

THE ROLE OF STEM CELLS IN ATHEROSCLEROSIS TREATMENT AND FUTURE PERSPECTIVES

İ Sıla Başak Gök¹, İ Kayra Kılıç¹, İ Yiğit Balıkçı¹, İ Cansel Şahin¹, İ Aleyna Kılıç¹, İ Muhammet Gürdoğan²

¹Trakya University School of Medicine, Edirne, TÜRKİYE

²Trakya University School of Medicine, Department of Cardiology, Edirne, TÜRKİYE

ABSTRACT

Atherosclerosis remains a primary driver of global cardiovascular morbidity and mortality, characterized by the progressive accumulation of lipids and inflammatory infiltrates within the arterial wall. This multifaceted pathology originates with endothelial dysfunction, particularly in regions subjected to disturbed hemodynamic flow, and evolves into the formation of unstable plaques that frequently culminate in acute clinical events such as myocardial infarction and stroke. While current pharmacological interventions—primarily statins and antiplatelet agents—effectively reduce mortality, they exhibit significant limitations in stabilizing advanced lesions and preventing post-interventional restenosis. Consequently, stem cell-based therapies have emerged as a transformative strategy in regenerative medicine, aiming to modulate the disease's underlying cellular mechanisms rather than merely addressing its clinical manifestations. Various cell populations, including mesenchymal stem cells, adipose-derived stem cells, and induced pluripotent stem cells, are currently being investigated for their roles in vascular repair, mediated through immunomodulation, endothelial restoration, and exosome-driven paracrine signaling. Although preliminary findings indicate the safety of these interventions, the successful translation of such regenerative approaches into routine clinical practice necessitates the standardization of protocols and the execution of large-scale clinical trials to establish long-term efficacy and stability.

Keywords: Angiogenesis, atorvastatin, induced pluripotent stem cells, vascular endothelial growth factors

INTRODUCTION

Atherosclerosis is the chronic inflammation that causes the vast majority of cardiovascular disease and mortality globally. It is pathologically defined by the formation of atheromatous plaques consisting of a fibrous cap over a necrotic core that underlie most fatal cardiovascular events, including myocardial infarction, stroke, and peripheral arterial disease (1, 2).

The disease is initiated by endothelial dysfunction, particularly in arterial regions of disturbed hemodynamic flow. This dysfunction reduces the synthesis of beneficial vasodilators, such as nitric oxide (NO), while upregulating pro-atherogenic adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). This is followed by the accumulation and oxidation of low-density lipoproteins (LDL) within the subendothelial space, a defining event in

the process. This mechanism recruits circulating monocytes, which travel into the intima, develop into macrophages, and internalize modified LDL via scavenger receptors (such as CD36) to form foam cells. Persistent inflammation mediated by the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome accelerates foam cell death and disrupts the efferocytosis clearance process. This cycle fuels the expansion of the plaque's pro-thrombotic necrotic core (2-4).

The most severe clinical outcomes, such as acute coronary syndromes, are precipitated by plaque rupture (particularly of vulnerable, thin-capped plaques) or erosion, which leads to acute thrombosis (5). Although conventional therapies, including statins and antiplatelet agents, have significantly reduced cardiovascular mortality; their utility is limited. These treatments can have severe effects, such as statin-induced myopathy, and



Address for Correspondence: Sıla Başak Gök, Trakya University School of Medicine, Edirne, TÜRKİYE

e-mail: sbasakgok@gmail.com

ORCID ID of the authors: SBG: 0009-0008-9490-3572; KK: 0009-0000-9453-0384; YB: 0009-0000-0667-4063; ÇŞ: 0009-0008-4813-0900; AK: 0009-0002-2195-9133; MG: 0000-0001-5650-9066

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often fail to sufficiently stabilize advanced plaques or prevent post-interventional restenosis (6). Given these limitations, there is a critical need for innovative therapeutic approaches. Stem cell therapies have thus been recognized as a revolutionary strategy for overcoming these challenges. Unlike conventional therapies, stem cells have the unique ability to target the root cause of atherosclerosis by stabilizing plaques and restoring damaged vessels. This changes the treatment paradigm from managing the disease to seeking a biological cure.

