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Exosomes as Modulators of Atherosclerosis: Pathogenetic Insights and Therapeutic Potential

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ABSTRACT

Atherosclerosis remains a leading cause of cardiovascular morbidity and mortality worldwide. It is driven by a cascade of pathogenetic events, including chronic endothelial dysfunction and lipid accumulation, culminating in critical complications such as plaque instability, thrombus formation, and thromboembolism. Current treatment strategies, including statin therapy and drug-eluting stents, primarily act by slowing disease progression or mechanically restoring vessel patency rather than actively regenerating damaged endothelium. In recent years, exosomes - nanoscale extracellular vesicles derived from endothelial, mesenchymal, and immune cells—have emerged as potent mediators of intercellular communication, capable of modulating inflammation, promoting endothelial repair, inhibiting foam cell formation, and stabilizing vulnerable plaques through their cargo of microRNAs, proteins, and lipids. These findings introduce the transformative concept of exosome-based vascular therapeutics that can restore endothelial integrity. Furthermore, the integration of exosomes into scaffold-based delivery systems has generated considerable interest in developing biological stent models that harness endogenous regenerative pathways, rather than relying solely on metallic structures. This review synthesizes current pathogenetic insights of atherosclerosis and treatment strategies, evaluates translational progress from the bench to the bedside, and proposes exosome-driven vascular repair as a novel conceptual framework for treating atherosclerosis, ultimately facilitating the development of advanced, regenerative biological stent technologies.

Keywords: Atherosclerosis; drug-eluting stents; exosomes.

INTRODUCTION

Atherosclerosis is a progressive, multifactorial vascular disorder characterized by endothelial dysfunction, lipid deposition, chronic inflammation, and plaque formation, ultimately leading to peripheral artery disease, ischemia, myocardial infarction, and stroke - the leading causes of global mortality. Endothelial injury is recognized as one of the earliest triggers of atherogenesis, initiating a cascade of events that includes oxidative stress, leukocyte recruitment, foam cell formation, and arterial wall structural remodeling.[1] Despite significant advances in pharmacotherapy, including statins, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, and anti-inflammatory agents, most existing treatments mainly aim to decelerate plaque progression rather than actively regenerate damaged vascular tissue.[2]

Similarly, conventional revascularization techniques, such as percutaneous coronary intervention (PCI) and drug-eluting stents (DES), mechanically restore luminal patency but fail to promote true endothelial healing. Late complications such as neoatherosclerosis, restenosis, and stent thrombosis reflect the limited regenerative capability of current strategies. As a result, there is growing interest in developing novel therapeutic approaches that shift the focus from simply stabilizing the condition to actively repairing blood vessels.[3]

Exosomes, nanoscale extracellular vesicles secreted by endothelial cells, mesenchymal stem cells, and immune cells, have recently emerged as critical mediators of intercellular communication. Owing to their cargo of microRNAs, proteins, and lipids, exosomes play a pivotal role in modulating endothelial homeostasis, reducing vascular inflammation, promoting angiogenesis, and enhancing plaque stability. These regenerative capabilities of exosomes have generated considerable interest in their potential as novel biological agents for the clinical management of atherosclerotic disease, with applications extending to exosome-integrated scaffolds or “biological stent” systems.[4-6]

This review focuses on the active roles of exosomes in atherosclerosis development and how they might be reversed. It further examines the current challenges, future research needs, and the clinical viability of using exosomes to facilitate vascular endothelial repair, as well as their potential integration into advanced biological stent designs.

REVIEW

Pathophysiological basis of atherosclerosis: endothelial inflammation and hyperlipidemia

It is well known that atherosclerosis is a chronic, progressive disease of the arterial wall, characterized by lipid accumulation, oxidative stress, and immune system activation, leading to plaque formation and vascular obstruction. The initiating event in this process is endothelial dysfunction - a loss of the endothelium’s ability to maintain vascular homeostasis and regulate the balance between vasodilation, coagulation, and inflammation.[7]

Under physiological conditions, endothelial cells produce nitric oxide (NO), prostacyclin, and other mediators that inhibit

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leukocyte adhesion and smooth muscle proliferation. When exposed to risk factors such as hyperlipidemia, hypertension, diabetes, and smoking, the endothelium becomes activated, expressing adhesion molecules like VCAM-1 and ICAM-1, which recruit monocytes into the intima.[7,8]

