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Atherosclerosis and inflammation – from pathogenesis to treatment: current state of affairs (Part I)

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ABSTRACT

Atherosclerosis and atherosclerosis-related cardiovascular diseases are a significant public health concern and a rapidly evolving area of research in both fundamental and clinical medicine. Despite the extensive history of studying, many aspects of atherosclerosis etiology and pathogenesis remain unclear.

Traditionally, the pathogenesis of atherosclerosis has been viewed in terms of the localized accumulation of specific lipoprotein fractions in the arterial wall. However, both innate and adaptive immunity play active roles in atherogenesis. Cells and mediators of the immune system engage in intricate interactions with cellular and extracellular components in all layers of the vascular wall. For this reason, scientific community have reached a consensus on the crucial role of inflammation in the onset, progression, and destabilization of an atherosclerotic plaque.

Therefore, atherogenesis can be considered not only as a metabolic disorder, but also as an immunoinflammatory process. The aim of this lecture was to summarize contemporary data regarding the role of inflammation at various stages of the atherosclerotic continuum.

Keywords: atherosclerosis, atherogenesis, lipoproteins, inflammation, atherosclerotic plaque, atheroma

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Атеросклероз и воспаление – путь от патогенеза к терапии: обзор современного состояния проблемы (часть 1)

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РЕЗЮМЕ

Атеросклероз и ассоциированные с ним болезни системы кровообращения являются актуальной проблемой общественного здравоохранения, а также активно развивающимся направлением исследований как в фундаментальной, так и клинической медицине. Несмотря на многолетнюю историю изучения заболевания, до сих пор многие аспекты этиологии и патогенеза атеросклероза остаются неясными.

Традиционно патогенез атеросклероза рассматривают с позиции очагового накопления отдельных фракций липопротеинов в сосудистой стенке артерий. Однако в атерогенезе активное участие принимают факторы как врожденного, так и адаптивного иммунитета. Клетки и медиаторы иммунной системы вступают в сложное взаимодействие с клеточным и внеклеточным компонентами всех слоев сосудистой стенки. Вследствие этого большинство исследователей пришли к консенсусу о ключевой роли воспаления в инициации, прогрессировании, а также дестабилизации атеросклеротической бляшки.

Таким образом, атерогенез можно рассматривать не только как дисметаболический, но и как иммуновоспалительный процесс. Целью настоящей лекции является обобщение новейших данных о роли воспаления на разных этапах атеросклеротического континуума.

Ключевые слова: атеросклероз, атерогенез, липопротеины, воспаление, атеросклеротическая бляшка, атерома

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of premature death and disability in economically developed countries,and impose a significant burden on healthcare systems, resulting in substantial economic consequences [1].

Diseases associated with atherosclerosis contribute significantly to CVD mortality [2–4]. Despite advancements in modern lipidology, including the implementation of high-intensity statin therapy, its combination with ezetimibe and proprotein convertase subtilisin / kexin type 9 (PSCK9) inhibitors in clinical practice, the challenge of achieving target lipid profile values and addressing residual cardiovascular risk remains pertinent [5]. Notably, approximately half of the patients receiving high-intensity statin therapy in combination with ezetimibe continue to exhibit an elevated risk of adverse cardiovascular outcomes [6]. As of 2024, atherosclerosis remains an idiopathic, multifactorial disease. Concurrently, a consensus has been reached among researchers regarding the pivotal role of inflammation in the pathogenesis of atherosclerosis [7].

Historically, the initiation of atherogenesis was conceptualized through the lens of endothelial dysfunction within the framework of the «endothelial response to injury» hypothesis. However, subsequent investigations revealed no damage, but rather activation of the endothelium due to biomechanical stress and the initiation of associated molecular cascades [8]. These findings do not negate but rather complement and expand upon the involvement of inflammation in the pathogenesis of all stages of atherogenesis [9].

CVD prevention encompasses a complex algorithm comprising a set of measures aimed at lifestyle modification and management of modifiable risk factors [10]. However, optimal pharmacological intervention and reduction of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) do not provide comprehensive protection against cardiovascular complications [11].

It is imperative to consider comorbid conditions represented by relatively novel (non-classical) risk factors for CVD, such as cancer and associated chemotherapy [12], HIV infection (irrespective of viral load levels) [13], *Helicobacter pylori* [14], and oral microbiome dysbiosis [15].