The Therapeutic Potential of Mesenchymal Stem Cells in Atherosclerosis

Given that chronic inflammation is a major cause of atherosclerosis, mesenchymal stem cells (MSCs) have emerged as a highly promising treatment option. They target different phases of disease development via potent immunomodulatory, regenerative, and metabolic regulatory pathways (7). The systemic administration of MSCs significantly reduces the inflammatory response following Ischemia, resulting in a reduction in infarct size (8). A central mechanism of action involves modulating central immune cells and pathways; for instance, human amniotic-derived MSCs reduce atherosclerosis by shifting the cytokine environment from pro-inflammatory to anti-inflammatory, notably by reducing tumor necrosis factor alpha (TNF- α) and increasing interleukin (IL)-10 (9). MSCs also directly affect T-cell function by inhibiting T-cell proliferation and facilitating the essential conversion from pro-inflammatory T helper 1 and T helper 17 cells to anti-inflammatory regulatory T-cells (Tregs) with high IL-10 production (10-12). Specifically, MSC-derived microRNA 125b-1-3p induces T-cell apoptosis by downregulating the T-cell survival gene *B-cell lymphoma/leukemia 11B* (13).

Beyond systemic immunomodulatory effects, MSCs and their products directly target the vascular endothelial dysfunction triggering atherosclerosis. MSC-derived exosomes loaded with miR-145 suppress leukocyte transendothelial migration by reducing junctional-adhesion molecule-A expression, thereby strengthening endothelial barrier integrity (14). Furthermore, MSC-derived extracellular vesicles reverse endothelial-to-mesenchymal transition (EndMT), while miR-126 mimics can further enhance MSC proliferation, migration, and endothelial differentiation, facilitating vascular repair (15, 16). Alongside these mechanisms, MSC immunomodulatory properties influence lipid metabolism, leading to a significant decrease in plasma cholesterol concentrations primarily through a reduction in very low-density lipoprotein secretion (17). Crucially, MSC therapy promotes plaque stabilization, the primary determinant of acute cardiovascular events. This stabilization is driven by the aforementioned cytokine microenvironment shift (decreased TNF- α , increased IL-10) (18). MSCs are specifically attracted to atherosclerotic plaques, and once localized, their exosomes directly modulate plaque biology (19). Bone marrow MSC exosomes, for example, promote plaque stabilization by inhibiting pyroptosis—a highly inflammatory form of cell

death—indicated by decreased expression of NLRP3, caspase-1, and gasdermin D (20).

Therapeutic Targeting of the Endothelium and Its Progenitor Cells in Atherosclerosis

Endothelial progenitor cells are essential for vascular repair and re-endothelialization. They have the ability to differentiate into functional endothelial cells (ECs), promoting neovascularization and replacing damaged endothelium, a therapeutic potential supported by clinical applications in cardiovascular and ischemic diseases (21). However, in atherogenic environments, this regenerative capacity is overwhelmed, and mature ECs undergo a pathological conversion. Instead of promoting vascular health, ECs maintain inflammation by upregulating GATA binding protein 6, which directly targets cytidine/uridine monophosphate kinase 2 to activate the NLRP3 inflammasome and increase IL-1 β production, thereby driving monocyte recruitment and vascular inflammation (22). Furthermore, ECs can promote plaque formation by acquiring a foam cell-like phenotype, a transition characterized by the excessive accumulation of lipid droplets and the subsequent expression of adhesion molecules such as VCAM-1 (23). This inflammatory environment eventually drives EndMT, where ECs lose their healthy phenotype by degrading their intercellular junctions, acquire invasive mesenchymal properties, and promote fibrosis and vascular calcification (24). Emerging therapeutic strategies aim to reverse this pathological transition. Targeted interventions that repair the endothelial barrier can inhibit immune cell infiltration and reverse EndMT, restoring the vessel to a healthy phenotype. This restorative potential is further supported by recent genetic reprogramming strategies, such as OSK transcription factor overexpression, which reverses cellular senescence and inhibits pro-atherosclerotic EndMT (25).

