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Complex regulation of cardiac fibrosis: insights from immune cells and signaling pathways

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Abstract

Cardiac fibrosis is a physiological process that involves the formation of scar tissue in the heart in response to injury or damage. This process is initially a protective measure characterized by enhanced fibroblasts, which are responsible for producing extracellular matrix proteins that provide structural support to the heart. However, when fibrosis becomes excessive, it can lead to adverse outcomes, including increasing tissue stiffness and impaired cardiac function, which can ultimately result in heart failure with a poor prognosis. While fibroblasts are the primary cells involved in cardiac fibrosis, immune cells have also been found to play a vital role in its progression. Recent research has shown that immune cells exert multifaceted effects besides regulation of inflammatory response. Advanced research techniques such as single-cell sequencing and multiomics have provided insights into the specific subsets of immune cells involved in fibrosis and the complex regulation of the process. Targeted immunotherapy against fibrosis is gaining traction as a potential treatment option, but it is still unclear how immune cells achieve this regulation and whether distinct subsets are involved in different roles. To better understand the role of immune cells in cardiac fibrosis, it is essential to examine the classical signaling pathways that are closely related to fibrosis formation. We have also focused on the unique properties of diverse immune cells in cardiac fibrosis and their specific intercommunications. Therefore, this review will delve into the plasticity and heterogeneity of immune cells and their specific roles in cardiac fibrosis, which propose insights to facilitate the development of anti-fibrosis therapeutic strategies.

Keywords Cardiac fibrosis, Signaling pathway, Immune cell, Heart injury

Background

Although the mortality from cardiovascular disease (CVD) has fluctuated in recent years, cardiac disease remains the leading cause of death and a serious threat to human health [1]. Along with CVD, cardiac fibrosis results from an abnormal reparative programme, such as the excessive extracellular matrix (ECM) deposition and remodelling, impaired matrix metalloproteinase (MMP) suppressive function, and aberrant elevation of infiltrating immune cells, which are present in diverse cardiac diseases including hypertensive heart disease, ischemic heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy and heart disease related with diabetes or

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aging [2]. For example, myocardial infarction, a typical ischemic heart disease, is induced by a blockage of blood supply to the heart, with the eventual replacement of dead cardiomyocytes by a fibrotic scar. There are some crucial events characterizing cardiac fibrosis, of which the proliferation and activation of fibroblasts are the key parts. Activated fibroblasts, which undergo myofibroblast transformation, produce and secrete superfluous ECM proteins by initiating a plethora of pro-fibrotic signaling pathways.

Recent studies have manifested that immune cells are involved in the regulation of the pro-fibrotic inflammatory response. Whereas the effect of fibroblasts has been extensively studied, the concrete implications of immune cells on cardiac fibrosis are still unclear. Since the current therapeutic strategies for cardiac fibrosis are unsatisfactory, it is urgent to deepen our comprehensive understanding of immune cells in cardiac fibrosis. Single cell spectrum research has revolutionized our capability to investigate the immune system and explore potential molecular mechanisms [3, 4]. This review will focus on the intricate functions and crosstalk of immune cells in cardiac fibrosis, as well as the well-known fibrotic signaling pathway.

Overview of cardiac fibrosis

Mainly developing in the chronic diseases or repair phase of acute injury, cardiac fibrosis is characterized by the excessive deposition of ECM widely perceived to be composed of collagens I/III, glycoproteins, and proteoglycan [2], which is mediated and secreted by various cells, especially fibroblasts. During normal wound healing procedures, a sophisticated regulating network maintains the balance between ECM protein synthesis and degradation and favors the formation of moderate fibrosis to protect heart from further damage like lethal cardiac capture rupture [5]. Nevertheless, once the balance is broken, aberrant fibrosis destroys and changes the structure and function of heart, also referred to as cardiac remodeling, which leads to elevated stiffness, falling compliance, and ultimately deteriorated systolic and diastolic function [6].

