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Review Article

# Structural-Metabolic Characteristics of Cells and Their Functional Opportunities

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The regulation of the vital activity of any cell is carried out mainly due to the state of the structural subunits of the membrane, their interaction and mutual arrangement. As a result of structural rearrangements, almost all functions of biomembranes, organelles and cells as a whole can change: the activity of membrane-bound enzymes, the permeability and transport of ions and substrates, the activity of the genome, reproduction.

Although all biomembranes have the same basic phospholipid bilayer structure and certain common functions, each type of cellular membrane also has certain distinctive activities determined largely by the unique set of proteins associated with that membrane. The most abundant lipid components in most membranes are phospholipids, which are amphipathic molecules (i.e., they have a hydrophilic and a hydrophobic part). In phosphoglycerides, a principal class of phospholipids, fatty acyl side chains are esterified to two of the three hydroxyl groups in glycerol, and the third hydroxyl group is esterified to phosphate [1,2].

Phospholipids (PL) refer to complex, or complex, lipids, which contain nitrogenous bases, alcohols (glycerin, inositol, sphingosine), fatty acids (FA), carbohydrates, phosphoric or sulfuric acid. This group includes glycerophospholipids and sphingolipids.

Glycerophospholipids are represented by phosphatidic acids, phosphatidylcholines, phosphatidylethanols, phosphatidylinositides and other compounds, the initial substrate for which is glycerophosphoric acid. Sphingolipids are represented by sphingomyelin and glycosphingolipids: cerebrosides, sulfates, gangliosides, ceramid polyhexosides [1,3].

Lipids are located asymmetrically in the membrane, but this feature is not absolute, with the exception of glycolipids, for which it is mandatory, this fraction involved in the formation of receptors is always on the outside of the cell membrane. It should be noted that, as necessary, the molecules of a particular lipid fraction can move quickly from their layer to the opposite one. For example, phosphatidylcholine in erythrocyte membranes can move from the outer to the inner layer (a phenomenon called the «flip-flop») in 8 hours [1,3]. For membrane structures, phospholipids (PL) are the main dynamic component that maintains the optimal structural and functional state by balanced reactions of disintegration and synthesis, exchange between subcellular formations [1-3].

It is believed that the consistency of the qualitative and quantitative composition of PL in human cell membranes has a genetic basis. Maintenance of the permanence of membrane PL occurs due to a sufficiently intensive exchange in the structures formed by them, when the destroyed molecules are replaced by identical ones. The degradation products PL - free fatty acids (FFA) and glycerol-3-phosphate - are either used again in the processes of biosynthesis in the cell, or are removed from it by exocytosis.

Phospholipids are functionally active compounds for many membrane-bound lipid-dependent and lipid-containing enzyme systems. Being the precursors of many biologically active substances (prostaglandin, prostacyclin, inositol triphosphate), they can modulate the activity of membrane proteins, primarily enzymes. For many enzymes, the determining value is not so much the fluidity of the lipid environment, due to the presence of cholesterol (COL) and its relationship with PL, but rather the presence of specific forms of the latter. Some enzymes require the presence of a certain phospholipid, that is, they have absolute specificity, others have partial specificity and are activated or inhibited by the PL group. For example, the activity of Na-, K-ATP-as is significantly influenced by the presence of phosphatidylserine or other negatively charged PL; the activity of monoamine oxidase of mitochondria is also affected by negatively charged phosphatidylserine and phosphatidylinositol; the activity of glucose-6-phosphotase is determined by phosphatidylethanolamine; pyruvate dehydrogenase - phosphatidylserine; cytochrome P-450 - phosphatidylcholine; the activity of respiratory chain enzymes depends on the optimal ratio in the cellular structures of phosphatidylethanolamine and phosphatidylcholine, the saturation of LC membrane lipids; the activity of adenylate cyclase (the main enzyme that regulates the level of cAMP and cell activation) decreases with the change in the cholesterol / PL ratio, which is due to the fluidity of the membranes reflected by this ratio [1,3].

It is established that the PL content in cells is related to the functional state and age of the latter: the concentration of these forms of lipids is higher in young, growing tissues.

