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INTERACTIONS BETWEEN IMMUNE CELLS, CARDIAC FIBROBLASTS, AND ENDOTHELIAL CELLS IN THE IMMUNE REGULATION OF CARDIAC FIBROSIS

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ABSTRACT

Cardiac fibrosis is a central pathological feature of adverse myocardial remodeling and a key contributor to the development and progression of heart failure. Increasing evidence indicates that fibrosis is not a passive consequence of injury but a dynamic, regulated process driven by complex interactions between immune cells, fibroblasts, and endothelial compartments. The objective of this review is to synthesize current mechanistic insights into immune–stromal regulation of cardiac fibrosis, with particular emphasis on fibroblasts as central integrators of inflammatory, mechanical, metabolic, and vascular signals.

This narrative review integrates findings from experimental, translational, and clinical studies addressing immune cell–fibroblast crosstalk, neutrophil extracellular trap formation, endothelial plasticity including endothelial-to-mesenchymal transition, and epigenetic and metabolic mechanisms that stabilize fibroblast activation. The literature was thematically analyzed to construct a unified conceptual framework rather than to perform a quantitative synthesis.

The reviewed evidence highlights macrophage–fibroblast interactions as a dominant regulatory axis governing fibrotic remodeling, with distinct immune cell subsets exerting divergent effects on fibroblast activation and extracellular matrix deposition. Neutrophil extracellular traps and endothelial dysfunction further amplify profibrotic signaling, while epigenetic and metabolic reprogramming preserves activated fibroblast phenotypes beyond the acute injury phase. Circulating biomarkers of fibrosis reflect these underlying biological processes but capture remodeling dynamics rather than fixed fibrotic burden.

In conclusion, cardiac fibrosis should be viewed as the outcome of regulated immune–stroma–endothelium communication rather than irreversible scarring. Targeting key interaction nodes within these networks may enable more precise strategies to limit pathological remodeling while preserving essential reparative responses.

KEYWORDS

Cardiac Fibrosis, Immune–Fibroblast Crosstalk, Macrophages, Neutrophil Extracellular Traps (NETs), Endothelial-To-Mesenchymal Transition (EndMT), Extracellular Matrix Remodeling

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Introduction

Cardiac fibrosis represents a fundamental pathological hallmark of nearly all forms of structural heart disease, including ischemic, hypertensive, valvular, and diabetic cardiomyopathies [1]. It develops as a maladaptive consequence of wound-healing responses that are initially reparative but, when chronically engaged, lead to excessive extracellular matrix (ECM) deposition, ventricular stiffening, and progressive heart-failure development [2]. Over recent years, the understanding of cardiac fibrosis has shifted from a passive scarring process to a dynamic, multicellular interaction orchestrated by fibroblasts, immune cells, and endothelial compartments [3].

From passive scarring to an interactive multicellular network

In the healthy myocardium, fibroblasts maintain ECM homeostasis by balancing collagen synthesis and degradation through matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) [3]. These quiescent fibroblasts occupy specialized anatomical niches—epicardial, endocardial, and perivascular—where they preserve myocardial architecture and contribute to electrical and mechanical coupling with cardiomyocytes [4]. Upon injury or sustained hemodynamic overload, fibroblasts rapidly transdifferentiate into myofibroblasts, characterized by expression of α-smooth-muscle actin (α-SMA), periostin, and connective tissue growth factor (CTGF) [5]. These cells acquire contractile and secretory phenotypes, driving excessive ECM accumulation.

High-resolution single-cell and spatial transcriptomic studies have uncovered substantial heterogeneity among cardiac fibroblast populations, including inflammatory (IL-6$^+$, CCL2$^+$), reparative, and scar-forming (POSTN$^+$/ACTA2$^+$) subsets [3]. This diversity is spatially organized within discrete fibroblast niches that integrate mechanical stress and immune-derived signals. Together, these observations support the concept that fibroblasts act as integrative hubs—cellular translators that convert environmental inputs into structural and inflammatory remodeling.

The immune system as a double-edged regulator

Inflammation constitutes the initiating and sustaining force of myocardial remodeling. Following tissue injury, damage-associated molecular patterns (DAMPs) such as HMGB1 and ATP activate Toll-like receptors (TLRs) on both immune cells and fibroblasts, triggering cytokine cascades [2]. Monocyte-derived macrophages infiltrate the injured myocardium and produce IL-1β, TNF-α, IL-6, and TGF-β—potent drivers of fibroblast activation [6]. As inflammation resolves, macrophages normally transition toward reparative phenotypes secreting IL-10 and VEGF; failure of this polarization prolongs fibrogenic signaling and promotes maladaptive ECM deposition [7].

Beyond macrophages, other immune cells—including T cells, neutrophils, and mast cells—participate in fibrogenic regulation. CD4$^+$ T-cell subsets modulate fibroblast activity through IL-17A and interferon-γ, while neutrophil extracellular traps (NETs) release histones and proteases that activate fibroblast TLR4 pathways [6]. These findings establish fibrosis as a coordinated outcome of persistent immune–stromal communication rather than a purely fibroblast-autonomous process [1].

Endothelial–stromal crosstalk and the vascular niche

Endothelial cells contribute actively to cardiac remodeling through paracrine signaling and endothelial-to-mesenchymal transition (EndMT), a process by which endothelial cells lose junctional integrity and acquire mesenchymal features [4]. Under stimuli such as TGF-β/Smad, Notch, and Wnt/β-catenin, endothelial cells begin to express fibroblast markers (FSP1, α-SMA) and produce collagens, thus expanding the fibroblast pool [8]. EndMT is also induced by metabolic stress, oxidative injury, and inflammatory cytokines, linking microvascular dysfunction with interstitial fibrosis [2]. Moreover, fibroblast-derived endothelin-1 (ET-1) and

PDGF-B reciprocally stimulate endothelial activation and proliferation, reinforcing the paracrine loop between stroma and vasculature [8].

Recent studies of the cardiac vascular niche highlight the proximity between fibroblast clusters and microvascular endothelial cells, suggesting that capillary rarefaction and fibroblast activation are spatially and functionally coupled [4]. This bidirectional signaling provides a structural basis for chronic remodeling in heart failure.