Simply put, cardiac fibrosis can be divided into two groups with distinct pathophysiologic processes, interstitial fibrosis and replacement fibrosis [7, 8]. In the absence of abundant cardiomyocytes loss, interstitial fibrosis appears to alter the ECM composition and the microenvironment of cardiac parenchymal cells, commonly induced by non-ischemic cardiomyopathy such as hypertensive heart disease [8]. Though replacing the necrotic cardiomyocytes with interstitial tissue and cells to preserve the heart integrity, replacement fibrosis is employed to compensate for the defective cardiomyocytes [9] due to the negligible ability of myocardial regeneration in adults [10]. Cardiac fibrosis also significantly impacts the pathophysiology of both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), accompanied by some differences. In HFrEF, fibrosis is primarily caused by replacement fibrosis that occurs after the death of cardiomyocytes, often due to ischemic injury such as myocardial infarction or chronic pressure overload. This leads to focal scarring and impaired contractility, contributing to systolic dysfunction [11, 12]. In contrast, in HFpEF, fibrosis is more commonly associated with interstitial and perivascular fibrosis. This type of fibrosis increases myocardial stiffness, leading to diastolic dysfunction. It is frequently linked to systemic inflammation, metabolic stress factors like obesity and diabetes, and endothelial dysfunction [12, 13]. The classification, albeit rough and simple, delineates a deeper understanding of cardiac fibrosis, suggesting unique signaling pathways and cell types are involved in different kinds of fibrosis.

Signaling pathway in cardiac fibrosis

Several key signaling pathways are commonly observed and involved in the pathogenesis of heart fibrosis, regardless of whether it is induced by acute ischemic cardiac disease or prolonged chronic inflammatory injury. These pathways play a significant role in the progression of fibrosis, in addition to the predominant events such as fibroblast phenotypic transition, recruitment of various immune cells, and changes in ECM composition (see Fig. 1). These signaling pathways mediate the expression of numerous interactive genes in fibrosis that not only directly affect ECM secretion, but also indirectly trigger the transformation of diverse cells such as fibroblasts, macrophages, and endothelial cells. A large and growing number of studies have shown that regulation of these signaling pathways contributes significantly to changes in the severity of cardiac fibrosis and cardiac function.

TGF-β signaling pathway

Transforming growth factor-β (TGF-β) is one of the most significant cytokines involved in cardiac fibrosis with abundant studies completed. It is the central link of fibrosis formation and is produced by a diverse number of cell types reacting to adverse events, including endothelial cells, epithelial cells, fibroblasts, and immune cells such as macrophages [14]. There are three isoforms of TGF-β, TGF-β1, TGF-β2 and TGF-β3. The TGF-β precursor synthesized in the Endoplasmic reticulum forms dimerization via a disulfide bond and then binds to the latency-associated peptide in secretory vesicle [7]. Latency-associated peptide with mature TGF-β becomes disulfide-linked to latent TGF-β binding protein and the complex is secreted to the ECM in which

