

BIOTECHNOLOGY

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Katerina Garkava**MOLECULAR ASPECTS OF THE IMMUNOBIOLOGICAL STABILITY OF THE ORGANISM**

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Abstract. *The analysis of molecular mechanisms of regulation of immunobiological stability of the organism was carried out. Conclusion made that immunobiological stability of the organism requires consistency of lipid peroxidation, a range of lymphocyte receptors, interleukins and regulation of these processes by lymphocytic chalone system.*

Keywords: interleukins, lipid peroxidation, lymphocytes, lymphocytic chalone, receptors.

1. Introduction

The basic property of living matter is the ability to maintain a steady state at different levels depending on the conditions in which the organism exists. All pathological processes are related to the violation of this steady state.

Homeostasis of the internal organism environment (Lebedev, Ponyakina 1990; Petrov, Ataulakhanov 1997; Khaitov et al. 1995) is provided by the immune system, which is basically a multicomponent, but very dynamic and clear in responding system (Fedorich et al. 1992). Many important processes of immune reaction occurs on the cell membrane caused by the operation of immunocytes and their receptors (Petrov, Ataulakhanov 1997).

The **purpose** of work – to analyze literature data concerning the molecular mechanisms of immunobiological stability of an organism.

2. Literature analysis

Biological membranes separating the cells from the external environment, allow them to exist as a single whole. They regulate the transport of substances through the membrane and provide the link of external environment with the cell (Stenina et al. 1986).

Discovering of certain substances by a cell occurs via complex proteins – glycoprotein that are embedded in the cell membrane, and molecular weight of which is around 10^5 daltons (Boldirev 1986). Regardless of the nature of the ligand that they bind, membrane proteins have the same body plan – part of the protein is located outside the cell, another part – in the membrane, and the other – in

the cytoplasm. The selectiveness of these ligands binding to membrane proteins helps identify them as receptors (Cullberg 1987). Interaction of receptor with ligand leads eventually to a change in a state of membranes (Petrov, Ataulakhanov 1997).

Receptors for the same ligand may differ from each other in structural organization, depending on which cells they are expressed, such as the insulin receptor differ from those that are expressed on cells of the brain and liver. The main difference between the receptors to the same ligand structure associated with intracellular receptor sites responsible for their effector functions, but sometimes there can be changes and of a carbohydrate component. Receptor proteins have isoelectric point (pH 5.0–5.5) and in these conditions become stable conformation (Petrov, Ataulakhanov 1997). If receptor proteins interact with the ligand, the proteins that interact with the antibody (AT) against ligand are termed “antireceptor”. Binding of receptor with antireceptor is happens similarly to idiotype – anti-idiotype. Exchange rate depends on the density of receptors on the cell membrane receptor molecules and antireceptors.

3. Receptors of lymphocytes in immunobiological stability

Receptor proteins of lymphocytes can bind antigen, antibody, components of the complement system, mediators of the immune system, various hormones as well as neurotransmitters (Boldirev 1986; Cullberg 1986; Lebedev, Ponyakina 1990). Some types of lymphocyte receptors are the same as in other cells. The main characteristic of receptor is bifunctionality (Drannik 2003).

Recognition of antigen via membrane receptors is the first step in a chain of successive actions of the body immune response. Upon ligand binding, the receptors activate effector mechanisms, which then give a signal inside the cells of the ligand that is on its surface (Cullberg 1987; Petrov, Ataullakhanov 1997).

This membrane signals trigger a chain of biochemical reactions that alter the metabolism of cells that eventually leads to division and differentiation or to the effective functioning (Cullberg 1987; Petrov, Ataullakhanov 1997).

The exchange rate of the immunoglobulin receptors rise very rapidly during the activation of lymphocyte and turning them into blasts. Receptor clustering and capping in the membrane of cells after exposure to the ligands is not the only process that occurs in the first minutes of ligand binding to the membrane. Known several early reactions that result from the aggregation of molecules on the cell surface (Petrov, Ataullakhanov 1997):

- 1) activation of cyclase;
- 2) changing of insight membranes, lipids;
- 3) changing of viscosity;
- 4) intensification of phospholipid metabolism and activation of enzymes that break down and synthesize membrane lipids.

