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Dyslipidemia-Induced Cellular Senescence in Atherosclerosis: Mechanisms and Therapeutic Implications

James David*

Department of Pathology and Biochemistry, University of Vermont, Burlington, United States

Introduction

Atherosclerosis is a prevalent age-related condition characterized by the accumulation of lipid-rich plaques in the walls of arteries. This significant global health issue stands as a leading cause of mortality worldwide. Despite its significance, the specific mechanisms behind atherosclerosis remain complex and multifaceted [1]. Recently, emerging evidence has shed light on the role of cellular senescence in various cell types, including endothelial cells (ECs), vascular smooth muscle cells (VSMCs), macrophages, endothelial progenitor cells (EPCs), and adipose-derived mesenchymal stem cells (AMSCs), contributing to the development of atherosclerosis [2]. Both cellular senescence and atherosclerosis share various causative stimuli, with dyslipidemia gaining considerable attention. Dyslipidemia, characterized by elevated plasma levels of atherogenic lipids or lipoproteins, or functional impairment of anti-atherogenic lipids or lipoproteins, plays a pivotal role in promoting cellular senescence and atherosclerosis. This review aims to provide a comprehensive summary of the current evidence regarding dyslipidemia-induced cellular senescence in atherosclerosis. The focus will be on low-density lipoprotein (LDL) and its modifications, the hydrolysate of triglyceride-rich lipoproteins (TRLs), and high-density lipoprotein (HDL) [3,4]. Moreover, we will discuss potential senescence-related therapeutic strategies for atherosclerosis, with particular emphasis on the anti-atherosclerotic effects of promising geroprotectors and the anti-senescence effects of current lipid-lowering drugs. Understanding the interplay between dyslipidemia, cellular senescence, and atherosclerosis could pave the way for innovative approaches to tackle this prevalent and life-threatening condition. Atherosclerosis is a chronic immune-inflammatory disorder, linked to aging and characterized by the accumulation of lipid-rich plaques in arterial walls. Despite advancements in cardiology, atherosclerosis remains the leading cause of mortality worldwide [5,6]. Consequently, monocytes are recruited and cross the endothelial barrier, differentiating into macrophages to clear accumulated lipids and lipoproteins. However, these macrophages transform into foam cells when overloaded, intensifying atherosclerotic plaque formation and eliciting an inflammatory response through the release of pro-inflammatory factors. In parallel, vascular smooth muscle cells (VSMCs) from the arterial media migrate into the intima, surrounding the inflammatory factors and lipids. These highly proliferative VSMCs contribute to the stabilization of atherosclerotic plaques by forming a fibrous cap, but they also secrete various matrix metalloproteinases (MMPs) that promote plaque rupture. In advanced atherosclerotic plaques, VSMCs may adopt a foam-cell-like phenotype, further exacerbating plaque progression and instability. Endothelial progenitor cells (EPCs), a crucial source of new ECs, play a vital role in vascular repair and atherosclerosis [7]. Additionally, perivascular adipose tissue (PVAT), which surrounds blood vessels, modulates vascular function and atherosclerosis. The paracrine secretion of various bioactive factors by adipose-derived mesenchymal stem cells (AMSCs) may be crucial in this process. Hence, the dysfunction of all these types of cells plays a pivotal role in atherosclerosis. Aging is an independent risk factor contributing to the increased morbidity and mortality associated with atherosclerosis. At the cellular level, aging is marked by the accumulation of senescent cells. Cellular senescence is characterized by irreversible cell cycle arrest and distinct phenotype alterations, including flattened and enlarged morphology, elevated activity of senescence-associated β-galactosidase (SA-β-gal), and upregulated senescence-related proteins like p53, p21, and p16. Significantly, senescent cells are known for producing senescence-associated secretory phenotype (SASP) factors, including pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and other factors. Cellular senescence can arise from telomere shortening-dependent replicative senescence and/or stress-induced premature senescence (SIPS) in response to various endogenous and exogenous stimuli, such as DNA damage, oncogene signals, mitochondrial dysfunction, and certain cardiovascular risk factors. Interestingly, cellular senescence shares multiple causative stimuli with atherosclerosis, such as hyperlipidemia, hypertension, diabetes, and obesity, making it a crucial driver of atherosclerosis. Emerging evidence indicates the presence of various types of senescent cells in atherosclerotic arteries, including endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and macrophages [8-10]. Notably, senescence in other cell types, such as endothelial progenitor cells (EPCs) and adipose-derived mesenchymal stem cells (AMSCs), also contributes to atherosclerosis. All these senescent cells play an active role in the pathophysiological process of atherosclerosis.

Conclusion

In conclusion, the interplay between dyslipidemia, cellular senescence, and atherosclerosis represents a complex and multifaceted network of processes. Understanding the specific mechanisms driving cellular senescence in various cell types can provide valuable insights into the pathophysiology of atherosclerosis. Targeting dyslipidemia-induced cellular senescence holds great promise as a potential therapeutic strategy for preventing and managing atherosclerosis. Promising geroprotectors and lipid-lowering drugs may offer new avenues for combating this prevalent and life-threatening condition. Moreover, as research progresses in the fields of precision medicine, genome editing, and gut microbiota modulation, novel and innovative approaches may emerge to tackle atherosclerosis more effectively. By addressing the intricate relationship between dyslipidemia, cellular

***Corresponding author:** James David, Department of Pathology and Biochemistry, University of Vermont, Burlington, United States, E-mail: david_j@yahoo.com

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senescence, and atherosclerosis, we can pave the way for more targeted and personalized interventions, ultimately reducing the burden of this age-related disorder on global health.

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Conflict of Interest

Author declares no conflict of interest.

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