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STATE-OF-THE-ART REVIEW

Emerging Role of Macrophage-Fibroblast Interactions in Cardiac Homeostasis and Remodeling

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HIGHLIGHTS

- **Interactions between cardiac macrophages and fibroblasts significantly affect cardiac homeostasis and remodeling, offering potential therapeutic targets of heart failure.**
- **This review presents the current evidence regarding the heterogeneity and plasticity of cardiac macrophages and fibroblasts, elucidates the diverse molecular mechanisms potentially governing macrophage-fibroblast interactions in cardiac homeostasis and remodeling, and assesses the key mediators involved from a translational perspective.**
- **Despite advances in basic research, translating experimental findings into effective clinical treatment strategies remains challenging. We emphasize that interventions targeting cardiac macrophage-fibroblast interactions should be based on understanding their dynamics across the pathophysiologic spectrum of cardiac homeostasis and remodeling.**

SUMMARY

As major noncardiomyocyte components in cardiac tissues, macrophages and fibroblasts play crucial roles in maintaining cardiac homeostasis, orchestrating reparative responses after cardiac injuries, facilitating adaptive cardiac remodeling, and contributing to adverse cardiac remodeling, owing to their inherent heterogeneity and plasticity. Recent advances in research methods have yielded novel insights into the intricate interactions between macrophages and fibroblasts in the cardiac context. This review aims to comprehensively examine the molecular mechanisms governing macrophage-fibroblast interactions in cardiac homeostasis and remodeling, emphasize recent advancements in the field, and offer an evaluation from a translational standpoint. (JACC Basic Transl Sci 2025;10:113-127) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Macrophages and fibroblasts, the major noncardiomyocyte components of cardiac tissues, play crucial roles in inflammation and fibrosis progression. Their diverse functions in cardiac homeostasis and remodeling arise from their inherent heterogeneity and plasticity (Figure 1). Complex interactions between macrophages and fibroblasts have long been acknowledged owing to their

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ABBREVIATIONS AND ACRONYMS

Ang = angiotensin

CCL = C-C chemokine ligand

CCR = C-C chemokine receptor

CSF = colony-stimulating factor

CXCL = C-X-C motif chemokine ligand

CXCR = C-X-C motif chemokine receptor

ECM = extracellular matrix

Gal = galectin

GM-CSF = granulocyte/macrophage colony-stimulating factor

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IL = interleukin

I/R = ischemia/reperfusion

MI = myocardial infarction

miR = microRNA

moMφ = monocyte-derived macrophage

OPN = osteopontin

PDGF = platelet-derived growth factor

RCM = resident cardiac macrophage

TAC = transverse aortic constriction

TGF = transforming growth factor

TREM2 = triggering receptor expressed on myeloid cells 2

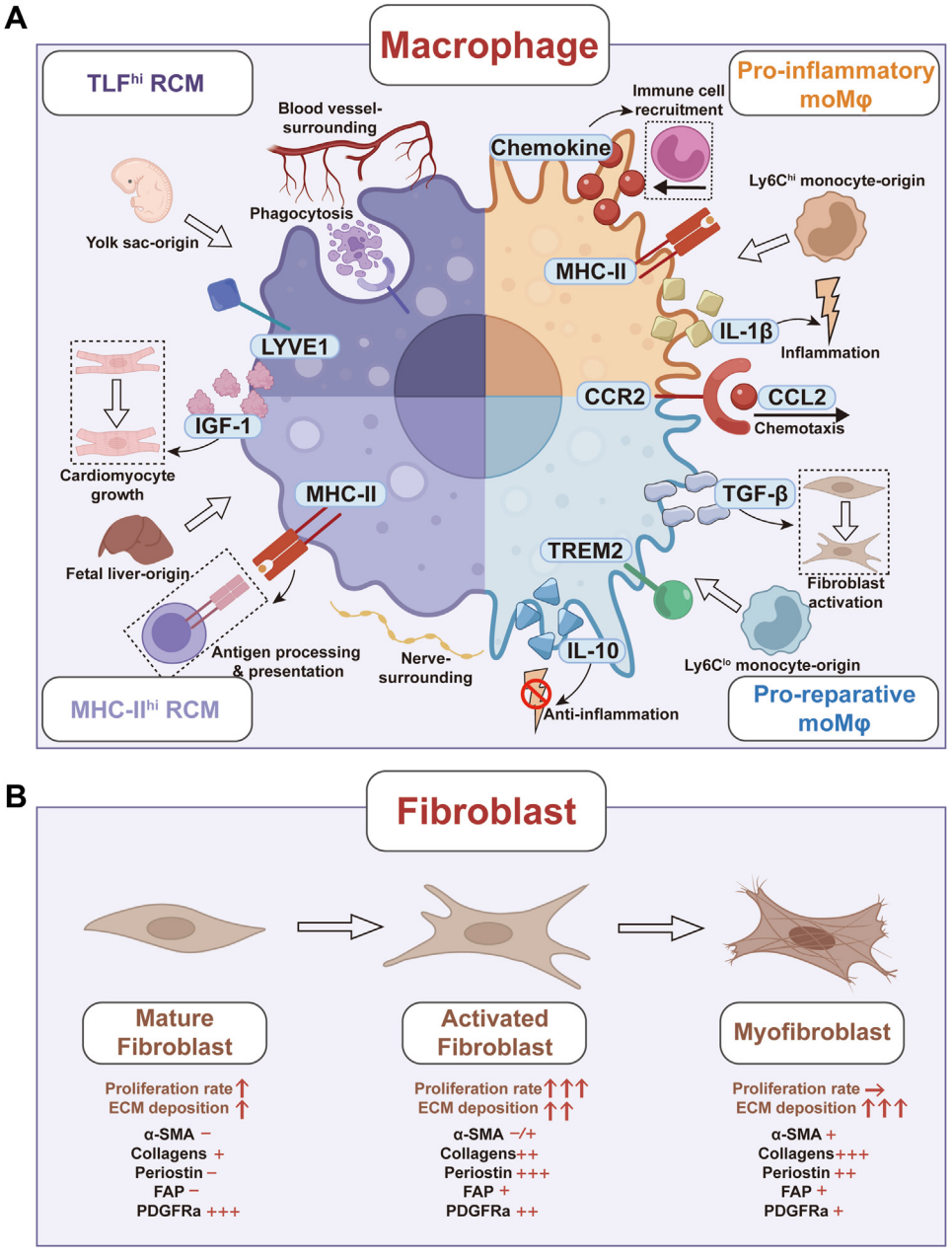
coexistence in various organs and close spatial proximity.[1] Advances in lineage tracing and multi-omics techniques have facilitated a thorough comprehension of macrophage-fibroblast interactions, encompassing phenotypic aspects, origin, and spatial relationships. Cardiac remodeling is commonly characterized as an adaptive or maladaptive process.[2] Adaptive cardiac remodeling enables the heart to initiate reparative cascades and compensatory adaptations to preserve its "pump" function in response to acute injury or stimuli, and is therefore deemed to be cardioprotective.[2] However, persistent cardiac injury or stimuli can trigger a prolonged inflammatory cascade coupled with a progressive fibrotic response, which can further induce reactive fibrosis and lead to adverse cardiac remodeling and chronic heart failure (HF).[3-5] Understanding the reciprocal interactions between macrophages and fibroblasts in cardiac homeostasis and remodeling holds significant potential for identifying therapeutic targets capable of mitigating adverse cardiac remodeling and contributing to precision medicine. This review aims to comprehensively examine the molecular mechanisms governing macrophage-fibroblast interactions in cardiac homeostasis and remodeling, emphasize recent advancements in the field, and offer an evaluation from a translational standpoint.