Monocytes differentiate into macrophages, internalize oxidized LDL (oxLDL), and transform into foam cells, generating pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which further amplify local inflammation. This cycle of endothelial activation, leukocyte recruitment, and cytokine release maintains a chronic inflammatory milieu that promotes smooth muscle cell migration and extracellular matrix remodeling, leading to the development of fibrous plaques. The instability of these plaques—characterized by a thin fibrous cap and a large lipid core—is responsible for most acute coronary syndromes through plaque rupture and thrombosis.[9,10]

While current therapies like statins and antiplatelet agents reduce systemic inflammation and lipid levels, they do not reverse endothelial injury or restore vascular integrity. This limitation has stimulated interest in regenerative and cellular mechanisms—particularly those mediated by extracellular vesicles—that could induce true vascular healing rather than mere disease stabilisation.[11]

Exosome biology: biogenesis and functional relevance in vascular systems

Exosomes are nanosized (30–150 nm) extracellular vesicles of endosomal origin released by nearly all cell types, including endothelial cells, smooth muscle cells, platelets, and macrophages. They are generated through the inward budding of multivesicular bodies (MVBs) and subsequently secreted upon fusion of MVBs with the plasma membrane.[12] Exosomes contain a complex cargo of bioactive molecules, including microRNAs (miRNAs), messenger RNAs, proteins, lipids, and signaling molecules that reflect the physiological or pathological state of their parent cells.[4]

According to findings, endothelial-derived exosomes play a crucial role in maintaining vascular tone, angiogenesis, and intercellular signaling. They mediate communication between endothelial cells, smooth muscle cells, and immune cells, thereby influencing vascular remodeling and inflammatory responses. For example, exosomes enriched in miR-126 and miR-21 play prominent roles in enhancing endothelial proliferation, migration, and angiogenic capacity. They enhance endothelial repair, promote NO production via the PI3K/Akt/eNOS pathway, and suppress NF-κB–mediated inflammation. Similarly, mesenchymal stem cell (MSC)-derived exosomes exert anti-inflammatory and anti-apoptotic effects on endothelial cells, reducing oxidative stress and improving angiogenesis.[13-15]

The uptake of exosomes by recipient cells occurs through multiple mechanisms - endocytosis, micropinocytosis, and receptor-mediated fusion - facilitated by surface molecules such as tetraspanins (CD9, CD63, CD81) and integrins that determine target-cell specificity. Once internalized, exosomal cargo can reprogram gene expression in target cells, effectively restoring endothelial homeostasis and function.

Because of these properties, exosomes have emerged as natural nanocarriers capable of delivering regenerative signals in cardiovascular diseases. Their ability to traverse biological barriers, low immunogenicity, and intrinsic targeting capacity make them promising tools for vascular repair and as prototypes for the development of biological stent platforms that combine mechanical support with molecular regeneration.[16]

Exosome-mediated endothelial repair: anti-inflammatory effects of exosomal cargo

Endothelial repair is a critical determinant of vascular homeostasis, particularly during atherosclerotic plaque development and progression. Exosomes derived from endothelial cells, mesenchymal stem cells, and cardiac progenitor cells have been increasingly recognized as key mediators of vascular regeneration by delivering bioactive cargo to dysfunctional endothelial cells.

Beyond cellular repair, exosomes contribute to plaque stabilization by modulating the balance between lipid accumulation and extracellular matrix formation. Studies in ApoE$^{-/-}$ mice have demonstrated that the administration of MSC-derived exosomes leads to reduced aortic plaque burden, increased fibrous cap thickness, and decreased necrotic core size.[17] These effects were partly attributed to reduced macrophage infiltration and enhanced collagen deposition, suggesting that exosomes facilitate the transition from an unstable, rupture-prone plaque towards a more stable phenotype. Furthermore, exosomes enriched in miR-143/145 clusters have been shown to regulate smooth muscle cell phenotypic switching, promoting a contractile rather than synthetic phenotype and thereby contributing to plaque stabilization.[18,19]

In vitro scratch-wound and tube formation assays have consistently confirmed the pro-reparative effects of exosomes on endothelial cell monolayers, demonstrating accelerated wound closure, enhanced vascular network formation, and improved endothelial barrier integrity following exosome exposure.[20] In addition, exosomal cargo has been reported to attenuate endothelial-to-mesenchymal transition (EndMT), a key process in plaque progression that results in loss of endothelial identity and acquisition of a pro-fibrotic, pro-inflammatory phenotype.[21] By preserving endothelial lineage markers such as CD31 and VE-cadherin, exosomes help maintain vascular stability and reduce plaque vulnerability.

