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Atherosclerosis and Inflammation the Path from Pathogenesis to Treatment: Review of the Current State of the Issue (Part 2)

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ABSTRACT

Numerous studies addressing the fundamental aspects of atherosclerosis emphasize the importance of systematically organizing the accumulated data. The second part of this lecture provides an analysis of the critical mechanisms involved in the development of atherosclerosis. This analysis includes a discussion on the roles of inflammasomes, hemodynamic disorders within the vascular wall, vasa vasorum pathology, endothelial cell dysfunction, matrix metalloproteinases, and the Notch and Wnt signaling pathways in the process of atherogenesis. Additionally, it explores the specific characteristics of the pathogenesis of vascular calcification associated with atherosclerosis. A dedicated section thoroughly reviews contemporary pharmacotherapeutic strategies for managing atherogenic dyslipidemia. A comprehensive analysis of current concepts regarding the pathogenesis of atherosclerosis, along with promising approaches to drug therapy, will facilitate the identification of future research directions within the field of lipidology. This endeavor has the potential to elevate preventive cardiology to a new standard.

Keywords: atherosclerosis, inflammation, inflammasome, atheroma, PCSK9 inhibitors

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Атеросклероз и воспаление – путь от патогенеза к терапии: обзор современного состояния проблемы (часть 2)

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РЕЗЮМЕ

Достижения многочисленных исследований в изучении фундаментальных аспектов атеросклероза диктуют необходимость систематизации накопленных данных. Во второй части лекции представлен анализ роли ключевых механизмов реализации воспалительного процесса в развитии атеросклероза. Рассмотрена роль инфламмасомы, нарушений гемодинамики в сосудистой стенке, патологии *vasa vasorum*, дисфункции эндотелиоцитов, матриксных металлопротеиназ, сигнальных путей Notch и Wnt в атерогенезе, а также ассоциированные с атеросклерозом особенности патогенеза кальцификации сосудов.

Отдельным разделом представлен обзор современных фармакотерапевтических подходов к лечению атерогенной дислипидемии. Комплексный анализ современных представлений о патогенезе атеросклероза и перспективных методов лекарственной терапии позволит обозначить дальнейшие направления исследований в липидологии и вывести возможности профилактической кардиологии на потенциально новый уровень.

Ключевые слова: атеросклероз, воспаление, инфламмасома, атерома, ингибиторы PCSK9

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Atherosclerosis is one of the primary challenges in preventive cardiology, which has traditionally received significant attention in the development of national programs for the primary and secondary prevention of atherosclerosis-associated cardiovascular diseases (aCVD) and cardiac rehabilitation programs [1-4].

According to data from the multicenter study ESSE-RF, which included respondents aged 25-64 years from 13 regions of the Russian Federation (RF), the prevalence of hypercholesterolemia (total cholesterol (TC) in the blood ≥5.0 mmol/L) averaged 58.40±0.34%. This indicates an extremely high frequency of atherogenic dyslipidemia within the study population [5]. In the United States, data from the National Health and Nutrition Examination Survey revealed that levels of TC over 200 mg/dL and low-density lipoprotein cholesterol (LDL) ≥130 mg/dL were found in 32.8% and 36.2% of examined individuals, respectively [6]

According to the multicenter, cross-sectional, observational study EURIKA (European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice), which included data from 12 countries (Austria, Belgium, Germany, France, Greece, Turkey, and others, including Russia) with a final sample size of 7,641 patients, the proportion of individuals with atherogenic dyslipidemia was over20% [7]. The EURIKA population comprised European patients aged at least 50 years who had at least one risk factor for cardiovascular disease (CVD) but no history of CVD in their medical records. Additionally, the STEPs 2021 study reported that the proportion of individuals with atherogenic dyslipidemia (based on all lipidogram indicators) among the population of the Islamic Republic of Iran was 81.0% [8].

A cross-sectional study conducted as part of the China-PEACE project involved 2,660,666 individuals aged 35 to 75 years from all provinces of the People's Republic of China between 2014 and 2019. Among those examined, the prevalence of atherogenic dyslipidemia was found to be 33.8% [9].

These findings indicate that atherogenic dyslipidemia is a global problem, as evidenced by the prevalence rates of lipid metabolism disorders observed across diverse populations with varying national dietary habits. Consequently, studying the pathogenesis of atherosclerosis and developing new therapeutic methods aimed at normalizing lipid metabolism and stabilizing inflammatory status are critically important. The role of inflammation in the development of ASCVD is well established and underscores the urgency of this research.

