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Modern Concepts About the Pathogenesis of Atherosclerosis

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Abstract: Atherosclerosis comes from the Greek word "Athero" meaning mush. Marchand coined the term "atherosclerosis" to describe the association of fatty degeneration and vascular stiffness. This is a patchy intramuscular thickening of the subintima. The earliest lesion is a fatty streak. Fatty streaks develop into fibrous plaques, and unstable plaques are responsible for various clinical manifestations. Damage to the endothelium of the arterial wall is an early pathogenetic event of atherosclerosis. The arterial wall is a dynamic regulatory system. However, damaging factors can disrupt normal homeostasis and cause the onset of atherosclerosis.

Key words: atherosclerosis, pathophysiology of atherosclerosis, pathogenesis, atherogenesis.

Relevance. Atherosclerosis is a chronic disease, the main manifestations of which are associated with the formation in the walls of arteries of atheromatous plaques specific to this pathology, causing disruption of blood flow in organs and tissues. The insidiousness of atherosclerosis lies in the fact that it is asymptomatic for a long time and does not manifest itself clinically until the blood circulation of the corresponding organ is disrupted. As a rule, symptoms of ischemia appear when the lumen of the vessel is stenotic by more than 50% (the so-called hemodynamically significant stenosis). Most often, the aorta, arteries of the heart, brain, lower extremities and kidneys undergo atherosclerotic changes. Therefore, among the causes of death, the first place is taken by coronary heart disease (CHD), myocardial infarction, rupture of aortic aneurysm, ischemic or hemorrhagic stroke [1, 2]. Atherosclerosis is a multifactorial disease, the risk of development of which is determined by a combination of several of them. The figurative expression of the German scientist M. Burger is known that "physiological sclerosis of old people is fate, and atherosclerosis is a disease." However, it is important to note that although atherosclerosis is not the result of the physiological process of aging of the body, there are certain relationships between atherosclerosis and age. The initial signs of atherosclerosis are detected on the section already at the age of 20. However, clinical manifestations of the disease are most often found in people over 30-40 years of age, when there is already hemodynamically significant vascular stenosis [1, 2]. Although the primary processes leading to the formation of fatty streaks are unknown, experiments conducted on animals suggest that early disturbances in endothelial function occur under stress exposure. At the same time, modified lipids enter the layers located behind the intima. They are mediators of inflammation and ensure the mobilization of leukocytes and the formation of foam cells, which is a characteristic pathogenetic feature of fatty streaks.

For many decades, unsuccessful attempts have been made to identify the underlying cause of atherosclerosis. It was not possible to create a unified scheme for the development of this disease. Currently, more than two dozen hypotheses and theories are known to explain the pathogenesis of atherosclerosis, but the main ones today are two of them: endothelial (based on

damage to vascular endothelial cells) and infiltration-combination (based on infiltration of the vascular wall with lipids) [2]. The form and content of progressive damage in atherosclerosis is demonstrated by the results of 3 fundamental biological processes: 1) accumulation of macrophages, T-lymphocytes and smooth muscle cells (SMCs) in the intima; 2) the formation by accumulated SMCs of a large amount of connective tissue matrix, including collagen, elastin and proteoglycans; 3) accumulation of lipids, mainly in the form of free cholesterol (cholesterol) and its esters both in cells and in the surrounding connective tissue [2, 8, 9]. The so-called mutagenic monoclonal theory put forward by E.P. aroused great interest. Benditt and J.M. Benditt (1976) [10]. Scientists proceeded from the fact that SMCs of fibrous plaques are always homozygous and homogeneous in composition and, obviously, originate from the same clone of cells.

