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An Integral Focus on the Pathogenesis of Atherosclerosis Based on Modern Data

Sergey Petrovich Lysenkov[1], Dmitriy Vitalevich Muzhenya*[1], Aminat Ramazanovna Tuguz[2], Dmitriy Sergeevich Shumilov[2]

[1]FSBEI HE "Maikop State Technological University", Medical Institute, 385000 Russia, Republic of Adygeya, Maikop;
[2]FSBEI HE "Adyghe State University", 385000 Russia, Republic of Adygeya, Maikop;

***Corresponding Author:** Muzhenya Dmitriy Vitalevich, candidate of biological sciences, Associate Professor at the Department of Pathomorphology and Clinical Pathophysiology, Medical Institute of the Maikop State Technological University.*

ABSTRACT

Atherosclerosis is a multifactorial disease, however, there is no consensus on the study of the onset of a disease and its progression. At the moment, there are six significant theories online posting on the internet (biomechanical theory; immunological or inflammatory theory; cholesterol theory; biochemical theory; genetic theory; theory of sulfate metabolism disorders).Each of them is based on the "main" forming factor, whereby a concept is developed that describes the possible pathophysiological insult of the onset of a disease and its progression. However, it does not give the integral understanding of all mechanism of disease pathogenesis, since the existent mechanisms have not been seen from a holistic perspective, but separately, in accordance with the hypothesis used for generalization. We have described a possible pathophysiological mechanism of the development and progression of atherosclerosis based on the analyzed literature data and taking into account the existing modern concepts. From this perspective, we assume that there is a possibility of influence on any component of the links presented in the given scheme in order to influence purposefully on the development of the pathological process.

Keywords: *atherosclerosis, inflammation, pathophysiology, theory of atherosclerosis.*

BACKGROUND

Atherosclerosis is a multifactorial disease that provokes vascular damage and, as a result, high disability and mortality rate of the population throughout the world. In the XX-XXI centuries, atherosclerosis has become the most common disease with a progressive course, in which lipid deposits – "atheromatous plaques" – are formed in the inner layers of the arteries. Endothelial damage precedes atherosclerotic changes in the vessel wall [1-4]. The next stage is accompanied by the formation of atherosclerotic plaques with the deposition of small crystals of cholesterol in the intima of the vessels and the underlying smooth muscles. Plaques grow with proliferation of fibrous tissue and surrounding smooth muscle, and then protrude into the arteries, resulting in reduced blood flow. The production of connective tissue by fibroblasts and the deposition of calcium in the lesion cause sclerosis or hardening of the arteries (arteriosclerosis). The uneven surface of the growing plaque in the artery reduces the efficiency of blood flow in the vessel, thereby increasing the risk of ischemia and thrombus formation [5-9].

The morphophysiological manifestations of atherosclerosis, studied over two centuries and supplemented from the standpoint of modern methods, nevertheless, do not give a holistic idea of the trigger factors for the development and progression of atherosclerosis. Possible triggering pathogenetic mechanisms are noted in the developed and most fully substantiated theories of atherogenesis:

1. Biomechanical theory. The triggering mechanism for the development of atherosclerosis, according to this theory, is mechanical or hydraulic damage to the vessel, due to high systemic pressure (hypertension), as well as some parts of the vascular bed with increased turbulent blood flow in places of arterial bifurcation;
2. Immunological or inflammatory theory. The participation of low-molecular-weight signaling proteins – cytokines in atherogenesis is confirmed by increased expression in the foci of fast formation of

atherosclerotic plaques of mRNA of pro and anti-inflammatory mediators IL-1β, TNF-α, IL-12, IL-4, IFN-γ, M-CSF;

3. Cholesterol or classical theory based on the violation of lipid metabolism in the body. According to this theory, a key role in the pathogenesis of atherosclerosis is assigned to low-density lipoproteins (LDL), which are actively involved in the formation of atherosclerotic plaques.
4. The biochemical theory of atherosclerosis is based on a violation of the metabolism of glucose and homocysteine in the blood, the increased concentrations of which have a toxic effect on the vascular endothelium, followed by the formation of atherosclerotic plaques;
5. The genetic theory of atherogenesis is consistent with modern ideas about the association of some genes with an increased risk of development and progression of atherosclerosis. Different types of mutations in genes can interfere with their function.
6. Theory of sulfate metabolism disorders. One of the latest theories based on changes in the balance of sulfate-ion in the membranes of endothelial cells. A decrease in the concentration of sulfate anion disrupts the functions of the endothelium and LDL transport, which ultimately leads to the accumulation of cholesterol crystals and the development of atheromatous plaque.

