



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 inflammatory disease affecting the large arteries and a leading cause of cardiovascular disease (CVD) and stroke. By examining the molecular, cellular, genetic, and environmental factors contributing to atherosclerosis, we gain insights from both individual pathway and systems perspectives. Our focus is on recent advances that have uncovered intriguing biology, such as the previously unrecognized heterogeneity of inflammatory and smooth muscle cells within atherosclerotic lesions. Additionally, we explore the roles of senescence and clonal hematopoiesis in atherosclerosis, as well as intriguing links to the gut microbiome. This comprehensive review aims to deepen our understanding of atherosclerosis and shed light on emerging discoveries that could shape future research and therapeutic approaches in combating this prevalent and detrimental disease.

Keywords: Atherosclerosis; Cardiovascular disease; Inflammation; Large arteries; Pathogenesis; Single-cell RNA sequencing; Cellular heterogeneity; Senescence; Clonal hematopoiesis; Macrophages

Introduction

Atherosclerosis, also known as coronary artery disease (CAD), stands as the most prevalent form of cardiovascular disease (CVD), characterized by lipid buildup and inflammation in the large arteries. This condition can eventually lead to serious clinical complications such as myocardial infarction (MI) and stroke [1]. Primarily affecting 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, inflammatory 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 significantly reduce blood flow 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 inflammatory composition. Ruptured lesions in the coronary arteries may lead to the formation of local clots, causing complete obstruction of blood flow 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 effective 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 significantly. Additionally, the diagnostic and therapeutic landscapes are witnessing exciting breakthroughs. This review offers an inclusive overview of atherosclerosis, with a focus on recent developments. The 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. The 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 offer a concise yet comprehensive perspective on this evolving field of study.

The arterial wall comprises a monolayer of endothelial cells (EC) lining the luminal blood flow, 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 fibrous layer known as the “adventitia.” The initiation of atherosclerosis primarily occurs due to the accumulation of specific plasma lipoproteins, such as low-density lipoproteins (LDLs) and remnants of triglyceride-rich lipoproteins, within the intimal region of the vessel. This leads to the activation of the overlying endothelial cells through a mechanism that is not yet fully understood but likely involves the generation of proinflammatory oxidized lipids [6]. Consequently, blood monocytes adhere to endothelial adhesion molecules, migrate into the intima, and transform into macrophages. These 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 flow, 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). The subsequent activation of ECs is triggered by

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the oxidation of lipoprotein lipids and other inflammatory mediators, leading to the expression of adhesion molecules such as P-selectin, E-selectin, VCAM1, and ICAM1. These molecules promote the adhesion of monocytes, other leukocytes, and chemotactic factors like CCR2 and CCR5, contributing to the inflammatory response. Disturbed blood flow can also trigger a different form of EC dysfunction known as erosion [7,8]. This mechanism involves TLR2-dependent EC apoptosis and the secretion of IL-8, leading to the recruitment and activation of neutrophils, and subsequent release of neutrophil extracellular traps, which exacerbate EC layer damage and may lead to thrombus formation. Atherosclerosis is a complex disease characterized by lipid accumulation and inflammation in the large arteries, leading to various cardiovascular complications such as myocardial infarction and stroke. The initiation and growth of atherosclerotic lesions are influenced by disturbed blood flow, particularly in regions like arterial bifurcations with turbulent flow, which increases the permeability of endothelial cells (ECs) and promotes the accumulation of lipoproteins in the intimal region. Lipids like low-density lipoproteins (LDL) and triglyceride-rich remnant lipoproteins can become trapped and modified in this area, contributing to lesion development. Lipid oxidation in the vessel wall produces proinflammatory species, leading to leukocyte recruitment and inflammation. Monocytes are recruited to the vessel wall, where they differentiate into macrophages and take up modified lipoproteins, forming cholesterol-engorged foam cells. The accumulation of foam cells gives rise to necrotic cores within the lesions. Advanced atherosclerotic lesions involve the accumulation of foam cells, migration of smooth muscle cells (SMCs) to form a fibrous cap, and infiltration of T cells, which interact with macrophages. Additionally, SMCs can differentiate into bone-like cells, contributing to lesion calcification [9]. Ultimately, the formation of a clot triggered by lesion rupture or endothelial erosion can lead to severe clinical consequences like myocardial infarction. Single-cell sequencing has revealed cellular heterogeneity within lesions, shedding light on the intricate cellular interactions underlying atherosclerosis pathogenesis. Understanding these mechanisms is crucial for developing targeted therapeutic strategies to combat this major global health concern.