MACROPHAGES IN THE HEART: EVOLVING CONCEPTS ON HETEROGENEITY

Macrophages constitute the majority of cardiac-resident immune cells.[6] Rather than adhering to oversimplified functional M1/M2 paradigms proposed primarily based on in vitro polarization evidence,[7] extensive research has been conducted to unveil the heterogeneity of cardiac macrophages, with a specific focus on cell origin and life cycle (**Table 1**). C-C chemokine receptor 2 (CCR2) is a chemokine receptor and can be used to distinguish embryonic or monocyte-derived macrophages (moMφs).[8,9] CCR2$^-$ macrophages, primarily derived from embryonic progenitors, constitute the majority of resident cardiac macrophages (RCMs) in stable murine hearts. They demonstrate enhanced proficiency in efferocytosis, cardiac extracellular matrix (ECM) organization, and tissue repair.[8,10,11] In contrast, CCR2$^+$ macrophages are predominantly derived from peripheral monocytes.[10,11] Advances in single-cell RNA sequencing technologies and genetic lineage tracing have significantly enhanced the classification and characterization of RCMs. Chakarov et al[12] identified 2 distinct RCM subsets: an LYVE1^{lo}MHC-II^{hi} population surrounding the nerves with antigen presentation function, and an LYVE1^{hi}MHC-II^{lo} population closely associated with blood vessels exhibiting antifibrotic properties. Similarly, Dick et al[13] identified 3 RCM subsets, each displaying unique expression profiles and hierarchic contributions from monocytes. Among CCR2$^-$ RCMs, the TLF^{hi} population (characterized by high expression of *Timd4*, *Lyve1*, and *Folr2*) exhibits minimal reliance on monocyte replenishment and maintains itself as a self-renewing population, whereas the MHC-II^{hi} population receives modest contributions from monocytes throughout its life cycle.[13] In terms of function, there is an increasing appreciation that RCMs play a critical role in cardiac development and homeostasis (comprehensively reviewed by Zaman et al[14]).

On encountering various types of cardiac injuries or stimuli, cardiac macrophages undergo dramatic changes in both abundance and phenotype (**Figure 2**). CCR2$^-$ RCMs, which are enriched in the proreparative pathways, experience a significant reduction in the acute phase and demonstrate slow recovery through local proliferation after myocardial infarction (MI).[15] The depletion of CCR2$^-$ RCMs results in impaired infarct healing and adverse remodeling after ischemic injury.[11,15] Conversely, CCR2$^+$ RCMs with relative proinflammatory features play a crucial role in monocyte recruitment and neutrophil extravasation into the ischemic myocardium. The depletion of CCR2$^+$ RCMs before ischemia/reperfusion (I/R) injury improves cardiac systolic function and results in a smaller infarct size.[11,16] Ly6C^{hi} moMφs enriched for proinflammatory pathways are recruited to the infarct zone to facilitate efferocytosis, antigen presentation, and clearance of necrotic tissues after MI.[11,17] After the removal of cellular debris, environmental stimuli induce the polarization of Ly6C^{lo} moMφ toward a proreparative and antiinflammatory phenotype. This process aids in attenuating the post-MI inflammatory response and promoting cardiac repair.[17,18] A group of profibrotic *Trem2*^{hi} moMφs with high expression of osteopontin (OPN) (encoded by *Spp1*) becomes dominant in the late phase after MI and exhibits proreparative features[18] (**Figure 2A**). Although the majority of recruited moMφs gradually diminish after the formation of cardiac scar tissues,[15] low-level

FIGURE 1 **The Phenotypic and Functional Characteristics of Cardiac Macrophages and Fibroblasts**



(A) Current mainly investigated macrophage subtypes in cardiac homeostasis and remodeling. RCM (resident cardiac macrophage) refers to macrophage subsets that exist in the heart under steady state and are derived primarily from embryonic progenitors. During cardiac remodeling, peripheral monocyte-derived macrophage (moMφs) dominate the injured heart. (B) Fibroblast dynamics in cardiac homeostasis and remodeling. The steady-state heart is populated by resident mature fibroblasts. On cardiac injury, mature cardiac fibroblasts transform into activated fibroblasts and exhibit elevated proliferation and collagen production. A proportion of activated fibroblasts undergo transdifferentiation into myofibroblasts, a more profibrotic and contractile phenotype characterized by significantly increased synthesis of contractile proteins. CCR2 = C-C chemokine receptor 2; ECM = extracellular matrix; FAP = fibroblast activation protein; IGF = insulin-like growth factor; IL = interleukin; Ly6C = lymphocyte antigen 6C; LYVE1 = lymphatic vessel endothelial hyaluronan receptor 1; MHC-II = major compatibility complex II; OPN = osteopontin; PDGFR = platelet-derived growth factor receptor; SMA = smooth muscle actin; TLF = expression of *Timd4*, *Lyve1*, and *Folr2*; TREM2 = triggering receptor expressed on myeloid cells 2.