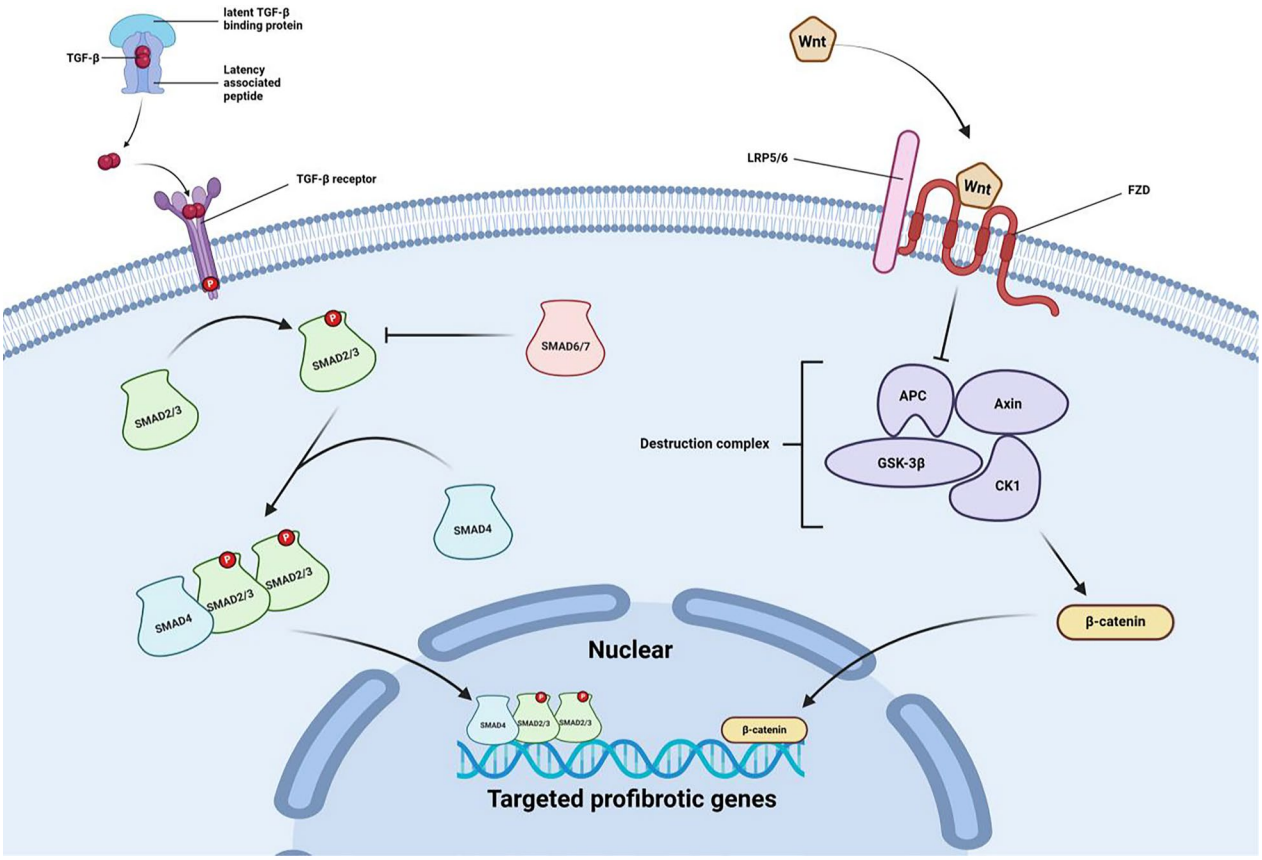

Fig. 1 Overview of canonical TGF-β/SMAD and Wnt/β-catenin signaling pathway. Released from TGF-β complex, active TGF-β binding to TGF-β receptor initiates SMAD-dependent signaling pathway and promotes the transcription of profibrotic genes. SMAD6/7 exerts an inhibitory role in TGF-β signaling pathway. Wnt protein binds to receptor (complex receptor comprised of FZD and LRP5/6), which results in instability of destruction complex and subsequent increase of β-catenin. Increased β-catenin translocates into nuclear to enhance targeted profibrotic genes expression. *APC* adenomatous polyposis coli protein, *CK1* casein kinase1, *GSK-3β* glycogen synthase kinase-3β, *LRP5/6* low-density lipoprotein receptor-related protein 5/6, *FZD* frizzled, *TGF-β* transforming growth factor-β

latency-associated peptide becomes disulfide-linked alternatively to glycoprotein A repetitions predominant (GARP) or leucine rich repeat-containing protein 33 in special cell types and the complex is remain on the cell surface [15, 16]. When injury events happen, to activate latent TGF-β, the latent TGF-β binding protein or GARP complex interacts with various αv integrins on adjacent cells resulting in changes that the complex is cleaved and the active TGF-β is released [17, 18]. But unlike other types of αv integrins, αv β 8 integrins can activate TGF-β signaling pathway through precise Latent TGF-β/ GARP complex without the need for mature TGF-βrelease and diffusion [19].

Signaling is initiated by activated TGF-β through binding to transmembrane serine/threonine kinases, TGF-β type I receptor (TβRI), and TGF-β type II receptor on the cell surface [20]. The signaling is mainly divided into canonical and non-canonical signaling or called SMAD-dependent and SMAD-independent signaling [21]. In the canonical signaling, activated TβRI phosphorylates the receptor-SMAD such as SMAD2, SMAD3, SMAD1, SMAD5, and SMAD8 [20], and promotes active receptor-SMAD binding to SAMD4, forming a trimeric complex which is able to translocate to the nucleus and increase transcription of fibrogenic genes [22]. However, activated TβRI not only phosphorylates the SMADs, but also activates other signalings to modify cell function such as PI3K/AKT, mitogen-activated protein kinase (MAPK) pathways, and JAK/ STAT (known as non-canonical signaling) [23]. In addition, SMAD6 and SMAD7 are inhibitory cytokines that exert suppressive function on receptor-SMAD signaling and SMAD-independent signaling (interact with receptor tyrosine kinase ErbB2 to inhibit the activation of ErbB) to reduce the expression of ECM genes and the transformation of fibroblasts into myofibroblasts [24]. After myocardial infarction, TGF-β/ SMAD3 upregulates the expression of programmed cell death 5, which promotes histone deacetylase 3

ubiquitination to inhibit histone deacetylase 3 and alleviates cardiac fibrosis suggesting programmed cell death 5 is a TGF-β negative feedback cytokine in signaling pathways [25].