Therefore, the primary purpose of our research is a complex study of physiopathology mechanism of development of atherosclerosis, including the use of clinical outcomes and existent concepts in this area. Taking into account the analysis of scientific information sources, pathogeny of atherosclerosis can be presented as follows (Fig. 1).

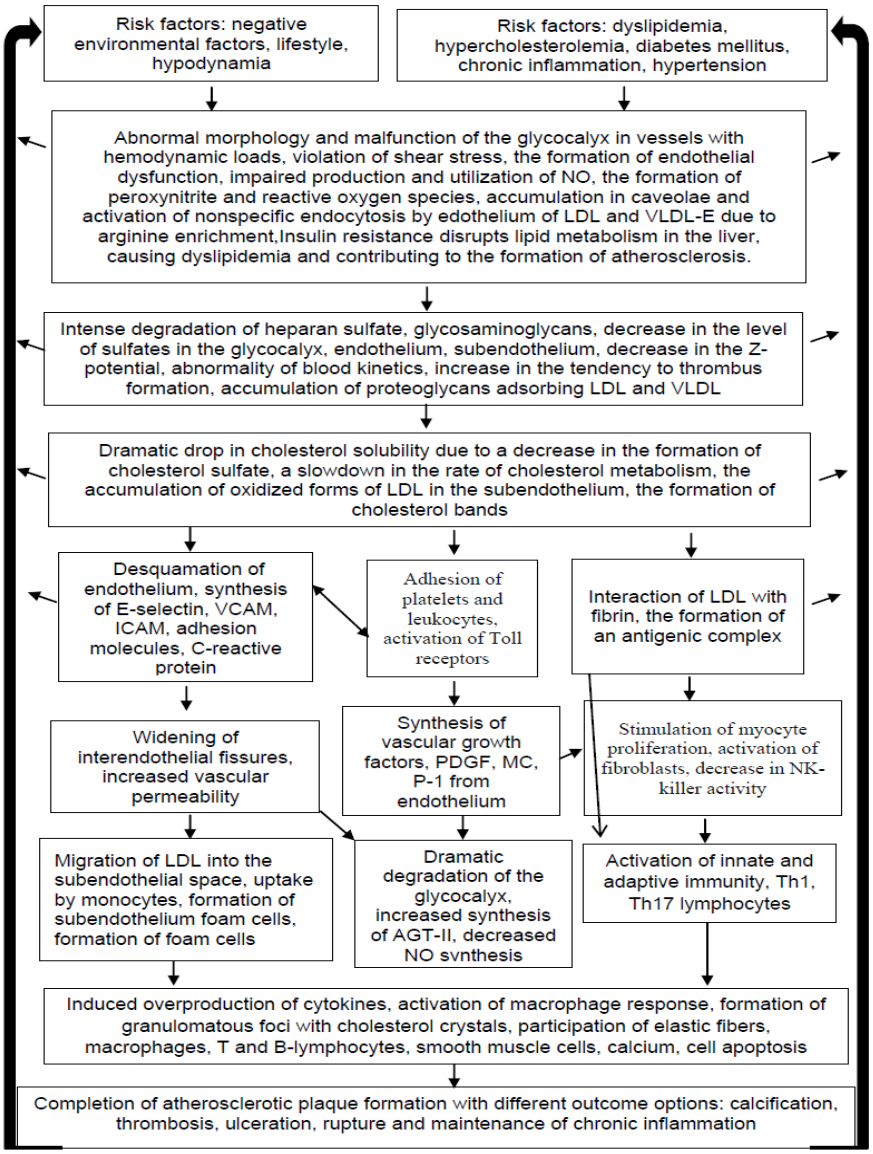

Figure1. *The pathogenesis of atherosclerosis.*

MAIN TEXT

The modern lifestyle in economically developed countries is associated with constantly increasing loads, chronic stress, against the background of a decrease in physical activity, a change in the type of diet, as well as the negative impact of bad habits, which together significantly increase the risk of developing cardiovascular diseases and in particular atherosclerosis. On the other hand, according to the classical concepts dominating for a long time, the key role in the pathogenesis and progression of atherosclerosis is assigned to LDL and elevated LDL cholesterol, which are of undoubted importance as the markers of an increased risk of diseases of the heart continuum. [1;2].

Plasma LDL, which deliver bound cholesterol to all tissues of the body, play a key role in the metabolism of the main morphological sign of atherosclerosis - deposition of cholesterol crystals. One of the cholesterol transport methods is energy-dependent vesicular traffic between the endoplasmic reticulum, the plasma membrane, and endocytic vesicles. Membrane contact pads and lipid transfer proteins are involved in non-vesicular lipid traffic, which is mediated by receptor-mediated endocytosis [1-7].

Cholesterol can also diffuse between cell membranes, liposomes, and emulsions through the aqueous phase. The gradient of cholesterol concentration between the plasma membrane and the membranes of intracellular organelles is maintained by a constant redistribution of cholesterol in volatile vesicular traffic and energy-independent transport by lipid transfer proteins. The efficiency of nondirectional diffusion transfer of cholesterol is determined by the cholesterol capacity of the membrane and kinetic factors - the rate of desorption and the concentration gradient [8-10].