TABLE 1 Cardiac Macrophage Classification Based on Cell Origin and Life Cycle

Paradigm	Classifications	Specialized Markers	Ref. #
Origin	Embryonic-origin	$CCR2^{-}$	8,156
	Monocyte-origin	$CCR2^{+}$	
Life cycle	Self-renewal	$CCR2^{-}$, $CX3CR1^{lo}$, *Timd4*^{hi}, *Lyve1*^{hi}, *Folr2*^{hi}, MHC-II^{lo}	13-15
	Self-renewal and monocyte supplement	$CCR2^{-}$, $CX3CR1^{hi}$, *Timd4*^{lo}, *Lyve1*^{lo}, *Folr2*^{lo}, MHC-II^{hi}	
	Monocyte supplement	$CCR2^{+}$, $CX3CR1^{hi}$, MHC-II^{hi}	

CCR2 = C-C chemokine receptor 2; CX3CR1 = C-X3-C motif chemokine receptor 1; *Folr2* = folate receptor β; *Lyve1* = lymphatic vessel endothelial hyaluronan receptor 1; MHC-II = major compatibility complex II; *Timd4* = T-cell immunoglobulin and mucin domain containing 4.

inflammation persists, leading to adverse cardiac remodeling by facilitating progressive fibrosis in the noninfarcted myocardium. Accordingly, sustained CCR2-dependent monocyte recruitment, accompanied by enhanced collagen deposition, has been observed in the remote post-MI myocardium, potentially contributing to HF progression.[19]

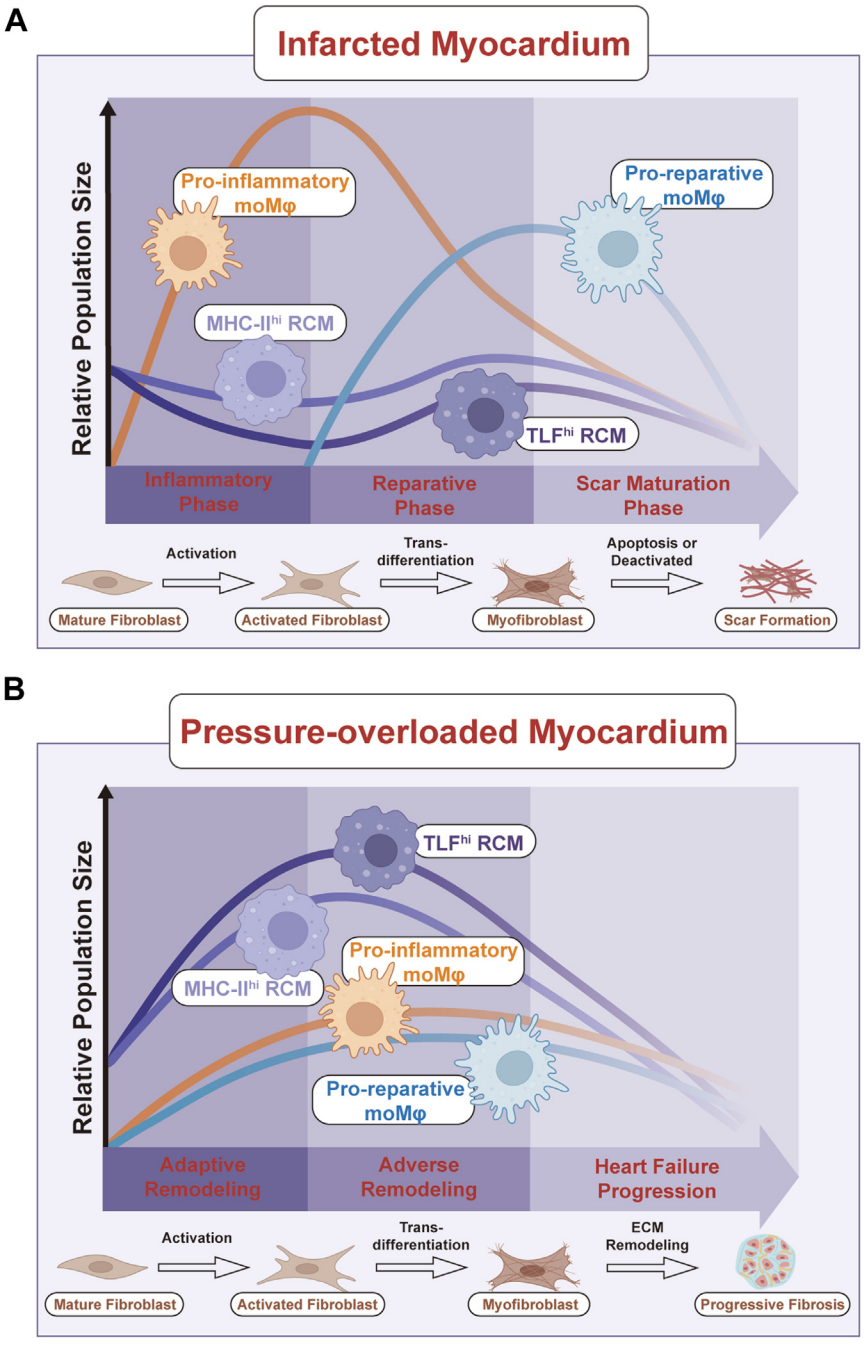
In pressure-overloaded cardiac hypertrophy induced by transverse aortic constriction (TAC), $CCR2^{-}$ RCMs proliferate in response to adaptive cardiac hypertrophy but decline during maladaptive HF progression.[20,21] $CCR2^{-}$ RCMs in the TAC model prevent cardiac fibrosis by reducing moMφ recruitment, stimulating angiogenesis, and thus slowing the progression of HF.[20,21] Concurrently, moMφs persist in infiltrating and eventually dominating the heart, leading to long-term damage[22] (**Figure 2B**). In angiotensin (Ang) II-induced cardiac hypertrophy, $CCR2^{-}$ RCMs expand and mediate compensatory myocardial growth through the action of insulin-like growth factor (IGF)-1, and the selective loss of RCM-derived IGF-1 leads to a decline in cardiac systolic function.[23] While evidence elucidating the dynamics of cardiac macrophages in animal models of heart failure with preserved ejection fraction (HFpEF) is still lacking, the enrichment of activated moMφs and the reduction of embryonic RCMs appear to be a common scenario in the failing hearts, regardless of the underlying causes.[24-26] On the other hand, HFpEF-associated risk factors, such as metabolic disorders and systematic inflammation, may further promote the infiltration and polarization of proinflammatory and profibrotic moMφs, potentially exacerbating adverse ventricular remodeling.[27] In the adult human heart, macrophage subsets displaying transcriptional features of $CCR2^{-}$ RCMs (eg, MHC-II^{lo} or $LYVE1^{hi}$) or moMφs (eg, MHC-II^{hi} or *TREM2*^{hi} or *SPP1*^{hi}) observed in mice have also been identified.[15,28-32] $CCR2^{+}$ moMφs represent an inflammatory population, and their abundance is associated with persistent systolic cardiac dysfunction.[10]