Molecular and epigenetic regulation of fibroblast plasticity

Persistent fibroblast activation depends on transcriptional and epigenetic programs that sustain profibrotic gene expression even after the initial injury resolves [9]. Histone acetylation (H3K27ac) and methylation (H3K4me3) at promoters of COL1A1, COL3A1, and ACTA2 are characteristic of a "fibrotic memory." The bromodomain protein BRD4 functions as a chromatin reader that assembles super-enhancers and supports prolonged transcription of ECM genes; pharmacologic BRD4 inhibition (JQ1) reverses fibrosis in pre-clinical models [9]. DNA methylation changes, non-coding RNAs (miR-21, miR-133a, lncRNA H19/Meg3), and metabolic cues (acetyl-CoA, α-ketoglutarate) further integrate environmental stress into durable epigenomic reprogramming [9].

Therapeutic implications and translational perspective

Recognition of fibroblasts as central integrators of immunological and endothelial signals positions them as promising therapeutic targets [10]. Strategies aiming to modulate fibroblast activation include inhibition of TGF-β/Smad and IL-11 signaling, macrophage-directed immunotherapies, and metabolic reprogramming. Clinical translation will require precise identification of fibroblast subsets driving pathology, as underscored by recent multi-omics profiling [3]. The concept of "immune–stroma checkpoints"—defined as ligand–receptor interactions (e.g., CCL2/CCR2, CSF1/CSF1R, ET-1/EDNRA)—offers a framework to rationally target fibrosis at its cellular communication nodes [1].

In summary, cardiac fibrosis arises from the convergence of immune dysregulation, fibroblast activation, endothelial plasticity, and epigenetic memory. Understanding how these processes integrate across spatial and temporal scales will be crucial for developing next-generation anti-fibrotic therapies that not only suppress scar formation but also restore tissue homeostasis and cardiac function [7].

Methodology

This narrative review synthesizes current experimental, translational, and clinical literature on immune–stromal mechanisms of cardiac fibrosis. Relevant publications were identified through targeted searches of PubMed, Web of Science, and Scopus using keywords related to cardiac fibroblasts, immune regulation, extracellular matrix remodeling, and heart failure. Studies providing mechanistic insight into fibroblast activation, immune–stromal interactions, and fibrotic remodeling were prioritized. The literature was critically appraised and thematically integrated to develop a coherent conceptual framework rather than a quantitative synthesis.

Results

1. Cardiac fibroblasts as an integrative hub

Cardiac fibroblasts constitute the central cellular regulators of myocardial homeostasis and pathological remodeling. Rather than acting as passive structural elements, they function as highly specialized integrators of immunological, mechanical, and metabolic cues within the cardiac microenvironment. This integrative capacity is closely linked to the pronounced heterogeneity of the fibroblast population, which displays distinct phenotypic states, transcriptional programs, and regulatory dependencies depending on anatomical location and pathophysiological context.

The heterogeneity of cardiac fibroblasts originates early during development. Single-cell lineage tracing studies have demonstrated that adult cardiac fibroblasts arise from three principal embryonic sources: the epicardium, the endocardium and endothelium, and the neural crest [5,11,12]. Epicardial-derived fibroblasts constitute the dominant population in the adult heart and undergo epithelial-to-mesenchymal transition during embryogenesis, acquiring characteristic transcriptional profiles defined by Tcf21, Tbx18, and Wt1 expression before migrating into the developing myocardium [5]. This lineage gives rise to the majority of interstitial fibroblasts and contributes to vascular smooth muscle cell populations in the adult heart [11,12].

In contrast, endocardial-derived fibroblasts originate through endothelial-to-mesenchymal transition and retain features of their endothelial lineage, including expression of receptor tyrosine kinases such as TIE2 [11]. These cells preferentially localize to perivascular regions and the interventricular septum, where they

participate in region-specific fibrotic responses and valvular pathology. Neural crest–derived fibroblasts represent a smaller but functionally relevant subset, primarily enriched in the outflow tract and proximal great vessels, where they may preserve distinct regulatory properties and contribute to localized remodeling processes [11].

Although developmental origin alone does not fully determine fibroblast behavior in adult disease, it provides a foundational framework upon which microenvironmental signals act. During myocardial injury or chronic stress, fibroblasts undergo rapid phenotypic transitions that reflect integration of immune-derived mediators, mechanical loading, and metabolic stress. Activated fibroblasts express contractile and extracellular matrix–producing programs, proliferate, and engage in bidirectional communication with immune and endothelial cells, positioning them as cellular hubs that coordinate structural remodeling.

At the tissue level, fibroblast populations are organized into discrete anatomical and functional niches. Perivascular fibroblasts reside in close proximity to endothelial cells and immune infiltrates, allowing rapid sensing of inflammatory and hemodynamic changes. Interstitial fibroblasts integrate mechanical strain generated by cardiomyocyte contraction with paracrine signals derived from macrophages and endothelial cells. This spatial organization enables fibroblasts to translate localized microenvironmental cues into regionally distinct remodeling responses, contributing to the heterogeneous pattern of fibrosis observed in different forms of heart disease.

Importantly, fibroblast activation is not a binary process but encompasses a spectrum of intermediate states. Single-cell transcriptomic analyses have identified inflammatory fibroblast subsets characterized by expression of cytokines and chemokines, as well as reparative and scar-forming populations defined by extracellular matrix synthesis and contractile gene programs [3]. These phenotypic states are dynamically regulated and reflect ongoing communication with immune and vascular compartments rather than fixed cell identities.

Through this combination of developmental diversity, spatial organization, and phenotypic plasticity, cardiac fibroblasts function as integrative hubs that coordinate immune responses, vascular remodeling, and extracellular matrix turnover. This central positioning allows fibroblasts to determine whether myocardial injury resolves through adaptive repair or progresses toward maladaptive fibrosis, establishing them as key regulators of cardiac remodeling across disease contexts.

2. Epigenetic and metabolic regulation of fibroblast activation

The activation of cardiac fibroblasts and their transition into myofibroblasts is controlled by coordinated epigenetic and metabolic programs that reshape cellular identity from a quiescent to a highly secretory and matrix-producing state. These mechanisms help determine whether fibroblasts support physiological repair or drive maladaptive remodeling [9,13].

Epigenetic regulation is a central determinant of fibroblast plasticity and governs transitions between quiescent and activated states. The major regulatory layers include histone acetylation and methylation, DNA methylation, and control by non-coding RNAs, which together shape the accessibility of profibrotic gene loci and stabilize transcriptional programs [9,13]. Histone acetylation, mediated by histone acetyltransferases, generally increases chromatin accessibility and promotes transcriptional activation. The p300 complex has been highlighted as a key co-activator in this context, and experimental inhibition of p300 reduces fibrogenesis by limiting acetylation at promoters of profibrotic genes [9,13].

