Atherosclerosis: Open Access

Coppe, Atheroscler Open Access 2023, 8:4

Mini Review Open Access

Cellular Senescence in Atherosclerosis: A Comprehensive Review of Mechanisms and Implications

Glory Coppe*

Department of Cardiovascular Medicine, Florida State University, United States

Abstract

Atherosclerosis, a chronic immune-inflammatory and age-related disorder characterized by lipid-rich plaques in arterial walls, remains the leading cause of global mortality. While advances in cardiology have improved our understanding of atherosclerosis, the underlying mechanisms continue to be complex. Recently, emerging evidence has shed light on the critical role of cellular senescence in this pathological process. Cellular senescence is characterized by irreversible cell cycle arrest and distinct phenotypic alterations, along with the production of senescence-associated secretory phenotype (SASP) factors, contributing to pro-inflammatory and pro-atherosclerotic responses. This review aims to provide an extensive examination of the current evidence regarding cellular senescence in atherosclerosis, focusing on its role in endothelial cells (ECs), vascular smooth muscle cells (VSMCs). We discuss the various causative stimuli for cellular senescence in atherosclerosis, including hyperlipidemia, hypertension, diabetes, obesity, DNA damage, oncogene signals, and mitochondrial dysfunction. Moreover, we explore the interplay between cellular senescence and atherosclerosis, emphasizing the involvement of senescent cells in the pathophysiological process. This comprehensive review aims to enhance our understanding of the molecular mechanisms underlying atherosclerosis and shed light on potential therapeutic strategies targeting cellular senescence for the prevention and treatment of this life-threatening disease.

Keywords: Atherosclerosis; Secretory phenotype; Chronic immune-inflammatory; Cellular senescence; Inflammatory cytokines

Introduction

Atherosclerosis is a complex and progressive inflammatory disease characterized by the accumulation of lipid-rich plaques in the arterial walls. It is a leading cause of global mortality, accounting for a significant burden on public health systems worldwide. Understanding the underlying mechanisms of atherosclerosis is crucial for developing effective prevention and treatment strategies [1-5]. In recent years, the concept of cellular senescence has garnered increasing attention in the field of atherosclerosis research. Cellular senescence refers to a state of irreversible growth arrest that cells enter in response to various stressors, including DNA damage and telomere shortening. Senescent cells display distinct phenotypic alterations, such as changes in morphology and the upregulation of specific proteins, as well as the secretion of a unique set of pro-inflammatory molecules collectively known as the senescence-associated secretory phenotype (SASP) [3,6]. The relevance of cellular senescence in atherosclerosis has become a focal point of investigation, as it plays a pivotal role in plaque formation and progression.

Senescence-associated β-galactosidase (SA-β-gal) activity and morphology changes: One of the defining features of senescent cells is the increased activity of SA-β-gal, an enzyme that cleaves a specific substrate and can be detected using a colorimetric assay. This marker has become widely used to identify senescent cells in atherosclerotic plaques and serves as a reliable indicator of cellular senescence. Additionally, senescent cells often exhibit changes in morphology, becoming flattened and enlarged, which can contribute to altered functions within the arterial wall [7].

Upregulation of senescence-related proteins: The tumor suppressor protein p53, cell cycle regulator p21, and cyclin-dependent kinase inhibitor p16 are crucial players in the regulation of cellular senescence. These proteins act in concert to enforce cell cycle arrest and inhibit cell proliferation, preventing the replication of damaged or dysfunctional cells. In atherosclerotic lesions, increased expression of these senescence-related proteins has been observed, signifying the presence of senescent cells [8].

Senescence-associated secretory phenotype (SASP) factors and their role in inflammation: The SASP is a characteristic feature of senescent cells and comprises a diverse array of pro-inflammatory cytokines, chemokines, growth factors, and MMPs. These SASP factors contribute to the chronic inflammation seen in atherosclerotic lesions and can promote the recruitment of immune cells, including macrophages and T cells, exacerbating plaque formation and instability.

Causes of cellular senescence in atherosclerosis

Telomere shortening-dependent replicative senescence: Telomeres, the protective caps at the end of chromosomes, undergo gradual shortening with each cell division. As telomeres reach a critically short length, cells enter a state of replicative senescence, which is thought to play a role in atherosclerosis due to the high cell turnover in the arterial wall.

Stress-induced premature senescence (SIPS) in response to endogenous and exogenous stimuli: Cells can also undergo premature senescence in response to various stressors, such as oxidative stress, DNA damage, and exposure to inflammatory cytokines. These stimuli trigger the activation of specific signaling pathways that induce senescence as a protective response [9].