FIBROBLASTS IN THE HEART: EMBRACING OLD-SCHOOL CLASSIFICATION

Unlike macrophages, comprehensive phenotypic and functional studies on cardiac fibroblasts have encountered challenges due to the absence of specific cellular markers and their greater heterogeneity.[33] Although the expression profiles of cardiac fibroblasts vary based on their anatomic location[28,34] and embryonic origin,[35] these features are insufficient to distinguish fibroblast populations under pathologic cardiac conditions.[36] A simplified classification of cardiac fibroblasts has been proposed based on their plasticity.[37] In the steady-state heart, resident mature fibroblasts with a low proliferation rate and limited collagen production predominate in the myocardium.[37] They orchestrate the dynamic remodeling of the ECM network and are essential for maintaining cardiac conductivity and rhythmicity.[38] During cardiac injury, cardiac resident fibroblasts transform into an activated and profibrotic phenotype.[39,40] Notable distinctions in fibroblast populations are observed only between the steady state (resident mature phenotype) and disease state (activated phenotype).[41]

After cardiac injury, resident mature cardiac fibroblasts are activated and undergo rapid proliferation in response to intracellular signaling regulated by the interplay between specific growth factors and ECM proteins.[42] Furthermore, a subset of activated fibroblasts undergo transdifferentiation into myofibroblasts, a more secretory and contractile phenotype distinguished by a notably elevated synthesis of contractile proteins.[37,42,43] The replacement of necrotic tissue with an infarct scar, whose formation is regulated by activated fibroblasts and myofibroblasts during acute post-MI remodeling, improves structural integrity and prevents heart rupture.[4] After the formation of cardiac scar tissues, a continuous process of maturation and expansion of dynamic remodeling occurs and persists for weeks to months.

FIGURE 2 Cardiac Macrophage and Fibroblast Dynamics in the Infarcted and the Pressure-Overloaded Myocardium



(A) Acute ischemic injury results in a significant reduction of RCMs and recruitment of proinflammatory moMφs in the infarcted myocardium, and mature resident fibroblasts are activated into a proliferative and more collagen-producing phenotype. During the reparative phase, moMφs exhibit a proreparative and antiinflammatory phenotype, that supports myofibroblast differentiation and scar formation, and RCMs show slow recovery through local proliferation. During the scar maturation phase, the majority of cardiac macrophages gradually diminish. (B) In the pressure-overloaded myocardium induced via transverse aortic constriction surgery, RCMs proliferate significantly during adaptive remodeling, while they decrease during adverse remodeling and heart failure progression. Recruited moMφs continue to infiltrate and induce proinflammatory and profibrotic cascades. MHC-II = major compatibility complex II; moMφ = monocyte-derived macrophage; RCM = resident cardiac macrophage; TLF = expression of *Timd4*, *Lyve1*, and *Folr2*.

TABLE 2 Crucial Cardiac Macrophage-Fibroblast Interactions and Their Roles in Cardiac Homeostasis and Remodeling

Macrophage-Derived Factor or Receptor	Fibroblast-Derived Factor or Receptor	Key Role	Ref. #
CSF-1R	CSF-1	Macrophage differentiation, survival, and proliferation	20
PDGF	PDGFRα	Fibroblast maintenance	64
TGF-β	TGF-βR	Fibroblast activation and myofibroblast transdifferentiation	72
TGF-βR	TGF-β	Promoting a phagocytic and antiinflammatory macrophage phenotype	80,81
CCR2	CCL2	Attracting monocyte/macrophage and promoting TGF-β signaling	88,89,91
CCL2	CCR2	Myofibroblast transdifferentiation	91
IL-1β	IL-1R	Promoting an ECM degrading phenotype in fibroblasts	101
OPN	CD44/Integrin	Myofibroblast transdifferentiation and collagen production	103
Gal-3	-	Fibroblast proliferation and collagen production	110,111
miR-21	-	Fibroblast survival, growth factor secretion, and promoting profibrotic signaling	122
miR-155	-	Suppressing cardiac fibroblast proliferation and collagen production	124

CCL2 = C-C chemokine ligand 2; CCR2 = C-C chemokine receptor 2; CSF = colony-stimulating factor ; CSF-1R = colony-stimulating factor 1 receptor; ECM = extracellular matrix; Gal = galectin; IL = interleukin; IL-1R = interleukin-1 receptor; miR = microRNA; OPN = osteopontin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; TGF = transforming growth factor; TGF-βR = transforming growth factor-β receptor.

This dynamic remodeling ultimately results in ventricular stiffness, weakening of pump function, and eventual progression to HF.[4] During cardiac hypertrophy, increased cardiomyocyte size during adaptive remodeling is coupled with ECM reorganization, which is characterized by the activation of cardiac fibroblasts and the deposition of ECM proteins.[44,45] Under persistent stress, cardiomyocyte apoptosis occurs, along with widespread interstitial fibrosis mediated by activated fibroblasts. These processes ultimately lead to a decline in heart function.[45] In HFpEF models associated with aging or metabolic disorders, the emergence of activated fibroblasts within the heart can also be observed, possibly involving the coordination of profibrotic signaling transduction induced by excessive oxidative stress, disrupted metabolites, and exacerbated cardiac and vascular inflammation, as comprehensively reviewed by Humeres and Frangogiannis.[46]

The elevated accumulation of activated fibroblasts has been associated with adverse cardiac remodeling in humans.[30,31,47] The application of ^{68}Ga-fibroblast activation protein inhibitor to visualize activated fibroblasts in vivo has shown significant uptake exclusively in the hearts of individuals with cardiovascular diseases associated with cardiac remodeling. In contrast, healthy control subjects exhibited no discernible uptake.[48-51] Although some evidence suggests that activated fibroblasts undergo apoptosis and revert to a less activated state after injury resolution,[39,52] persistent low-level cardiac inflammation and moMφ infiltration likely contribute to the progression of cardiac fibrosis and adverse remodeling.

MOLECULAR MECHANISMS GOVERNING CARDIAC MACROPHAGE-FIBROBLAST INTERACTIONS

Through intercellular mediators, macrophages and fibroblasts interact to regulate each other's abundance, location, phenotype, and function, participating in cardiac homeostasis and remodeling. In cardiac homeostasis, macrophage-fibroblast interactions are crucial for maintaining cell population and an inactive state. During cardiac repair and remodeling, both cardiac macrophages and fibroblasts undergo dynamic changes in their phenotype and subset composition, and the dominant intercellular mediators involved in macrophage-fibroblast interactions, along with their principal functions, exhibit notable distinctions from those involved in cardiac homeostasis (Table 2). Understanding the molecular mechanisms governing macrophage-fibroblast interactions is critical for developing strategies to alleviate myocardial inflammation and fibrosis, the major causes of HF.