The excess of synthesized cholesterol is eliminated by four main pathways, including: two ATP- binding cassette (ABC) transporters (ABCA1, ABCG1), SR-BI, and passive water diffusion. All proteins that mediate the outflow of cholesterol through the plasma membrane to the extracellular acceptor are also involved in intracellular movement and cholesterol distribution [11-13]. An increase in the level of cholesterol in the cell stimulates the production of ABCA1 and induces the expression of genes involved in the excretion of cholesterol [15-18].

According to the model of direct interaction between apolipoprotein and cholesterol transporter [19], the mechanism of indirect cholesterol release includes the following stages:

- diffusion across the cell membrane and ATP-dependent lipid attachment of the transporter;
- dimerization of the transporter with its subsequent fixation in the membrane with the participation of the cytoskeleton;
- interaction of apolipoprotein (Apo-A-I) with a dimer and the formation of a complex with lipid fractions,
- release of lipid-loaded Apo-A-I into the extracellular environment;
- dissociation of the dimer with the ABCA1 cyclization.

It should be noted that there is a direct relationship between ABCA1 activity and arterial wall thickness. It is assumed that an increase in ABCA1 concentration inhibits the process of atherogenesis by increasing the excretion of cholesterol into the extracellular space. It was found that stimulation of ATP production by macrophage mitochondria promotes an increase in ABCA1 expression and cholesterol excretion with a simultaneous decrease in the aortic sinus lesion area in mice prone to atherosclerosis, despite the absence of changes in high-density lipoprotein (HDL) cholesterol levels [16;20;21]. In addition, it has been suggested that there is a protective effect of activation of the ABCA1 pathway in reactive astrocytes in ischemic stroke [22;23].

Passive transportation is provided by water diffusion, but its contribution to the total cholesterol output for most cell types is relatively small. Excess exogenous and endogenous cholesterol expressed on the cell membrane is “removed” by HDL with the formation of active complexes transported to the intercellular space and blood. The speed of this process is limited not only by the “requests” of cells for cholesterol, the possibility of transport systems for ensuring its metabolism, but also by the participation of pro- and anti-inflammatory mediators of the immune system - interleukins [2, 24-26].