Currently, atherosclerosis is perceived by the scientific community as an inflammatory disease of the arteries that triggers the mechanisms of vascular aging and damage to target organs [10, 11]. Given this fact, the study of atherogenesis problems from the standpoint of inflammatory theory is a relevant fundamental direction with direct access to real clinical practice [12-16].

In the second part of this lecture, attention will be directed towards examining the clinically relevant aspects of inflammation pathogenesis in the context of atherosclerosis development. Furthermore, a summary of therapeutic methodologies, grounded in the latest progressions in clinical lipidology, will be presented.

The Role of Inflammasome in Atherogenesis

In the context of the leading role of inflammation in the pathogenesis of atherosclerosis, it is worth emphasizing the role of the inflammasome, since this intracellular multiprotein complex is known to play an crucial role in the relationship between lipid metabolism and low-grade inflammation of the vascular wall [17]. Cholesterol crystals and oxidized lipoproteins activate monocytes and macrophages, generating an inflammatory response followed by the production of proinflammatory interleukins (IL) - IL-1β and IL-18. Oxidized LDL is recognized by CD36 receptors on recruited monocytes, which leads to activation of the NLRP3 inflammasome [18]. In lipopolysaccharide (LPS)-treated monocytes, saturated fatty acids can induce the release of IL-1β, which is not observed with unsaturated fatty acids [19]. Like monocytes, endothelial cells also demonstrate NLRP1 activation after stimulation with plasma containing high levels of triacylglycerols and VLDL [20]. In addition to lipid metabolism disorders, other mechanisms are involved in triggering atherogenesis-associated inflammation.

Hypoxia and hypoxia-associated signaling through hypoxia-inducible factor (HIF)-1α in atherosclerotic plaques enhance NLRP3 expression in macrophages and slow the degradation of proIL-1β [21].Hemodynamically induced shear stress increases the expression of sterol regulatory element-binding protein 2 (SREBP2) via mechanotransduction, triggering a new wave of atherogenesis. In this context, elevated NLRP3 expression in endothelial

cells plays an crucial role in maintaining aberrant lipid metabolism [22]. The development of dysfunctional autophagy in atherosclerotic plaques is also significant in the process of atherogenesis, as evidenced by the increased expression of autophagy markers ATG13 and LC3 in aortic endothelial cells. Notably, in mice lacking the ATG5 protein which is essential for autophagy, there is an increase in inflammatory activity and plaque size. These findings underscore the importance of autophagy in the pathogenesis of ASCVD [23]. In mice fed a high-cholesterol diet, hematopoietic deletion of NLRP3, ASC, or IL-1α/IL-1β resulted in reduced atherogenesis and lower levels of IL-18 [24]. Furthermore, pharmacological inhibition of NLRP3 with colchicine increases the number of smooth muscle cells (SMCs) and collagen within the atherosclerotic plaque, promoting its transition to a more stable phenotype [25].

Vascular Shear Stress and Atherosclerosis

Under normal conditions, uniform laminar blood flow acting on the intima of the arteries induces the secretion of nitric oxide (NO). In turn, NO released under physiological conditions regulates the tone of the vascular wall and helps maintain the anti-inflammatory and antithrombotic properties of the endothelium. It is well established that the formation and progression of atheroma occurs focally, primarily around bifurcations or at the points where lateral branches depart from the artery, that is, in areas characterized by uneven (turbulent) blood flow [26]. This nature of the blood flow creates low wall shear stress (WSS), which induces vascular inflammation and contributes to the development of atherosclerosis. WSS refers to the tangential force of mechanical friction exerted by flowing blood, acting longitudinally on the endothelium surface of the arterial wall [27].

