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The role of calcium metabolism disorders in induction of hypersensitivity in cardiovascular diseases

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ABSTACT

Impairment of extracellular and intracellular calcium homeostasis can have a damaging effect on the functioning of both individual organs and systems and the whole organism. In the cardiovascular system, disorders of calcium metabolism trigger a cascade of auto-inflammatory responses, leading to persistent morphological and functional disturbances. In this review, impaired calcium homeostasis is defined as a predictor of the development of hypersensitivity in cardiovascular diseases. We analyzed the development of a cardiovascular pathology (atherosclerosis, aortic valve calcification, and essential hypertension) with impaired calcium metabolism and pathological mechanisms that cause the disturbances. Calcium sensors, polymorphic variants of genes, and hormones involved in calcium metabolism can reveal the features of calcium metabolism and contribute to a personalized approach to treatment of cardiovascular diseases.

Key words: calcium metabolism, atherosclerosis, aortic valve calcification, auto-inflammation, essential hypertension, allergic reactions.

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Роль нарушений обмена кальция в индукции иммунной гиперчувствительности при сердечно-сосудистых заболеваниях

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РЕЗЮМЕ

Нарушение внеклеточного и внутриклеточного гомеостаза кальция способно оказывать повреждающее

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действие на функционирование как отдельных органов и систем, так и на весь организм в целом. В сердечно-сосудистой системе дисбаланс кальциевого обмена запускает каскад реакций аутовоспалительного характера, приводящих к стойким морфологическим и функциональным нарушениям. В данном обзоре нарушение кальциевого гомеостаза рассматривается как предиктор развития иммунной гиперчувствительности при сердечно-сосудистой патологии. Проанализировано развитие патологии сердечно-сосудистой системы (атеросклероз, кальцификация клапанов сердца и эссенциальная гипертензия) при нарушении кальциевого обмена и патологических механизмах, которые данные нарушения вызывают. Кальциевые сенсоры, полиморфные варианты генов и гормоны, участвующие в обмене кальция, могут выявить особенности кальциевого обмена и внести свой вклад в персонализированный подход в лечение сердечно-сосудистой патологии.

Ключевые слова: метаболизм кальция, атеросклероз, кальцификация клапанов сердца, аутовоспаление, эссенциальная гипертензия, аллергические реакции.

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INTRODUCTION

Calcium is a macronutrient that plays a pivotal role in many biochemical reactions contributing to the vital activity [1]. Transplantology studies the role of calcium metabolism, including its effect on heart valve and vascular prostheses [2, 3].

The biological role of calcium is extremely diverse, since it is a part of nearly all physiological processes. Membrane stabilization, enzyme activation, blood clotting, and cell death are the processes that involve calcium ions. Moreover, transport across membranes, cell – cell communication, information transfer, intracellular and extracellular signaling, bone and cardiac remodeling, and gene expression involve calcium as well [3, 4].

In intracellular signaling, calcium acts as a second and third messenger. In intercellular signaling, calcium coordinates biochemical processes. Through this mechanism, calcium affects the efficiency of the immune system, and its dysregulation induces hypersensitivity reactions, some of the manifestations of which include immune inflammatory responses [1, 5].

In the absence of abnormalities, nutritional disorders, and micro- and macroecological imbalance, calcium regulates routine cellular processes, such as proliferation and differentiation. In case of any deviation from the norm, calcium metabolism can be significantly disrupted. The effect on the above-mentioned processes would be pathological, incorporating hypersensitivity / apoptosis. [1, 5, 6]. Therefore, calcium metabolism is essential for the body, and disorders of calcium metabolism underlie many chronic diseases, such as inflammatory responses that determine development of cardiovascular pathology [1, 3].

HYPERSENSITIVITY REACTIONS AS THE BASIS OF CARDIOVASCULAR PATHOLOGY

In 1968, P.G.H. Gell and R. Coombs proposed the following classification of hypersensitivity reactions: immediate hypersensitivity (IH, atopy), cytotoxic (cytolytic), immune complex-mediated, delayed hypersensitivity (DH, cellular), and antibody-mediated hypersensitivity [7, 8]. These reactions are important links in the pathogenesis of allergic and autoimmune diseases [7–9].

Hypersensitivity reactions include three parallel phases: 1) immunological (interaction of the antigen with antibodies and / or sensitized CD4+ T helper and CD8+ cytotoxic T lymphocytes); 2) pathochemical (release of inflammatory mediators); 3) patho-

physiological (stage of clinical manifestations). Hypersensitivity reactions are divided into five types due to the nature of the first, immunological phase. The effect of calcium metabolism is implemented via the pathochemical and pathophysiological stages [8].

In 1999, a new group of autoinflammatory diseases was introduced. Discovery of these diseases is associated with the identification of autosomal dominant and autosomal recessive disorders, as well as monogenic diseases manifested by familial periodic fevers, cold allergies, and non-infectious dermatitis [10]. The genes associated with these diseases encode the activity of inflammasomes and cause a hyperactive innate immune response [10].

Further studies made it possible to distinguish a group of polygenic autoinflammatory diseases that includes atherosclerosis [11]. Activation of innate immunity and development of a systemic inflammatory response and multi-organ damage are particularities of this pathology [12]. It is atherosclerosis that is the underlying pathology determining the cardiovascular disease continuum.