Conversely, histone deacetylases (HDACs), particularly class I and II enzymes, exert strong regulatory effects on fibrotic remodeling. HDAC inhibition can suppress fibroblast-to-myofibroblast transition by modulating chromatin states at regulatory regions involved in negative feedback on profibrotic signaling, including pathways converging on SMAD7 [9,13]. Histone lysine methylation provides an additional layer of control and is regulated by lysine methyltransferases and demethylases that fine-tune fibroblast activation states and responsiveness to profibrotic cues [9,13].

Among demethylases, KDM1A (LSD1) has been implicated as a relevant regulator, with perturbation of LSD1-related programs influencing TGF-β pathway activity and downstream Smad phosphorylation patterns in experimental settings [9,14]. DNA methylation–dependent mechanisms further contribute to fibroblast behavior, with methyl-CpG-binding protein 2 (MeCP2) acting as an important transcriptional modulator during cardiac fibrosis. Alterations in MeCP2-mediated repression have been linked to changes in hypertrophic and fibrotic responses under hemodynamic overload, while reduced MeCP2 activity has been associated with more regenerative phenotypes in specific contexts [9].

2.1 MicroRNA regulation of fibroblast activation

MicroRNAs represent critical post-transcriptional regulators of fibroblast gene expression and can exert either profibrotic or antifibrotic effects depending on their targets and expression dynamics during remodeling [9,13]. miR-21 is one of the most consistently reported profibrotic microRNAs in cardiac disease and is expressed across multiple cardiac cell types, including fibroblasts. It promotes collagen synthesis, fibroblast survival, and growth factor secretion in part by suppressing negative regulators of TGF-β signaling, such as SMAD7, and modulators of MAPK signaling, such as Spry1 [9]. Experimental inhibition of miR-21 using locked nucleic acid antagonists has attenuated angiotensin II–driven fibrogenic responses and reduced pathological remodeling in preclinical models [9].

In contrast, the miR-29 family (notably miR-29a and miR-29b) is downregulated during fibrotic remodeling and exerts antifibrotic effects by directly targeting transcripts encoding collagens and other extracellular matrix proteins. Restoration of miR-29 expression reduces myofibroblast markers and limits ECM accumulation. Additional microRNAs, including miR-155, have been linked to amplification of inflammatory signaling, while miR-208a, miR-125b, and miR-214 promote fibroblast proliferation and collagen production through modulation of TGF-β- and MAPK/ERK-associated pathways [9,13].

2.2 Long non-coding RNAs in fibroblast regulation

Long non-coding RNAs modulate fibrotic remodeling by recruiting chromatin-modifying complexes, shaping transcription factor availability, or functioning as competitive endogenous RNAs that sequester microRNAs. NEAT1 has been described as pro-fibrotic through effects that include repression of inhibitory regulators of TGF-β signaling, whereas other lncRNAs such as MALAT1 can influence fibrogenic programs indirectly by interacting with microRNA networks implicated in endothelial plasticity and stromal activation [13].

2.3 Metabolic reprogramming during fibroblast activation

Metabolic remodeling is a defining feature of fibroblast activation. While quiescent fibroblasts rely predominantly on oxidative phosphorylation, activated myofibroblasts exhibit a shift toward glycolysis, resembling a Warburg-like metabolic profile with increased glycolytic flux even under normoxic conditions [14]. Signaling intermediates including p38 MAPK have been implicated in coordinating metabolic adaptation alongside fibrogenic activation programs, and perturbations of mitochondrial regulatory nodes can further reinforce myofibroblast differentiation. For example, disruption of mitochondrial calcium handling has been associated with augmented profibrotic responses and increased abundance of activated fibroblasts in experimental models [14].

2.4 Integration of epigenetic and metabolic pathways

Epigenetic and metabolic pathways converge on shared regulatory nodes, allowing inflammatory, hypoxic, and mechanical stimuli to be translated into coordinated transcriptional outputs. In this integrated control system, p38 MAPK has been highlighted as a central hub linking environmental stress to both metabolic adaptation and chromatin-dependent gene regulation [13,14]. Metabolic regulators can influence the availability of key intermediates (including acetyl-CoA) that directly shape histone acetylation states, thereby coupling cellular metabolism to epigenetic remodeling [13,14]. TGF-β signaling occupies a particularly central position because it simultaneously engages epigenetic regulators, metabolic pathways (including mTOR and glycolysis), and Smad-dependent transcriptional programs that govern myofibroblast differentiation and ECM production [9,13,14].

Collectively, these observations support the concept that effective antifibrotic strategies may require combined targeting of epigenetic and metabolic mechanisms rather than isolated interference with single downstream effectors. In this context, the TGF-β–p38 MAPK axis emerges as a plausible integrator of fibroblast activation programs and a candidate focus for multi-layered therapeutic intervention [9,13,14]

3. Fibroblast–macrophage and fibroblast–endothelial communication

Cardiac fibroblasts act as central nodes of intercellular communication within the myocardial microenvironment, maintaining continuous bidirectional interactions with resident macrophages and endothelial cells. Through these interactions, fibroblasts regulate both physiological tissue homeostasis and pathological remodeling by integrating inflammatory signals, growth factors, and mechanical cues into coordinated stromal responses [8,15].

3.1 Fibroblast–macrophage communication

Reciprocal signaling between fibroblasts and macrophages is essential for myocardial function and repair. Activated cardiac fibroblasts express colony-stimulating factor 1 (CSF-1), which signals through CSF-1 receptor–expressing macrophages to support their survival, proliferation, and differentiation [15]. This CSF-1–CSF-1R axis operates under steady-state conditions and becomes further amplified during injury and fibrotic remodeling, establishing a persistent functional link between stromal and immune compartments. In turn, macrophages reinforce fibroblast activation by enhancing CSF-1 production and secreting growth factors such as platelet-derived growth factors and amphiregulin, which promote fibroblast proliferation and matrix synthesis [15].