The Therapeutic Role of Hematopoietic Stem Cells in Atherosclerosis

Hematopoietic stem cells (HSCs) are considered the prime progenitors of all circulating blood and immune cells, thus regulating the body's inflammatory response. However, recent breakthroughs suggest that HSCs are now recognized as key drivers of atherosclerosis. Evidence suggests that systemic conditions, such as hypercholesterolemia, can directly "prime" HSCs to become inflammatory cells (26). This pathophysiology can be best understood in the context of clonal hematopoiesis, where somatic mutations (e.g., tet methylcytosine dioxygenase 2) cause the clonal expansion of HSCs. This has been directly associated with the acceleration of atherosclerosis, primarily due to mechanisms such as the activation of the NLRP3 inflammasome (27, 28). Therefore, the focus of therapy has shifted from regeneration to the regulation of this pathologically aberrant behavior. The natural plasticity of the hematopoietic system makes this possible; for example, exercise can "reprogram" progenitors to reduce the inflammatory response (29). Thus, targeting the bone marrow

niche to alter HSC differentiation pathways is emerging as a novel therapeutic strategy.

The Therapeutic Role of Adipose-Derived Stem Cells in Atherosclerosis

Adipose-derived stem cells (ADSCs) are a type of multipotent MSCs that come from the stromal vascular fraction of fat tissue. They've gotten a lot of attention because they naturally have antioxidant, anti-inflammatory, and anti-apoptotic qualities. The main way ADSCs work is through their strong paracrine activity. Conditioned medium from ADSCs helped reduce atherosclerosis in low-density lipoprotein receptor-/- mice, mainly by reducing the inflammation in their blood vessels. The changes were linked more to reduced cell adhesion molecules and macrophage infiltration, rather than shifts in serum lipids. This effect happened because the mitogen-activated protein kinase and nuclear factor- κ B signaling pathways were turned down, and hepatocyte growth factor (HGF) was found to be an important secreted factor (30). Similarly, in ischemia-reperfusion injury models, ADSCs counteract oxidative stress by overexpressing antioxidant enzymes ((NAD(P)H quinone oxidoreductase 1, heme oxygenase-1), concurrently decreasing the expression of inflammatory mediators such as VCAM-1, ICAM-1, and TNF- α (31).

In addition to their secretory components, ADSCs possess strong immunomodulatory properties. They stimulate the production of regulatory Tregs and the differentiation of macrophages into the anti-inflammatory M2 phenotype through both direct and indirect signaling. This leads to a beneficial cytokine profile, decreasing pro-inflammatory TNF- α and IL-1 β , while increasing anti-inflammatory IL-10 (21).

Moreover, ADSCs possess strong regenerative properties. They have been shown to differentiate into viable ECs, expressing markers such as CD34, platelet endothelial cell adhesion molecule, and vascular endothelial-cadherin (32). Their differentiation capacity, along with their secretion of angiogenic factors (vascular endothelial growth factor, HGF), enables ADSCs to directly participate in neovascularization and the repair of the injured endothelial lining (21).

The Therapeutic Role of Induced Pluripotent Stem Cells in Atherosclerosis

By producing patient-specific induced pluripotent stem cell-derived ECs (iPSC-ECs), iPSCs have become a game-changing tool in cardiovascular medicine (33). Researchers can now produce high-fidelity, physiologically relevant models thanks to this technology. It has been confirmed that these iPSC-ECs are functionally competent and can appropriately react to intricate hemodynamic and inflammatory cues. For instance, they upregulate protective factors such as KLF2, KLF4, and endothelial nitric oxide synthase under atheroprotective shear stress. On the other hand, pro-inflammatory stimuli accurately mimic the start of vascular inflammation by inducing the expression of adhesion molecules like ICAM-1 and E-selectin (34).