Specific endothelial biomechanical receptors within the endothelial glycocalyx detect mechanical stimuli and differentiate between laminar and turbulent types of blood flow, converting WSS into biochemical signals [28]. Consequently, endothelial dysfunction induced by WSS is closely linked to inflammation and lipid metabolism disturbances in the vascular wall, thereby promoting the progression of atherosclerosis. It is worth noting that, although atherogenesis initially occurs in regions of the arterial wall exposed to low WSS, areas of high WSS that develop around growing atherosclerotic plaques are associated with the formation of an unstable plaque phenotype [29].As WSS increases, the functioning of the mechanoreceptor KLK10 diminishes, which mediates the transformation of the normal transcriptome signature of arteries into an emergency response profile [30]. Inflammatory changes within the plaque lead to hypoxia, initiating neovascularization from the adventitial vasa vasorum, which contributes to increased plaque vulnerability [31]. In discussing the vasa vasorum, it is important to highlight the theory that atherosclerosis may initiate specifically from these microvessels within the vascular wall of the arteries [32]. The microvascular network of the vasa vasorum (including arterial, venous, and lymphatic vessels of varying calibers) serves as a crucial anatomical and functional structure that meets the metabolic needs of the adventitia and perivascular adipose tissue, as well as the outer part of the medial layer of large arteries [33]. Dysregulation of blood flow in the vasa vasorum is implicated in the pathogenesis of atherosclerosis, as evidenced by the presence of multiple neuroimmune cardiovascular interfaces (NICIs) in the outer layers of atherosclerotic arteries. These interfaces are characterized by axon terminals located near the SMC media and macrophages in perivascular adipose tissue [34].Numerous newly formed vasa vasorum are abundant in lipid-rich plaques and express elevated levels of cell adhesion molecules, such as ICAM-1 and VCAM-1. This expression facilitates an excessive influx of immune cells and is associated with plaque instability [35].

Although the concept of initial vasa vasorum pathology in the initiation of atherogenic changes currently has several gaps, their role in atherogenesis is extremely important, both within the framework of the “outside-in” concept and in the classical approaches to study. During vascular wall inflammation, vascular endothelial (VE) cadherin is phosphorylated by Src kinase 3 at the intercellular junctions of the endothelium. Concurrently, dephosphorylation of VE cadherin by VE protein tyrosine phosphatase (VE-PTP) prevents its internalization and stabilizes the adhesive junctions between endothelial cells [36, 37].

Additionally, the dissociation of VE-PTP from VE cadherin leads to leukocyte diapedesis and increased vascular permeability in vivo, as demonstrated in a model induced by vascular endothelial growth factor (VEGF) and endotoxin [38]. It is known that lymphocyte binding to the adhesion molecule VCAM-1, along with the stimulation of endothelial cells by VEGF, triggers a common signaling cascade

that includes Ras-associated botulinum toxin substrate C3, NADPH oxidase, reactive oxygen species, and proline-rich tyrosine kinase 2 [39, 40]. However, the molecular mechanisms regulating the kinetics of the interaction between VE-PTP and VE-cadherin remain largely unexplored. Signaling protein 2 containing the CUB-EGF domain (SCUBE2) ensures the integrity of the vascular wall by recruiting VE-PTP to dephosphorylate VE-cadherin. This process promotes the stabilization of endothelial adherens junctions and preserves the barrier function of the intima [41]. Studies involving genetic overexpression and pharmacological induction of SCUBE2 further support the concept that therapeutic regulation of SCUBE2 may be beneficial for stabilizing the vascular bed [42].

Inflammation also stimulates the development of dystrophic calcification in the necrotic lesion of atherosclerotic plaques as a healing response to the inflammatory activation of macrophages [43]. The death of macrophages and SMCs releases vesicles that serve as "nucleation sites" for the deposition of hydroxyapatite crystals. Their aggregation leads to the formation of microcalcifications with diameters of less than 50 μm, which can penetrate the fibrous cap of the plaque [44, 45]. Microcalcifications significantly contribute to the instability of atherosclerotic plaques; furthermore, they induce mechanical stress within the fibrous capsule, generating new inflammatory impulses within the plaque [46]. It is also important to note that ectopic deposition of calcium hydroxyapatite salts occurs long before the onset of atherocalcinosis.

In atherosclerotic inflammation, various cell types, including vascular SMCs, resident pericytes, circulating stem cells, and adventitial cells, differentiate into osteoblastic cells, leading to vascular calcification [47]. For example, SMCs lose part of their contractile phenotype, as evidenced by downregulation of α-smooth muscle actin (α-SMA) and SM-22 expression, followed by abnormal upregulation of genes involved in osteogenesis, such as Runt-related transcription factor 2 (Runx2), osteopontin, osteocalcin, etc. [48, 49]. Vascular calcification is initiated by matrix vesicles produced by osteoblast-like cells that serve as deposition sites for hydroxyapatite crystals [50]. Meanwhile, the overexpression of matrix metalloproteinase MMP-9 leads to the degradation of elastin, which in turn promotes the transition of SMCs from a contractile to a producing phenotype [51].

The Role of Inflammation in Plaque Destabilization

Atherosclerotic plaques are primarily composed of extracellular matrix (ECM), which includes collagen, elastin, proteoglycans, and glycosaminoglycans synthesized by SMCs in the arterial wall [52]. Under conditions of atherogenic inflammation, cytokines such as IL-1β andtumor necrosis factor α (TNF-α) induce the secretion of metalloproteinases, particularly MMP-1, MMP-8, MMP-9, MMP-12, and MMP-13, by macrophages under the regulation of microRNA [53-55].