Macrophages further drive fibrogenic programs through secretion of cytokines and profibrotic mediators, including transforming growth factor-β, interleukin-6, interleukin-17, and amphiregulin. These factors collectively stimulate fibroblast activation, myofibroblast differentiation, and extracellular matrix deposition [15]. In parallel, the CCL2–CCR2 chemokine axis constitutes a major pathway linking immune recruitment with stromal remodeling. Fibroblast-derived CCL2 recruits monocyte-derived macrophages to sites of injury, where they proliferate and adopt profibrotic phenotypes. Beyond its chemotactic function, CCL2 directly promotes fibroblast transdifferentiation into myofibroblasts, thereby amplifying fibrotic remodeling through a feed-forward mechanism [8,15,16].

These interactions underscore that macrophages not only respond to fibroblast-derived signals but also actively shape fibroblast fate. Through coordinated CSF-1, CCL2, and cytokine signaling, macrophages regulate fibroblast proliferation, activation state, and spatial organization within the myocardium, positioning immune–stromal communication as a core determinant of remodeling outcomes [15,16].

3.2 Fibroblast–endothelial communication

Fibroblast–endothelial interactions are similarly complex and operate through both direct cell–cell contact and soluble mediators. Perivascular fibroblasts reside in close proximity to endothelial cells, allowing rapid exchange of signals that regulate vascular integrity, immune cell trafficking, and stromal activation [3,8]. NOTCH1-dependent signaling plays an important role in vascular homeostasis, while fibroblast-derived fibroblast growth factors and vascular endothelial growth factor promote endothelial proliferation and angiogenesis [3,8].

The extracellular matrix and basement membrane further modulate fibroblast–endothelial communication by providing structural support and integrin-mediated survival signals to endothelial cells. In turn, endothelial cells influence fibroblast behavior by producing angiotensin II, endothelin-1, insulin-like growth factor 1, and transforming growth factor-β, which collectively regulate fibroblast proliferation, contractile gene expression, and extracellular matrix synthesis [3,17]. These reciprocal interactions establish a tightly regulated paracrine network linking stromal activation with vascular remodeling.

During myocardial inflammation, this balanced crosstalk becomes profoundly altered. Endothelial cells rapidly upregulate proinflammatory cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor-α, which promote fibroblast activation and extracellular matrix reorganization [3,8,17]. Owing to their perivascular localization, fibroblasts function as gatekeepers that regulate immune cell access to deeper myocardial layers, thereby controlling the extent and distribution of inflammatory infiltrates within cardiac tissue [3,8,17].

3.3 Integration within the myocardial niche

Together, fibroblast–macrophage and fibroblast–endothelial interactions define specialized myocardial niches in which immune activation, vascular remodeling, and extracellular matrix turnover are spatially and temporally coordinated. Disruption of these interactions during chronic injury shifts fibroblast behavior toward persistent activation and maladaptive fibrosis. In this context, fibroblasts serve not only as responders to immune and endothelial signals but also as active organizers of the myocardial microenvironment, reinforcing the concept of fibroblasts as integrative hubs within immune–stroma–endothelium networks [8,15,17].

4. Macrophage–Fibroblast Crosstalk

Cardiac macrophages and fibroblasts represent two fundamental cellular populations that engage in continuous, bidirectional communication within the myocardial microenvironment. Through tightly regulated interactions, these cells exert a decisive influence on myocardial homeostasis, reparative responses, and pathological remodeling. Macrophage–fibroblast crosstalk is mediated by complementary mechanisms that include direct cell–cell contact, paracrine signaling via soluble mediators, and the exchange of extracellular vesicles containing regulatory proteins and RNAs [15–18].

Cardiac macrophages comprise a heterogeneous population that is commonly classified based on the expression of C–C chemokine receptor 2 (CCR2), a distinction that reflects developmental origin, tissue residency, and functional specialization [15–18]. This dichotomy between $CCR2^{-}$ and $CCR2^{+}$ macrophages represents a central determinant of their roles in maintaining cardiac homeostasis versus driving maladaptive remodeling.

$CCR2^{-}$ resident cardiac macrophages are derived from yolk sac and fetal liver progenitors and establish tissue residency early during development. Under steady-state conditions, they maintain their population predominantly through local self-renewal, with minimal contribution from circulating monocytes. Within this compartment, additional functional heterogeneity exists, including subsets characterized by high expression of TIMD4, LYVE1, and FOLR2, collectively referred to as TLF^{HI} macrophages, as well as $MHC\text{-}II^{HI}$ populations [15,16].

In physiological conditions, $CCR2^{-}$ resident macrophages display enhanced efferocytotic capacity, contribute to extracellular matrix organization, and support tissue repair. During pressure overload, these cells undergo local proliferation and promote adaptive hypertrophy by restraining excessive monocyte recruitment and supporting angiogenesis, thereby limiting fibrotic remodeling and delaying progression toward heart failure. Notably, depletion of $CCR2^{-}$ resident macrophages prior to ischemia–reperfusion injury has been shown to improve systolic function and reduce infarct size by limiting neutrophil extravasation, highlighting the context-dependent effects of this macrophage subset [15–17].

In contrast, $CCR2^{+}$ macrophages are largely bone marrow–derived and are recruited from circulating monocytes in response to acute injury or chronic stress. Following myocardial infarction, $Ly6C^{HI}$ $CCR2^{+}$ monocytes rapidly infiltrate the infarcted myocardium, where they participate in efferocytosis, antigen presentation, and clearance of necrotic tissue during the early inflammatory phase. Over time, these cells transition into $Ly6C^{LO}$ macrophages that exhibit pro-reparative and anti-inflammatory properties, supporting myofibroblast differentiation and scar formation [15–17].

While this phenotypic transition is essential for structural stabilization of the injured myocardium, sustained CCR2-dependent recruitment in chronic settings promotes progressive fibrosis in non-infarcted regions and contributes to adverse ventricular remodeling. In pressure-overloaded hearts, persistent accumulation of $CCR2^{+}$ monocyte-derived macrophages drives long-term tissue damage and accelerates heart failure progression. A distinct profibrotic macrophage subset characterized by high expression of triggering receptor expressed on myeloid cells 2 (TREM2) and secreted phosphoprotein 1 (SPP1, osteopontin) emerges during late post-infarction remodeling and exhibits particularly strong capacity to activate fibroblasts and promote extracellular matrix deposition [16].

At the molecular level, macrophage–fibroblast communication is orchestrated through several interconnected signaling axes. Among these, the colony-stimulating factor 1 (CSF-1)–CSF-1 receptor pathway represents a foundational interaction that governs macrophage survival, proliferation, and spatial organization. Cardiac fibroblasts, particularly when activated during inflammation and fibrosis, constitutively express CSF-1, while CSF-1R is predominantly expressed on macrophages [15–17].

