Fibrocytes in Atherosclerosis: Emerging Roles in Vascular Inflammation and Fibrosis

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Abstract

Atherosclerosis is a chronic inflammatory and progressive disease of the arterial wall and represents a major underlying cause of cardiovascular disorders such as coronary artery disease, stroke, and peripheral arterial disease. The development of atherosclerotic plaques involves complex interactions among endothelial cells, vascular smooth muscle cells, macrophages, and various immune mediators. In recent years, fibrocytes, a population of circulating bone marrow–derived progenitor cells, have emerged as important contributors to vascular inflammation and tissue remodelling associated with atherosclerosis. Fibrocytes possess characteristics of both hematopoietic cells and fibroblasts and are capable of migrating from the bloodstream to sites of vascular injury through chemokine-mediated signalling pathways. Within atherosclerotic lesions, fibrocytes contribute to disease progression by producing extracellular matrix components such as collagen and fibronectin, which promote fibrosis and fibrous cap formation. They also secrete inflammatory cytokines and growth factors that regulate immune responses and influence the proliferation and migration of vascular smooth muscle cells. Through these mechanisms, fibrocytes play a significant role in plaque formation, vascular remodelling, and plaque stability.

This chapter provides an overview of the origin, biological characteristics, recruitment mechanisms, and functional roles of fibrocytes in atherosclerosis. It also discusses their potential clinical significance as biomarkers and therapeutic targets for the prevention and management of atherosclerotic cardiovascular diseases.

Keywords: Atherosclerosis, Fibrocytes, Macrophage, Ischemic heart disease, Cardiac fibrosis

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, claiming over 17 million lives annually according to the World Health Organization. Atherosclerosis, the primary underlying pathology, drives this burden through progressive arterial narrowing and plaque instability. It manifests as lipid-laden plaques within the intimal layer of arteries, resulting from intricate interplay among endothelial dysfunction, dysregulated lipid metabolism, chronic inflammation, monocyte recruitment, foam cell formation, and vascular smooth muscle cell (VSMC) migration and proliferation. These processes culminate in luminal obstruction, ischemia, and acute events like myocardial infarction or stroke [1,2].

Traditionally, macrophages, endothelial cells, and VSMCs dominate discussions of plaque pathogenesis. Macrophages engulf oxidized low-density lipoprotein (ox LDL) to form foam cells, perpetuating inflammation via cytokine release (e.g., TNF-α, IL-6). Endothelial cells initiate the cascade through reduced nitric oxide bioavailability and expression of adhesion molecules like VCAM-1. VSMCs contribute to plaque fibrosis but also necrotic core expansion. However, emerging evidence spotlights fibrocytes as pivotal players in vascular inflammation and fibrosis, bridging innate immunity and stromal remodelling [2].

Fibrocytes originate from bone marrow-derived CD14+ monocyte precursors, exhibiting a hybrid phenotype: hematopoietic markers (CD45, CD34, CD11b) alongside mesenchymal features (collagen-I, α-SMA, vimentin, fibronectin). Under chemokine gradients such as CXCL12/SDF-1α, they traffic via diapedesis to injured tissues, differentiating into fibroblasts or myofibroblasts within 3–5 days. This plasticity enables dual roles in wound healing and pathological fibrosis [3,4].

In atherosclerosis, fibrocytes infiltrate plaques early, accumulating in the shoulder regions and fibrous cap. Human autopsy studies and ApoE-/- mouse models demonstrate 10–20% of plaque CD45+ cells as fibrocytes, correlating with lesion severity. They deposit collagen types I/III, stabilizing the fibrous cap—a thin collagen-rich layer overlying the necrotic core that prevents rupture. Fibrocyte-derived matrix metalloproteinases (MMP-2, MMP-9) paradoxically thin the cap during unstable phases, heightening vulnerability. Beyond structural contributions, fibrocytes amplify inflammation by secreting pro-inflammatory mediators (IL-1β, CCL2, TGF-β), recruiting monocytes and T cells, and promoting VSMC phenotypic switching [5,6].

CCL2 blockade reduces fibrocyte homing and plaque burden in hyperlipidaemic mice. In humans, elevated circulating fibrocytes predict adverse CVD outcomes in cohorts like the Framingham Heart Study. Their roles extend to post-injury remodelling, such as neointima formation after angioplasty [4].

Therapeutically, targeting fibrocytes holds promise. Inhibitors of CXCR4/SDF-1 axis (e.g., plerixafor) curtail recruitment, while anti-fibrotic agents like pirfenidone suppress differentiation. Nanoparticle-delivered siRNAs against fibrocyte-specific markers (e.g., CD45+Col1+) emerge in preclinical trials [4].
This chapter delves into fibrocyte biology—from ontogeny and trafficking to plaque-specific functions—highlighting their dual pro- and anti-atherogenic potential. Understanding these dynamics could unlock novel diagnostics (e.g., fibrocyte counts as biomarkers) and interventions, shifting paradigms in atherosclerosis management.