COLONY-STIMULATING FACTOR 1. The colony-stimulating factor-1 receptor (CSF-1R) is primarily expressed on macrophages. Colony-stimulating factor (CSF)-1 induces CSF-1R dimerization, initiating a signaling cascade vital for macrophage survival, differentiation, and proliferation.[53,54] Fibroblasts are the major producers of CSF-1 in the heart, whereas the alternative CSF-1R ligand interleukin (IL)-34 is predominantly expressed on cardiac pericytes.[55] The self-renewal of embryonic RCMs occurs in a CSF-1/CSF-1R-dependent manner: Anti-CSF-1R treatment significantly depletes RCMs in the steady-state

heart,[20] and the genomic deletion of the *Csf1r* enhancer results in RCM reduction.[56] In vitro co-culturing of lung-resident macrophages and fibroblasts with prominent *Csf1* expression promotes macrophage proliferation and induces polarization toward an M2 phenotype.[57] The selective loss of $Wt1^{+}$ stromal cell-derived CSF-1 significantly reduces the number of self-renewing $Lyve1^{hi}$ resident macrophages in the peritoneal mesothelium.[58] In addition, apart from its role in cell maintenance, CSF-1 produced by fibroblasts facilitates the spatial proximity between macrophages and fibroblasts.[59] *Csf1r*-expressing tendon-resident macrophages preferentially localize to *Csf1*-expressing fibroblasts,[60] and splenic red pulp macrophages are intricately embedded in the reticular meshwork of red pulp fibroblasts characterized by *Csf1* expression.[61] In the case of cardiac remodeling after MI, CSF-1/CSF-1R signaling is essential for reparative $Ly6C^{lo}$ moMφ proliferation, with CSF-1R inhibition resulting in reduced post-MI angiogenesis in the infarct border myocardium.[62,63] In the murine TAC model, early CSF-1R blockade markedly reduces the expansion of $CCR2^{-}$ RCMs, leading to increased moMφ infiltration and accelerated HF development.[20]

PLATELET-DERIVED GROWTH FACTOR. The platelet-derived growth factor (PDGF) family, which can be produced by macrophages, is essential for fibroblast maintenance: The selective loss of PDGF receptor (PDGFR) α leads to a rapid reduction in resident cardiac fibroblasts.[64] Although increased PDGF signaling may induce fibroblast activation,[65,66] in vitro evidence suggests that the concomitant elevation of fibroblast-derived CSF-1 in turn inhibits the transcriptional activity of *Pdgfb* in macrophages,[59] ensuring the stability of macrophage-fibroblast circuits under steady condition. Increased PDGF signaling has been associated with various cardiac pathologies, typically involving fibroblast activation and increased collagen deposition.[65,66] Increased PDGF-C and PDGF-D signaling between profibrotic $SPP1^{hi}$ moMφs and fibroblasts has been identified in human post-MI hearts,[31] potentially mediating fibroblast phenotypic transition in ischemic conditions.[67] Similarly, in a murine model of diabetic cardiomyopathy, the expression of *Pdgfc* was significantly elevated in cardiac macrophages, and the inhibition of PDGFRα phosphorylation significantly reduced myocardial fibrosis.[68] Hamid et al[69] found that moMφs facilitate the transdifferentiation of cardiac mesenchymal stem cells into myofibroblasts in a PDGF/PDGFRβ manner, and PDGFR inhibition via imatinib attenuated post-MI cardiac remodeling and fibrosis. Moreover, Hume et al[70] reported that PDGF-AB promotes a unique migratory phenotype of cardiac fibroblasts, accelerating post-MI scar maturation and reducing cardiac inflammation. Mechanistically, the administration of exogenous PDGF-AB in animal models of MI improves scar mechanics and vascularity, resulting in increased scar anisotropy and improved heart function.[71] Currently, the role of PDGF in cardiac remodeling remains controversial, potentially involving intricate interactions among different members of the PDGF family.

TRANSFORMING GROWTH FACTOR-β. Transforming growth factor (TGF)-β, a well known profibrotic growth factor that can be expressed by both macrophages and fibroblasts, undergoes significant activation during cardiac remodeling.[42] Among cardiac macrophage subsets, $Trem2^{hi}$ moMφ is characterized by an elevated expression of *Tgfb1*, aligning with its profibrotic features.[18] Recognized as a crucial regulator of fibroblast phenotype and function, TGF-β primarily induces myofibroblast transdifferentiation, matrix protein synthesis, and ECM organization through SMAD-dependent signaling.[72] Loss of fibroblast-specific *Smad3* results in defective cardiac repair and an increased incidence of heart rupture after MI, primarily owing to the disrupted alignment of myofibroblast assemblies and impaired scar formation.[73] In pressure-overloaded cardiac hypertrophy, increased TGF-β/SMAD signaling is necessary for adaptive cardiac remodeling.[74] The loss of myofibroblast-specific *Smad3* in the TAC model resulted in accelerated systolic dysfunction along with enhanced ECM degradation and macrophage-induced inflammation, and these effects can be reversed by suppressing matrix metalloproteinase activity.[75] Although TGF-β plays a protective role in cardiac repair and adaptive remodeling, it also triggers unrestrained fibroblast activation, exacerbating the progression of adverse remodeling. In the late phase of post-MI remodeling, inhibiting TGF-β signaling prevents prolonged fibroblast activation and progressive interstitial fibrosis in the non-infarcted myocardium, thereby alleviating cardiac dilatation and contractile dysfunction.[76]

In addition, TGF-β directly regulates cardiac macrophages. In vitro evidence suggests that TGF-β promotes CSF-1-induced macrophage proliferation.[77] The activation of TGF-β/SMAD3 signaling in macrophages promotes an M2-like phenotype and inhibits C-C chemokine ligand (CCL) 2 expression.[78,79] In the infarcted heart, TGF-β/SMAD3 signaling modulates the behavior of moMφs by mediating a phagocytic and antiinflammatory phenotype. This modulation

facilitates the resolution of excessive inflammation and promotes the transition to an anti-inflammatory and proreparative phase in infarct healing.[80,81]

CHEMOKINES. Chemokines are chemotactic cytokines that guide cell migration, positioning, and gathering and are essential for intercellular interactions in tissues. The elevated expression of *Ccl5* and *Cx3cl1*, which aid in the recruitment of peripheral monocytes, has been identified as a hallmark of activated fibroblasts in the infarcted heart.[82] Moreover, cardiac fibroblasts, in response to activating signals, produce various macrophage/monocyte attractants, including CCL2, C-X-C motif chemokine ligand (CXCL) 12, CCL3, and CCL4.[83-85] Particularly, CCL2 has been identified as a major attractant for $CCR2^{+}$ monocytes and moMφs after sustaining cardiac injuries.[86-88] Beyond its role in recruitment and orientation, CCL2 also exerts direct regulatory effects, promoting fibrosis. In vitro studies demonstrate that CCL2 stimulation increases the expression of TGF-β and ECM proteins in monocytes,[89] regulates profibrotic moMφ polarization,[90] and directly promotes the transdifferentiation of fibroblasts into myofibroblasts.[91] CCL2 deficiency decreases the expression of proinflammatory cytokines, leads to defective macrophage differentiation, and reduces myofibroblast accumulation after MI.[92]