***Corresponding author:** Glory Coppe, Department of Cardiovascular Medicine, Florida State University, United States, E-mail: glorycop@yahoo.com

Received: 28-Jun-2023, Manuscript No. asoa-23-107742; **Editor assigned:** 30-Jun-2023, PreQC No. asoa-23- 107742(PQ); **Reviewed:** 14-Jul-2023, QC No. asoa-23-107742; **Revised:** 20-Jul-2023, Manuscript No. asoa-23-107742(R); **Published:** 27-Jul-2023, DOI: 10.4172/asoa.1000214

Citation: Coppe G (2023) Cellular Senescence in Atherosclerosis: A Comprehensive Review of Mechanisms and Implications. Atheroscler Open Access 8: 214.

Endothelial cells (ECs) and their role in atherosclerosis: Endothelial dysfunction is a critical early event in atherosclerosis development. Senescence of ECs can impair their barrier function, promote leukocyte adhesion, and contribute to the formation of fatty streaks and atherosclerotic lesions.

Vascular smooth muscle cells (VSMCs) and their contribution to plaque stability and rupture: Senescence of VSMCs can influence plaque stability and rupture by promoting matrix degradation and weakening the fibrous cap, making it more susceptible to rupture and thrombosis.

Macrophages and their dual role in plaque formation and inflammation: Senescent macrophages in the plaque contribute to both plaque formation and inflammation. While they can promote lipid accumulation and foam cell formation, they also secrete pro-inflammatory cytokines that exacerbate inflammation and plaque progression [10].

Endothelial progenitor cells (EPCs) and their impact on vascular repair and atherosclerosis: EPCs play a crucial role in vascular repair and regeneration. However, their senescence can compromise their regenerative potential, impairing endothelial repair and contributing to atherosclerosis.

Adipose-derived mesenchymal stem cells (AMSCs) and their involvement in atherosclerosis: AMSCs have the potential to differentiate into various cell types, including ECs and VSMCs. Senescence of AMSCs may hinder their regenerative capacity, leading to impaired vascular repair and promoting atherosclerosis.

Hyperlipidemia: A key driver of cellular senescence and atherosclerosis: Dyslipidemia, particularly elevated levels of atherogenic lipids and lipoproteins, is a major contributor to the development of atherosclerosis and has been shown to induce cellular senescence in various cell types within the arterial wall.

Hypertension, diabetes, and obesity are well-established risk factors for atherosclerosis. These conditions can trigger cellular senescence in ECs, VSMCs, and other cell types, further promoting plaque formation and inflammation. In conclusion, cellular senescence plays a significant role in the pathophysiology of atherosclerosis, affecting multiple cell types within the arterial wall [11]. Understanding the mechanisms and implications of cellular senescence in atherosclerosis is essential for developing novel therapeutic strategies aimed at targeting senescent cells and preventing plaque formation and progression. Further research in this area is warranted to identify potential senescence-related therapeutic targets and interventions to combat atherosclerosis effectively. In atherosclerotic lesions, senescent endothelial cells (ECs) exhibit impaired barrier function and increased adhesion molecule expression, promoting leukocyte recruitment and inflammation. Senescent vascular smooth muscle cells (VSMCs) are found within the fibrous cap of plaques, contributing to plaque stability and rupture through matrix degradation. Senescent macrophages in the plaque secrete pro-inflammatory cytokines, perpetuating inflammation and plaque progression [12]. Senescence of endothelial progenitor cells (EPCs) impairs their regenerative capacity, hindering endothelial repair and contributing to atherosclerosis. Additionally, senescent adipose-derived mesenchymal stem cells (AMSCs) may compromise their differentiation potential into vascular cell types, leading to impaired vascular repair and further promoting atherosclerosis.

Geroprotectors are compounds that target cellular aging processes and have shown promising effects in combating age-related diseases, including atherosclerosis [13]. These compounds, such as rapamycin and metformin, have been investigated for their potential to mitigate cellular senescence and reduce atherosclerotic plaque burden. Certain lipid-lowering drugs, such as statins and PCSK9 inhibitors, have been found to exert anti-senescence effects beyond their lipid-lowering capabilities [14,15]. These drugs can attenuate cellular senescence in various cell types within the arterial wall, offering potential additional benefits in treating atherosclerosis.

Discussion

The discussion of this comprehensive review highlights the crucial role of cellular senescence in atherosclerosis and its potential implications for therapeutic interventions. Senescent cells, particularly in endothelial cells (ECs), vascular smooth muscle cells (VSMCs), macrophages, endothelial progenitor cells (EPCs), and adipose-derived mesenchymal stem cells (AMSCs), have been identified within atherosclerotic plaques and play significant roles in plaque formation, progression, and stability. The presence of senescent ECs promotes inflammation and leukocyte recruitment, while senescent VSMCs contribute to plaque stability and rupture. Additionally, senescent macrophages perpetuate inflammation, further driving plaque progression. Dysfunction in EPCs and AMSCs due to cellular senescence compromises vascular repair mechanisms, exacerbating atherosclerosis. The review also sheds light on shared risk factors, such as hyperlipidemia, hypertension, diabetes, and obesity, which contribute to both cellular senescence and atherosclerosis. It discusses the potential therapeutic strategies that target cellular senescence, such as geroprotectors and anti-senescence properties of lipid-lowering drugs. The integration of these interventions into atherosclerosis management holds promise for improved patient outcomes. As research in this field progresses, the identification of novel therapeutic targets may offer new avenues to combat cellular senescence and its detrimental effects on atherosclerosis, ultimately leading to innovative approaches for preventing and treating this life-threatening cardiovascular disease.