4. Metabolites of lymphocytes in immunobiological stability

Among the factors that regulate immunoglobulin production are cyclic nucleotides. In the first hours after the activation of lymphocytes, cAMP splits and when it is lowered the activation of protein synthesis happens. During the extension of the growth of the AMP concentration, cells lose the ability to activate and to synthesize the protein (Cullberg 1987).

A cell can be represented as a system of interconnected membranes, because there is much evidence that the outer membrane of the cell, cytoplasmic, mitochondrial, lysosomal and nuclear are closely related. One function of the outer cell membrane is the regulation of metabolism between the intracellular space and the extracellular environment (Petrov, Ataullakhanov 1997).

Mutual influence of immune cells happens with the active participation of their membranes (Cullberg 1987; Petrov, Ataullakhanov 1997). Membrane proteins more or less interact with lipid bilayer membranes. In this case, the proteins do not only affect the bilayer, but also have the action of the surrounding lipids. Membrane structure is very

dynamic. Significant changes in the membranes occur during cell development and transformation (Liashenko, Molotkovskaya 1988; Liashenko et al. 1988). The relative composition of lipid membranes and the viscosity of the carbohydrate part of the bilayer depend on the functional activity of these membranes. In the cells, which grow and divide, the membranes tend to be more liquid and have more lipids, but in tumor cells are vice versa. It is possible that the cell membranes of organisms, standing at all levels of evolutionary hierarchy, have a distinctive ability to homeoviscous adaptation by changing the fatty acid composition of membrane lipids.

There are several ways to change the metabolism of immune cells – the opening of tubular structures, the change of enzyme activity (Khaitov, Pinegin 2000), the change of microviscosity of the membranes and the change of receptor structures (Robinson et al. 1986). Immune cells have their own range of receptors and enzymes that are active, the composition and status depends on many conditions of existence of the body and its function. Composition and state of receptors and enzymes of immunocompetent cells is changed during the proliferation, differentiation and cooperative interactions (Robinson et al. 1986; Stenina et al. 1986). It is known that the optimal spectral and functional relation of membrane systems exists under normal physiological conditions (Lebedev, Ponyakina 1990). Imbalance at different levels of these systems leads to the development of immunopathological states of the organism (Lebedev, Ponyakina 1990). Under the influence of external factors the transition of plasma membrane from one state to another is occurred, and changes in the content of intracellular cAMP, cGMP, Ca⁺⁺ ion, and others are happened (Khaitov, Pinegin 2000).

A tender spot of autoregulating mechanism is lipid stroma cells, through which the electrons are transported and in which enzymes and receptor proteins are deployed. The cell membrane of lipids is involved in the implementation of their functions, which also applies to cells and cells monophagocytic system (Petrov et al. 1997). Lipids are part of the endogenous regulatory factors produced by immunocompetent (Nikitin 1986) cells and alter membrane microviscosity, their permeability, activity of enzymes and receptor mobility.

In membranes of lymphocytes there are lipo- or cyclooxygenase cascade conversion of arachidonic acid metabolites in the highly-prostaglandins, leukotrienes and thromboxanes (Devels et al. 2006),

which are involved in the regulation of immune response. It is known that lipids are part of some receptors of immune cells, in particular Fc-receptor is phospholipoprotein and has phospholipase activity.

It is believed that the markers of subpopulations of lymphocytes – glycopospholipids involved in cooperative interactions. The human body can form antibodies to phospholipids causing pathological states – systemic lupus erythematosus, thrombosis or thrombocytopenic purpura (Khaitov, Pinegin 1996). Lipid matrix plays an important role in signal transduction. After acceptance of lymphocytes ligands the fluidity of the lipid bilayer is changed. Microviscosity decrease leads to the opening of channels for entry of Ca^{2+} , activation of phospholipase A and C, which determine the direction of the metabolism of immune cells. It is known that high concentrations of Ca^{2+} in the lymphocyte membrane cause increased permeability of ion sugar nucleosides through the membrane, which is necessary for synthetic processes in the lymphocytes (Liashenko, Molotkovskaya 1988; Liashenko et al. 1988). It is found that the mechanisms of B-lymphocytes activation are depended on Ca^{2+} (Robinson et al. 1986). When immune cells are activated then free unsaturated fatty acids are built in their membrane phospholipids (Baybakov et al. 1988). In the transition of lymphocytes from the resting phase in presynthetic phase of the cell cycle an increase in the level of cAMP and decrease in the level of GMP is observed. Lymphocytes in the phase of transition synthesis require signal that increases the content of cGMP. Such initiating factor may be the insulin, but for the differentiation of immune cells the activation of guanylate cyclase is required.