It should be noted that the inflammatory reaction can also develop with mechanical or hydraulic damage to the glycocalyx, desquamation of the vascular endothelium, especially in areas with significant deformation

shifts in the places of arterial bifurcation, pressure drops and shear stresses, mechanical vascular compression, anomalies in vascular development, etc. The walls of blood vessels undergo damage, inflammation and the development of chronic endotheliosis, causing tissue hypoxia [27-30].

A factor aggravating the course of the pathological process is the effect of pro-inflammatory cytokines and chemokines on the vascular endothelium, which leads to a deficiency in the synthesis of heparan sulfate by endotheliocytes and hyaluron [31;32]. As a result, cholesterol sulfate metabolism is disrupted, and peroxide processes are activated due to a decrease in the synthesis of superoxide dismutase (SOD). SOD deficiency is observed both in the apical part of the glycocalyx and in the subendothelial matrix, where HDL is most actively oxidized [33;34].

The change in the structure of endothelium is accompanied by a violation of the synthesis of local regulators of blood circulation, in particular nitrogen monoxide. Failure in the process of synthesis and utilization of NO in endotheliosis contributes to the accumulation of peroxide compounds and, in particular, peroxynitrite, which has a powerful oxidative capacity, which aggravates endothelial damage [35-40]. Oxidation of HDL occurs already at the stage of contact with the endothelial glycocalyx and sub endothelial matrix, and the presence of proinflammatory cytokines significantly enhances this process, which should not normally occur. It was found in model experiments on animals, that the administration of high doses of oxidized HDL causes the destruction of the smooth muscle of the vessels of the cremistor muscle, and also increases the formation of new compounds in the “intima media” in mice with knockout of the apolipoprotein E gene [41;42]

The progression of atherosclerosis is accompanied by a significant decrease in NO expression due to changes in translation or increased instability of eNOS mRNA. The activity of eNOS in atherosclerosis can be inhibited by various mechanisms, for example, pro-atherogenic lipids such as oxidized forms of HDL and lysophosphatidylcholine, which interfere with the signal transmission from the activated receptor to eNOS[43-45].

Hyper cytokine background and these factors stimulate the production of adhesion molecules, the synthesis of E-selectin, inter-cellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and also increase the adhesion of leukocytes and platelets, causing microthrombosis with impaired vascular permeability and expansion of interendothelial spaces [46-49].

The key stage in the formation of an atherosclerotic plaque at the site of endothelial injury is inflammation caused by monocytes recruited from the bloodstream of VCAM-1. An important role in this process is played by the biologically active form of angiotensin - 2 (AGT2), which stimulates apoptosis of endothelial cells and smooth muscle cells - SMCs [50;51], induces impaired endothelial relaxation and vascular function, contributing to abnormal vasoconstriction, procoagulant state and transmigration lymphoimda cells into the vascular wall. It has been shown that high levels of AGT2 are regulated by both classical systemic and local tissue production, including intracellular production [52].

In the cell, the endogenous renin-angiotensin system (RAS) activates NAD (P) H oxidase, enhancing AGT2 signaling and the production of reactive oxygen intermediate (ROI) in both endothelial and vascular smooth muscle cells. This leads to activation of gene expression of proinflammatory cytokines, increased migration and proliferation of cells, production of extracellular matrix, apoptosis of endothelial cells, and vascular damage [53-58].

The proatherogenic effects of AGT2 are also manifested in an increase in vascular permeability due to the activation of adhesion molecules VCAM-1, ICAM-1, and VEGF on endotheliocytes [4; 55-58], which enhance the binding with ligands on leukocytes. Under the influence of pro-inflammatory cytokines, the expression of selectins and integrins is enhanced. Selectins mediate the free interaction of leukocytes with activated areas of endothelial cells, and integrins - the formation of strong connections with intracellular signaling to target genes. Expression of chemokines enhances the chemotactic stimulus in the inflammation focus and attracts leukocyte populations to the forming plaque (at the dolipid stage), stimulating their migration into the vascular intima. Along with the specific functions, PBMCs produce first-wave inflammatory mediators, participate in the differentiation and proliferation of certain subpopulations of lymphocytes and, in particular, natural killer cells [48;49]. In the vascular intima, monocytes

mature into macrophages under the influence of macrophage colony-stimulating factor (M-CSF), which enhances macrophage expression of scavenger-receptor (SR) members of the hazard pattern recognition receptor super family. SR facilitates the absorption of modified lipoproteins by macrophages (lipoidosis) through receptor-mediated endocytosis [36; 37; 49; 59].