Acquired heart diseases are another significant pathology, formed due to immune inflammatory responses and constitutional symptoms. This pathology is manifested though acute rheumatic fever in children and rheumatic disease in adults. The etiology and pathogenesis of acquired heart diseases are being actively studied.

The concepts of specific rheumatogenic M types of streptococcus pyogenes, autoimmune damage to myocardial autoantigens, and immune complex-mediated inflammatory responses remain relevant [13]. According to the classification, this disease can be attributed to a mixed group [14]. High autoinflammatory activity is intrinsic in acquired heart diseases after infectious endocarditis [15]. Prerequisites for acquired heart diseases remain the same by the time of surgical treatment. Therefore, these factors can determine early and long-term consequences, such as calcification of the implant [16].

Multi-omics approaches to analysis of genomic, epigenomic, transcriptomic, and microbiome markers of immune inflammatory diseases create new prospects for their treatment [9]. At the same time, calcium metabolism disorders can make a significant contribution to the understanding of the molecular, cellular, and genetic mechanisms of this pathology.

The main focus of the study will be the role of calcium in maintaining hypersensitivity responses, implemented both through classical allergic (immunopathological) reactions and autoinflammatory reactions associated with activation of innate immunity. As mentioned above, the role of calcium in these reactions consists in its extracellular and intracellular regulatory functions.

EXTRACELLULAR CALCIUM METABOLISM

Calcium concentration in the blood is regulated by several hormones. Intracellular and extracellular concentration is controlled by a complex system of pumps, channels, exchangers, and a wide range of Ca^{2+}-binding proteins [6]. Parathyroid hormone (PTH), synthesized in the parathyroid gland (PTG), regulates extracellular calcium homeostasis. The calcium-sensing receptor (CaSR) expressed on the surface of PTG cells activates synthesis and secretion of PTH. In the bloodstream, PTH binds to the G protein-coupled parathyroid hormone 1 receptor (PTH1R), increasing osteolytic activity of osteoclasts and bone resorption. In the renal nephron, PTH promotes reabsorption of calcium [17].

By stimulating production of calcitriol in the kidneys, PTH promotes a vitamin D-mediated increase in calcium absorption in the intestine. Calcitriol (Vitamin D – $1,25(OH)_2D$) is synthesized from the inactive precursor of vitamin D3 (cholecalciferol) through double subsequent hydroxylation by the enzyme 1 α-hydroxylase in the kidneys and the liver. PTH stimulates CYP27B1 gene transcription, which encodes 1α-hydroxylase [18] and fibroblast growth factor-23 (FGF-23). In contrast, FGF-23 has an inhibitory effect on 1α-hydroxylase and stimulates synthesis of 24-hydroxylase (CYP24), thus converting calcitriol to inactive metabolites [18, 19].

Vitamin D plays an important role in regulating calcium metabolism. Vitamin D stimulates expression of protein transporters (transient receptor potential cation channel subfamily V member 5 (TRPV 5), transient receptor potential cation channel subfamily V member 6 (TRPV 6), calcium-binding protein calbindin – CaBP-9k, CaBP-28k, etc.), which promote calcium absorption in the intestine, stimulate osteoclastic resorption, and enhance calcium reabsorption in the renal tubules [6, 18]. Another effect of PTH and vitamin D is an increase in the serum calcium concentration.

However, calcitonin has an opposite effect on calcium regulation. It is a calcium-lowering hormone secreted by parafollicular cells of the thyroid gland. The signal for its secretion is hypercalcemia. Calcitonin inhibits osteoclastic activity in the bone, reducing bone resorption and increasing excretion of calcium ions in the renal tubules [6, 17].

In addition to the three main hormones regulating calcium homeostasis, new regulators of calcium metabolism have been discovered, such as klotho. Klotho is a protein hormone that has two forms: membrane and secreted. It is synthesized by the kidneys, intestines, brain, and other organs. Membrane-bound klotho is a cofactor for FGF-23, synthesized by osteocytes. By binding together, klotho and FGF-23 interact with and biologically affect receptors of organs and tissues.

FGF-23 regulates vitamin D by inhibiting 1α-hydroxylase, thereby indirectly affecting calcium metabolism [18, 19]. Moreover, the association of klotho deficiency with atherosclerosis and vascular calcification was revealed. Decreased klotho levels are known to correlate with the severity of coronary artery stenosis. Decreased plasma klotho concentration and low klotho expression in the vascular wall are associated with high risk of coronary artery disease. At the same time, increased plasma klotho concentration is associated with low risk of developing cardiovascular diseases [20].

Besides calcium and phosphorus metabolism, vitamin D is involved in other physiological processes in the body. Vitamin D can have an extra-skeletal effect due to the presence of vitamin D receptors (VDR) in almost all cells and tissues of the body – cells of the immune system, vascular smooth muscle cells, endothelial cells, and cardiomyocytes [18]. Similar to thyroid and steroid hormone receptors, VDR is one of the transcription factors that regulates protein synthesis; thus, an active form of vitamin D is equivalent to steroid hormones [21].