Similarly, CXCL12, which is elevated in patients with pathologic cardiac conditions, regulates cell homing, trafficking, and differentiation in multiple cell types by binding to its cognate C-X-C motif chemokine receptor (CXCR) 4.[83] CXCL12-CXCR4 blockade efficiently alleviates cardiac function deterioration in various cardiopathologic models by reducing cardiac fibrosis and inflammation.[93-96] We observed elevated CXCL12 expression in cardiac fibroblasts of HF patients compared with healthy control subjects, potentially contributing to the recruitment of moMφs.[32] In addition to attracting immune cells, the CXCL12-CXCR4 axis facilitates the influx of circulating fibroblast progenitor cells into the murine TAC heart,[97] potentially serving as an additional source for myofibroblasts and contributing to adverse cardiac remodeling.

INTERLEUKIN-1β. Proinflammatory cytokines are consistently expressed during cardiac remodeling, indicating persistent cardiac inflammation.[42] Although the activated cardiac $Ly6C^{hi}$ moMφ is commonly considered to be a reservoir of proinflammatory cytokines,[98] existing evidence also supports the ability of activated cardiac fibroblasts to produce proinflammatory mediators.[35] IL-1β, a key proinflammatory cytokine in cardiac inflammation, induces a proinflammatory, promigratory, and ECM-degrading phenotype in cardiac fibroblasts and directly inhibits fibroblast proliferation, myofibroblast transdifferentiation, and collagen synthesis.[99-101] Despite promoting an antifibrotic phenotype in cardiac fibroblasts, the overall effect of IL-1β also involves the induction of tissue damage. This leads to the subsequent infiltration of moMφs and the increased expression of profibrotic mediators in these cells, ultimately leading to enhanced cardiac fibrosis.[99] Accordingly, the *IL-1β*-expressing macrophages and activated $FAP^{+}POSTN^{+}$ fibroblasts were found in close spatial proximity in the infarcted hearts of patients with acute MI.[102] The selective loss of IL-1 receptor (IL-1R) in fibroblasts alleviates Ang II-induced cardiac interstitial fibrosis, and the inhibition of IL-1β impedes the emergence of activated $Fap^{+}Postn^{+}$ cardiac fibroblasts by disrupting their differentiation trajectory.[102]

OSTEOPONTIN. OPN, encoded by *Spp1*, is expressed in various cardiac cell types and plays a multifunctional role in orchestrating cell-ECM interactions during cardiac repair and remodeling.[103] Increased OPN expression has been observed in both ischemic and nonischemic models of cardiac remodeling and is associated with extensive interstitial fibrosis.[104-106] OPN is crucial for TGF-β-induced myofibroblast transdifferentiation[107] and serves as an accessory signal that induces collagen synthesis and inhibits matrix metalloproteinase activity.[103,108] OPN deficiency prevents fibrosis in Ang II-induced cardiac hypertrophy,[105] protects the heart from myocardial aging, and induces the reverse modulation of fibroblast senescence.[104] A subset of $Trem2^{hi}$ moMφs with high expression of *Spp1* has been found to infiltrate into the myocardium during atrial fibrillation in a CCR2-dependent manner and contribute to adverse cardiac remodeling by promoting progressive cardiac fibrosis.[109] Accordingly, a close spatial correlation was observed between $SPP1^{hi}$ macrophages and myofibroblasts in human post-MI hearts.[31] The selective loss of *Spp1* in bone marrow–derived cells led to a reduction in cardiac inflammation and fibrosis in a murine atrial fibrillation model.[109]

GALECTIN-3. Galectin (Gal)-3, newly considered to be a mediator and biomarker of HF progression, is primarily produced by proreparative moMφs and directly induces cardiac fibroblast proliferation and collagen synthesis in vitro.[110,111] The pericardial administration of Gal-3 increases cardiac fibrosis and ventricular dysfunction in healthy rats.[110] The induction of Gal-3 in moMφs may be due to the activation of STAT3 signaling in response to the

expression of IL-10. This induction could function in an autocrine manner by inducing the transcriptional activity of the OPN-encoding gene *Spp1*, thereby promoting profibrotic *Spp1*^{hi} moMφs differentiation and TGF-β signaling activation in the infarct myocardium.[111] The inhibition of Gal-3 reduces the profibrotic polarization of cardiac macrophages during the reparative phase after MI and can prevent the exacerbation of fibrosis in the peri-infarct myocardium.[112] In the pressure-overloaded myocardium, Gal-3 is localized in activated macrophages and myofibroblasts.[113] The genetic deletion of Gal-3 prevents ventricular dysfunction in Ang II-induced remodeling.[114] Furthermore, Hu et al[115] identified that cardiac macrophage-derived Gal-3 was up-regulated in response to cardiomyocyte-derived IL-18 signaling after acute β-adrenergic receptor activation, which may promote excessive cardiac inflammation and injury.

GRANULOCYTE/MACROPHAGE COLONY-STIMULATING FACTOR. Granulocyte/macrophage colony-stimulating factor (GM-CSF), primarily released during inflammation, is a multifunctional growth factor that regulates the maturation and activation of bone marrow–derived leukocytes.[116] It has been identified that GM-CSF plays an active role in cardiac moMφ recruitment and proliferation under pathologic conditions.[117,118] Anzai et al[118] found that cardiac fibroblasts exhibit the highest expression of GM-CSF after acute ischemic injury, promoting the accumulation of moMφs by inducing CCL2 production in Ly6C^{hi} moMφs. Furthermore, a group of activated Sca-1^{+} cardiac fibroblasts with prominent expression of CCL2 serve as potent producers of GM-CSF during cardiac inflammation and may mediate the recruitment of moMφs under conditions such as myocarditis and ischemic cardiomyopathy.[119]

MicroRNA. Emerging evidence underscores the regulatory role of microRNA (miR) in cardiac remodeling.[120] miR-21, which is up-regulated during cardiac injury, is one of the most extensively examined miRs.[121] In the murine pressure-overloaded myocardium, miR-21 exhibits high expression levels in cardiac macrophages and may trigger a proinflammatory macrophage phenotype while promoting the transition from resting fibroblasts to myofibroblasts.[122] miR-21 regulates fibroblast survival and growth factor secretion by activating the MAP signaling in fibroblasts, thus contributing significantly to fibroblast activation.[121] Both global anti–miR-21 treatment and selective deletion of miR-21 in macrophages have proven to be effective in preventing cardiac interstitial fibrosis under both ischemic and nonischemic conditions by reducing inflammation and fibroblast activation.[122,123] Furthermore, macrophage-derived miR-155 is a suppressor of cardiac fibroblast proliferation and collagen production, and anti–miR-155 treatment can prevent post-MI cardiac rupture.[124]

TRANSLATIONAL PERSPECTIVE TARGETING CARDIAC MACROPHAGE-FIBROBLAST INTERACTIONS

Although our understanding of the roles of macrophages, fibroblasts, and their interactions in cardiac homeostasis and remodeling is gradually improving, translating these experimental findings into effective clinical treatment strategies remains a formidable challenge. In this context, we briefly introduce the translational perspective regarding targets associated with cardiac macrophage-fibroblast interactions, considering the current status of both basic and translational research progress.