The phospholipid composition of biomembranes is largely susceptible to regulatory influences of the body. For example, under stressful effects, excess catecholamines cause activation of lipid peroxidation (LPO), which changes or damages the lipid layer.

Phospholipids play an important role in the activation of a number of cellular enzymes and in the reaction of target cells with hormonal stimulation; they, participating in the formation of acetylcholine and in the transfer of ions through cellular and subcellular membranes, provide a nerve impulse. The phenomenon of desensitization (a decrease in sensitivity to mediators, for example, catecholamines) is associated with a change in the lipid microenvironment of adrenoreceptors in repeated stressors.

Phospholipids can be used by the cell and as a source of energy in the absence of oxygen and in other extreme situations [4]. Taking into account the large energy capacity of the PL, Miselsaar H. *et al.* Proved the possibility of a dynamic equilibrium in the PL-ATP system.

The so-called simple lipids consist of alcohol (more often glycerin or COL) and LC; these are acylglycerol (or neutral fats), which are glycerol esters, bile acids, wax. The bulk of neutral fats in the body are triglycerides or triacylglycerol (TAG).

Cholesterol is not only a precursor of bile acids, steroid hormones of the adrenal glands, ovaries, testes and placenta, but also takes an active part in the formation of membranes: up to 90% of its content falls on the cellular structures in the body. The presence of cholesterol determines electrical potential, fluidity, permeability and other biophysical parameters of membranes [2]. The participation of cholesterol in the construction of cellular structures is due to its ability to interact easily with lipids, forming complexes. Being part of cell membranes, cholesterol provides the necessary stability to structures, protecting them from the action of enzymes. Modulating effect of cholesterol on permeability, viscosity, membrane potential is due to its ability to change the angle of inclination of hydrocarbon chains to the plane of the membrane, as a result of which the area occupied by lipid molecules changes and the membrane is compacted.

Increasing the level of the steroid affects the functional state of the cells by changing the viscosity of the membranes and reducing their reactivity and cellular receptor activity. The effect of cholesterol content in biomembranes on the functional state of the cells is manifested in a change in the activity of many cellular enzymes.

Free fatty acids. (FFA) and TAG are largely used as energy substrates; there is a close relationship between the interconversion of these two groups of lipids in the body. SFA sources are TAG fat stores, where LCs are released by sequential hydrolysis with lipases, as well as PL cell membranes, in the process of continuous renewal of which FFA are formed. The LCs freed of hydrolysis with more than 10 atoms are newly synthesized in TAG in epithelial cells. Most of the glycerol of triglycerides is formed from glucose or hexophosphates in the glycolytic or pentose cycle. Synthesis of TAGs that make up the bulk of neutral fats in the body occurs in the liver, fatty tissue and other organs. Three ways of biosynthesis of these lipids are known: α-glycerophosphate, dihydroxyacetone phosphate and monoacylglycerophosphate, whose name indicates the substances used as precursors in the synthesis. In addition, activated saturated and unsaturated LCs are used in biosynthesis. Their activation is catalyzed by acyl-CoA synthetases, which are localized in microsomes; This occurs in the presence of CoA and ATP [1,3].

Lipolysis (hydrolysis of TAG) is stimulated in the body by the lipomobilizing factor of the pituitary gland, ACTH, STH, TSH, catecholamines, thyroxine, hydrocortisone, heparin. Adrenaline, ACTH, glucagon depress the inclusion of FFA in the synthesis of TAG [1,3]. Noradrenaline and epinephrine antagonists, which increase the rate of lipolysis and mobilization of the LC, are corticotropin and glucocorticoids produced under its influence, as well as insulin, which inhibits the release of TAG and FFA from adipose tissue.

The vegetative nervous system also exerts an important influence on the exchange of TAG: the impulses applied to the sympathetic nerves, inhibit their synthesis and intensify the decay, and the increase in the tone of the parasympathetic nervous system contributes to the deposition of fat.

There are two ways of synthesis of fatty acids - mitochondrial, in which the carbon chain of these compounds extends and the conversion of palmitate into stearate, linoleate into arachidonate, and non-mitochondrial, localized in the cytoplasm and catalyzing the conversion of acetyl-CoA to palmitate. Oxidation of the liquid crystal is one of the fastest reactions of the body, and this fact determines the importance of FFA in providing energy for various stress states: stress, exercise and other conditions, accompanied by an increase in activity of the sympathetic-adrenal system.