Conclusion

In this comprehensive review, we have explored the intricate relationship between cellular senescence and atherosclerosis. Senescent cells in various cell types, including ECs, VSMCs, macrophages, EPCs, and AMSCs, play crucial roles in plaque formation, progression, and stability. Understanding the pathophysiological implications of cellular senescence in atherosclerosis provides valuable insights into potential therapeutic interventions. Future perspectives for therapeutic interventions in atherosclerosis should focus on developing strategies to target senescent cells. Geroprotectors show promise in reducing cellular senescence and mitigating atherosclerosis. Additionally, lipid-lowering drugs, which are commonly used in clinical practice, have demonstrated anti-senescence properties, suggesting their potential as adjunct therapies in atherosclerosis management. As research in this area continues to advance, the identification of novel therapeutic targets and interventions to combat cellular senescence in atherosclerosis holds great potential. By developing targeted therapies to mitigate the detrimental effects of senescent cells, we may be able to revolutionize the treatment and prevention of atherosclerosis, offering hope for improved cardiovascular health and reduced global morbidity and mortality.

Acknowledgement

Not applicable.

Conflict of Interest

Author declares no conflict of interest.

References

1. Ahmad F, Leake DS (2019) Lysosomal oxidation of LDL alters lysosomal pH, induces senescence, and increases secretion of pro-inflammatory cytokines in human macrophages. J Lipid Res 60: 98-110.
2. Ai D, Jiang H, Westerterp M, Murphy AJ, Wang M, et al. (2014) Disruption of mammalian target of rapamycin complex 1 in macrophages decreases chemokine gene expression and atherosclerosis. Circ Res 114:1576-1584.
3. Akhmedov A, Rozenberg I, Paneni F, Camici GG , Shi Y, et al. (2014) Endothelial overexpression of LOX-1 increases plaque formation and promotes atherosclerosis in vivo. Eur Heart J 35:2839-2848.
4. Akhmedov A, Camici GG , Reiner MF, Bonetti NR, Costantino S, et al. (2017) Endothelial LOX-1 activation differentially regulates arterial thrombus formation depending on oxLDL levels: role of the Oct-1/SIRT1 and ERK1/2 pathways. Cardiovasc Res 113:498-507.
5. Akhmedov A, Sawamura T, Chen CH, Kraler S, Vdovenko D, et al. (2021) Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1): a crucial driver of atherosclerotic cardiovascular disease. European Heart Journal 42:1797-1807.
6. Allahverdian S, Chaabane C, Boukais K, Francis GA, Bochaton-Piallat ML (2018) Smooth muscle cell fate and plasticity in atherosclerosis. Cardiovas Res 114:540-550.
7. Arsenault BJ, Rana JS, Stroes ES, Despres JP, Shah PK, et al. (2009) Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol 55:35-41.
8. Arunachalam G, Samuel SM, Marei I, Ding H, Triggle CR (2014) Metformin modulates hyperglycaemia-induced endothelial senescence and apoptosis through SIRT1. Br J Pharmacol 171:523-535.
9. Assmus B, Urbich C, Aicher A, Hofmann WK, Haendeler JR, et al. (2003) HMG-CoA reductase inhibitors reduce senescence and increase proliferation of endothelial progenitor cells via regulation of cell cycle regulatory genes. Circ Res 92:1049-1055.
10. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, et al. (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479:232-236.
11. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, et al. (2007) Effects of torcetrapib in patients at high risk for coronary events. New Engl J Med 357:109-2122.
12. Basatemur GL, Jorgensen HF, Clarke MCH, Bennett MR, Mallat Z (2019) Vascular smooth muscle cells in atherosclerosis. Nat Rev Cardiol 16:727-744.
13. Bekkering S, Quintin J, Joosten LA, van der Meer JW, Netea MG, et al. (2014) Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. Arterioscler Thromb Vasc Biol 34:1731-1738.
14. Belcastro E, Rehman AU, Remila L, Park SH, Gong DS, et al. (2021) Fluorescent nanocarriers targeting VCAM-1 for early detection of senescent endothelial cells. Nanomedicine 34:102379.
15. Bennett MR, Macdonald K, Chan SW, Boyle JJ, Weissberg PL (1998) Cooperative interactions between RB and p53 regulate cell proliferation, cell senescence, and apoptosis in human vascular smooth muscle cells from atherosclerotic plaques. Circ Res 82:704-712.