The concentration of cholesterol is regulated by solubility in water (depends on the group of phospholipids of the head and the length of the acyl chain) and the degree of saturation of the cytoplasmic membrane, which has a limit to the ability to solubilize excess cholesterol, which precipitates in the form of crystals from the bilayer [2; 24;25;60]. Thus, the accumulation of cholesterol esters in the cytoplasm transforms macrophages into foam cells (lipid-loaded macrophages with cholesterol crystals), characteristic of the early stage of atherosclerosis [61-63]. This is confirmed in experimental studies: cytoplasmic concentrations of cholesterol are five times higher than its content in cell membranes [61].

Some of the intimal foam cells in the inflammatory focus die as a result of apoptosis, forming a lipid-rich necrotizing nucleus. In the center of the forming atherosclerotic plaque, lipid droplets accumulate, forming a yellow fat layer. In this case, the drainage functions of the extracellular matrix in relation to lipoproteins and their oxidized forms are disrupted [4;32;64].

One of the possible causes of impaired transport in the vascular endothelium is a deficiency of sulfate anions. According to the latest data, sulfate anions attached to glycosamine-glycans of the glycocalyx are required to maintain structured water, which is key for normal endothelial function. A decrease in the concentration of sulfates is associated with the accumulation of cholesterol and the development of atheroma, since the transport of cholesterol through aqueous media depends on the level of sulfurylation [35].

It should be noted that a large number of $CD4^+$ T cells migrate to the site of atherosclerotic plaque formation, which recognize antigens presented in the form of fragments of lipid fragments associated with the main molecules of the class II histocompatibility complex, which are activated by oxidative HDL [39]. The focus of inflammation also contains cytokines that induce the activation of T cells to differentiate into Th-1 and other effector cells that enhance the local inflammatory response by stimulating the production of pro-inflammatory mediators (TNF-a, IL-6, IL-17A, IL-1B), as well as CD40 (CD40L, CD154) ligands [31-35]. It has been shown that some of these cytokines are secreted by the adipose tissue surrounding the vessels. The close relationship of adipose tissue with adventitia suggests its significant role in the development of atherosclerosis [65-67].

A very important factor at this stage of atherogenesis, as shown in our studies, is a decrease in the activity of NK-killers, the failure of the macrophage reaction in the sanitation of the extracellular and subendothelial space from oxidized forms of lipids [68;69]. In turn, this process is accompanied by the proliferation of myocytes and the activation of fibroblasts (stage of liposclerosis), due to the stimulation of the production of interleukin 1 (IL-1B) and TNF-a, INF-γ, IL-4, TGF-β, and IL-10. The presence of these factors promotes the migration of smooth muscle cells to the luminal side of the vessel wall, as well as the synthesis of the extracellular matrix, which forms a fibrous layer of collagen-rich fibrous tissues, SMCs, macrophages and T-lymphocytes [1;36;55;67].

The progressive course of atherosclerosis is accompanied by further activation of pro-inflammatory cytokines, weakening of the nervous control of the anti-inflammatory system, increased macrophage response, the formation of granulomatous foci containing cholesterol crystals (stage of atheromatosis), elastic fibers, T and B-lymphocytes, smooth muscle cells, high concentrations of calcium and cell apoptosis products (stage of atherocalcinosis) [30-35]. All this ends with the formation of an atherosclerotic plaque. Impaired stability and subsequent rupture of the plaque may be due to the participation of macrophages, which secrete meta-proteinases and lyse the extracellular matrix. T lymphocytes produce TNF-α, which blocks collagen synthesis in the SMC. These processes enhance the destabilization and destruction of the fibrous layer. The released substances (collagen and lipids) in the breakthrough area promote platelet adhesion and thrombus formation, which in turn can lead to malperfusion [4; 59-60].