MMPs catalyze the destruction of interstitial collagen, leading to thinning and weakening of the fibrous capsule, which contributes to plaque instability [56]. In addition, the stability of the fibrous capsule is influenced by the cross-linking of collagen fibers, a process mediated by the enzyme lysyl oxidase (LOX), which is expressed by endothelial cells [57]. Endothelial dysfunction and the phenotypic transition of SMCs are associated with a decrease in LOX activity, resulting in abnormal collagen cross-linking. This weakens the fibrous capsule and increases the presence of soluble collagen forms that are subject to MMP-mediated degradation [58].

In unstable atherosclerotic plaques, the activity of MMP-7 and MMP-9 is increased, and tissue expression of MMP-2 and MMP-9 raises alongside a decrease in the expression of type IV collagen [59]. Among the three types of unstable atheromas, lipid-type plaques exhibit the highest tissue expression of MMP-9 compared to dystrophic-necrotic and inflammatory-erosive types, while type IV collagen expression is predominant in dystrophic-necrotic atherosclerotic plaques. In addition to MMPs, an 8-fold significant increase in APOE gene expression ($p<0.001$) was observed in unstable atherosclerotic plaques of the dystrophic-necrotic type. In contrast, stable atherosclerotic plaques showed an 8-fold statistically significant increase in LDLR and APOB gene expression ($p<0.001$) [60].

Interestingly, the level of adiponectin in an atherosclerotic plaque is directly proportional to serum levels of HDL-C, while secretin levels are inversely proportional. Furthermore, the glucagon levels in conditionally intact intima are 2.1 times lower than those in fragments with stable atherosclerotic plaque; it has also been established that secretin levels are directly associated with plaque stability [61].

In recent decades, more and more attention has been paid by researchers to such a phenomenon as atherosclerotic plaque erosion. Plaques that have undergone superficial erosion demonstrate less lipid accumulation, a less pronounced necrotic core, a moderate number of inflammatory cells, and an intact fibrous capsule [62]. Thrombi formed as a result of superficial erosions are white and rich in platelets, while thrombi associated with plaque rupture are red (rich in fibrin and erythrocytes) [63].

Parallels between Notch and Wnt Signaling Pathways and Atherosclerosis

Notch is a cellular signaling pathway that mediates intercellular communication and is involved in the regulation of homeostasis [64]. The Notch cascade protects against endothelial dysfunction induced by pro-inflammatory cytokines and regulates the phenotypic transition of cells [65]. Increasing evidence suggests that Notch plays a crucial role in signaling related to changes in WSS [66].

Activation of the Notch pathway creates an anti-inflammatory, anti-atherogenic environment that helps maintain endothelial integrity, including the preservation of adherens junctions between endothelial cells [67]. Additionally, Notch is a key signaling cascade for regulating the structure and function of SMCs. Expression of Notch receptors 2 and 3, as well as the primary ligand Jagged1, has been observed in SMCs [68]. Mutations in Notch 2 and 3 can lead to defects in SMC development, providing a strong evidence for the involvement of Notch signaling in regulating vascular differentiation during angiogenesis [69]. Furthermore, Jagged1-Notch3 signaling mediated through nidogen-2 is essential for maintaining the contractile phenotype of SMCs in vitro and in vivo [70].

Wnt is a multitarget signaling cascade characterized by three main intracellular signaling pathways: the canonical pathway (Wnt/β-catenin), the non-canonical Wnt/PCP pathway (which regulates cytoskeletal dynamics through the activation of JNK (C-Jun N-terminal kinase) by small G proteins), and the Wnt/Ca^{2+}-dependent pathway [71]. In addition to its roles in cell proliferation and differentiation, the Wnt pathway is also involved in regulating lipid metabolism [72]. The stabilization of β-catenin via Wnt signaling, along with the activation of fatty acid synthesis via Akt/mTOR signaling, plays a central role in lipid metabolism in steatotic liver [73]. An inverse relationship has been demonstrated between Wnt activation and the severity of atherosclerosis. Specifically, activation of the Wnt pathway following lipid depletion enhances the IL-4 response in macrophages via the PGE2/STAT3 axis. Dickkopf-2 (DKK2),a negative regulator of Wnt/β-catenin signaling, is implicated in macrophage activation during atherosclerosis [74].