Observational studies have demonstrated the potential anti-atherogenic properties of disease-modifying and/or targeted anti-inflammatory drugs used to treat autoimmune diseases [16]. It has been established that the beneficial effect of statins in reducing cardiovascular risk is associated not only with their primary lipid-lowering effect, but also with anti-inflammatory effects [17].

In contemporary clinical lipidology, the critical importance of inflammation in atherogenesis is directly confirmed by the inclusion of colchicine in the clinical guidelines for cardiovascular prevention prepared by the Russian National Society of Preventive Cardiology in collaboration with the Russian Society of Cardiology [5]. Low-dose colchicine therapy in patients with coronary artery disease has been approved by the U.S. Food and Drug Administration as an efficacious method for reducing residual cardiovascular risk [18].

A subsequent step in improving therapeutic algorithms is the use of nanotechnology to produce novel dosage forms of drugs that can be delivered to specific tissues or cell populations. Thus, a comprehensive study of the pathogenesis of atherosclerosis in combination with the application of a multi-omics approach is highly relevant, as a detailed understanding of the molecular mechanisms of atherogenesis forms the basis for developing

a «signature,» the impact on which will provide more precise control of atherogenic inflammation and facilitate the development of a vaccine against atherosclerosis [19, 20], which will likely require more than one decade.

The aim of this lecture was to synthesize potentially clinically significant data on the role of inflammation at different stages of atherogenesis, including destabilization of atherosclerotic plaques. An international multidisciplinary team of experts prepared the materials. Within the concept «from pathogenesis to therapy,» the presented lecture is divided into two parts.

CONTRIBUTION OF IMMUNE CELLS TO THE DEVELOPMENT OF ATHEROGENIC ENDOTHELIAL DYSFUNCTION

Advances in fundamental scientific research have enabled to reevaluate traditional perspectives on the endothelium, which was previously regarded in the scientific community solely as a conventional layer of flat cells of mesenchymal origin lining the inner surface of blood and lymphatic vessels as well as cardiac cavities [21, 22]. Contemporary understanding considers the endothelium as an active morphological subunit (or, according to some authoritative scientific schools, a distinct organ) that produces a diverse array of biologically active substances with autocrine, paracrine, and juxtacrine activity [23, 24].

Under physiological conditions, the endothelium predominantly exhibits antithrombotic, anti-inflammatory, and vasoactive properties, regulating vascular wall permeability for circulating biologically active molecules and vascular tone through the balance between the release of vasodilators (e.g., nitric monoxide (NO) and prostaglandin E2 (PgE2)) and vasoconstrictors (e.g., endothelin-1 and thromboxane (Tx) A2) [25]. The development of proinflammatory and vasospastic endothelial dysfunction leads to a pathological increase in vascular permeability and a decrease in the bioavailability of atheroprotective NO, contributing to the subendothelial accumulation of atherogenic (ApoB100-containing) lipoprotein fractions (primarily low-density lipoproteins [LDL]) and the development of so-called sterile inflammation [26–30].

Recent research has led to a re-evaluation of the role of perivascular adipose tissue. It has been demonstrated that perivascular adipose tissue produces a diverse group of cytokines and biologically active substances, including tumor necrosis factor α (TNFα), interleukins (IL) IL-1, IL-6, and IL-8, adipocyte-derived relaxing factor, macrophage chemotactic protein-1, plasminogen activator inhibitor-1, complement component C3, apelin, leptin, resistin, visfatin, carbon monoxide (CO), and hydrogen sulfide (H_2S). These biologically active substances can modulate the endothelial state and vascular tone, and exhibit both pro- and antiatherogenic effects [31–34]. Considering the contribution of perivascular adipose tissue to atherogenesis, it is important to note the role of the inflammatory microenvironment in its metabolic reorganization as well as in the development of structural and functional dysfunction of the vasa vasorum and significant dystrophic changes in the perivascular nerve plexus [35, 36]. Furthermore, functional dysregulation of stem/progenitor cells of perivascular adipose tissue (a stem cell niche located at the medial-adventitial interface) has been observed, including adipocyte progenitor cells, smooth muscle cells (SMCs), endothelial cells, mesenchymal stem cells (MSCs), and myeloid progenitor cells [37].