State of the system of cyclic nucleotides immune cells depends on thymus hormones (Borisova et al. 1988), and can be regulated by prostaglandin E_2 or histamine. The content of cAMP in lymphocytes changes when stimulated with PHA, Con A, pokeweed mitogen (Khaitov, Pinegin 2000) under the differentiation and division. Hydrolysis of phospholipids and the release of fatty acids is also one of the mechanisms that control the state of immune cells. Increased levels of fatty acids in the membranes of liposomes activates cyclooxygenase cascade and leads to increased production of high-type metabolites of eicosanoids type.

In many pathological conditions of the body lipid peroxidation of biological membranes is activated,

the levels of free radicals are increased and free radical processes are enhanced. This happens as result of radiation injury, during the development of tumors, avitaminosis (Stephanie, Valtischev 1996) and other states.

In operation of the normal physiological cell systems lipid peroxidation plays an important role in the regulation of membrane permeability, in the speed of cell division, in the state of oxidative phosphorylation and in the synthesis of prostaglandins and steroids (Stephanie, Valtischev 1996).

Products of lipid peroxidation are intracellular metabolites, the stationary concentration of which varies in different physiological conditions, as well as in extreme and pathological conditions.

The existence of regulatory mechanisms of immunological reactivity, including different populations and subpopulations of lymphocytes, lymphokines and interleukins does not preclude the existence of other systems involved in these processes (Stephanie, Valtischev 1996; Coico et al. 2003; Devels et al. 2006; McGeachy et al. 2009; Santili, Zurier 1989; Yoshimura et al. 2010) for the cellular and humoral homeostasis. There are many known works, which indicate involvement of membrane lipids in the regulation of the immune response.

Especially important is the regulatory role of the lipid phase of membranes of lymphocytes in the immune processes. Lipids are synthesized in the immunocompetent cells captured with receptors or phagocytosis and moved from cell to cell transmembrane. Free radical oxidation is a universal mechanism of modification changes all types of immune cells, as well as the structure of the lipid phase of the cell membrane.

Thus, in the study of the state of lipid peroxidation in the development of the humoral immune response in mice (Grinevich et al. 1990), it was found that the products of lipid peroxidation play an important role in the regulation of immunogenesis. The number of malondialdehyde grew in the early immune response and peaked in the proliferative phase, the maximum number of it was registered a day earlier of the growth of antibodies and antibody forming cells. 24 hours before a maximum value of antibody LPO began to fall, indicating a significant relationship between these processes. The introduction of antioxidant ionol showed that in chronic administration of it block lipid peroxidation and antibody genesis.

According to, inhibition of lipid peroxidation may be associated with certain neurotransmitters, which are shown or formed by the interaction of antigen-antibody and lipid peroxidation plays an important role in the regulation immunogenesis.

Y.A. Grinevich (1990), when studying lipid peroxidation in the membranes of lymphocytes after exposure to immunostimulants of different nature – PHA, splenin, timostimulin and microbial antigens nature, have come to a conclusion that the mechanisms of the immune response activation LPO cells plays an essential role in the early stages of development of the immune response. The maximum accumulation of malondialdehyde, the end product of lipid peroxidation occurs at 2–3 days after antigenic stimulation, and the peak of spontaneous chemiluminescence was recorded already next day after immunization, while antibody titers in mice peaked on 5–7 days, and in rats on 9–11 days of experiment (Grinevich et al. 1990).

When introducing the T-dependent and T-independent antigens, free radical processes occur in the early stages of immunogenesis, which is confirmed in the literature. Elevated levels of secondary products of lipid peroxidation in the membranes of immune cells were recorded in the early immune response to sheep red blood cells.