During the growth of atherosclerotic lesions, smooth muscle cells (SMCs) within the media undergo a transformation from a contractile to a proliferative state and migrate into the intima, the inner layer of the artery wall. In this intimal region, SMCs secrete an extracellular matrix mainly composed of collagen, forming a fibrous cap that plays a critical role in protecting the lesion against rupture. Only a limited number of SMCs migrate into the intima, where they undergo clonal expansion before redifferentiating into contractile SMCs. Studies using lineage tracing techniques have revealed that these SMCs can also undergo trans-differentiation, giving rise to macrophage-like and osteochondrogenic cells [10]. The macrophage-like SMCs have the ability to take up lipids and become foam cells, contributing to the accumulation of cholesterol in the lesion. These foam cells may undergo apoptosis and impaired efferocytosis, leading to secondary necrosis and inflammation. Moreover, SMCs can acquire cholesterol from neighboring macrophage foam cells through a recently identified pathway involving membrane-derived particles. Notably, SMC-derived foam cells have been suggested to account for up to 50% of the total foam cells in animal models. Additionally, SMCs are responsible for producing macrophage colony-stimulating factor (M-CSF), a cytokine that drives the proliferation of macrophages within the lesions. Furthermore, osteochondrocytes derived from SMCs can contribute to the formation of calcification granules, which can coalesce and form calcium nodules. These dynamic processes involving SMCs play crucial

roles in the progression and complexity of atherosclerotic lesions. Both adaptive and innate immunity play critical roles in driving the chronic inflammation observed in atherosclerosis, with T cells being key contributors to disease progression. T cells are present at all stages of atherosclerosis, and their infiltration into the lesions is facilitated by chemokine receptors (CCR5 and CXCR6) and their corresponding ligands (CCL5 and CXCL16). These T cells have diverse functions, including activation and suppression of immune responses, as well as assisting B cells in producing antibodies. Among the T cell subsets, TH1 cells that secrete interferon γ are most abundant in lesions and promote plaque growth and instability. Conversely, Treg cells express anti-inflammatory cytokines such as IL-10 and TGF β , promote macrophage efferocytosis (clearance of apoptotic cells), and show a negative correlation with atherosclerosis, indicating their protective role. Additionally, TH2 cells express IL-5 and IL-13, both of which exhibit protective effects in atherosclerosis [11,12]. Both T cells and B cells are activated by antigens present within the lesions. Moreover, dendritic cells that have acquired atherosclerosis-related antigens can leave the lesion site and stimulate immune responses at other locations. The intricate interactions of these T cell subsets and their impact on inflammation and lesion progression highlight their importance in atherosclerosis pathogenesis.

B cells play a crucial role in both local and systemic immune responses that contribute to the chronic inflammation observed in atherosclerosis. Originating from bone marrow progenitors, B cells mature in the spleen. Each B cell generates a unique B cell receptor that recognizes specific antigens, leading to its transformation into an antibody-producing plasma cell [13]. Within the B cell population, both antiatherogenic and proatherogenic subsets have been identified. Certain B cells produce "natural" antibodies that bind to oxidized epitopes present in oxidized lipoproteins and necrotic debris, exerting an inhibitory effect on inflammation. Antibodies targeting various antigens, such as LDL, oxidized LDL, apolipoprotein B (the primary protein of LDL), and pathogens like cytomegalovirus, have been associated with atherosclerosis [14,15]. Notably, recent research suggests that elevated levels of IgE immunoglobulins, capable of stimulating proinflammatory responses in macrophages, are significantly linked to increased atherosclerosis. Furthermore, B cell autoimmunity can also contribute to atherosclerosis, as demonstrated by some mouse models of lupus showing an augmented development of atherosclerotic lesions. Understanding the diverse functions of B cells in atherosclerosis provides valuable insights into their potential as therapeutic targets for modulating the disease's inflammatory processes.