Chronic low-grade inflammation of the vascular wall also induces accumulation of senescent cells. In this context, the inflammatory microenvironment acquires a senescence-associated secretory phenotype, which plays a crucial role in the development of both early vascular aging syndrome and aging heart [38]. Senescent cells are characterized by mitochondrial damage, telomere shortening, epigenetic alterations, metabolic dysregulation (particularly protein metabolism), stem cell dysfunction, and impaired intercellular communication. The key molecules associated with the initiation of aging processes are NF-kB, C/EBP beta, GATA4, mTOR, and p38MAPK, as well as disturbances in the functioning of signaling mechanisms involving cyclic GMP-AMP synthetase (cGAS) and cyclic GMP-AMP (cGAMP) [39]. The accumulation of senescent cells leads to a decrease in the activity of antioxidant systems, particularly the inactivation of the Nrf2/ARE/sestrin-2 cascade [40]. These alterations underlie the development of the early aging syndrome of blood vessels, which presents a significant challenge in the field of internal medicine [41].

As a consequence of the interaction between positively charged amino acids, specifically

arginine and lysine in LDL, and negatively charged proteoglycans in the arterial wall, atherogenic lipoproteins are retained within the vessel wall [42]. Acute activation of the endothelium induces the expression of cell adhesion molecules, resulting in the attachment of monocytes to the endothelial cells [43–45].

Monocytes adhere to endothelial cells via PSGL-1/CD162 receptors (receptors for P-selectin and E-selectin on the surface of endothelial cells), CD11b and CD18 (subunits of the Mac-1 receptor for ICAM1), LFA-1/CD11a (receptor for ICAM1), CD29, and CD49d (subunits of the VLA-4 receptor for VCAM1) [46]. Following cell adhesion, MCP-1 stimulates monocyte migration and infiltration. Upon migration into the endothelium, monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF) [47].

Upon entering the subendothelial space, LDL undergoes not only oxidation, but also aggregation. In the context of an inflammatory microenvironment and the accompanying decrease in pH within the vascular wall, the composition of lipoproteins shifts from the large and medium fractions to the small and dense subfractions. These subfractions exhibit lower affinity for LDL receptors (which impede their removal), greater mobility in the extracellular matrix, and consequently, higher atherogenicity [48].

The accumulation of atherogenic LDL in the subendothelial space of monocytes and resident macrophages that have migrated from circulating blood results in the release of a wide range of proinflammatory cytokines (IL-1β, IL-6, IL-12, IL-15, IL-18, and TNFα) [49]. It is worth noting that under the pathological conditions of an atherogenic microenvironment, macrophages can acquire both proinflammatory and anti-inflammatory phenotypes, characterized by the release of corresponding molecules (IL-4, IL-10, IL-13, and transforming growth factor 1β (TGF-1β)) [50].

Therefore, irrespective of the causal relationship between oxidized LDL and atherosclerosis, atherosclerotic changes in arterial walls can develop in the presence of a normal lipid profile. The increasing prevalence of type 2 diabetes mellitus and metabolic syndrome in the population, coupled with the control of LDL levels through lipid-lowering therapy, has altered the lipid risk profiles. Notably, a significant contribution is observed from elevated levels of desialylated, electronegative, small dense, and multiply modified LDL [51, 52].

In the subendothelial space, modified lipoproteins are captured by macrophages and dendritic cells, which are mononuclear phagocytes that are resident in the normal arterial wall since fetal development. Additionally, circulating monocytes originating from the bone marrow or spleen adhere to the endothelial layer, migrate into the intima via diapedesis, and differentiate into macrophages [50]. In addition, endothelial cells can migrate into the intima and undergo endothelial – mesenchymal transition, thereby promoting thickening (intimal remodeling) and exacerbating inflammation [53].

The endothelial reaction, a key component of the inflammatory response, encompasses the coordinated activation of both innate immunity (macrophages) and adaptive immunity (T- and B lymphocytes). Upon entering the subendothelial space, recruited monocytes differentiate into macrophages and polarize, adopting diverse functional phenotypes in response to alterations in the microenvironment [54].