During immunization there is an occurrence of typical dynamics of fatty acid composition of membrane lipids of lymphocytes with increasing unsaturation of acyl residues in phospholipids, activation of desaturation processes with higher levels of free cholesterol. Similar results were obtained in studies in rabbits LCD under stress, indicating the analogy between stress and antigenic stimulation. Accumulation of cholesterol causes an increase in the area of membrane structures. Its growth on high antibody probably has a physiological adaptation in nature, providing along with the increase of cell mass, increasing the resistance of membrane lipids to repeated oxidative action and was confirmed by the authors who studied the sensitivity of B-cells to free radical oxidation processes.

Activation of free radical processes in the membranes of immune cells in the early stages of immunization determines the transmembrane transport of uridine, sugars, amino acids, nucleosides, and other substances that promote the entry of lymphocytes in the synthetic phase of the cell cycle (Petrov et al. 1997). Increase in the early stages of immune response in the membranes of

cells of lipid peroxidation products may be indicative of metabolic disorders and possible changes in the DNP-complex through the formation of DNA crosslinks with aldehydes and ketones. It is known that this mechanism may include some parts of the genome and determine the expression of traits that are programmed to a particular period and accelerate entry into the processes of cell proliferation and differentiation (Drannik 2003). Change in short-term free radical processes, and 2 weeks after immunization, these rates return to normal, maintenance of secondary and final products of lipid peroxidation are normalized, and it can be assumed that on the 14th day after antigenic stimulation there is renovated population of immune cells (Robinson et al. 1986). Free radicals may block the broadcast of free DNA, change the phase state of the lipid bilayer, on which the conformation and mobility of receptors is depended (Petrov et al. 1997; Khaitov, Pinegin 2000), as well as the processes of activation of lymphocytes and phagocytes (Petrov et al. 1997; Khaitov, Pinegin 2000). Since the activation by antigen accompanied by the increases of level lipid metabolism in membranes and free radical oxidation, possibly receptors of committed lymphocyte populations become resistant to lipid peroxidation (Liashenko et al. 1988).

Regulation of intensity of cell division occurs at the level of the body and tissues. The integrated systems are responsible for the regulation at the body level, and chalone – for the tissue level.

Chalones when they reach the cells, form the complex “chalones + receptor”, which is due to the vertical mobility of membrane receptors causes excitation of adenylate cyclase, located on the inner surface of the membrane and increases the formation of cAMP in the cells in vivo after 30 minutes (Garkava 2001). After 1.5 hours, inhibition of protein synthesis is marked, which plays an important role in the preparation and implementation of mitosis. And in 3–4 hours after administration of chalones there is inhibition in cell proliferation. Chalones molecules in vitro combine with the receptor during one minute, then in 30 minutes enter the cell, and after 4 hours split and release from the cell in the form of small-molecule products. After primary treatment cells cannot respond to the re-introduction chalones within 2 hours. Chalones have surface-membrane origin and released from the cells by calcium-dependent proteases (Nikitin 1986).

5. Conclusions

The analysis of the molecular mechanisms of regulation of immunobiological stability of the organism were carried out. It is shown that the stability of immunobiological body requires consistency of lipid peroxidation, a range of lymphocyte receptors, interleukins and regulation of these processes by lymphocytic chaperones system.

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К.Г. Гаркава. Молекулярні аспекти імунобіологічної стабільності організму

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Проведено аналіз молекулярних механізмів регуляції імунобіологічної стабільності організму. Показано, що для імунобіологічної стабільності організму необхідна узгодженість процесів перекисного окиснення ліпідів, певного спектру рецепторів лімфоцитів, інтерлейкінів та регуляції цих процесів лімфоцитарною кейлонною системою.

Ключові слова: інтерлейкіни, лімфоцитарні нейлони, лімфоцити, перекисне окиснення ліпідів, рецептори.

К.Г. Гаркавая. Молекулярные аспекты иммунобиологической стабильности организма

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Проведен анализ молекулярных механизмов регуляции иммунобиологической стабильности организма. Показано, что для иммунобиологической стабильности организма необходима согласованность процессов перекисного окисления липидов, определенного спектра рецепторов лимфоцитов, интерлейкинов и регуляция этих процессов лимфоцитарной кейлонной системой.

Ключевые слова: интерлейкины, лимфоцитарные кейлоны, лимфоциты, перекисное окисление липидов, рецепторы.

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