Fatty acids are an important regulator of the metabolism of carbohydrates at the cellular level, they are able to stimulate the reactions of the pentose phosphate pathway, inhibit the glycolysis enzymes, inhibit glucose transport through intracellular membranes, block glycogenolysis and activate gluconeogenesis. Activation of key enzymes of gluconeogenesis can be regarded as a favorable phenomenon for the cell, since they help compensate for glucose deficiency from available substrates - lactate, amino acids, glycerol.

Considering that fatty acids have the ability to increase the electrical conductivity of lipid membranes and, consequently, to separate oxidative phosphorylation, V. P. Skulachev suggested that any increase in the concentration of free fatty acids in the mitochondrial membrane, resulting from an increase in the level of these compounds in the cell, should be accompanied by a certain disconnection of oxidation and phosphorylation. Free fatty acids, like the lysoforms of PL, can increase the rate of LPO.

In the opinion of several authors, the disruption of the properties of the lipid bilayer in many cases is the primary cause of the development of the pathological process in cells, tissues and the organism as a whole. The effect of the lipid spectrum of cells (the content of cholesterol, free fatty acids and TAG) on their functions was studied most extensively on blood lymphocytes, and the results of these studies indicated that the a pronounced relationship between the lipid composition of lymphocyte membranes and their ability to respond to external stimuli [2]. An increase in the level of COL in the cell and, as a consequence, an increase in the viscosity of the membrane makes the latter less reactive, which is mediated by the activity of surface receptor systems and the ability of cells to transform.

The greatest number of studies devoted to the study of the dependence of the functional capabilities of cells on their metabolic characteristics was carried out on lymphocytes. This can be explained by the fact that the lymphocyte has a complex intracellular exchange, reflecting almost all the metabolic processes peculiar to the body, in connection with which RP. Narcissov called lymphocyte – «an enzymatic mirror of the body» [5,6].

More extensive opportunities for studying the characteristics of intracellular processes appeared with the development of the determination of the activity of intracellular enzymes by the bioluminescence method with bacterial luciferase.

Among the most informative reflecting the main parameters of intracellular metabolism of lymphocytes are several dehydrogenases [7,8].

Glucose-6-phosphate dehydrogenase (G6PDG) is the key enzyme of the pentose phosphate pathway (PFP) and plays an important role in the metabolism of sugars - this enzyme depends on whether glucose will undergo glycolysis or be disposed of in PFP. The physiological significance of the latter is that in this cycle, which is the main competitor of glycolysis for glucose-6-phosphate, ribozo-5-phosphate and NADPH are formed, used in the reactions of macromolecular synthesis: nucleotide coenzymes, nucleic acids, fatty acids, steroids; In addition, NADPH is a cofactor for NADP-dependent enzymes. Glucose-6-phosphate dehydrogenase is closely interrelated with enzymes of antioxidant protection and catabolism of xenobiotics (known about the cofactor relationship between G6PDH and glutathione reductase). The activity of G6PDH increases in growing and proliferating cells, as, for example, in lymphocytes under the state of activation of the immune system [9-11].

Glycerol-3-phosphate dehydrogenase (G3PDG), exists in two forms - cytoplasmic and intramitochondrial. In the cytoplasm, the NAD-dependent enzyme interacts between the lipid exchange system and glycolysis through a reaction of the interaction of glycerol-3-phosphate and dihydroxyacetone phosphate. In the interaction of NAD-dependent G3PDH and its intramitochondrial FAD-dependent form, the alpha-glycerophosphate shuttle mechanism is realized, which ensures the transfer of hydrogen into the mitochondria; the latter's activity depends on the production of NADPH in the cytoplasm of cells and on the oxidation of substrates in the mitochondria. Activation of the FAD-dependent form of the enzyme under the influence of thyroid hormones and the dependence of G3PDH activity on the level of cortisol and insulin concentration in the blood serum were noted [9].