T lymphocytes transform monocytes into proinflammatory M1 macrophages, which produce proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12, IL-15, IL-18, and TNFα) involved in the progression of atherosclerosis, or into «alternative» anti-inflammatory M2 macrophages, which produce anti-inflammatory cytokines (IL-4, IL-10, IL-13, and TGFβ) capable of modulating the inflammatory response. Consequently, T lymphocytes regulate the continuum of inflammation resolution [55]. Although macrophages are the primary source of cytokines, other cells, such as lymphocytes, polymorphonuclear leukocytes, and endothelial cells, which play a significant role in atherosclerosis, also contribute to cytokine production.

Neutrophilic granulocytes are directly implicated in the development of oxidative stress in endothelial cells and the formation of erosion on plaque surfaces [56]. Furthermore, neutrophils directly activate neighboring cells, such as macrophages and T lymphocytes, thereby intensifying the inflammatory reaction in atheroma [57].

T lymphocytes are present in atherosclerotic plaques to varying degrees at nearly all stages of their formation and associated complications. The process of atheroma development and weakening is accompanied by an immunoallergic reaction of delayed-type hypersensitivity, associated with

significant activation of the CD4+ T lymphocyte subpopulation and secretion of interferon γ (IFNγ) by the latter [13]. Direct receptor-mediated contact occurs between T lymphocytes and macrophages, promoting activation of the latter and increased production of proinflammatory cytokines and proteolytic enzymes, potentiating the development of destructive processes in the plaque [58].

IFNγ and TNFα mediate atherosclerotic changes, affecting macrophages and the endothelium and increasing the level of fractalkine (CX3CL1), a chemokine that regulates the migration and adhesion of leukocytes [59]. IFNγ destabilizes atherosclerotic plaques by inhibiting collagen synthesis, promoting SMC apoptosis, and increasing endothelial permeability [60]. By activating matrix metalloproteinases (MMPs), IFNγ and TNFα promote the degradation of collagen and extracellular matrix, thereby disrupting the stability of atherosclerotic plaques [61].

Typical atheromas contain a lipid core, dying macrophages that form a necrotic core, and a developing thick fibrous cap, which is facilitated by the production of collagen, elastin, fibronectin, and other components of the extracellular matrix by SMC [62]. Macrophage activation results in the release of numerous cytokines and their transformation into foam cells [63]. Activated macrophages release additional inflammatory stimuli and stimulate the formation of the necrotic core in the atherosclerotic plaque. Unstable atheromas are commonly classified into three types [64]:

1. Lipid type – fibroatheroma with a massive lipid core and a thin fibrous cap.

2. Inflammatory and erosive – atheromas with an increased content of proteoglycans and inflammatory or erosive damage to the cap.

3. Dystrophic necrotic type – atheromas with a calcified core and pronounced dystrophic and necrotic changes in the cap.

THE ROLE OF MACROPHAGES IN ATHEROSCLEROSIS

Macrophages catabolize oxidized LDL in the arterial wall to form foam cells. The fate of macrophages varies depending on the concentration of cytokines and their combination as well as the quantity of oxidized LDL [65, 66]. Deceased macrophages coalesce, forming a lipid-rich necrotic core that stimulates the migration of smooth muscle cells from the media to the intima, encapsulated by a collagen cap, with subsequent formation of fibroatheroma [67]. Under conditions of chronic low-grade inflammation, macrophages exhibit catabolic effects, degrading and thinning the fibrous cap, thereby thinning the fibroatheroma (< 65 μm) [68]. These pathological changes, characterized by the presence of a large lipid-rich necrotic core separated from the arterial lumen by a thin fibrous cap, render the plaque unstable and susceptible to rupture [69].

M1 macrophages are classically activated by proinflammatory cytokines, particularly INFγ and bacterial lipopolysaccharides, and produce, as previously mentioned, proinflammatory cytokines, such as IL-1β, IL-6, and TNFα, as well as inducible nitric oxide synthase (iNOS) and NADPH oxidase, with subsequent development of nitrosative and oxidative stress [70]. M2 macrophages, conversely, are alternatively activated by anti-inflammatory cytokines, such as IL-4 and IL-13, and produce elevated levels of IL-10 and TGF-1β [71]. M2 macrophages also express scavenger receptors, such as CD163 and CD206, which play a significant role in atherogenesis [72]. Notably, macrophages in the fibrous capsule of an atherosclerotic plaque express both proinflammatory and anti-inflammatory cytokines, indicating a mixed M1/M2 phenotype [73].