Directly or indirectly, vitamin D regulates about 200 genes. It controls secretion of proinflammatory cytokines, adhesion molecules, proliferation of vascular smooth muscle cells and cardiomyocytes, exerting an inhibitory effect on the processes associated with atherosclerosis and vascular calcification and suppressing renin gene expression, thereby regulating the activity of the renin-angiotensin-aldosterone system (RAAS) [16, 18]. Indirectly, vitamin D reduces synthesis of matrix metalloproteinases (MMPs), which significantly limits the growth of atherosclerotic plaque [22] and blocks synthesis of proinflammatory cytokines and cell adhesion molecules, preserving the integrity of the vascular wall and its components and limiting the process of vascular calcification [16].

Therefore, disorders of extracellular calcium metabolism can be associated with individual genomic and epigenomic characteristics that must be taken into account during assessment of hypersensitivity responses and cardiovascular pathology. In this regard, genetic polymorphisms in the PTH genes, calcitonin, CYP27B1, CYP24, TRPV 5, TRPV 6, cabp-9k, cabp-28k, FGF-23, VDR and others make an important contribution to calcium metabolism [15, 18, 21]. Moreover, chromosomal microdeletions, monogenic disorders, and thyroid surgery may affect extracellular calcium metabolism as well [23]. Disorders of extracellular calcium metabolism create prerequisites for changes in both intercellular and intracellular signaling.

INTRACELLULAR CALCIUM METABOLISM

In the cell, calcium can exist in three forms: 1) ionized (free); 2) localized in intracellular organelles (endoplasm, sarcoplasmic reticulum, nucleus, mitochondria); 3) chelated (bound). Intracellular calcium concentration is about 10,000 times less than extracellular calcium concentrations. Under resting conditions, the cytosolic free calcium concentration is 100–200 nM, which is facilitated by Ca^{2+}-ATPase and Na / Ca^{2+}-exchangers. Moreover, many proteins in the cytoplasm bind calcium ions, acting as buffers [6].

More than 200 genes in the human genome encode Ca^{2+}-binding proteins [5]. The biochemical action of calcium in the cell is mediated by the EF-hand Ca^{2+}-binding motif and other Ca^{2+}-binding proteins (calcium sensors) associated with the regulation of ion currents, signal transmission, and cell proliferation and differentiation [24]. With calcium ions, troponin C regulates the interaction between actin and myosin in striated muscles. Mutations in troponin C are associated with some forms of congenital heart diseases [5, 25].

Calsequestrin, calregulin, and calreticulin regulate calcium transport and act as a buffer for calcium. Calcium ions and annexin V, which belongs to phos-

pholipid-binding proteins, can selectively and affinely bind to phosphatidylserine, reaching the surface of the cell membrane during apoptosis. Annexin V is used as a specific marker of apoptosis [26]. Calmodulin is one of the most important calcium sensors, it has four high-affinity Ca^{2+}-binding centers, making it a multifunctional regulatory element [24].

Thus, calcium ions can regulate the activity of more than 100 enzymes, ion pumps, and cytoskeletal components. Increased serum calcium concentration triggers exocytosis of mediators in presynaptic nerve terminals, reduction of myocytes, hormone release of endocrine and exocrine glands, and migration of white blood cells, tumor cells, etc. A significant number of diseases have been described associated with defected Ca^{2+} transporters, channels, sensory proteins, as well as enzymes modulated by them [5]. Some Ca^{2+}-binding proteins are diagnostic markers for cancer [5, 27].

A complex system of intracellular calcium metabolism regulation plays a crucial role in regulating many biochemical processes and developing immune-mediated inflammatory and cardiovascular diseases [3, 28, 29]. Polymorphic variants of Ca^{2+} transporter genes and sensory proteins determine disorders of intracellular calcium metabolism. In the following parts of the work, the focus will be placed on the role of calcium in maintaining autoinflammatory diseases associated with activation of innate immunity through apoptosis and pyroptosis.

THE ROLE OF CALCIUM IN THE REGULATION OF APOPTOSIS

Certain individual characteristics can contribute to a significant increase in the serum calcium concentration in the cell up to 1000 nM. This results from Ca^{2+} channels opening in the plasma membrane or the endoplasmic reticulum via dihydropyridine and ryanodine receptors [30, 31].

The above-mentioned mechanisms lead to a drastic and short-term increase in the concentration of calcium in the cytoplasm, the so-called "calcium peaks" [5]. Certain signals increase the frequency of these peaks, leading to prolonged elevation of the level of calcium in the cytosol. Prolonged elevation has a cytotoxic effect on the cell, which is extremely sensitive to changes in the calcium concentration. Located on the inner membrane of mitochondria, phospholipase A2 is activated by cytosolic calcium, damaging the phospholipids in the mitochondrial membranes and disrupting their work [30]. At the beginning of this process, the mitochondria successfully cope with an acute rise in cytosolic calcium, since they accumulate it in the form of an insoluble salt – hydroxyapatite. However, this is only a temporary measure. While the mitochondria "hide" calcium, they cannot synthesize adenosine triphosphate (ATP), a lack of which prevents excess calcium from leaving the cell through pumps. Following disruption in the respiratory chain, oxidative stress develops, forming pores in the mitochondrial membrane. Hydrolysis of membrane phospholipids leads to accumulation of free fatty acids in the mitochondria, which correlates with the degree of their damage. If this vicious circle is not broken, the cell will die [5].