2. Biology of Fibrocytes

2.1 Discovery and Origin

Fibrocytes were first identified in the mid-1990s as a unique population of circulating cells that participate in wound healing and tissue remodelling. These cells originate from bone marrow–derived monocyte precursors and circulate in peripheral blood before migrating to sites of tissue injury or inflammation [3]. Fibrocytes represent a small proportion of circulating leukocytes but play an important role in tissue repair and fibrogenesis. Upon reaching injured tissues, they can differentiate into fibroblasts or myofibroblasts and produce extracellular matrix components that contribute to tissue remodelling [7,8]

2.2 Phenotypic Characteristics

Fibrocytes possess a distinctive phenotype that combines characteristics of immune and connective tissue cells. Key markers expressed by fibrocytes include:

- CD34
- CD45
- Collagen I
- Vimentin
- α-smooth muscle actin (in differentiated cells):This unique phenotype allows fibrocytes to participate in both immune responses and structural tissue remodelling [9-11].

2.3 Functional Properties

Fibrocytes exhibit several important biological functions:

1. **Extracellular matrix production** – They synthesize collagen and other matrix proteins.
2. **Cytokine secretion** – Fibrocytes release inflammatory mediators such as TNF-α, IL-1β, and TGF-β.

3. **Antigen presentation** – These cells can present antigens and modulate immune responses.
4. **Differentiation into myofibroblasts** – Under profibrotic signals such as TGF-β, fibrocytes differentiate into contractile myofibroblasts involved in fibrosis. Through these mechanisms, fibrocytes contribute to the inflammatory and fibrotic processes observed in many chronic diseases [9-11].

3. Pathogenesis of Atherosclerosis

Atherosclerosis is a progressive inflammatory disease of large and medium-sized arteries. The process begins with endothelial dysfunction, which allows the accumulation of low-density lipoproteins (LDL) in the arterial wall. Oxidized LDL triggers the recruitment of immune cells such as monocytes and T lymphocytes, which infiltrate the vessel wall and transform into macrophages. These macrophages engulf lipids and become foam cells, forming fatty streaks within the arterial intima [12,13].

As the disease progresses, smooth muscle cells migrate from the media to the intima and produce extracellular matrix proteins, contributing to plaque formation and fibrous cap development.

Chronic inflammation and oxidative stress drive plaque progression and vascular remodelling. In advanced stages, plaque rupture can lead to thrombosis and acute cardiovascular events such as myocardial infarction or stroke. Recent evidence suggests that fibrocytes participate in these processes by contributing to both vascular inflammation and fibrosis [14]

4. Recruitment of Fibrocytes to Atherosclerotic Lesions

Fibrocytes migrate from the bloodstream to sites of tissue injury through chemokine-mediated signalling pathways. Several chemokines and growth factors are involved in fibrocyte recruitment, including:

- CCL2 (MCP-1)
- CXCL12 (SDF-1)
- Platelet-derived growth factor (PDGF)
- Transforming growth factor-β (TGF-β)

These signalling molecules are produced by activated endothelial cells, macrophages, and vascular smooth muscle cells within atherosclerotic lesions.

Once recruited to the arterial wall, fibrocytes differentiate into fibroblasts and myofibroblasts, contributing to extracellular matrix deposition and vascular remodelling.

Evidence from animal models and human studies indicates that fibrocytes accumulate within the fibrous caps of atherosclerotic plaques, where they contribute to plaque stability and repair mechanisms [15,16]

5. Fibrocytes and Vascular Inflammation

Inflammation is a central feature of atherosclerosis, and fibrocytes play an important role in modulating inflammatory responses within vascular tissues.

Fibrocytes produce a wide range of cytokines and chemokines that regulate immune cell recruitment and activation. These include:

- Tumor necrosis factor-α (TNF-α)
- Interleukin-1β (IL-1β)
- Interleukin-6 (IL-6)
- Transforming growth factor-β (TGF-β)

These mediators amplify inflammatory signalling within the vascular wall and influence the behaviour of endothelial cells, macrophages, and smooth muscle cells.

Fibrocytes can also function as antigen-presenting cells, interacting with T lymphocytes and promoting adaptive immune responses. Through these mechanisms, fibrocytes contribute to the chronic inflammatory environment that drives atherosclerosis [16].