IL-6 plays a crucial role in atherogenesis; specifically, it stimulates the production of acute-phase response proteins and enhances the proliferation and differentiation of lymphocytes [74]. Furthermore, IL-6 activates cyclooxygenase-2 (COX-2), which increases the concentration of IL-1β, TNFα, and high-sensitivity C-reactive protein (hs-CRP) in blood plasma by augmenting the activity of NF-κB, JAK/STAT3, and MAPK transcriptional cascades [75].

Recent studies have identified several novel subtypes of macrophages that may be present in atherosclerotic plaques, including MMe, Mox, M(Hb), Mhem, M4, and HA-mac macrophages. Metabolically activated (MMe) macrophages predominantly reside in the adipose tissue. Their primary function is to eliminate the dead adipocytes [76].

Mox macrophages are inflammatory macrophages that produce high levels of the enzyme Hmox1 (heme oxygenase 1). The M1, MMe, and Mox macrophages are activated by LDL and INFγ [77].

M4 macrophages are proinflammatory macrophages that mature and are activated by the platelet chemokine CXCL-4 (arterial thrombosis companion) and can participate in the degradation of the fibrous cap and plaque rupture by producing the enzyme MMP-12 [78].

Macrophages HA-mac, M(Hb) (hemoglobin-stimulated), and Mhem are anti-inflammatory macrophages with pronounced atheroprotective effects activated by the hemoglobin – haptoglobin complex (hb – hp), which is involved in the clearance of hemoglobin from the hemorrhagic zones [79]. Macrophages with the Mhem phenotype, in addition to participating in erythrophagocytosis, suppress the development of oxidative stress, accumulation of lipid droplets, and formation of foam cells [80]. The role of M(Hb) macrophages in the pathogenesis of atherosclerosis is also associated with the induction of cholesterol efflux, leading to a sharp decrease in foam cell formation [81].

MMe macrophages are characterized by high activity of NADPH oxidase-2 and iNOS, which play important roles in inflammation and generation of reactive oxygen species [65]. In turn, the Mox macrophage phenotype, which is often found in already developed atherosclerotic plaques, activates the expression of Srnx-1 and Txnrd-1 [82].

PLAQUE DESTABILIZATION FACTORS

The main mechanism through which existing atherosclerotic lesions begin to shrink is through a decrease in circulating plasma lipid concentrations and stabilization of inflammatory cascades [83–85]. In animal models, this is often followed by an increase in cholesterol efflux from foam cells via the ATP-binding cassette transporter (ABCA)1 into apoA1/HDL (high-density lipoprotein) via the reverse cholesterol transport pathway.

When cholesterol efflux is induced in high-HDL environments, atherosclerotic plaque macrophages adopt a pro-resolving M2-like phenotype, producing anti-inflammatory cytokines, such as IL-10 and TGF-1β, supporting connective tissue cell proliferation and angiogenesis [86]. The pro-resolving phenotype also enhances phagocytosis of debris and efferocytosis of apoptotic cells, which contributes to the reduction of the necrotic core. Indeed, efferocytosis and apoptosis of atherogenic field cells enhance macrophage proliferation, increasing the number of macrophages available for efferocytosis and potentiating the plaque regression process [87].

Polyunsaturated fatty acids (PUFAs) have been shown to have pronounced atheroprotective properties, which are associated with their anti-inflammatory action [88]. Linoleic acid suppresses the expression of proinflammatory genes in macrophages and inactivates NF-κB, CCL2, and COX-2 through PPARγ receptors, thereby reducing the progression of atherosclerosis [89]. In addition, PUFAs can modulate the atherogenic effects of saturated fatty acids, such as palmitate-induced expression of the lectin-like receptor for oxidized LDL-1 (LOX1) [90].

The atheroprotective functions of HDL are associated with stimulation of cholesterol catabolism and efflux. The antioxidant and anti-inflammatory properties of HDL and its anti-apoptotic effects on endothelial cells and endothelial progenitor cells are worth noting [91]. HDL enhances the proliferation and migration of endothelial cells and endothelial progenitor cells, thereby contributing to the restoration of endothelial integrity [92].