Self-renewal of embryonically derived $CCR2^{-}$ resident macrophages critically depends on intact CSF-1–CSF-1R signaling, as pharmacological blockade of CSF-1R leads to marked depletion of resident macrophages in the steady-state heart. Following myocardial infarction, this pathway is also required for expansion of reparative $Ly6C^{LO}$ monocyte-derived macrophages and for angiogenesis within the infarct border zone. In pressure-overload models, early CSF-1R inhibition limits expansion of $CCR2^{-}$ macrophages, increases infiltration of $CCR2^{+}$ populations, and accelerates progression toward heart failure, underscoring the context-specific effects of this signaling axis [15,16].

The CCL2–CCR2 chemokine axis constitutes the principal mechanism by which circulating monocytes are recruited to the injured myocardium. Activated fibroblasts upregulate CCL2 in response to inflammatory and mechanical cues, thereby promoting accumulation of $CCR2^{+}$ monocytes and macrophages at sites of injury. Beyond its chemotactic role, CCL2 directly enhances fibrogenesis by increasing transforming growth factor-β expression, shaping profibrotic macrophage polarization, and inducing fibroblast transdifferentiation into myofibroblasts [15–18].

Genetic or pharmacological disruption of CCL2–CCR2 signaling reduces inflammatory cytokine production, limits macrophage recruitment, and attenuates myofibroblast accumulation in experimental models of myocardial infarction. Therapeutic interventions targeting this pathway, including CCL2 inhibitors and CCR2 antagonists, consistently reduce infarct size, inflammatory burden, and fibrotic remodeling, supporting the relevance of this axis as a therapeutic target [16,18].

Transforming growth factor-β represents the most potent profibrogenic cytokine within the cardiac microenvironment and is produced by macrophages, cardiomyocytes, and fibroblasts. Among macrophage subsets, TREM2^{HI} monocyte-derived macrophages exhibit particularly high expression of TGF-β1, consistent with their profibrotic phenotype. In fibroblasts, TGF-β drives myofibroblast transdifferentiation, extracellular matrix synthesis, and matrix organization predominantly through SMAD-dependent signaling pathways [15–17].

Loss of fibroblast-specific SMAD3 impairs cardiac repair and increases susceptibility to myocardial rupture following infarction due to defective myofibroblast alignment and scar formation. Conversely, during pressure overload, intact TGF-β–SMAD signaling is required for adaptive remodeling, whereas myofibroblast-specific SMAD3 deficiency accelerates systolic dysfunction by enhancing extracellular matrix degradation and macrophage-driven inflammation [16].

Importantly, TGF-β also exerts direct effects on macrophages. Through SMAD3-dependent mechanisms, it promotes CSF-1–driven macrophage proliferation, suppresses excessive CCL2 expression, and favors an anti-inflammatory, phagocytic phenotype that facilitates resolution of inflammation and transition toward reparative remodeling. In the infarcted heart, macrophage TGF-β–SMAD3 signaling supports efficient efferocytosis and limits prolonged inflammatory activation [16,17].

Beyond these core pathways, additional mediators further refine macrophage–fibroblast communication. Platelet-derived growth factors produced by macrophages support fibroblast migration and maintenance, while excessive PDGF signaling can amplify fibroblast activation. In human post-infarction myocardium, enhanced PDGF-C and PDGF-D signaling between profibrotic SPP1^{HI} macrophages and fibroblasts has been implicated in ischemia-driven fibroblast phenotypic transitions [15,16].

Osteopontin, encoded by Spp1, plays a central role in coordinating cell–matrix interactions during repair and remodeling. Elevated osteopontin expression is observed in both ischemic and non-ischemic cardiac disease and closely associates with interstitial fibrosis. Osteopontin facilitates TGF-β–induced myofibroblast differentiation, promotes collagen synthesis, and suppresses matrix metalloproteinase activity, thereby stabilizing fibrotic tissue architecture [15–17].

Galectin-3 has emerged as both a mediator and biomarker of immune-driven cardiac remodeling. Primarily produced by monocyte-derived macrophages, galectin-3 directly stimulates fibroblast proliferation and collagen synthesis. Its induction may involve interleukin-10–dependent STAT3 activation, functioning within an autocrine loop that reinforces profibrotic macrophage differentiation and amplifies stromal activation [15–17].

MicroRNAs further modulate macrophage–fibroblast interactions during cardiac remodeling. miR-21, which is upregulated after cardiac injury, is highly expressed in cardiac macrophages during pressure overload and promotes proinflammatory macrophage phenotypes while facilitating fibroblast-to-myofibroblast transition. In contrast, macrophage-derived miR-155 suppresses fibroblast proliferation and collagen synthesis, and experimental inhibition of miR-155 has been shown to prevent post-infarction cardiac rupture [15–18].

5. Therapeutic implications of macrophage–fibroblast crosstalk

Given the central role of macrophage–fibroblast interactions in cardiac remodeling, the molecular pathways governing this crosstalk have emerged as attractive therapeutic targets. Among these, transforming growth factor-β signaling has received particular attention due to its pivotal role in fibroblast activation, myofibroblast differentiation, and extracellular matrix deposition [1,15,16]. Pharmacological inhibition of TGF-β–dependent pathways has consistently demonstrated antifibrotic effects in preclinical models. However, translation into clinical benefit has proven challenging, reflecting the pleiotropic and context-dependent functions of TGF-β in cardiac repair. In patients with heart failure with preserved ejection fraction, treatment with pirfenidone resulted in modest reductions in myocardial extracellular volume without clear improvement in functional outcomes, underscoring the importance of disease stage and timing when targeting profibrotic signaling cascades [19].

Targeting immune cell recruitment represents an alternative strategy with more selective effects on fibrotic remodeling. Inhibition of the CCL2–CCR2 axis has produced robust experimental results by attenuating monocyte recruitment, reducing macrophage-driven inflammation, and limiting fibroblast

activation. Pharmacological suppression of CCL2 synthesis using bindarit or blockade of CCR2 with selective antagonists has been shown to reduce pressure overload–induced fibrosis, ventricular hypertrophy, and adverse remodeling in multiple experimental settings, thereby slowing progression toward heart failure [2,15–17].