According to the autoimmune theory of the pathogenesis of atherosclerosis, proposed by A.N. Klimov et al. (1987) the launch of the atherosclerotic process is caused not so much by lipoproteins as by autoimmune complexes containing lipoproteins as an antigen [11, 12, 13]. Theories about the role of inflammation. We now know that subclinical chronic inflammation plays a crucial role in the pathophysiology of atherosclerosis. According to her, the fundamental role of inflammation in the development of atherosclerosis may lead to new therapeutic approaches that selectively affect the inflammatory process that slowly "smolders" atheroma [14]. The target of inflammation is usually the so-called vulnerable atherosclerotic plaques (AB) with a significant lipid core, an abundance of macrophages and a thin fibrous cap [15, 16, 17, 18, 19, 20]. Inflammation is the phylogenetically oldest type of the body's defense response to various damage and the introduction of foreign agents [2, 5]. The hypothesis that the occurrence and progression of atherosclerosis may be based on an inflammatory process cannot be called new. This assumption was put forward by R. Virchow back in 1856 [21]. R. Ross et al. emphasize the significant similarities between inflammation and atherosclerosis. [22] Inflammation plays a major role in all stages of atherosclerosis [23]. The process of atherogenesis is similar to normal inflammation. Both processes consist of the same functional reactions, where the main active component is cells of loose connective tissue: endothelial, SMC, monocytes, macrophages, neutrophils, platelets, T - and B-lymphocytes. Signs of a local nonspecific inflammatory process in atherosclerosis are detected at the initial stages of the development of arterial pathology, as well as in the phase of destabilization and damage to arterial arteries. The role of inflammation in the process of AB destabilization has been studied to a greater extent and it has been proven that lipids are not involved in the mechanism of AB destruction [23]. Pathophysiology. We will discuss the major pathways involved in the pathophysiology of atherosclerosis. Atherosclerosis begins with the fatty streak, which is an accumulation of lipid-laden foam cells in the intimal layer of the artery [24]. Lipid retention is the first step in the pathogenesis of atherosclerosis, followed by chronic inflammation in sensitive areas of the walls of large arteries, leading to fatty streaks, which then progress to fibrotic formations [25, 26]. Atherosclerosis is a continuous progressive development. Fatty streaks develop at the age of 11-12 years, and fibrous plaques at the age of 15-30 years [27]. Fatty streaks evolve into atherosclerotic plaques, which are composed of three components: inflammatory cells, smooth muscle cells, a fibrous connective tissue component, and a fatty lipid component [28]. Endothelial injury plays an inciting role. Turbulent blood flow leads to endothelial dysfunction; it suppresses the production of NO, a powerful vasodilator, and stimulates the production of adhesion molecules that attract inflammatory cells. Other risk factors contribute to this move. As a result, monocytes and T cells bind to endothelial cells and migrate into the subendothelial space. Lipids in the blood, LDL, VLDL bind to endothelial cells and are oxidized in the subendothelial space. Monocytes in the subendothelial space take up oxidized LDL and

become foam cells. This is the first stage, that is, the fatty (fatty) strip. Macrophages also produce proinflammatory cytokines that recruit SMCs. Smooth muscle cell replication occurs and the density of the extracellular matrix increases. The end result of the lesion is a subendothelial fibrous plaque consisting of a lipid core surrounded by smooth muscle cells and connective tissue fibers [29, 30].

Atherosclerotic lesion of the arterial wall. The arterial wall is a dynamic regulatory system. However, damaging factors can disrupt normal homeostasis and cause the onset of atherosclerosis. For example, as described below, vascular endothelial and smooth muscle cells actively respond to inflammatory mediators such as IL-1 and TNF-α. These mediators can also activate choroidal cells, which begin to produce IL-1 and TNF-a, this fact does not fit into the framework of the previous idea that only cells of the immune system are capable of synthesizing these cytokines. Based on the data that immune cells are not the only source of inflammatory mediators, further research began to be carried out on the role of "activated" endothelial and smooth muscle cells in the pathogenesis of atherosclerosis. As a result of such basic research, several key components involved in the process of atherosclerotic inflammation have been identified. These components include: endothelial dysfunction; accumulation of lipids in the intima; mobilization of leukocytes and smooth muscle cells on the vascular wall; formation of foam cells and formation of extracellular matrix deposits. Cells at sites of atherosclerotic damage constantly and randomly interact with each other on a competitive basis, which after decades leads to the formation of fibrous plaques that form one of several possible profiles. This mini-review examines three pathogenetically significant stages of this process: 1) fatty stripe; 2) formation of fibrous plaques 3) destruction of atherosclerotic plaques. 1) Accumulation of lipoprotein particles in the intima. Modified lipoproteins (for example, oxidized or glycosylated) are highlighted in darker colors. 2) Under oxidative stress, as well as under the influence of modified LDL components (mLDL), a local release of cytokines occurs. 3) These cytokines promote the expression of adhesion molecules that bind leukocytes and chemoattractant molecules (eg, monocyte chemoattractant protein 1 [MCP1]) that guide leukocytes into the intima. 4) After entering the arterial wall under the influence of chemoattractants, blood monocytes interact with such a stimulator as macrophage colony stimulating factor (M-CSF), which enhances the expression of scavenger receptors (scavenger receptors) in them. 5) These receptors ensure the capture of modified lipoprotein particles and ensure the development of foam cells. The latter serve as an additional source of cytokines and effector molecules such as superoxide anion and matrix metalloproteinases. 6) Smooth muscle cells migrate into the intima from the media. Note that this increases the thickness of the intima. 7) Intimal smooth muscle cells divide and form an extracellular matrix, ensuring its accumulation in growing atherosclerotic plaques. Thus, fatty streaks are converted into fibrolipid formations [20, 29]. In later stages, calcification occurs and fibrosis continues. Sometimes the process is accompanied by the death of smooth muscle cells (including through the mechanism of apoptosis). As a result, fibrous capsules are formed, containing relatively few cells and surrounding a lipid-rich core containing dying or no longer viable cells.

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