At the same time, the atheroprotective effect of HDL is partly mediated by its anti-inflammatory effect. Studies using a mouse model of atherogenesis have shown that HDL promotes the polarization of macrophages from the M1 phenotype to the M2 phenotype and inhibits the reverse polarization of cells to the M1 phenotype [79].

The migration of monocytes through the endothelium into atherosclerotic plaques is mediated by chemokines (CCR2–CCL2 (or MCP-1), CX3CR1–CX3CRL1, and CCR5-CCL510) secreted by endothelial cells, intimal macrophages, and smooth muscle cells [93]. Vascular endothelial adhesion molecules CD31 (also known as von Willebrand factor) and VCAM1 are involved in monocyte transmigration [93].

It is worth noting that neural guidance signals are involved in the recruitment of monocytes in atherosclerosis; in particular, netrins, semaphorins, and ephrins are expressed by endothelial cells in the arterial wall [94]. Their effects depend on the vascular wall microenvironment. For example, ephrin B2 expression increases under proatherosclerotic conditions and enhances leukocyte recruitment to atherosclerosis-prone areas of the arterial wall, even in the absence of additional chemokines [95]. In contrast, netrin 1 and semaphorin 3A expression inhibits chemokine-directed migration of human and mouse monocytes *in vitro* [96].

The uptake of lipoproteins by monocyte-derived macrophages is considered as one of the earliest stages of atheroma development, leading to the formation of foam cells. Although macrophages can clear ApoB-containing lipoproteins via the LDL receptor, the expression of this receptor is reduced early in foam cell formation, owing to increased cholesterol levels in the cells [97]. These observations have led to the well-established hypothesis that lipoproteins must undergo modification of the arterial wall and be taken up by alternative mechanisms.

Macrophage-expressed scavenger receptors, a type of pathogen pattern recognition receptor (PRR), play a significant role in atherosclerosis and were initially described for their ability to recognize and process modified LDL. Numerous members of the scavenger receptor family include scavenger receptor A (SRA; encoded by MSR), MARCO, CD36, scavenger receptor class B member 1 (SRB1), lectin-type oxidized low-density lipoprotein receptor 1 (LOX1), scavenger receptor class 1 member 1 (SREC1), and scavenger receptors for phosphatidylserine and oxidized low-density lipoprotein (SRPSOX; also known as CXCL16). These receptors bind oxidized LDL and promote foam cell formation [98]. These receptors internalize lipoproteins; in lysosomes, lipoprotein-cholesterol esters are hydrolyzed to free cholesterol and fatty acids [99]. Free cholesterol from the endolysosomal apparatus is subsequently transported to the endoplasmic reticulum, where it is re-esterified by cholesterol ester acyl-CoA transferase to fatty acid esters, which constitute the «foam» of foam cells [77].

Modification of LDL by various proteases and lipases present in the intima can also mediate its aggregation. Glycoproteins of the extracellular matrix contribute to this process by retaining lipoproteins and modulating the activity of various lipolytic enzymes (secretory phospholipase A2 group IIA and secretory sphingomyelinase), which produce modified forms of LDL that are taken up by a scavenger receptor-independent pathway [100].

In understanding the concept of atherogenesis, the necrotic core is of great importance, playing a major role in the vulnerability of atherosclerotic plaques. It is essential to consider the role of primary and secondary inflammation, cell death, and debris removal as well as other factors that may be involved in the formation of the necrotic core, such as MMP activation and diapedetic hemorrhage [101]. The free cholesterol content in the necrotic cores of high-risk plaques is significantly higher than that in low-risk plaques [102]. Free cholesterol is deposited largely because of the extravasation of erythrocytes, which increases with intimal neovascularization, as new vessels are highly permeable, and erythrocyte membranes are rich in free cholesterol [103].

CONCLUSION

Inflammation plays a crucial role in all stages of atherogenesis. Elucidating and investigating intricate cellular and subcellular interactions in atherogenesis in greater detail will provide a foundation for the development of novel strategies for targeted anti-inflammatory therapy of atherosclerosis aimed at mitigating primary cardiovascular and residual cardiovascular risk.

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