroxide reactions, thereby exerting an antioxidant effect.

One such process is the interaction of radicals and lipid hydroperoxides, which leads to the formation of "non-radical" compounds. Enzymatic and non-enzymatic mechanisms play a leading role in the cellular antioxidant defense system.

Recent research has shown that excessive activation of free radical and peroxide reactions is one of the main factors causing damage to cell membranes and enzymes. The following processes are of primary importance:

1) a change in the physicochemical properties of membrane lipids, which causes a disruption in the conformation of their lipoprotein complexes and, in connection with this, a decrease in the activity of proteins and enzyme systems that ensure the reception of humoral effects, transmembrane transfer of ions and molecules, and the structural integrity of membranes;

2) changes in the physicochemical properties of protein micelles that perform structural and enzymatic functions in the cell;

3) the formation of structural defects in the membrane—the so-called simple channels (clusters)—due to the introduction of PSOL products. These processes, in turn, disrupt processes essential to cellular functioning—excitability, generation and conduction of differential impulses, metabolism, perception and implementation of regulatory effects, intercellular interactions, etc.

B) Activation of hydrolases (lysosomal , membrane-bound and free).

Normally, the composition and condition of membranes and enzymes are modified not only by free-radical and lipid peroxide processes, but also by membrane-bound , free (solubilized), and lysosomal enzymes: lipases, phospholipases , and proteases. Under the influence of pathogenic factors, their activity or content in the cell's hyaloplasm may increase (in particular, due to the development of acidosis, which promotes increased enzyme release from lysosomes and their subsequent activation).

As a result, glycerophospholipids and membrane proteins, as well as cellular enzymes, undergo intense hydrolysis. This is accompanied by a significant increase in membrane permeability and a decrease in the kinetic properties of enzymes [4-16].

B) Introduction of amphiphilic compounds into the lipid phase of membranes.

As a result of the action of hydrolases (mainly lipases and phospholipases), free fatty acids and lysophospholipids accumulate in the cell , in particular, glycerophospholipids : phosphatidylcholines , phosphatidylethanolamines , phosphatidylserines . They are called amphiphilic compounds due to their ability to penetrate and fix in both hydrophobic and hydrophilic environments of cell membranes (amphi means “both”, “two”). At a relatively low level of amphiphilic compounds in the cell, they, penetrating into biomembranes, change the normal sequence glycerophospholipids , disrupt the structure of lipoprotein complexes, increase permeability , and also change the configuration of membranes due to the “wedge-shaped” shape of lipid micelles.

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