Knockdown of DKK2 significantly reduces the expression of genes associated with the polarization of macrophages toward the pro-inflammatory M1 phenotype while increasing the level of polarization markers associated with the anti-inflammatory M2 phenotype. This knockdown also significantly attenuates the formation of foam cells [75].

The Role of Microrna in the Pathogenesis of Atherosclerosis

The role of microRNA in atherosclerosis is multifaceted. For example, miR-520c-3p protects endothelial cells from damage and stabilizes endothelial function by regulating key aspects of pathogenesis, such as cell proliferation, apoptosis, and endothelial cell adhesion [76]. Moreover, miR-181a-5h, miR-181a-3p, and miR-250bmodulate the severity of chronic low-grade inflammation in the vascular wall by suppressing the expression of the nuclear factor NF-κB, thereby slowing the progression of stromal-vascular dystrophic changes [77]. Conversely, miR-488 [78] and miR-183-5p [79] exhibit proatherogenic effects by stimulating functional reorganization of SMCs and exacerbating inflammatory infiltration in the vascular wall. MicroRNAs also demonstrate a dual effect on macrophages. Thus, miR-10a, miR-210, and miR-383 stabilize mitochondrial metabolism and the redox status of cells, leading to a reduction in apoptosis and necroptosis [80]. Notably, miR-181a-3p/5p and miR-155-5p have pronounced atheroma-stabilizing effects [81]. However, high levels of miR-155 correlate with NLRP3 activation via ERK1/2 kinase [82]. In addition, miR-216a exhibits proatherogenic potential by enhancing inflammation through the Smad3/NF-κB cascade [83].

A Look at Lipid-Lowering Therapy through the Prism of the Inflammatory Theory of Atherogenesis

In parallel with the active study of the molecular mechanisms of atherogenesis, the drug arsenal of lipid-lowering therapy is expanding, which increases the capabilities of modern cardiology.

The basic drugs of lipid-lowering therapy are traditionally considered to be HMG-CoA reductase

inhibitors – statins (in particular, rosuvastatin, pitavastatin and atorvastatin) both without and in combination with ezetimibe - a selective inhibitor of cholesterol absorption targeting the sterol transporter Neimann-Pick-like1 (NPC1L1) [84]. This combination is considered generally accepted and complies with the recommendations of both the Russian and European Cardiology Societies.

In the context of this lecture, it is important to focus on the anti-inflammatory potential of statins. Analyzing the mechanism of action of statins reveals that part of their pleiotropic effects can be attributed to the blockade of the mevalonate pathway of cholesterol synthesis, which reduces the levels of isoprenoid intermediates such as farnesyl pyrophosphate and geranyl-geranyl pyrophosphate. A decrease in these levels changes the prenylation of proteins, influencing the effects of statins on autophagy and inflammation [85]. Moreover, statins can suppress the adhesion and migration of inflammatory cells by reducing the expression of the integrin dimer CD11, the immunoglobulin superfamily protein VCAM-1, and leukocyte functional antigen-1 (LFA-1). They also decrease the expression of monocyte chemotactic protein-1 (MCP-1) and interleukin-8 (IL-8) [86].

Another anti-inflammatory mechanism of statins is their ability to reduce the levels of interferon γ (INF-γ), oxidized LDL (oxLDL), and serum apoA-I [87, 88]. Several potential mechanisms through which statins exert their anti-inflammatory effects via Toll-like receptor (TLR) signaling pathways have also been identified: inhibition of the prenylation of regulatory proteins, direct or indirect inhibition of NF-kB and MyD88/NF-kB axis, and activation of antioxidant response elements (ARE) [89]. In addition, statins can reduce signaling mediated by transforming growth factor TGF-1β in T lymphocytes, suppress oxLDL-induced maturation of human dendritic cells, impair T lymphocyte activation, and stimulate the pool of regulatory T lymphocytes [90]. Further studies are needed to elucidate the complete molecular mechanisms and multifaceted anti-inflammatory potential of statins.At the same time, several issues persist regarding statin use, particularly their side effects, such as statin-induced myopathy and hyperglycemia. Other concerns include partial and complete resistance to statins, the presence of residual cardiovascular risk, and elevated levels of triglyceride-rich lipoproteins, despite achieving target levels of total cholesterol, LDL cholesterol, and triacylglycerols [91-97]. In light of these challenges, new drugs aimed at normalizing cholesterol metabolism are currently being actively developed and introduced into clinical practice. Among the extensive list of lipid-lowering agents, the most promising include