Due to cytosolic calcium overload, the intrinsic (mitochondria-dependent) apoptotic pathway is triggered. The intrinsic pathway stimulates changes in the membrane potential and release of pro-apoptotic B-cell lymphoma-2 (Bcl-2) family proteins: Bcl-2-associated X-protein (BAX) and Bcl-2 homologous antagonist / killer (BAK) [5, 32]. These events disrupt the integrity of the mitochondrial membrane, forming apoptotic pores and promoting the release of mitochondrial proteins, such as cytochrome C and apoptosis-inducing factor (AIF), which is capable of initiating caspase-independent cell death [28, 30, 32]. Cytochrome C binds to the apoptosis protease-activating factor-1 (APAF-1), resulting in the formation of an apoptosome that converts procaspase-9 to active caspase-9. Then, the elements of the apoptotic cascade activate effector caspases (caspase-3, -6, -7) [5, 32].

Activated caspases break down plasma membrane calcium pumps (PMCA), overloading the cell with calcium and leading to even greater activation of proteases and caspases [5]. Thus, activated caspases trigger a chain of biochemical processes that lead to cell death.

Literature data suggest that the level of calcium determines what mechanism of cell death will be used – apoptosis or necrosis. A small increase in the level of calcium initiates apoptosis, however, a sudden rise in calcium is related to necrosis [28]. Progression of necrosis is associated with activation, increased levels of calcium, Ca^{2+}-dependent phospholipases and nucleases, as well as calpains, which cause destructive changes in cells. Energy supply

for the cell is another essential factor: with big ATP reserves, cell death happens via apoptosis, and with energy depletion – via necrosis [28, 30].

THE ROLE OF CALCIUM IN THE REGULATION OF PYROPTOSIS

Pyroptosis is a protective innate immune mechanism, a type of a programmed form of necrosis of leukocytes, more often, monocytes / macrophages [33]. However, unlike apoptosis, pyroptosis proceeds with development of inflammation, as it is accompanied by the release of proinflammatory cytokines. This process is possible due to the formation of a multiprotein complex – inflammasome. The inflammasome has sensory molecules, which bind caspase-1 to the apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (PYCARD / ASC CARD). Activation of caspase-1 cleaves interleukin (IL)-1β and IL-18 [34].

Moreover, the pore-forming protein gasdermin D is activated during pyroptosis [33]. Due to the difference in the osmotic pressure, Na^+ ions and water rush into the cell. Cell lysis occurs, and all the content, including proinflammatory cytokines and damage-associated molecular patterns (DAMPs), burst into the intercellular space and potentiate local inflammation. As a type of programmed cell death, pyroptosis is activated by pathogen-associated molecular patterns (PAMPs) and aimed at eliminating infectious agents that have entered the cell [34, 35].

The NLRP3 inflammasome is the most studied and of the greatest interest for us. There are intracellular and extracellular pathways of NLRP3 inflammasome activation. The intracellular activation mechanism is related to calcium levels. When dehydration occurs due to changes in the osmotic pressure as potassium and chlorine ions leave the cell, calcium mobilization is stimulated through transient receptor potential channels (TRP channels) [36]. An increase in the intracellular concentration of calcium leads to activation of one of its targets – TGF-β-activated kinase 1 (TAK1), which is associated with deubiquitination of NLRP3 [5, 34].

Changes in the extracellular calcium concentration result in a decrease in cyclic adenosine monophosphate (cAMP) by inhibiting adenylate cyclase. Besides, due to these changes, intracellular calcium increases through activation of phospholipase C and synthesis of second messengers associated with calcium mobilization. The effect of cAMP on the activation of the inflammasome remains controversial [37].

The peculiarity of the NLRP3 inflammasome is that it requires two signals to become activated. The first signal is products of microorganisms and cytokines and the second one is various crystalline substances, including cholesterol crystals. Cholesterol crystals and oxidized low-density lipoproteins (LDL) stimulate caspase-1, which, in turn, activates the NLRP3 inflammasome, resulting in inflammation [38–40].

LDL is oxidized by reactive oxygen species in endothelial cells. Macrophages not only actively capture oxidized LDL, but also play a pivotal role in the atherogenesis [39, 40]. NLRP3 activation results in synthesis of IL-1β, associated with the atherosclerosis. IL-1β stimulates adhesion of leukocytes and monocytes to endothelial cells and their procoagulant activity, increasing synthesis and activity of tumor necrosis factor (TNF), chemokines, nitric oxide, etc. [41]. Excessive activation of the NLRP3 inflammasome can cause uncontrolled systemic inflammation that underlies the pathogenesis of a wide range of inflammatory diseases, such as atherosclerosis, rheumatoid arthritis, Crohn`s disease, obesity, diabetes mellitus, Alzheimer`s disease, etc. [40].

Therefore, calcium ions can be attributed to non-protein mediators that initiate cell death, either through apoptosis or through pyroptosis. Selecting the mechanism of cell death is quite complex and multifaceted, since it depends on the type and strength of the stimulus that activates cell death. Moreover, calcium ions affect the activity of the inflammasome and, hence, the autoinflammatory process. Currently, the most significant autoinflammatory disease is atherosclerosis [40].

THE ROLE OF CALCIUM METABOLISM DISORDERS IN THE PATHOGENESIS OF CALCIFICATION AND ATHEROSCLEROSIS

The role of calcium metabolism disorders in the development of atherosclerosis, arterial hypertension, ischemic heart disease, and cerebrovascular diseases has been established, making it possible to refer these diseases to the “calcium deficiency” category [29]. Genetic mechanisms associated with the intracellular calcium concentration both in cardiomyocytes and in smooth muscle cells and neurons of

the brain are similar in the pathogenesis of these diseases. The detected polymorphisms of genes responsible for calcium metabolism would explain genetic susceptibility to bioprosthetic heart valve calcification [15].