Interleukin-1β signaling represents another immune-regulatory pathway with complex and context-dependent effects on fibroblast behavior. IL-1β promotes a proinflammatory and migratory fibroblast phenotype while stimulating extracellular matrix degradation and inhibiting collagen synthesis and fibroblast proliferation. Despite these seemingly antifibrotic effects at the cellular level, sustained IL-1β signaling exacerbates tissue injury, promotes secondary monocyte recruitment, and increases production of profibrotic mediators [15–18]. Clinically, this dual role is reflected in the beneficial effects observed with IL-1β–targeted therapies. Treatment with canakinumab has been associated with reduced heart failure–related hospitalization and mortality, while administration of anakinra following ST-segment elevation myocardial infarction has been linked to a lower incidence of subsequent heart failure [1,15–18].

Beyond suppressing inflammatory signaling, increasing attention has focused on strategies aimed at preserving or restoring resident cardiac macrophage populations. Expansion of proinflammatory or profibrotic monocyte-derived macrophages correlates with disease progression, whereas recovery of $CCR2^{-}$ resident macrophages has been associated with functional improvement. In experimental models of sepsis-induced cardiomyopathy, adoptive transfer or expansion of resident macrophage subsets improved cardiac performance and attenuated myocardial inflammation, highlighting the therapeutic potential of approaches designed to rebalance macrophage populations rather than indiscriminately deplete immune cells [15,16].

6. Role of Neutrophil Extracellular Traps and NETosis in Post-Myocardial Infarction Cardiac Remodeling

6.1 Neutrophil extracellular traps (NETs) and NETosis: definition and molecular mechanisms

Neutrophil extracellular traps (NETs) are web-like structures composed of decondensed chromatin, extracellular DNA, histones, and antimicrobial proteins released by activated neutrophils. The process underlying NET formation, termed NETosis, represents a distinct form of neutrophil activation that differs fundamentally from classical apoptotic cell death. Two principal NETosis pathways have been described. Suicidal, or lytic, NETosis depends on reactive oxygen species (ROS) generation through NADPH oxidase activation and culminates in neutrophil death, whereas vital NETosis occurs independently of ROS and allows neutrophils to remain viable following NET release [17,20,21].

At the molecular level, NETosis is orchestrated by three key enzymes: peptidylarginine deiminase 4 (PAD4), neutrophil elastase (NE), and myeloperoxidase (MPO). PAD4 catalyzes histone citrullination, converting arginine residues into citrulline and thereby weakening histone–DNA interactions to facilitate chromatin decondensation. Neutrophil elastase subsequently translocates to the nucleus, where it cleaves histones and further promotes chromatin relaxation, while MPO acts synergistically with NE to enable extensive nucleosomal remodeling. Beyond their mechanistic roles, PAD4, NE, and MPO are widely used as biomarkers of NET formation in cardiac tissue and circulation [20,21].

6.2 Temporal dynamics of NETosis after myocardial infarction

Following acute myocardial infarction, neutrophils rapidly infiltrate the injured myocardium, with peak accumulation typically observed within the first 24 to 72 hours. During this early inflammatory phase, circulating markers of NETosis, including citrullinated histone H3, MPO–DNA complexes, and cell-free DNA, are markedly elevated. Increased NET formation has been directly associated with infarct size, impaired left ventricular remodeling, and the no-reflow phenomenon.

Clinical and experimental evidence has highlighted the spatial and functional relevance of NETs at culprit lesion sites. In patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, markers of neutrophil activation and NETosis are enriched within coronary thrombi and correlate positively with infarct size while inversely correlating with ST-segment resolution. NETs have been identified as structural components of coronary thrombi retrieved during thrombectomy, underscoring their contribution to thrombotic occlusion and microvascular dysfunction [6,20,21].

6.3 NETs as drivers of post-infarction cardiac fibrosis

Beyond their role in acute inflammation and thrombosis, NETs actively contribute to post-infarction cardiac fibrosis through multiple interconnected mechanisms. Excessive NETosis amplifies local inflammatory signaling by releasing cytokines, chemokines, and damage-associated molecular patterns that activate innate immune cells via pattern recognition receptors. NET components themselves, particularly extracellular DNA and histones, directly engage Toll-like receptors, most notably TLR4 and TLR2, thereby triggering downstream inflammatory and fibrogenic signaling cascades within the myocardium [6,17,20,22].

At the stromal level, NETosis promotes fibroblast-to-myofibroblast differentiation through both direct and indirect mechanisms. NET-derived DNA and histones can directly activate cardiac fibroblasts, while neutrophil-associated mediators such as PAD4 and midkine further enhance fibroblast activation, proliferation, and extracellular matrix production. Experimental exposure of fibroblasts to purified NETs increases expression of connective tissue growth factor, augments collagen synthesis, and enhances migratory capacity. Importantly, these profibrotic effects are significantly attenuated by NET degradation using DNase I, heparin, or MPO inhibition, supporting a causal role for NETs in fibrogenic signaling [6,17,20–22].

6.4 Interactions between NETs, immune cells, and fibrotic signaling

During the post-infarction healing phase, NETs participate in complex crosstalk with resident and infiltrating immune cells that shapes fibrotic remodeling. Monocyte-derived macrophages entering the infarct zone are exposed to a NET-rich microenvironment that influences their phenotypic polarization. PAD4-dependent histone citrullination within NETs has been shown to promote interleukin-17 expression, which subsequently activates cardiac fibroblasts through IL-17 receptor signaling. This establishes a feed-forward loop in which NETosis-driven immune activation amplifies fibroblast-mediated fibrosis [6,17,20–22,23].

Emerging evidence also supports a bidirectional regulatory relationship between neutrophils and fibroblasts. Activated fibroblasts can secrete midkine, which enhances neutrophil activation and NET formation. This reciprocal interaction generates a self-sustaining profibrotic circuit in which neutrophil-derived mediators activate fibroblasts, and activated fibroblasts further promote NETosis, reinforcing chronic inflammation and extracellular matrix deposition [6,21].

6.5 Therapeutic implications and future directions

The pathogenic role of excessive NETosis in post-infarction fibrosis has stimulated interest in therapeutic strategies targeting NET-associated pathways. Recombinant human DNase effectively degrades extracellular DNA scaffolds within NETs and has been shown in preclinical models to reduce NET-associated inflammation and fibrosis. Pharmacological inhibition of PAD4, including the selective inhibitor GSK484, reduces infarct size, neutrophil infiltration, NET formation, and citrullinated histone H3 levels while preserving cardiac function in murine models of myocardial infarction [6,21].