6. Fibrocytes in Vascular Fibrosis

Fibrosis is an important component of vascular remodelling in atherosclerosis. It involves excessive deposition of extracellular matrix proteins such as collagen and fibronectin within the arterial wall. Fibrocytes contribute to vascular fibrosis in several ways:

6.1 Differentiation into Myofibroblasts

Under the influence of profibrotic cytokines such as TGF-β, fibrocytes differentiate into myofibroblasts that produce large amounts of extracellular matrix proteins.

6.2 Extracellular Matrix Production

Fibrocytes synthesize collagen types I and III, which contribute to the formation of the fibrous cap that stabilizes atherosclerotic plaques.

6.3 Matrix Remodelling

Fibrocytes secrete matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), regulating extracellular matrix turnover and

vascular remodelling. These processes contribute to vascular fibrosis and arterial wall thickening associated with advanced atherosclerosis. [2–4]

7. Interaction of Fibrocytes with Other Vascular Cells

Fibrocytes interact with multiple cell types within the vascular microenvironment.

7.1 Endothelial Cells

Endothelial cells regulate fibrocyte recruitment through chemokine production and adhesion molecule expression.

7.2 Macrophages

Macrophages release cytokines that stimulate fibrocyte activation and differentiation.

7.3 Smooth Muscle Cells

Fibrocytes influence smooth muscle cell proliferation and migration, contributing to neointima formation and plaque development.

These interactions create a complex network of signalling pathways that regulate inflammation and fibrosis within atherosclerotic lesions.

8. Fibrocytes and Plaque Stability

One of the most important roles of fibrocytes in atherosclerosis is their contribution to plaque stability. The fibrous cap of an atherosclerotic plaque is composed primarily of collagen and smooth muscle cells. This structure prevents rupture of the plaque and exposure of thrombogenic material to circulating blood. Fibrocytes contribute to fibrous cap formation by producing extracellular matrix proteins and differentiating into myofibroblasts. Studies have identified fibrocytes within the fibrous caps of human atherosclerotic plaques, suggesting that they play an important role in stabilizing these structures. However, excessive fibrosis can also contribute to vascular stiffness and reduced arterial elasticity [16].

9. Clinical Implications

The recognition of fibrocytes as contributors to vascular inflammation and fibrosis has important clinical implications. Elevated levels of circulating fibrocytes have been associated with several cardiovascular conditions, including:

- Atherosclerosis
- Ischemic heart disease
- Cardiac fibrosis
- Peripheral vascular disease

Measurement of circulating fibrocyte levels may serve as a potential biomarker for cardiovascular disease progression. Furthermore, targeting fibrocyte recruitment or differentiation may provide new therapeutic approaches for preventing vascular fibrosis and plaque progression [16].

10. Therapeutic Perspectives

Several potential therapeutic strategies are being investigated to target fibrocyte-mediated pathways in cardiovascular disease.

10.1 Inhibition of Fibrocyte Recruitment

Blocking chemokine receptors such as CCR2 and CXCR4 may prevent fibrocyte migration to vascular tissues.

10.2 Targeting Profibrotic Cytokines

Inhibition of signalling pathways mediated by TGF-β and PDGF may reduce fibrocyte differentiation and fibrosis.

10.3 Serum Amyloid P Therapy

Serum amyloid P has been shown to inhibit fibrocyte differentiation and may reduce fibrotic responses.

10.4 Anti-Inflammatory Therapies

Targeting inflammatory signalling pathways may limit fibrocyte activation and plaque progression. These strategies may help prevent excessive vascular fibrosis and improve cardiovascular outcomes [7–9].

11. Future Directions

Although significant progress has been made in understanding fibrocyte biology, many aspects of their role in atherosclerosis remain unclear.

Future research should focus on:

- Identifying specific fibrocyte markers in vascular tissues
- Understanding mechanisms of fibrocyte recruitment
- Determining the balance between protective and pathogenic roles of fibrocytes
- Developing targeted therapies to modulate fibrocyte activity

Advances in molecular biology and imaging technologies will help clarify the role of fibrocytes in cardiovascular disease.

Conclusion

Fibrocytes represent an important link between inflammation and fibrosis in the pathogenesis of atherosclerosis. These bone marrow-derived cells migrate to sites of vascular injury, where they contribute to inflammatory signalling, extracellular matrix deposition, and vascular remodelling. Through their ability to differentiate into fibroblasts and myofibroblasts, fibrocytes participate in fibrous cap formation and plaque stabilization. However, excessive fibrocyte activity can also promote vascular fibrosis and arterial stiffening.

Understanding the complex roles of fibrocytes in vascular inflammation and fibrosis may lead to new therapeutic strategies for preventing and treating atherosclerotic cardiovascular disease.

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