1) PCSK9-modifying agents

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, particularly evolocumab and alirocumab, are innovative drugs that are actively utilized in modern clinical practice [98-100]. The pivotal studies demonstrating the lipid-lowering potential of evolocumab and alirocumab are FOURIER [101] and ODYSSEY-OUTCOMES [102] trials. According to a meta-analysis of 41 randomized clinical trials, which included a cumulative sample of 76,304 patients(49,086 received evolocumab and 27,218 received alirocumab), PCSK9 inhibitors significantly reduce the risk of myocardial infarction, coronary artery restenosis, and ischemic stroke. Furthermore, these agents are well-tolerated and considered safe drugs while effectively lowering LDL cholesterol levels [103]. In addition to their significant beneficial effects on lipid metabolism and the the reduction of major adverse cardiovascular outcomes (MACE) [104], PCSK9 inhibitors also demonstrate significant anti-inflammatory effects. A study from the European Collaborative Project on Inflammation and Remodeling of the Vascular Wall in Intravascular Ultrasound (ATHEROREMO-IVUS) demonstrated that serum PCSK9 levels are associated with increased absolute inflammatory plaque volume and necrotic core size [105]. A clear correlation was also observed between serum PCSK9 levels and the concentrations of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, macrophage colony-stimulating factor (M-CSF), and high-sensitivity C-reactive protein (hs-CRP) [106]. It has been established that PCSK9 enhances the infiltration of inflammatory monocytes into the vessel wall due to the interaction of PCSK9-LDLR (less pronounced with LRP5) with plaques. This interaction directly contributes to plaque destabilization [107]. PCSK9 itself induces inflammation and exacerbates atherosclerosis independently of the LDL receptor. Research has shown that PCSK9 worsens atherosclerosis in mice with a knockout of the LDL receptor gene. Adenylate cyclase-associated protein 1 (CAP1) serves as the primary transducer for mediating the inflammatory actions of PCSK9, including the induction of cytokines, Toll-like receptor 4, scavenger receptors, and the lectin-type oxidized low-density lipoprotein receptor

1 (LOX-1) [108]. Key mediators of this inflammatory cascade include spleen tyrosine kinase (Syk) and protein kinase C delta (PKCδ), which are activated following the formation of the PCSK9-CAP1 complex [109]. In human peripheral blood mononuclear cells, it has been established that PCSK9 levels positively correlate with the phosphorylation of Syk, PKCδ and p65 [110]. Thus, the anti-inflammatory effect of PCSK9 inhibition is evident and holds significant clinical relevance. In discussing drug approaches targeting PCSK9, it is important to highlight inclisiran, a drug based on small interfering RNA (siRNA) [111, 112]. Inclisiran is a double-stranded modified siRNA linked to N-acetylgalactosamine (GalNAc), which acts as a ligand for the asialoglycoprotein receptor expressed by hepatocytes. The drug specifically binds to the matrix RNA transcribing the sequence of the gene encoding PCSK9 [113]. By disrupting the translation of PCSK9 through mRNA cleavage, inclisiran effectively reduces its production. The ORION study series [114] provides robust evidence regarding its hypolipidemic potential, supported by meta-analyses [115, 116] that confirm its clinical efficacy in achieving target lipidogram indicators and reducing adverse cardiovascular outcomes. It is worth noting that some studies within the ORION series are still ongoing today.

2) Lipoprotein (a) inhibitors

Lipoprotein (a) or Lp(a), is an independent factor contributing to both overall and residual risk of CVD [117, 118]. Individuals with elevated Lp(a) levels (>125 nmol/L; >50 mg/dL) exhibit increased activity of arterial inflammation, characterized by endothelial activation due to oxidized phospholipids carried by Lp(a). This process leads to the recruitment of circulating monocytes, resulting in heightened secretion of chemoattractants and pro-inflammatory cytokines, increased expression of adhesion molecules, and enhanced leukocyte migration through the vascular wall [119]. Unfortunately, lifestyle modifications have minimal impact on Lp(a) levels; therefore, extracorporeal therapies, such as namely lipoprotein apheresis may be necessary. This approach is supported by latest American Heart Association consensus on LP(a) apheresis published in 2024 [120]. Lp(a) particles can cross the endothelial barrier, persist in the arterial wall, and promote the development of atherosclerotic plaques [121]. The oxidized phospholipids carried by Lp(a) can trigger macrophage apoptosis and contribute to the "instability" of atheromas [122]. Additionally, Lp(a) promotes inflammation within the arterial wall by increasing monocyte extravasation and endothelial activation [123].

