Advancements in Atherosclerosis Research: Unraveling Complexity and Charting Therapeutic Avenues

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Abstract

In this review, we delve into the complexities of atherosclerosis, an inþammatory disease a ecting the large arteries and a leading cause of cardiovascular

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Atherosclerosis, also known as coronary artery disease (CAD), stands as the most prevalent form of cardiovascular disease (CVD), characterized by lipid buildup and in ammation in the large arteries. is condition can eventually lead to serious clinical complications such as myocardial infarction (MI) and stroke [1]. Primarily a ecting older individuals due to its gradual progression, atherosclerosis remains a leading global cause of mortality, despite a declining incidence in some regions. Atherosclerotic lesions develop over a lifetime, involving the accumulation and transformation of lipids, in ammatory cells, smooth muscle cells, and necrotic debris within the intimal space beneath a monolayer of endothelial cells (ECs) that line the interior of the blood vessels. As these lesions grow, they can signi cantly reduce blood ow within the lumen, leading to angina, especially during physical exertion or stress. Moreover, lesions can become unstable and prone to rupture, particularly if they possess a fatty and in ammatory composition. Ruptured lesions in the coronary arteries may lead to the formation of local clots, causing complete obstruction of blood ow and resulting in a myocardial infarction [2]. Alternatively, the clot may dislodge and travel to the brain, causing a stroke. Understanding the complexities of atherosclerosis and its potential clinical outcomes is crucial for e ective management and prevention of its life-threatening complications. In recent times, there have been remarkable strides in understanding the intricate molecular and cellular interactions underlying atherosclerosis. Advancements in single-cell RNA sequencing (scRNA-seq) have unveiled previously unknown cellular heterogeneity within atherosclerotic lesions [3-5]. Moreover, aging-related processes, such as senescence and clonal hematopoiesis, have emerged as crucial contributors to the disease. Furthermore, the intricate links between the gut microbiome and atherosclerosis are becoming increasingly evident. Progress in comprehending the interplay of genetic and environmental risk factors in a systems context, along with their connection to cardiometabolic traits, continues to advance signi cantly. Additionally, the diagnostic and therapeutic landscapes are witnessing exciting breakthroughs. is review o ers an inclusive overview of atherosclerosis, with a focus on recent developments. e discussion begins with the growth of atherosclerotic lesions, covering their initiation, progression to advanced stages, and the impact of aging. Subsequently, genetic approaches and the key genetic and environmental risk factors associated with the disease are explored. e review concludes with a comprehensive assessment of clinical aspects and potential future directions. Given the space constraints, we refer primarily to recent reviews, rather than original research articles, to o er a concise yet comprehensive perspective on this evolving eld of study.

e arterial wall comprises a monolayer of endothelial cells (EC) lining the luminal blood ow, with an underlying acellular layer consisting of glycosaminoglycans and collagen known as the “intima.” Beneath the intima are layers of smooth muscle cells (SMCs) forming the “media,” followed by a brous layer known as the “adventitia.” e initiation of atherosclerosis primarily occurs due to the accumulation of speci c plasma lipoproteins, such as low-density lipoproteins (LDLs) and remnants of triglyceride-rich lipoproteins, within the intimal region of the vessel. is leads to the activation of the overlying endothelial cells through a mechanism that is not yet fully understood but likely involves the generation of proin ammatory oxidized lipids [6]. Consequently, blood monocytes adhere to endothelial adhesion molecules, migrate into the intima, and transform into macrophages. ese macrophages can then take up the accumulated lipoproteins, leading to the formation of cholesterol ester-laden “foam cells.” Endothelial cells (ECs) form a continuous single cell layer connected by tight junctions, serving as a barrier between the blood and the vessel wall. Under conditions of disturbed blood ow, the ECs and their tight junctions become more permeable, facilitating the uptake of plasma low-density lipoproteins (LDL) and triglyceride-rich lipoproteins (TG-rich lipoproteins). e subsequent activation of ECs is triggered by

the oxidation of lipoprotein lipids and other in ammatory mediators, leading to the expression of adhesion molecules such as P-selectin, E-selectin, VCAM1, and ICAM1. ese molecules promote the adhesion of monocytes, other leukocytes, and chemotactic factors like CCR2 and CCR5, contributing to the in ammatory response. Disturbed blood ow can also trigger a di erent form of EC dysfunction known as

through statins, ezetimibe, and PCSK9 inhibitors have shown e cacy in reducing LDL levels, while antisense oligonucleotides targeting Lp(a) present a promising approach for treating high Lp(a) levels. In ammation plays a critical role in atherosclerosis, and clinical trials targeting IL-1β with neutralizing antibodies have shown promising results. Additionally, modulating B cells and T cells through depletion or vaccination strategies o er potential therapeutic avenues. e advent of CRISPR-based technologies presents exciting possibilities for targeted genome editing, potentially reducing cholesterol levels and exploring gene expression modulation. Age-related processes, such as senescence, have been implicated in atherosclerosis, and senolytics and CAR T cells targeting senescent cells show promise as therapeutic approaches. Modulating gut microbiota through dietary changes and inhibiting speci c bacterial lyases may also impact CAD. A holistic understanding of atherosclerosis requires integrating various genetic and environmental factors into a systemic network view. Systems studies based on gene-regulatory coexpression networks allow for the identi cation of key driver genes, which may be potential targets for novel interventions. ese approaches o er the potential to de ne molecular signals in blood associated with atherosclerosis and identify therapeutic opportunities. In summary, the advancements in understanding atherosclerosis and technical developments present numerous opportunities for the development of novel medical applications. Emphasizing prevention, precision medicine, and targeting key pathways o er hope for more e ective therapies and better management of this complex and life-threatening disease.

Not applicable.

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