Coronary artery calcification and valvular calcification increase the risk of cardiovascular events, in addition to being a prognostic factor for coronary artery disease. Sclerosis of the vascular wall and calcium mineralization change the architectonics of the vessel resulting in narrowing of its lumen up to obliteration. This process is similar to osteogenesis, with the same participants and principles of progression [16].

The nature of calcium salt deposition is important in the calcification of atherosclerotic plaques. With homogeneous calcium deposition, the strength of the plaque cap increases, reducing the risk of its rupture. Uneven deposition has the opposite effect. Therefore, it is difficult to assess whether calcium has a stabilizing or destabilizing effect.

Vascular calcification may occur due to deficiency of calcification inhibitors (osteopontin, pyrophosphates) produced by vascular smooth muscle cells. The osteoprotegerin (OPG) / receptor activator of nuclear factor-kappaB (NF-kB) ligand (RANKL) / receptor activator of NF-kB (RANK) system is also involved in the development of vascular calcification [42]. OPG is found in some tissues and organs, including the heart. OPG takes part in synthesis of monocyte chemoattractant protein-1 (MCP-1) and MMPs, thereby supporting inflammation in the atherosclerotic plaque [43]. Studies show that deletion of the *OPG* gene in mice causes aortic calcification.

Other studies showed that elevated OPG levels in the blood correlate with the severity of atherosclerosis, heart failure, unstable angina, and acute myocardial infarction [42, 43]. Bioprosthetic heart valve calcification can also be stimulated by the underlying immune inflammatory process that induced formation of acquired heart disease.

As mentioned above, rheumatic disease is not only a streptococcal infection, but also an autoimmune disease that develops according to the second and third types of hypersensitivity responses (allergic: cytoxic and immune complex-mediated) [7]. The pathogenesis of this disease is associated with hypersensitivity developing according to these allergic patterns and linked to particular human leukocyte antigen (HLA) genes and alleles. The immune response (Ir) genes of the HLA class II determine immune dysregulation via autoimmune T lymphocyte clones [8]. At the same time, disorders of calcium metabolism may influence the pathochemical and pathophysiological phases of hypersensitivity.

In particular, the process of degranulation of cells involved in allergic inflammation is associated with calcium ions. Thus, calcium ions and complement components C3a and C5a (anaphylotoxins) are secondary liberators of histamine and other active molecules of cell granules [44]. Through phosphorylation by spleen tyrosine kinase (Syk), phospholipase Cγ (PLCγ) is activated, which catalyzes breakdown of phosphatidylinositol bisphosphate (PIP2) to inositol trisphosphate (IP3) and diacylglycerol (DAG).

In inflammatory cells, IP3 mediates an increase in intracellular calcium, depleting the intracellular calcium deposits. The increased amount of calcium activates transcription factors, leading to granule exocytosis. In the presence of DAG, calcium ions activate protein kinase C, which phosphorylates myosin light chains, reducing the cytoskeletal elements and initiating degranulation [7]. Calcium ions are involved in activation of an esterase, leading to hydrolysis of phospholipids through phospholipase D. These phospholipids comprise the basis of the cell wall. Thinning of the membrane facilitates exocytosis of granules and secretion of mediators [45]. Moreover, calcium ions and Syk activate phospholipase A2 (PLA2), which is involved in synthesis of arachidonic acid, followed by eicosanoid formation. Eicosanoids are known to mediate the late phase of allergic inflammation [7, 8].

Therefore, the precise mechanism of calcification is not fully understood. However, theories exist about an imbalance between stimulants and inhibitors of calcification that trigger this process. Many studies are dedicated to the role of disorders of intracellular calcium metabolism as a basis for the pathochemical phase in immune hypersensitivity. The latter should be taken into account in case of surgical correction of valvular heart disease resulting from rheumatic fever.

Belonging to the group of metabolic disorders, atherosclerosis is considered to be a result of sterile inflammation. Sterile inflammation consists of accumulation of DAMPs inside and outside the cell, inflammasome assembly, hyperproduction of reactive

oxygen species and autophagy, and local synthesis of proinflammatory cytokines IL-1 β and IL-18. These events contribute to local accumulation of immunocompetent cells – macrophages and lymphocytes, followed by tissue injury and the development of fibrosis [40].

Therefore, the basis of atherosclerosis is the inflammatory response of innate immunity, aimed at maintaining metabolic homeostasis via recognition of DAMPs. The literature describes extreme stages of sterile inflammation, where an adaptive immune response can be characterized by the presence of autoreactive T and B lymphocytes and antibodies [46].

Chronic inflammation within the vascular wall is maintained by mediators of cell – cell interaction, particularly by IL-1, IL-6, and TNF [22]. Proinflammatory and proatherogenic mediators are involved in the induction of apoptosis, contributing to the development and further progression of atherogenesis. In terms of physiology, apoptosis is not associated with inflammation. However, apoptosis can have a proinflammatory effect in the atherogenesis. Released from the apoptotic cells, DNA is immediately absorbed by phagocytes that release the proinflammatory cytokines [47].