It is also necessary to pay attention to the factors that are not determinant, but contribute to the development of atherosclerosis. First of all, it is obesity syndrome, since adipose tissue itself is a powerful endocrine organ that produces a large amount of biologically active substances. For

example, adiponectin, which affects the concentration and activity of enzymes responsible for catabolism of triglyceride-rich lipoproteins and HDL, lipoprotein lipase and hepatic lipase [45-47]. Adiponectin also directly affects endothelial cell function by decreasing the expression of VCAM-1 and scavenger receptors, as well as TNF-α production. Accordingly, adiponectin plays a restraining role in the development and progression of atherosclerosis, regulating the balance of atherogenic and antiatherogenic components in blood plasma [70-72]. On the other hand, adipose tissue actively produces pro-inflammatory cytokines, contributing to the formation and development of atherosclerosis.

The next factor sensitizing and chronically maintaining the inflammatory response in the vascular endothelium is the activation of Toll receptors [73;74]. A wide range of both exogenous and endogenous TLR ligands expressed in atherosclerotic lesions has been described. A large number of exogenous bacterial products, including nucleic acids, peptidoglycans, and heat shock proteins, were found in the sites of inflammation of the vascular endothelium. There is growing evidence that TLR signaling can be triggered in the absence of infection, due to the production of endogenous ligands at sites of tissue remodeling and inflammation. An active role in this process is played by the intestine, the barrier function of which is impaired with age, as well as under the influence of unfavorable factors. The accumulation of lipoproteins and degradation products of extracellular matrix macromolecules, as well as necrotic cells formed in an atherosclerotic plaque, can act as TLR ligands [75-79]. For example, hyaluronan, one of the main glycosaminoglycans of the extracellular matrix, which undergoes rapid degradation at sites of inflammation, is another ligand for TLR2 and TLR4, which has been confirmed in a number of studies. In the ApoE - / - mouse strains, it was found that a decrease in the concentration of TLR4 or TLR2 contributed to a 55% decrease in the development of atherosclerotic lesions and a 65% decrease in macrophage infiltration [80-82].

Earlier studies in C3H / HeJ mice have shown resistance to atherosclerosis compared to C57BL/6 mice on a high cholesterol diet. This is due to the fact that this C3H/HeJ line carries a point mutation in the cytoplasmic TLR4 gene encoding a non-functional receptor. The presence of this mutation blocks the activation of leukocytes at the initial stages of the development of atherosclerosis in response to an increase in the concentration of oxidized forms of LDL, which confirms the important role of TLR4 in atherogenesis [83;84], which can directly affect the metabolism of cholesterol in macrophages. TLR4 deficiency contributes to a decrease in the area of vascular lesion, as well as a decrease in lipid content and macrophage infiltration in response to a high-cholesterol diet for six months in apoE - / - mice [74;85;86]. Against the background of increased activity of a number of pro-inflammatory cytokines, synthesis of C-reactive protein, the activity of Toll receptors in the endothelium contributes to the maintenance of endotheliosis [73;74].

The connection of atherosclerosis with infectious diseases and the escalation of pathogenetic mechanisms, based on the prevailing infectious process, is explained by the presence of common antigenic determinants of pathogens. Thus, murine cytomegalovirus, a ligand for TLR3 and TLR9, provokes the progression of atherosclerosis [83;87], while Coxsackie B virus acts as an agonist for TLR7 and promotes lipid accumulation in the myocardium of mice [88]. Herpes simplex virus is a TLR9 ligand [89] and promotes the development of atherosclerosis in mice [90].

In turn, immune complexes with endogenous RNA and DNA are considered to be triggers of autoimmune diseases, and there is a strong link between autoimmune disease and atherosclerosis, but under the condition of dyslipidemia with a violation of the ratio of atherogenic and non-atherogenic lipoprotein fractions [30-33;83;84].