Induced pluripotent stem cells are an essential preclinical tool because they enable researchers to examine disease pathways and test treatments on a patient's own cells. Research on accelerated atherosclerosis in relation to Hutchinson-Gilford Progeria Syndrome (HGPS) provides the finest example of this utility. By using HGPS-derived iPSC-ECs, researchers were able to test investigational drugs (like Everolimus) and show a partial restoration of endothelial function and NO production in cells with that specific disease background (35).

Consequently, the therapeutic role of iPSCs in atherosclerosis is currently defined not by direct cellular transplantation, but by their indispensable function as a discovery engine for identifying and validating new pharmacological strategies.

Stem Cell Mechanisms in Atherosclerosis Therapy

Stem cell therapies intervene in the atherosclerotic process through several key, often overlapping, mechanisms (Figure 1) (18,25,36-39).

Clinical Translation and Future Perspectives

Early clinical trials of MSCs have shown encouraging results in terms of safety and efficacy. For example, Phase I clinical trials of autologous adipose-derived MSCs (AD-MSCs) showed marked attenuation of key pro-inflammatory cytokines such as IL-1 α , IL-6, and TNF- α in patients with systemic inflammation, with no adverse effects reported (40). These findings are consistent with those of other diseases, such as HGPS and congestive heart failure, in which MSC infusions were found to reduce arterial stiffness and improve cardiac function (41-43). While these findings suggest the therapeutic potential of MSCs, the challenge of long-term efficacy, particularly in atherosclerosis, still persists. A key issue is the variability of existing studies in terms of cell type, administration routes, and patient selection, making direct comparison of results difficult (Table 1). Furthermore, it is important to emphasize that the current clinical management of atherosclerosis heavily relies on established pharmacological interventions, as outlined in the contemporary ACC/AHA and ESC guidelines for the management of dyslipidemias and cardiovascular risk. Due to the limited availability of robust human data and the absence of large-scale randomized phase III clinical trials, stem cell therapies remain investigational and have not yet been incorporated into these major guideline recommendations or routine clinical practice. Looking ahead, the successful translation of stem cell therapy into the clinical setting must address several key issues. The foremost among these is the lack of standardized protocols for cell processing and administration, which is a limitation in terms of reproducibility (37).

Moreover, long-term safety data must be carefully evaluated, particularly in terms of the genomic integrity and tumorigenicity of iPSCs (44). To address these limitations, there is an increasing trend in research towards cell-free therapies such as MSC exosomes although the mechanisms and targeted delivery of these exosomes need further optimization (45). Moreover, to maximize the therapeutic potential, there may be a need