An increase in the expression and activity of proinflammatory cytokines destabilizes the atherosclerotic plaque due to enlargement of the lipid core, thickening of the fibrous cap, and accumulation of macrophages [22], eventually leading to plaque rupture and triggering the mechanism of atherothrombosis.

An association of genetic variations in Toll-like receptor (TLR) genes in the innate immune response (particularly TLR4) with development of atherosclerosis and associated vascular complications was revealed [48]. The expression of these receptors is presented on the surface of cardiomyocytes, macrophages, smooth muscle cells, and vascular endothelial cells. Interaction with bacterial lipopolysaccharides and other proatherogenic ligands can activate the transcription factor NF-kB, resulting in synthesis of a wide range of inflammatory mediators, including proatherogenic ones [22, 46].

The role of disorders of intracellular calcium metabolism that stimulate apoptosis, pyroptosis, and inflammation has been described above. These pathological changes in calcium metabolism contribute to maintenance of atherosclerosis. Moreover, an imbalance between stimulants and inhibitors of calcification makes a significant contribution to the progression of atherosclerotic lesions.

Therefore, atherosclerosis is an inflammatory process that involves immune inflammatory mechanisms of innate and adaptive immunity. Atherosclerosis encompasses processes and factors that lead to growth and later destabilization of the atherosclerotic plaque, atherothrombosis, and other complications. In the meantime, calcium is involved in calcification, as well as in initiation and maintenance of chronic inflammation [22, 40, 47].

THE ROLE OF CALCIUM IN THE DEVELOPMENT OF ESSENTIAL HYPERTENSION

The development of essential hypertension is associated with disorders of intracellular calcium metabolism. The experiments on spontaneously hypertensive rats (SHR) showed the significance of hereditary defects of Na^+ and Ca^{2+} ion channels in the membrane of resistance artery smooth muscle cells. These changes result in increased vascular tone and high sensitivity to various pressor stimuli, with further development of endothelial dysfunction [49]. Moreover, changes in the water and electrolyte balance with reduction of natriuretic peptide levels were discovered [50].

Genetic defects were detected in dihydropyridine receptors (DHPR) localized on the cardiomyocyte membrane. Allowing calcium to enter the cell, these receptors are closely related to ryanodine receptors (RyRs), which regulate the release of calcium from the sarcoplasmic reticulum. By triggering the mechanism of calcium-induced calcium release (CICR), these receptors participate in cardiac muscle contraction. Disruptions in the process can lead to a persistent increase in blood pressure [31]. Moreover, any mutation in the *RyR2* gene, which leads to a disorder of calcium balance in the cell, is associated with heart failure, arrhythmogenic right ventricular dysplasia, and an increased risk of sudden cardiac death [51].

Therefore, a disorder of calcium metabolism is associated with increased vascular tone. Disruption of intracellular calcium homeostasis affects not only the cardiovascular system, but other systems as well.

CONCLUSION

The biological role of calcium is extremely diverse. Calcium ions activate and suppress immune

and inflammatory responses and regulate extracellular and intracellular metabolism. A countless number of biochemical reactions involving calcium confirm its uniqueness.

According to some authors, up to 150 different diseases are associated with impaired calcium metabolism. In relation to atherosclerosis and bioprosthetic valve calcification, the role of calcium consists in the initiation of a hypersensitivity response via apoptosis and pyroptosis. From the perspective of a personalized approach to management of cardiovascular diseases, it is necessary to monitor the serum calcium concentration and hormones involved in extracellular calcium metabolism. Features of intracellular calcium metabolism can be predicted by analyzing soluble OPG in the blood serum, calcium-sensing receptor gene polymorphism, and calcium transport proteins.