Conclusion

The understanding of atherosclerosis and its underlying mechanisms has seen significant progress in recent years. Despite this, there remain critical knowledge gaps, particularly in understanding the contributions of environmental factors in coronary artery disease (CAD). Studies in animal models are vital for bridging this gap, as human studies face challenges in controlling or measuring long-term environmental factors. Efforts like the MOTRPAC consortium and large population studies focusing on gut microbes and their metabolites offer promising avenues to enhance our understanding of the disease. In the pursuit of precision medicine and novel therapies, prevention and early diagnosis of atherosclerosis are of paramount importance, given its largely irreversible nature. Incorporating nontraditional risk factors and high-density genotyping-based polygenic genetic risk scores can improve CAD risk prediction. Targeting lipid metabolism

through statins, ezetimibe, and PCSK9 inhibitors have shown efficacy in reducing LDL levels, while antisense oligonucleotides targeting Lp(a) present a promising approach for treating high Lp(a) levels. Inflammation plays a critical role in atherosclerosis, and clinical trials targeting IL-1 β with neutralizing antibodies have shown promising results. Additionally, modulating B cells and T cells through depletion or vaccination strategies offer potential therapeutic avenues. The 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 specific 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 identification of key driver genes, which may be potential targets for novel interventions. These approaches offer the potential to define 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 offer hope for more effective therapies and better management of this complex and life-threatening disease.

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Conflict of Interest

Author declares no conflict of interest.

References

1. Bermudez B, Lopez S, Pacheco YM, Villar J, Muriana FJ, et al. (2008) Influence of postprandial triglyceride-rich lipoproteins on lipid-mediated gene expression in smooth muscle cells of the human coronary artery. *Cardiovasc Res* 79:294-303.
2. Bhayadia R, Schmidt BM, Melk A, Homme M (2016) Senescence-induced oxidative stress causes endothelial dysfunction. *J Gerontol A Biol Sci Med Sci* 71:161-169.
3. Bian W, Jing X, Yang Z, Shi Z, Chen R, et al. (2020) Downregulation of LncRNA NORAD promotes ox-LDL-induced vascular endothelial cell injury and atherosclerosis. *Aging (Albany NY)* 12:6385-6400.
4. Shen H, Oesterling E, Stromberg A, Toborek M, MacDonald R, et al. (2008) Zinc deficiency induces vascular pro-inflammatory parameters associated with NF-kappaB and PPAR signalling. *J Am Coll Nutr* 27:577-587.
5. Tomat AL, Insera F, Veiras L, Vallone MC, Balaszczuk AM, et al. (2008) Moderate zinc restriction during fetal and postnatal growth of rats: effects on adult arterial blood pressure and kidney. *Am J Physiol Regul Integr Comp Physiol* 295:543-549.
6. Tomat A, Elesgaray R, Zago V, Fasoli H, Fellet A, et al. (2010) Exposure to zinc deficiency in fetal and postnatal life determines nitric oxide system activity and arterial blood pressure levels in adult rats. *Br J Nutr* 104:382-389.
7. Patrushev N, Seidel-Rogol B, Salazar G (2012) Angiotensin II requires zinc and down regulation of the zinc transporters ZnT3 and ZnT10 to induce senescence of vascular smooth muscle cells. *PLoS One* 7:33211.
8. McCord MC, Aizenman E (2014) The role of intracellular zinc release in aging, oxidative stress, and Alzheimer's disease. *Front Aging Neurosci* 6:77.
9. Granzotto A, Sensi SL (2015) Intracellular zinc is a critical intermediate in the excitotoxic cascade. *Neurobiol Dis*.
10. Chowanadisai W, Kelleher SL, Lonnerdal B (2005) Zinc deficiency is associated with increased brain zinc import and LIV-1 expression and decreased ZnT-1 expression in neonatal rats. *J Nutr* 135:1002-1007.
11. Baker DJ, Wijshake T, Tchkonja T, LeBrasseur NK, Childs BG, et al. (2011) Clearance of p16Ink4a-positive senescent cells delays ageing associated disorders. *Nature* 479:232-236.
12. Coppe JP, Desprez PY, Krtolica A, Campisi J (2010) The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol* 5:99-118.
13. Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, et al. (2008) Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371:243-260.
14. Little PJ, Bhattacharya R, Moreyra AE, Korichneva IL (2010) Zinc and cardiovascular disease. *Nutrition* 26:1050-1057.
15. Beattie JH, Gordon MJ, Duthie SJ, McNeil CJ, Horgan GW, et al. (2012) Suboptimal dietary zinc intake promotes vascular inflammation and atherogenesis in a mouse model of atherosclerosis. *Mol Nutr Food Res* 56:1097-1105.