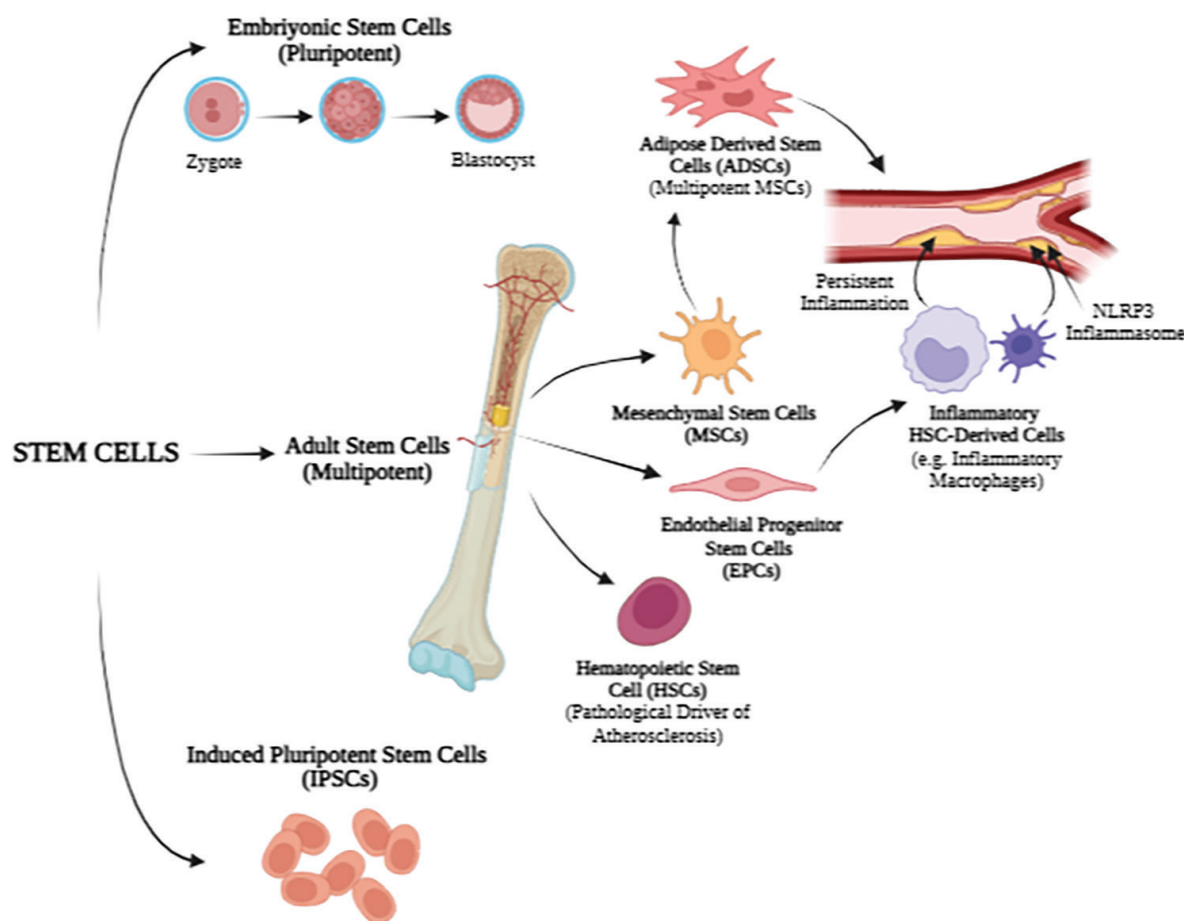


Figure 1: Overview of different stem cell types. **1. Immunomodulation:** MSCs and ADSCs are strong anti-inflammatory agents. They do this by inhibiting key signaling pathways such as NF- κ B, which in turn changes the cytokine environment from pro-inflammatory (TNF- α) to anti-inflammatory (IL-10) (18). **2. Endothelial Repair:** These cells contribute to the repair of the damaged inner lining of blood vessels. This is achieved by enhancing the integrity of the endothelial layer to prevent leukocytes from migrating through and potentially reversing the detrimental process of endothelial-to-mesenchymal transition (25). **3. Plaque Stabilization:** MSCs are attracted to the site of injury. At the site, they contribute to the stabilization of unstable plaques by inhibiting pyroptosis (an extremely pro-inflammatory form of cell death) by suppressing the NLRP3 inflammasome and caspase-1 activation, and by modulating metabolic gene expression in the plaque (36). **4. Regeneration and Angiogenesis:** By secreting angiogenic factors (HGF, VEGF) and having the ability to differentiate into functional endothelial cells, ADSCs and MSCs contribute to neovascularization and the regeneration of damaged tissue (37). **5. Exosome-Mediated Signaling:** Stem cells release exosomes that act as paracrine messengers. These vesicles deliver regulatory cargo, such as microRNAs (e.g., miR-145, miR-125b), which can enhance endothelial barrier integrity, induce T-cell apoptosis, or suppress inflammation by activating other pathways (e.g., SIRT1) (38). **6. iPSC-Based Discovery:** iPSCs serve a different role as a preclinical discovery engine. They provide high-fidelity, patient-specific models (iPSC-ECs) essential for dissecting disease mechanisms and validating new pharmacological strategies (39).