REFERENCES

1. Ahmedzhanova Z.I., Zhiemuratova G.K., Danilova E.A., et al. Macro- and micronutrients in the life of the body and their relationship with the immune system. *Journal of Theoretical and Clinical Medicine.* 2020; 1: 16–21 (in Russ.).
2. Antonova L.V., Kudryavtseva Y.A. Development of a tissue engineered small-diameter vascular graft for cardiovascular surgery. *Complex Issues of Cardiovascular Diseases.* 2016; 5 (3): 6–9 (in Russ.).
3. Majlyan D.E., Kolomiec V.V. The role of calcium dysmetabolism in the pathogenesis of cardiovascular diseases. *Russian Journal of Cardiology.* 2019; 9: 78–85 (in Russ.). DOI: 10.15829/1560-4071-2019-9-78-85.
4. Blaine J., Chonchol M., Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clin. J. Am. Soc. Nephrol*. 2015; 10 (7): 1257–1272. DOI: 10.2215/CJN.09750913.
5. Schaub M.C., Heizmann C.W. Calcium in health and disease. In: Kretsinger R.H., Uversky V.N., Permyakov E.A. (eds). Encyclopedia of metalloproteins. Springer, New York, 2013: 478–484. DOI: 10.1007/978-1-4614-1533-6.
6. Ahpolova V.O., Brin V.B. Calcium metabolism and its hormonal regulation. *Fundamental Medicine and Biology.* 2017; 2: 38–46 (in Russ.).
7. Yarilin A.A. Immunology. M.: Geotar – Media. 2010: 615–617 (in Russ.).
8. Haitov R.M., Garib F.Yu. Immunology. Atlas. M.: Geotar – Media.2020: 387–402 (in Russ.).
9. Gudima G.O. Strategies of precision medicine in modern clinical immunology and allergology. *Immunology.* 2019; 40 (4): 83–87 (in Russ.).
10. Figueras-Nart I., Mascaró J.M. Jr., Solanich X. et al. Dermatologic and dermatopathologic features of monogenic autoinflammatory diseases. *Front. Immunol.* 2019; 10: 2448. DOI: 10.3389/fimmu.2019.02448.
11. Nasonov E.L., Popkova T.V. Anti-inflammatory therapy for atherosclerosis: contribution to and lessons of rheumatology. *Rheumatology Science and Practice.* 2017; 55 (5): 465–473 (in Russ.). DOI: 10.14412/1995-4484-2017-465-473.
12. Nasonov E.L., Eliseev M.S. The role of interleukin-1 in the development of human diseases. *Rheumatology Science and Practice*. 2016; 54 (1): 60–77 (in Russ.). DOI: 10.14412/1995-4484-2016-60-77.
13. Carapetis J.R., Beaton A., Cunningham M.W. et al. Acute rheumatic fever and rheumatic heart disease. *Nat. Rev. Dis. Primers.* 2016; 2: 15084. DOI: 10.1038/nrdp.2015.84.
14. Nasonov E.L., Aleksandrova E.N., Novikov A.A. Autoimmune rheumatic diseases: results and prospects for researches. *Rheumatology Science and Practice.* 2015; 53 (3): 230–237 (in Russ.). DOI: 10.14412/1995-4484-2015-230-237.
15. Ponasenko A.V., Kutikhin A.G., Khutornaya M.V., et al. The association of rs13290979 polymorphism within Notch1 gene with severe bioprosthetic mitral valve calcification. *Fundamental and Clinical Medicine.* 2018; 3 (4): 12–21 (in Russ.). DOI: 10.23946/2500-0764-2018-3-4-12-21.
16. Wang J., Zhou J.J., Robertson G.R. et al. Vitamin D in vascular calcification: a double-edged sword? *Nutrients.* 2018; 10 (5): 652. DOI: 10.3390/nu10050652.
17. Centeno P.P., Herberger A., Mun H.C. et al. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. *Nat. Commun*. 2019; 10 (1): 4693. DOI: 10.1038/s41467-019-12399-9.
18. Christakos S., Dhawan P., Verstuyf A. et al. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiol. Rev*. 2016; 96 (1): 365–408. DOI: 10.1152/physrev.00014.2015.
19. Richter B., Faul C. FGF23 actions on target tissues-with and without Klotho. *Front Endocrinol. (Lausanne).* 2018; 9: 189. DOI: 10.3389/fendo.2018.00189.
20. Navarro-González J.F., Donate-Correa J., Muros de Fuentes M. et al. Reduced Klotho is associated with the presence and severity of coronary artery disease. *Heart*. 2014; 100 (1): 34–40. DOI: 10.1136/heartjnl-2013-304746.
21. Bukhalko M.A., Skripchenko N.V., Skripchenko E.Yu., et al. Significance of gene polymorphism of vitamin D receptor in human pathology. *Russian Bulletin of Perinatology and Pediatrics.* 2017; 62 (6): 23–28 (in Russ.). DOI: 10.21508/1027-4065-2017-62-6-23-28.
22. Aimagambetova A.O. Atherogenesis and inflammation. *Science and Healthcare.* 2016; 1: 24–39 (in Russ.). DOI: 0000-0003-1496-3281.
23. Kim J.H., Shin Y.L., Yang S. et al. Diverse genetic aetiologies and clinical outcomes of paediatric hypo-