There is evidence that this process develops against the background of systemic inflammation or oxidative stress associated with an increased content of triglycerides in plasma, rich in lipoproteins and their residues, as well as an excess of oxidized lipophilic phospholipids. The unfavorable course of atherosclerosis is aggravated by the loss of anti-inflammatory mediators, antioxidant and atheroprotective properties of HDL and apoprotein. Common clinical manifestations include atherogenic dyslipidemia and hypertriglyceridemia with an increased level of ApoB or hypertriglyceridemic “junk background”, which are accompanied by a significant increase in the production of nonspecific markers of inflammation: C-reactive protein (CRP), C3 component of complement and uric acid [2;36;37;91]. Dyslipoproteinemia

due to mutations in the genes of apoproteins A, B and genetically determined familial hypercholesterolemia with defective genes of LDL receptors can be powerful amplifying factors. In the absence of these receptors, the liver is unable to absorb HDL, which leads to an imbalance in the production and utilization of cholesterol and, as a consequence, to hypercholesterolemia [92-96].

Increased levels of cytokine secretion entail the phenomenon of insulin resistance, especially in organs with intensive lipid metabolism: liver, intestines, adipose tissue, etc. For example, TNF-α acts on the type 1 insulin receptor (IRS-1). As a result of its phosphorylation, the affinity of the receptor for insulin decreases, which leads to a significant decrease in the concentration of the insulin-dependent glucose carrier protein (GLUT4) [97-103]. This sequence causes impaired glucose uptake and utilization by cells and, as a consequence, the progression of hyperglycemia, damage to the vascular wall and the development of type 2 diabetes mellitus. The aminoglycans formed in the area of vascular lesions in diabetes mellitus are antigens that are also involved in immunological processes. Against the background of excess insulin levels, glycated HDL proteins are more rapidly captured by the cells of the vascular wall and macrophages [2;36;33-37].

In the proposed scheme of atherogenesis, hypercholesterolemia is assigned a secondary role, but it enhances the production of free superoxide radicals in the vessels, thereby reducing the synthesis of vasodilators and deactivating nitric oxide (NO) produced by the endothelium. It is possible that hypercholesterolemia (a familial hereditary form) becomes a trigger of the atherosclerotic process, but according to our views, it is realized with a combination of several important pathogenetic components: overexpression of proinflammatory cytokine genes, weakening of central and peripheral nervous anti-inflammatory mechanisms, endothelial dysfunction, the decrease in the activity of macrophage killers (Fig. 1).

At the end of the review, we would like to add that another aspect in the studied subject area is the search for molecular genetic markers associated with atherosclerosis. Nowadays there is a large number of scientific paperson the Internet related to this topic. Thus, 3536 papers were proposed for the keyword "atherosclerosis" from the HuGE Literature Finder database, in which 1473 candidate genes were analyzed [104].However, it should be noted that at the moment no one hundred percent markers associated with atherosclerosis have been found, a limited range of polymorphisms has been established that can increase the risk of developing this disease in combination with other factors. Therefore, at the moment thefurther comprehensive research to this point is required in order to understand the role of the genetic component in the development and progression of the disease.

Conclusion

An analytical review of the existing theories of atherogenesis made it possible to generalize the data and present a scheme that includes the most significant factors influenced on the development of pathology. It should also be remarked that we tried to combine the most significant components of various theories for a comprehensive understanding of the process from different positions. This concept is not an axiom, and each of its elements can be subjected to changes as scientific knowledge accumulates. The presented scientific generalization opens up the horizons for the development of a targeted impact on the pathologic behavior.

Abbreviations

ABC: ATP- binding cassette

AGT2: angiotensin – 2

CRP: C-reactive protein

CVD: cardiovascular diseases

HDL: High-density lipoprotein

ICAM: inter-cellular adhesion molecule

IHD: ischemic heart disease

IL: interleukin

LDL: low-density lipoproteins

M-CSF: macrophage colony-stimulating factor

NK: natural killer cells

PBMC: Peripheral blood mononuclear cell

RAS: renin-angiotensin system

ROI: reactive oxygen intermediate

SMCs: smooth muscle cells

SOD: superoxide dismutase

VCAM: Vascular cell adhesion molecule

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