TARGETING TGF-β SIGNALING. As the primary mediator of fibroblast activation and ECM deposition, the TGF-β signaling pathway remains an attractive target for impeding the progression of cardiac fibrosis.[125] Although demonstrating efficacy in animal models of cardiac fibrosis,[126,127] pirfenidone, known for its ability to reduce TGF-β expression, yielded only a marginal reduction in myocardial extracellular volume in patients with HFpEF.[128] Given the multifaceted impacts of TGF-β signaling and its dynamic role in myocardial pathology, further studies are needed to identify patients who could potentially benefit from anti–TGF-β treatment, as comprehensively reviewed by Frangogiannis.[74] The challenges encountered by existing strategies targeting TGF-β signaling underscore the need to discover pathology-driven stratification methods and antifibrotic agents within the complex signaling network.[125]

TARGETING THE CCL2-CCR2 AXIS. The pivotal role of the CCL2-CCR2 axis in coordinating monocyte/macrophage trafficking and fibroblast transdifferentiation makes it a promising target for alleviating cardiac inflammation and fibrosis.[129] Animal studies have provided compelling evidence of the therapeutic potential of the CCL2-CCR2 axis in various cardiovascular diseases, but its efficacy in humans awaits conclusive validation.[130] Bindarit, a small-molecule drug that selectively inhibits CCL2 production, albeit with limited specificity, is effective in improving pressure-induced cardiac fibrosis.[131] The administration of the CCL2-mutant competitor PA508 reduced infarct size, monocyte recruitment, and fibrotic content in a murine I/R model.[132] On the other hand, CCR2 blockade with the CCR2 antagonist

RS-504393 inhibited early macrophage infiltration and ventricle hypertrophy in TAC mice, thereby preventing late adverse remodeling and progression to HF.[133] The intricate role of the CCL2-CCR2 axis within the immune network, coupled with the complexity of its molecular structure, poses challenges in identifying suitable pharmacologic targets.[129] Although further in-depth investigation is required, the CCL2-CCR2 axis remains a prominent target for antiinflammatory interventions in cardiac remodeling, warranting continued exploration.

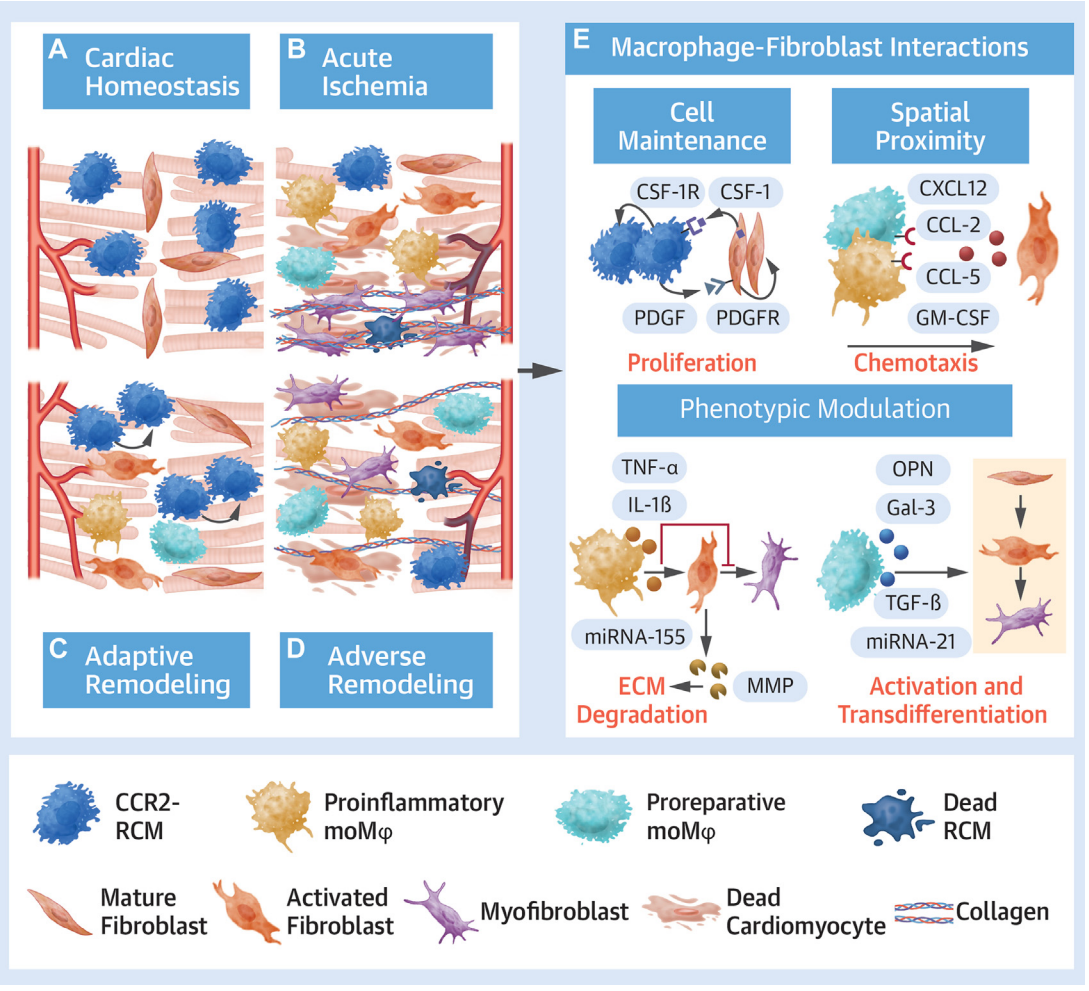
TARGETING THE NLR FAMILY PYRIN DOMAIN–CONTAINING 3–IL-1β AXIS. The increased understanding of innate immune pathways underscores the potential for targeting the NLR family pyrin domain–containing 3 (NLRP3)-IL-1β axis in antiinflammatory therapies for cardiovascular diseases.[134,135] Considering the crucial role of the NLRP3 inflammasome in IL-1β production,[136] colchicine, a nonspecific inhibitor of the NLRP3 inflammasome, has demonstrated the ability to alleviate cardiac inflammation, reduce fibrosis, and enhance heart function in murine models of cardiac remodeling.[137-139] In patients with chronic HF, the antiinflammatory effects of colchicine were demonstrated through the reduction of high-sensitivity C-reactive protein and IL-6 levels, but no significant improvement in either cardiac function or prognosis was observed.[140] The selective NLRP3 inflammasome inhibitor MCC950 has shown efficacy in resolving cardiac inflammation and may improve heart function in nonhuman animal models by reducing cardiac fibrosis.[141,142] In a murine clonal hematopoiesis model characterized by hematopoietic or myeloid *Tet2* deficiency, MCC950 reversed the deterioration of cardiac function after MI.[143] However, recent applications of MCC950 in humans have revealed liver toxicity, prompting the discontinuation of further testing.[144]