parathyroidism. *Clin. Endocrinol. (Oxf.).* 2015; 83 (6): 790–796. DOI: 10.1111/cen.12944.
24. Kolobynina K.G., Solov'eva V.V., Slepak V.Z., et al. The role of the EF-hand Ca2 + / Mg2 + -binding protein of tescalcin in cell proliferation and differentiation. *Genes and Cells.* 2015; 10 (1): 28–34 (in Russ.).
25. Guhathakurta P., Prochniewicz E., Thomas D.D. Actin-myosin interaction: structure, function and drug discovery. *Int. J. Mol. Sci*. 2018; 19 (9): 2628. DOI: 10.3390/ijms19092628.
26. Valencia-Nuñez D.M., Kreutler W., Moya-Gonzalez J. et al. Endothelial vascular markers in coronary surgery. *Heart Vessels*. 2017; 32 (11): 1390–1399. DOI: 10.1007/s00380-017-1006-3.
27. Chiang J.M., Tan R., Wang J.Y. et al. S100P, a calcium-binding protein, is preferentially associated with the growth of polypoid tumors in colorectal cancer. *Int. J. Mol. Med*. 2015; 35 (3): 675–683. DOI: 10.3892/ijmm.2015.2065.
28. Bahar E., Kim H., Yoon H. ER stress-mediated signaling: action potential and Ca($^{2+}$) as key players. *Int. J. Mol. Sci.* 2016; 17 (9): 1558. DOI: 10.3390/ijms17091558.
29. Veronese N., Stubbs B., Crepaldi G. et al. relationship between low bone mineral density and fractures with incident cardiovascular disease: a systematic review and meta-analysis. *J. Bone Miner. Res.* 2017; 32 (5): 1126–1135. DOI: 10.1002/jbmr.3089.
30. Orlova D.D., Tribulovich V.G., Garabadzhiu A.V.., Barlev N.A., Martin S. The role of mitochondrial dynamics in cell death. *Cytology.* 2015; 57 (3): 184–191 (in Russ.).
31. Zakharov E.A., Klyueva N.Z., Belostotskaya G.B. The mechanisms of Ca 2+ -dependent hypertension formation on the model of rat cardiomyocytes in the culture. *Arterial Hypertension.* 2009; 15 (6): 683–687 (in Russ.). DOI: 10.18705/1607-419X-2009-15-6-683-687.
32. Deev R.V., Bilyalov A.I., Zhampeisov T.M. Modern ideas about cell death. *Genes and Cells.* 2018; 8 (1): 6–19 (in Russ.). DOI: 10.23868/201805001.
33. Shi J., Gao W., Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem. Sci.* 2017; 42 (4): 245–254. DOI: 10.1016/j.tibs.2016.10.004.
34. Guo H., Callaway J.B., Ting J.P. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat. Med.* 2015; 21 (7): 677–687. DOI: 10.1038/nm.3893.
35. Feng S., Fox D., Man S.M. Mechanisms of gasdermin family members in inflammasome signaling and cell death. *J. Mol. Biol*. 2018; 430 (18 Pt. B): 3068–3080. DOI: 10.1016/j.jmb.2018.07.002.
36. Pirozhkov S.V., Litvitskiy P.F. Inflammasomal diseases. *Immunology.* 2018; 39 (2-3): 158–165 (in Russ.). DOI: 10.18821/0206-4952-2018-39-2-3-158-165.
37. Lee G.S., Subramanian N., Kim A.I. et al. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca^{2+} and cAMP. *Nature*. 2012; 492 (7427): 123–127. DOI: 10.1038/nature11588.
38. Duewell P., Kono H., Rayner K.J. et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature.* 2010; 464 (7293): 1357–1361. DOI: 10.1038/nature08938.
39. Victor V.M., Apostolova N., Herance R. et al. Oxidative stress and mitochondrial dysfunction in atherosclerosis: mitochondria-targeted antioxidants as potential therapy. *Curr. Med. Chem.* 2009; 16 (35): 4654–4667. DOI: 10.2174/092986709789878265.
40. Strowig T., Henao-Mejia J., Elinav E. et al. Inflammasomes in health and disease. *Nature.* 2012; 481 (7381): 278–286. DOI: 10.1038/nature10759.
41. Ridker P.M. From C-reactive protein to interleukin-6 to interleukin-1: Moving upstream to identify novel targets for atheroprotection. *Circ. Res.* 2016; 118 (1): 145–156. DOI: 10.1161/CIRCRESAHA.115.306656.
42. Rattazzi M., Faggin E., Bertacco E. et al. RANKL expression is increased in circulating mononuclear cells of patients with calcific aortic stenosis. *J. Cardiovasc. Transl. Res.* 2018; 11 (4): 329–338. DOI: 10.1007/s12265-018-9804-2.
43. Mogelvang R., Pedersen S.H., Flyvbjerg A. et al. Comparison of osteoprotegerin to traditional atherosclerotic risk factors and high-sensitivity C-reactive protein for diagnosis of atherosclerosis. *Am. J. Cardiol.* 2012; 109 (4): 515–520. DOI: 10.1016/j.amjcard.2011.09.043.
44. Sidorovich O.I., Luss L.V. Food allergy: principles of diagnosis and treatment. *Medical Council.* 2016; (16): 141–147 (in Russ.). DOI: 10.21518/2079-701X-2016-16-141-147.
45. Delves P.J., Martin S.J., Burton D.R. et al. Roitt's essential immunology. Wiley-Blackwell.13th ed. 2017: 405–430.
46. Land W.G. The role of damage-associated molecular patterns in human disease. Part 1 – Promoting inflammation and immunity. *Sultan Quaboos Univer. Med. J.* 2015; 15 (1): e9–21.
47. Potapnev M.P. Immune mechanisms of sterile inflammation. *Immunology.* 2015; 36 (5): 312–317 (in Russ.).
48. Barbarash O.L., Golovkin A.S., Ponasenko A.V., et al. The role of Toll-like receptor polymorphism in atherosclerosis complications development. *Russian Journal of Cardiology.* 2015; 20 (12): 72–79 (in Russ.). DOI: 10.15829/1560-4071-2015-12-72-79.
49. Blagonravov M.L., Medvedeva E.V., Bryk A.A., et al. Features of electrolyte excretion in the early stages of hypertension in SHR rats. *Bulletin of Experimental Biology and Medicine.* 2017; 164 (7): 21–24 (in Russ.).
50. Carey R.M. Blood pressure and the renal actions of AT2 receptors. *Curr. Hypertens. Rep.* 2017; 19 (3): 21. DOI: 10.1007/s11906-017-0720-7.
51. Liu Y., Wei J., Wong King Yuen S.M. et al. CPVT-associated cardiac ryanodine receptor mutation G357S with reduced penetrance impairs Ca^{2+} release termination and diminishes protein expression. *PLoS One.* 2017; 12 (9): e0184177. DOI: 10.1371/journal.pone.0184177.

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