MSCs: Mesenchymal stem cells, ADSCs: Adipose-derived stem cells, TNF- α : Tumor necrosis factor alpha, IL-10: Interleukin-10, HGF: Hepatocyte growth factor, iPSC-ECs: Induced pluripotent stem cell-derived-endothelial cells, NF- κ B: Nuclear factor- κ B, VEGF: Vascular endothelial growth factor, NLRP3: NOD-like receptor family pyrin domain containing 3, SIRT1: Sirtuin 1.

Table 1: Summary of clinical studies evaluating the effects of stem cell-based therapies.

Cell type	Study population	Principal findings
Autologous adipose tissue-derived stem cells	Patients with aging-related low-grade inflammation	<ul style="list-style-type: none"> • Attenuation of pro-inflammatory cytokines such as IL-1α, IL-6, and TNF-α • No adverse effects reported
Allogeneic bone marrow-derived clonal MSCs	Patient with Hutchinson-Gilford Progeria Syndrome	<ul style="list-style-type: none"> • Reduced arterial stiffness • Decreased levels of sICAM-1, IL-18, and MCP-1. • Long-term efficacy limited by continued disease progression.
Allogeneic hMSCs delivered by transendocardial injections oto-hMSC ve allo-hMSC	Patients with nonischemic dilated cardiomyopathy	<ul style="list-style-type: none"> • Improved cardiac function • Reduced infarct size • Improved ventricular remodeling • Enhanced neovascularization
Allogeneic and autologous bone marrow-derived human mesenchymal stem cells	Patients with nonischemic dilated cardiomyopathy	<ul style="list-style-type: none"> • Greater improvement in ejection fraction • Improved 6-minute walk distance and endothelial function • Reduced pro-inflammatory TNF-α levels

allo-hMSC: Allogeneic human mesenchymal stem cells, hMSCs: Human mesenchymal stem cells, IL-1 α : Interleukin 1 alpha, IL-6: Interleukin 6, IL-18: Interleukin 18, MCP-1: Monocyte chemoattractant protein-1, MSC: Mesenchymal stem cells, oto-hMSC: Autologous human mesenchymal stem cells, sICAM-1: Soluble intercellular adhesion molecule-1, TNF- α : Tumor necrosis factor alpha.

for combination therapies that combine stem cells with conventional anti-inflammatory and lipid-lowering therapies (46). Ultimately, advancements in iPSC technology hold the key to personalized medicine, enabling the creation of patient-specific disease models to target unique molecular pathways (47).

CONCLUSION

The integration of stem cell biology into the management of atherosclerosis represents a significant advancement in cardiovascular medicine. By targeting the fundamental mechanisms of inflammation and endothelial decay, stem cell-based therapies offer a potential for disease modification that exceeds the capabilities of current pharmacological standards. However, despite encouraging preclinical and early clinical data, stem cell therapy for atherosclerosis remains investigational and has not yet entered routine clinical practice. The path to clinical integration still requires the standardization of isolation protocols, long-term safety monitoring, and the development of targeted delivery systems to ensure localized efficacy without systemic adverse effects.

Footnotes

Conflict of Interest: The authors declared no conflict of interest.

Author Contributions: Surgical and Medical Practices: M.G., Concept: S.B.G., M.G., Design: C.Ş., A.K., Data Collection or Processing: S.B.G., Analysis and/or Interpretation: S.B.G., K.K., M.G., Literature Search: K.K., Y.B., C.Ş., Writing: S.B.G., K.K., Y.B.

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