Lactate dehydrogenase (LDH) catalyzes the metabolism of lactate, thereby regulating the intracellular NAD / NADPH ratio. LDH catalyzes the reaction occurring at the branching of anaerobic and aerobic transformation of pyruvate. Most of this NAD-dependent enzyme, existing in five isoenzyme forms, is localized in the cytoplasmic matrix, and smaller - on the mitochondrial membranes. As a result of the aerobic reaction of LDH (lactate-pyruvate), which is one of the important parameters of the share of the energy potential of the metabolism in the cytoplasm provided by glycolysis, the bulk of NADH is produced. The important role of glycolysis in conditions of functional tension of lymphocytes (it acts as an «emergency» mechanism for the production of ATP in cells), which is confirmed by a number of authors who established, for example, its activation during the reactions of blast-transformation of lymphocytes.

More productive than glycolysis, in terms of production in ATP cells, is a cycle of tricarboxylic acids (Krebs cycle). The characteristics of the reactions of this cycle can be obtained by examining the activity indices of enzymes catalyzing the initial stages (NADITsDG and NADFICHDG) and the final stages (NADDMG and NADPMDG) of its stages.

Two isocitrate dehydrogenases (NAD- and NADP-dependent) control the metabolism of the corresponding substrate (isocitrate) of the tricarboxylic acid cycle (CTC), converting it to α-ketoglutarate. The activity of the NADICH enzyme along with NADDMH reflects the volume of substrate flow along the cycle, which ensures the maintenance of the necessary concentration of NADH and the energy potential of the mitochondria. With a decrease in the intensity of the substrate flow and a lack of hydrogen in the mitochondria, one of the additional reactions of the cycle, regulated by NADFICHD, may be included; which catalyzes the inflow into the substrate cycle from the cell's cytosol. However, it should be borne in mind that such a compensatory mechanism is limited in time due to changes in the redistribution of intermediates between the mitochondria and the cytoplasm of the cell.

The two enzymes function at the final stage of the tricarboxylic acid cycle, they participate in the metabolism reactions, the malate formed in it; this is NADDMG and NADDMHDG. The enzyme NADDMH adjusts the substrate flow in the cycle and influences, together with glutamate dehydrogenases, oxidative phosphorylation. The second (NADPMDG or malic enzyme) controls one of the so-called shunt reactions, activated when it is necessary to accelerate the passage of substrates along metabolic pathways. During this reaction, malic acid is converted into pyruvate with the reduction of NADP + to NADPH, which is then used in the synthesis processes. Like the other already mentioned enzyme - G6PDG, involved in the production of NADPH in a cell, NADPMDH has functional links with intracellular antioxidant defense systems.

An important role in the functioning of the TSC belongs to the enzyme system of glutamate dehydrogenases, which control the flow of substrates along the cycle, affect oxidative phosphorylation and carry out the CTC linkage with the amino acid exchange. The processes controlled by enzymes of NAD- and NADP-dependent glutamate dehydrogenases (NADGDG and NADPHDG) are classified as auxiliary reactions of the CTC, they have an important role in regulating its activity through changes in the volumes of the substrate stream. Determination of the activity of these enzymes in reactions using as a substrate glutamate allows us to estimate the intensity of the admission of substrates from the amino acid exchange to the CTC (Yoshino M., 1993).

The enzyme glutathione reductase (GR) provides the regeneration of glutathione disulfide to reduced glutathione, which functions in the system of antioxidant protection of cells and participates in the transport of protein in them. GH is in direct cofactor association with G6PDH, and actively affects the vital activity of lymphocytes, especially the process of proliferation and blast transformation. GH participates in two major intracellular processes: first, it ensures the conversion of glutathione disulfide to reduced glutathione, thereby supporting the functioning of the glutathione system of antioxidant cell protection; Secondly, it participates in the active transport of amino acids in them [4,12].

Thus, the intracellular metabolism of lymphocytes is regulated by a wide range of enzymes and this provides the ability of cells to perform a variety of specific functions. The manifestation of their functional capabilities in the full volume of lymphocytes is possible only with the appropriate state of intracellular metabolism. The activity of enzymes in lymphocytes is a very sensitive indicator of their condition, they are used for differential diagnosis and development of the prognosis of the course of diseases [13].

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