The levels of circulating IL-1β in acutely decompensated HF patients correlate positively with myocardial damage indicators such as N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T.[145] In a murine MI model, early IL-1β neutralization reduced post-MI leukocyte production, cardiac inflammation, and cardiomyocyte apoptosis and improved cardiac function.[146,147] Either early or delayed post-I/R IL-1β neutralization improves myocardial perfusion and left ventricle function together with reduced collagen deposition and myocardial oxidative stress.[148] In an MI model, application of IL-1R antagonist reduced cardiomyocyte apoptosis and ameliorated cardiac remodeling.[149] In a TAC model, IL-1R antagonist prevented HF progression by decreasing macrophage infiltration and collagen deposition.[150] In patients with a history of MI and elevated high-sensitivity C-reactive protein levels, the IL-1β antibody canakinumab exhibited a dose-dependent decrease in HF-related hospitalization and mortality.[151] The IL-1R antagonist anakinra is linked to a reduced incidence of HF and HF-related hospitalization in patients with ST-segment elevation myocardial infarction.[152] However, it should be noted that the efficacy of reducing HF events in MI patients by targeting IL-1 may be related to the attenuation of both cardiac and vascular inflammation.

TARGETING RCM MAINTENANCE OR RECOVERY. The detailed categorization of cardiac macrophages and their unique interactions with cardiac fibroblasts offers innovative translational possibilities for manipulating the composition of cardiac macrophage subtypes with distinct phenotypic characteristics. The presence of proinflammatory or profibrotic moMφs indicates HF progression, whereas the restoration of $CD163^{+}$ (marker of TLF^{hi} RCMs) RCMs is a hallmark of HF recovery.[153] Therapeutic interventions supporting the maintenance or the recovery of embryonic RCMs have aroused great interest owing to their crucial roles in maintaining cardiac homeostasis and preventing excessive cardiac inflammation and fibrosis.[17] In a murine model of sepsis-induced cardiomyopathy, the intraperitoneal administration of TLF^{hi} RCMs improved cardiac function and inhibited cardiac inflammation.[154] Although evidence from other tissues has confirmed the crucial role of fibroblast-derived CSF-1 in orchestrating the self-renewal of resident macrophages,[58,155] the determinants of RCMs' fate in cardiac homeostasis and remodeling remain unclear.

SUMMARY AND FUTURE OUTLOOK. In this review, we have synthesized current knowledge on the roles of macrophages and fibroblasts and their interactions in cardiac homeostasis and remodeling (**Central Illustration**). We emphasize the heterogeneity and plasticity within cardiac macrophage and fibroblast populations, the interplay between inflammatory cascades and cardiac fibrogenesis, and the potential to alleviate adverse cardiac remodeling by targeting macrophage-fibroblast interactions. Despite recent advances, our understanding of the intricate landscape of macrophage-fibroblast interaction in the heart remains shallow. The heterogeneity and plasticity of macrophages and fibroblasts, along with their dynamic changes during cardiac remodeling induced

CENTRAL ILLUSTRATION **The Integrated Landscape of Macrophage-Fibroblast Interactions in Cardiac Homeostasis and Remodeling**



Zhang X-Z, et al. JACC Basic Transl Sci. 2025;10(1):113–127.

(A) In the steady-state heart, intramyocardial spaces are predominantly occupied by embryonic RCMs and mature fibroblasts, both of which play organ-specific roles in maintaining cardiac homeostasis. (B) Acute ischemic injury results in extensive cell death, including cardiomyocytes and RCMs. The subsequent release of damage-associated molecular patterns leads to the recruitment of monocytes and differentiation into moMφs, exhibiting a proinflammatory phenotype and participating in efferocytosis to clear cellular debris. Simultaneously, environmental growth factors activate fibroblasts, promoting their transition into a proliferative and more collagen-producing phenotype. Once cellular debris is removed, environmental cues drive moMφ polarization, adopting a proreparative and antiinflammatory phenotype that supports cardiac repair and scar formation. Profibrotic signaling further induces transdifferentiation of activated fibroblasts into myofibroblasts, contributing to the maturation of cardiac scars. (C) During adaptive cardiac remodeling, embryonic RCMs proliferate and produce insulin-like growth factor-1 to facilitate adaptive growth of cardiomyocytes. Simultaneously, mechanical stress activates fibroblasts, leading to ECM remodeling and the infiltration of moMφs. (D) In adverse cardiac remodeling, embryonic RCMs experience a significant reduction and are replaced by moMφs. Sustained profibrotic signals activate cardiac fibroblasts, affecting the uninjured myocardium, resulting in reactive fibrosis and the development of chronic heart failure. (E) Through intercellular mediators, cardiac macrophages and fibroblasts interact to mutually regulate their abundance, location, phenotype and function, participating in cardiac homeostasis and remodeling. CCL2 = C-C chemokine ligand 2; CCL5 = C-C chemokine ligand 5; CCR2 = C-C chemokine receptor 2; CSF = colony-stimulating factor; CSF-1R = colony-stimulating factor-1 receptor; CXCL12 = C-X-C motif chemokine 12; ECM = extracellular matrix; Gal = galectin; IL = interleukin; miR = microRNA; MMP = matrix metalloproteinase; moMφ = monocyte-derived macrophage; OPN = osteopontin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; RCM = resident cardiac macrophage; TGF = transforming growth factor; TNF = tumor necrosis factor.

by various stimuli, increase the complexity of comprehending their interactions, thus necessitating more in-depth exploration.

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