These effects are mediated through adhesion molecules such as ICAM-1 and are associated with an increase in the activity of the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB)-3 induced by Lp(a) [124]. The development of drugs targeting high Lp(a) levels represents an innovative approach to lipid-lowering therapy, as elevated Lp(a) levels are a strong and independent risk factor for ASCVD. As of 2024, several drugs have emerged in this category: pelacarsen [125], olpasiran [126], zerlasiran [127], lepodisiran [128], and muvalaplin [129]. Notably, clinical trials involving these agents have generated great interest within the scientific community, particularly studies such as OCEAN(a)-DOSE [130], KRAKEN [131], ALPACAR [132], among others.

3) Antisense oligonucleotides

Volanesorsen and olezarsen are antisense oligonucleotides targeting apolipoprotein C3 (APOC3) mRNA and are currently under active investigation for the treatment of familial chylomicronemia syndrome [133]. Volanesorsen blocks the synthesis of apolipoprotein C3 in the nucleus of hepatocytes by inhibiting APOC3 mRNA. Two main clinical trials have been conducted with volanesorsen: APPROACH [134] and its open-label extension (OLE) [135], as well as the COMPASS trial [136]. Olezarsen represents an advancement over volanesorsen, as it is conjugated to N-acetylgalactosamine, an aminosaccharide that exhibits a strong binding affinity for the asialoglycoprotein type 1 receptor, thereby enhancing its targeting to hepatocytes [137]. Evidence supporting the efficacy of olezarsen comes from a double-blind, placebo-controlled study [138], which demonstrated that olezarsen reduces levels of apolipoprotein C3, triacylglycerols, and atherogenic lipoproteins in patients with moderate hypertriacylglycerolemia who are at high risk or have established cardiovascular disease.

4) Bempedoic acid

Bempedoic acid is a long-chain tetramethyl-substituted ketodiac acid characterized by a linear molecule structure. It belongs to the family of "rogue" fatty acids [139].

As a hypolipidemic agent, bempedoic acid functions as an inhibitor of the enzyme ATP-citrate lyase, which catalyzes one of the key reactions in cholesterol synthesis [140]. It is the first drug in its

class to act by inhibiting adenosine triphosphate citrate lyase [141]. A significant aspect of bempedoic acid's mechanism of action is that its active metabolite is formed exclusively in the liver, which minimizes the risk of muscle-related adverse reactions [142]. The safety and efficacy of long-term use of bempedoic acid have been evaluated in the CLEAR (Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen) program, which encompasses four phase 3 studies: CLEAR Tranquility [143], CLEAR Harmony [144], CLEAR Wisdom [145], and CLEAR Serenity [146].

Bempedoic acid promotes the activation of LDL receptor expression, leading to lower LDL cholesterol levels, attenuation of atherogenesis, reduction in hepatocyte lipid levels and body weight, and improvement in glycemic control [147, 148]. In this regard, both genetic inhibition of ATP-citrate lyase (ACLY) in hepatocytes and pharmacological inhibition with bempedoic acid suppress fatty acid and cholesterol synthesis while enhancing fatty acid oxidation without increasing circulating triacylglycerol levels. Moreover, studies conducted on murine and human hepatic stellate cells have demonstrated that bempedoic acid also inhibits liver fibrosis by targeting pathways involved in collagen formation [149].

5) Evinacumab

Evinacumab is a monoclonal antibody that targets angiopoietin-associated peptide 3 (ANGPTL3), a circulating protein secreted by the liver that regulates the hydrolysis of very low-density lipoprotein (VLDL) triglycerides. This drug is typically used for the treatment of refractory homozygous familial hypercholesterolemia [150].

6) Lomitapide

Lomitapide lowers cholesterol levels by inhibiting microsomal triacylglycerol transfer protein (MTP) [151]. MTP is involved in loading triacylglycerols onto apolipoprotein B100, which is essential for VLDL assembly. After being secreted by hepatocytes, VLDL is converted to LDL. By blocking VLDL assembly, lomitapide reduces both VLDL release and VLDL-mediated triacylglycerol secretion, resulting in lower plasma LDL concentrations [152]. Lomitapide has been approved by the FDA and EMA for the treatment of adult patients with homozygous familial hypercholesterolemia as an adjunct to a low-fat diet and other lipid-lowering therapies, with or without LDL apheresis [151]. Despite the impressive therapeutic potential of new drugs, their use is limited due to the lack of large-scale double-blind randomized studies, insufficient clinical experience, and high costs. Consequently, they are considered reserve therapies and are prescribed in cases where target lipid profile indicators are not achieved with the maximum tolerated dose of statins combined with ezetimibe and/or when there is complete intolerance to statins [153, 154].