Taken together, exosomes exert a dual regenerative effect in atherosclerosis by promoting endothelial repair and plaque stabilization. Their ability to activate angiogenic pathways, enhance NO production, restore endothelial barrier function, and modulate extracellular matrix remodeling positions them as promising therapeutic agents in reversing vascular injury. These findings form a critical foundation for exploring

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exosome-based vascular regeneration strategies and support the development of future therapeutic strategies.

As mentioned before, exosomes have emerged as key modulators of inflammatory signaling pathways through their cargo of regulatory microRNAs, proteins, and lipids that suppress immune activation and promote plaque stabilization.

One of the most extensively studied exosome-derived microRNAs is miR-21, which reduces inflammation by inhibiting the PTEN/NF-κB pathway, thereby downregulating pro-inflammatory gene expression and reducing macrophage activation.[22]

Mesenchymal stem cell-derived exosomes have also been shown to shift macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, thereby enhancing tissue healing and reducing lesion progression.[23]

Similarly, exosomes containing miR-146a suppress toll-like receptor signaling and downstream NF-κB activation, attenuating endothelial and macrophage-mediated inflammatory responses.[24]

In animal models of atherosclerosis, treatment with exosomes carrying anti-inflammatory miRNAs resulted in decreased levels of circulating IL-1β, IL-6, and C-reactive protein, suggesting systemic immunomodulation.[25]

In addition to inflammatory control, exosomes contribute to lipid homeostasis and foam cell regulation, which are essential for reducing plaque lipid burden. For example, exosomes enriched in miR-33 and miR-758 have been reported to modulate cholesterol efflux by regulating ATP-binding cassette transporters ABCA1 and ABCG1, thereby reducing foam cell formation.

Moreover, endothelial-derived exosomes carrying miR-126 help maintain vascular integrity and prevent leukocyte adhesion, indirectly reducing lipid deposition and inflammatory infiltration.

In summary, exosome-based therapy holds promise as a therapeutic strategy that extends beyond traditional pharmacologic interventions focused solely on systemic lipid lowering or symptom control.

CONCLUSIONS

Current therapeutic strategies for atherosclerosis—including statins, PCSK9 inhibitors, anti-inflammatory agents, and drug-eluting stents (DES)—primarily aim to reduce risk factors or mechanically open stenotic vessels, but do not achieve true vascular regeneration. Statins remain the cornerstone of lipid-lowering therapy and have demonstrated significant reductions in major adverse cardiovascular events; however, they primarily target cholesterol synthesis and exert only indirect anti-inflammatory effects without actively repairing endothelial damage. PCSK9 inhibitors further enhance LDL reduction but remain limited to lipid control, without influencing endothelial regeneration or plaque stabilization at the cellular level. Anti-inflammatory strategies, such as canakinumab in the CANTOS trial, demonstrated that IL-1β blockade reduces cardiovascular risk independently of lipid levels. Yet, they do not reverse plaque architecture or restore endothelial function.

Drug-eluting stents (DES) provide temporary mechanical support and prevent restenosis through local drug delivery. Still, they can induce endothelial dysfunction, neoatherosclerosis, and delayed healing, with persistent risks of late thrombosis.

In contrast to widely used therapies that target single pathways, exosomes provide multidimensional vascular healing by delivering key microRNAs and proteins to damaged cells, enhancing nitric oxide bioavailability, suppressing NF-κB-driven inflammation, promoting cholesterol efflux, and stimulating angiogenesis, offering a comprehensive approach to vascular regeneration.

These regenerative capabilities suggest that exosome-based therapies serve not only as adjuncts but as foundational components of next-generation treatment strategies.

Future research should focus on optimizing exosome isolation, enhancing lesion-specific targeting, improving large-scale production, and validating long-term safety and efficacy in clinical trials. As the field evolves, exosome-based nanotherapeutics have the potential to redefine the future of cardiovascular intervention by restoring vascular health at the cellular and molecular levels.

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