Additional approaches target other components of the NETosis machinery. Myeloperoxidase inhibitors decrease inflammatory cell recruitment and attenuate left ventricular dilation in experimental heart failure, while neutrophil elastase inhibitors such as sivelestat and SSR69071 limit endothelial damage and preserve vascular integrity in ischemia–reperfusion and endotoxin-induced myocardial injury models [21].

Beyond direct inhibition of NETosis, several widely used pharmacological agents exhibit NET-modulating properties. Colchicine suppresses NET formation in vitro and attenuates myocardial inflammation and fibrosis in experimental heart failure models. Statins and metformin similarly reduce NET formation and circulating NETosis biomarkers, with metformin decreasing plasma MPO levels and preventing neutrophil infiltration in preclinical settings, and rosuvastatin lowering MPO levels and circulating neutrophil counts in patients with acute coronary syndromes [6,24].

Despite these promising findings, NETs also exert context-dependent protective functions during early post-infarction healing by contributing to pathogen defense and wound stabilization. Consistent with this dual role, PAD4-deficient mice exhibit impaired infarct healing and delayed resolution of inflammation. These observations highlight the need for temporally controlled and context-specific therapeutic strategies that selectively suppress pathological NETosis while preserving the reparative functions of neutrophils during myocardial healing [21,23].

7. Endothelial–Fibroblast Interactions and Endothelial-to-Mesenchymal Transition

Endothelial–mesenchymal transition (EndMT) describes a phenotypic reprogramming process in which endothelial cells progressively lose endothelial characteristics and acquire mesenchymal, fibroblast-like properties. Although EndMT was initially identified as a physiological mechanism during cardiac development, it is now recognized as an important contributor to fibrotic remodeling in adult tissues under pathological conditions [26,27].

A broad range of inflammatory, metabolic, and mechanical stimuli can initiate EndMT, including proinflammatory cytokines, oxidative stress, hypoxia, disturbed shear stress, and metabolic abnormalities [25,28]. Central to this process is transforming growth factor-β signaling. Members of the TGF-β family activate type I and type II TGF-β receptors, triggering downstream Smad-dependent and Smad-independent pathways that induce transcriptional programs favoring mesenchymal differentiation [29]. Canonical Smad signaling promotes expression of transcription factors such as Snail, Twist, Zeb, and Slug, which suppress endothelial junctional integrity and drive mesenchymal gene expression. The pathogenic relevance of this pathway is illustrated by fibrodysplasia ossificans progressiva, in which constitutive activation of TGF-β receptor signaling results in aberrant endothelial-derived mesenchymal transformation, as well as by experimental models demonstrating that disruption of Smad2, Smad3, or TGF-β receptor signaling effectively prevents EndMT [25,30].

EndMT does not rely on TGF-β signaling alone but emerges from integration of multiple regulatory pathways. Crosstalk with Wnt and Notch signaling, activation of Rho GTPase–dependent cytoskeletal pathways, and engagement of Smad-independent cascades such as Akt/NF-κB and MAPK/ERK collectively shape endothelial plasticity [25,31]. Environmental stressors further modulate these pathways. Hypoxia promotes EndMT through hypoxia-inducible factor–1α–dependent mechanisms, while reactive oxygen species amplify fibrogenic signaling by inducing TGF-β expression and activating NF-κB, thereby establishing reinforcing feedback loops [25]. Mechanical forces exert similarly potent effects: laminar shear stress suppresses EndMT via ERK5 signaling, whereas disturbed flow, cyclic strain, and hyperglycemia enhance EndMT by potentiating TGF-β- and Wnt-dependent responses [25,32,33].

At the cellular level, EndMT is executed through extensive cytoskeletal remodeling. Loss of vascular endothelial cadherin–mediated cell–cell junctions permits activation of small GTPases and reorganization of the actin cytoskeleton, enabling endothelial cells to adopt an elongated, migratory phenotype. Formation of actin stress fibers, recruitment of α-smooth muscle actin, and assembly of focal adhesion complexes confer contractile properties characteristic of mesenchymal cells. Importantly, actin dynamics are directly coupled to transcriptional reprogramming through the myocardin-related transcription factor–serum response factor axis, providing a mechanistic link between mechanical cues and fibrogenic gene expression [25].

Additional cytoskeletal systems reinforce EndMT progression. Microtubule remodeling, driven by changes in tubulin isoform composition and post-translational modifications, regulates cell polarity and directional migration. Intermediate filaments, particularly vimentin, play a central role in mechanosensing and stabilization of cell–matrix adhesions. Upregulation of vimentin enhances cellular plasticity and migratory capacity, further consolidating the mesenchymal phenotype and supporting extracellular matrix deposition [25].

Phenotypically, EndMT is characterized by downregulation of endothelial markers, including CD31, VE-cadherin, von Willebrand factor, TIE1/2, and endothelial nitric oxide synthase, alongside induction of mesenchymal markers such as α-smooth muscle actin, vimentin, fibronectin, collagens I and III, and matrix metalloproteinases MMP-2 and MMP-9. Because no single marker uniquely defines EndMT-derived cells, identification relies on combined molecular, spatial, and functional assessment [25,34].

Collectively, EndMT represents a signal-driven and mechanically reinforced process through which endothelial cells acquire fibrogenic properties. By integrating inflammatory, metabolic, and biomechanical inputs into coordinated cytoskeletal and transcriptional programs, EndMT contributes directly to fibroblast accumulation, extracellular matrix remodeling, and progression of cardiac fibrosis.

8. Biomarkers of cardiac fibrosis

Cardiac fibrosis constitutes a core component of adverse myocardial remodeling and contributes directly to the development and progression of heart failure. Importantly, fibrosis does not represent a single static entity but rather a dynamic process encompassing fibroblast activation, altered extracellular matrix turnover, inflammatory signaling, and myocardial stress responses. Because these mechanisms overlap and differ across heart failure phenotypes, including heart failure with reduced versus preserved ejection fraction, ischemic versus non-ischemic etiology, and acute versus chronic decompensation, no single circulating biomarker can comprehensively quantify "cardiac fibrosis" in clinical practice. Instead, available biomarkers predominantly reflect specific biological pathways within the broader remodeling continuum rather than fibrosis burden per se [35,36].