7) Colchicine

In the context of trends in contemporary cardiology, it is worthwhile to highlight the role of colchicine in the treatment of atherosclerosis. Colchicine is a significant medication whose mechanism of action is linked to its effects on cellular structure and function. This drug exhibits a biphasic effect on microtubules; at low concentrations, it inhibits microtubules growth, while at high concentrations, it promotes their depolarization [155]. Colchicine inhibits tubulin polymerization, disrupting the cellular cytoskeleton and leading to impairment of various intracellular processes, including mitosis, intracellular transport, and phagocytosis [156]. In addition, colchicine inhibits chemotaxis and the adhesion of neutrophils to inflamed endothelium, including indirectly through alterations in the expression of VE-selectin on endothelial cells [157]. Colchicine also inhibits L-selectin expression, preventing neutrophil recruitment, and affects neutrophil function by limiting their extravasation. Furthermore, colchicine normalizes macrophage activity and inflammasome functioning [158].Beyond its effect on neutrophils, colchicine exhibits antithrombotic activity by reducing leukocyte-platelet aggregation (including both monocytes and neutrophils) as well as lowering levels of surface markers associated with platelet activity, such as P-selectin and PAC-1 (activated GP IIb/IIIa) [159].

Thus, the diverse effects of colchicine, including modulation of the cell cytoskeleton, anti-inflammatory properties, and antithrombotic activity, determine its high clinical significance in reducing both overall and residual cardiovascular risk in atherosclerosis [160]. There is a substantial body of evidence supporting the use of colchicine in atherosclerosis; notable studies include COLCOT (COLchicine Cardiovascular Outcomes) [161], LoDoCo (Low Dose Colchicine) [162], COVERT-MI (Colchicine for Left Ventricular Infarct Size Reduction in Acute Myocardial Infarction) [163], and CONVINCE (Colchicine for prevention of Vascular Inflammation in Non-CardioEmbolic Stroke) [164].

8) Biologically active compounds in contemporary lipidology

In parallel with conventional drug therapy, the role of various biologically active substances with hypolipidemic activity is being actively studied. Notable examples include chitosan, ursolic acid, nattokinase, spermidine, taurine, grape and pomegranate seed extracts, as well as many other naturally derived compounds that are positioned as atheroprotective and hypolipidemic substances [165, 166]. This topic is traditionally considered controversial. Unfortunately, the available data on the effectiveness and safety of these compounds are limited, difficult to compare, and sometimes even contradictory. Nonetheless, this does not exclude their potential benefits, which have been supported by large placebo-controlled, double-blind randomized studies. For example, the COSMOS (COcoa Supplements and Multivitamin Outcomes Study) study demonstrated a 27% reduction in cardiovascular mortality rates associated with cocoa flavonoids [167]. Additionally, a network meta-analysis encompassing 131 studies with a total sample size of 13,062 patients compared the effectiveness of various dietary supplements such as artichoke, berberine, bergamot, garlic, green tea extract, plant sterols/stanols, policosanols, red yeast rice, silymarin, and spirulina. This analysis found that bergamot and red yeast rice extracts exhibited the most significant atheroprotective effect [168]. It is important to note that in the vast majority of cases, while the positive effects of these compounds are statistically significant compared to placebo groups, they are not comparable to those of statins. The interpretation of data from existing studies is further complicated by the high variability in the biological properties of natural raw materials. These properties can depend on factors such as the life cycle conditions of the producing organisms and the conditions under which they are harvested, processed, and stored. Therefore, caution should be exercised when interpreting these findings. However, the significance of these results should not be underestimated; they should be considered in clinical practice, particularly, when developing personalized dietary interventions that align with clearly defined treatment goals.

CONCLUSION

Our understanding of atherosclerosis has evolved significantly beyond the concept of a mere lipid metabolism disorder. Contemporary research highlights the pivotal role of inflammation throughout the entire atherosclerotic process. Notably, both innate and adaptive immune responses are activated in atherosclerosis, initiating inflammatory reactions that occur both locally and systemically, manifesting as chronic low-grade inflammation. Consequently, circulating cytokines not only serve as indicators of heightened cardiovascular risk but also actively contribute to the progression and destabilization of atherosclerotic plaques. Understanding the role of inflammation in the pathogenesis of atherosclerosis presents significant clinical implications. The pursuit of identifying a molecular signature of the inflammatory cascade in atherosclerotic cardiovascular disease (aCVD) may facilitate the development of targeted anti-inflammatory strategies in the future. When combined with personalized medicine approaches, this advancement could significantly enhance the capabilities of preventive cardiology.

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