Among circulating biomarkers associated with fibrotic remodeling, galectin-3 is one of the most extensively studied. This macrophage-derived lectin participates in inflammatory and extracellular matrix–related signaling pathways and has been linked to fibroblast activation and collagen deposition, supporting its role as a marker of adverse myocardial remodeling rather than acute hemodynamic stress [36,37]. From a clinical perspective, galectin-3 demonstrates limited utility for the diagnosis of acute heart failure but appears to provide prognostic information, particularly during the early phase following hospitalization. Elevated galectin-3 concentrations have been associated with an increased risk of short-term adverse outcomes, including heart failure–related rehospitalization, suggesting that galectin-3 reflects ongoing profibrotic and inflammatory activity predisposing to early clinical instability. In contrast, its ability to predict long-term mortality has been inconsistent across studies [36,38,39].

When compared with established heart failure biomarkers, such as natriuretic peptides or soluble suppression of tumorigenicity 2 (sST2), galectin-3 generally exhibits weaker prognostic performance in both heart failure with reduced and preserved ejection fraction populations. Interpretation of galectin-3 concentrations is further complicated by a strong dependence on renal function, which limits specificity for myocardial fibrosis in patients with concomitant kidney disease [36,40].

Beyond markers directly linked to fibroblast biology, myocardial remodeling is characterized by profound alterations in extracellular matrix turnover, governed by a tightly regulated balance between matrix metalloproteinases and their endogenous inhibitors. Disruption of this equilibrium reflects active remodeling processes rather than established fibrotic burden. Among circulating metalloproteinases, matrix metalloproteinase-2 has been most consistently associated with adverse myocardial remodeling, with elevated levels reported in patients with heart failure and linked to greater disease severity and worse clinical outcomes [41,42]. Experimental and clinical evidence suggests that increased MMP-2 activity accompanies maladaptive matrix turnover, contributing to structural disorganization and progressive ventricular remodeling [42].

Complementary insight into matrix remodeling dynamics is provided by matrix metalloproteinase-9, which is more closely coupled to inflammatory activation and immune-mediated matrix degradation. Elevated circulating MMP-9 concentrations have been observed in both acute and chronic heart failure settings, underscoring its role in dynamic remodeling rather than fixed fibrosis alone [43,44]. Although additional metalloproteinases, tissue inhibitors of metalloproteinases, and collagen degradation products participate in extracellular matrix regulation, their individual diagnostic specificity remains limited, and circulating levels are strongly influenced by systemic inflammatory states. Consequently, MMP-2 and MMP-9 are best interpreted as markers of ongoing remodeling biology, with enhanced clinical relevance when assessed longitudinally or incorporated into multi-marker strategies rather than used as isolated indicators of myocardial fibrosis [44].

In this context, soluble ST2 represents a complementary biomarker reflecting myocardial stress–driven remodeling rather than collagen accumulation itself. Soluble ST2 is the circulating isoform of the interleukin-33 receptor and acts as a decoy receptor that interferes with cardioprotective IL-33/ST2L signaling. Under physiological conditions, IL-33/ST2L signaling exerts anti-apoptotic, anti-fibrotic, and anti-hypertrophic effects within the myocardium. Elevated circulating sST2 levels attenuate these protective pathways and are predominantly driven by extracardiac release in response to hemodynamic overload, inflammatory activation, and profibrotic stimuli, explaining both its limited cardiac specificity and lack of diagnostic utility for heart failure [36,45].

Despite these limitations, sST2 has emerged as a robust prognostic biomarker. In acute heart failure, elevated sST2 concentrations measured at admission or discharge are associated with increased risk of all-cause and cardiovascular mortality, while temporal changes during hospitalization provide prognostic information independent of natriuretic peptide levels [36,46]. Similar findings have been reported in chronic

heart failure, where sST2 predicts adverse outcomes irrespective of NT-proBNP or high-sensitivity troponin concentrations, demonstrates reduced susceptibility to age-related variation, and shows comparable performance in heart failure with reduced and preserved ejection fraction. In multiple studies, sST2 has exhibited stronger prognostic discrimination than galectin-3 [46,47]. In line with these observations, current ACC/AHA guidelines support the use of sST2 for prognostic risk stratification in chronic heart failure, whereas ESC guidelines conclude that available evidence remains insufficient to justify routine clinical application [48].

Discussion

This review highlights cardiac fibrosis as a dynamic, regulated process driven by coordinated interactions between immune cells, fibroblasts, and endothelial compartments rather than a passive accumulation of extracellular matrix. Across experimental and translational studies, fibroblasts emerge as central integrators that translate immune, vascular, metabolic, and mechanical signals into remodeling programs that shape myocardial structure and function.

A major insight is the dominant role of immune–stromal communication in governing fibroblast activation. Macrophage–fibroblast crosstalk, in particular, appears to determine whether inflammatory responses resolve through adaptive repair or transition into chronic fibrogenesis. Neutrophil extracellular traps further amplify these responses, especially after myocardial infarction, by reinforcing inflammatory and profibrotic feedback loops. Endothelial plasticity, including endothelial-to-mesenchymal transition, links microvascular dysfunction with fibroblast expansion and interstitial fibrosis, underscoring the integrated nature of immune–stroma–endothelium networks.

At the molecular level, epigenetic and metabolic reprogramming stabilizes activated fibroblast phenotypes beyond the acute injury phase, providing a mechanistic explanation for the persistence of fibrosis and the limited efficacy of therapies targeting extracellular matrix deposition alone. Together, these observations suggest that effective antifibrotic strategies should focus on upstream regulatory pathways that control intercellular communication and fibroblast plasticity rather than downstream structural outcomes.

Conclusions

Cardiac fibrosis arises from dysregulated communication within immune–stroma–endothelium networks, with fibroblasts acting as central organizers of pathological remodeling. Key findings of this review include the pivotal role of macrophage–fibroblast crosstalk in determining fibrotic trajectories, the amplifying contribution of neutrophil extracellular traps, the involvement of endothelial plasticity in fibroblast accumulation, and the stabilization of profibrotic states through epigenetic and metabolic mechanisms.

Future research should prioritize the identification of context- and stage-specific immune–stromal interaction nodes that govern fibroblast behavior across different forms of heart disease. Integrating single-cell and spatial omics with functional and longitudinal human studies will be essential to define fibroblast subsets and immune phenotypes that drive disease progression. Additionally, the development of temporally targeted therapeutic strategies and pathway-informed biomarker panels may enable more precise modulation of fibrotic remodeling while preserving essential reparative processes. Advancing these approaches holds promise for improving the prevention and treatment of heart failure driven by pathological cardiac fibrosis.

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