TGF-β signaling promotes cardiac fibrosis through a wide range of mechanisms including inducing transformation of fibroblasts into myofibroblasts, cell proliferation, cell apoptosis, induction of epithelial-to-mesenchymal transition, and production of ECM [7, 8, 26]. The pathogenesis of fibrosis caused by TGF-β is diverse and involves many other key cytokines or signaling pathways. Bone morphogenetic Protein 9 inhibits TGF by increasing the level of phosphorylated SMAD1 and limiting SMAD3 activity, thereby attenuating cardiac fibrosis and improving cardiac function [27]. Researches show that protease-activated receptor 2 deletion, non-specific alkaline phosphatase, and NUAK family kinase 1 (one of the members of the AMP-activated protein kinase family) aggravate cardiac fibrosis via accelerating TGF-β signaling with the mechanism that increases collagen secretion by fibroblasts [28–31]. In contrast, the activation of cardiac fibroblasts is inhibited by high-temperature requirement A serine peptidase 3 and increased expression of TGF-β–induced factor homeobox 1 induced by natriuretic peptide receptor C deletion via degrading TGF-β [32, 33]. Besides, TGF-β has critical effects on the function and phenotype of immune cells, such as recruiting neutrophils and macrophages to injury tissues, instructing the differentiation of Tregs cells and inhibiting antigen presentation capability of dendritic cells [16, 20, 34].

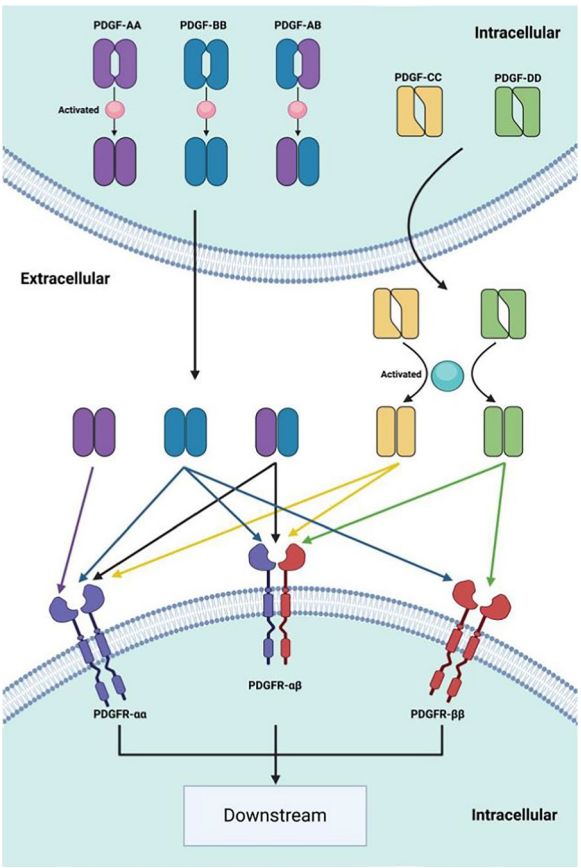

Fig. 2 The secretion, activation and ligand-receptor binding of PDGF signaling pathway. PDGF-A, and PDGF-B are activated intracellularly while PDGF-C and PDGF-D are secreted in a latent state and activated by matrix enzymes extracellularly. Distinct affinity exists in binding between PDGFs and receptors. PDGF: platelet-derived growth factor

PDGF family

The platelet-derived growth factor (PDGF) family participates in a wide range of pathophysiological activities including the inflammatory reaction and wound healing after cardiac injury, resulting in adverse remodeling and cardiac fibrosis with aberrant regulation [9, 35]. PDGFs are comprised of four distinct monomers (PDGF-A, PDGF-B, PDGF-C, and PDGF-D) and all of them accomplish homodimerization of which PDGF-A and PDGF-B can additionally heterodimerize, leading to five various isoforms (AA, BB, CC, DD, and AB) [36]. The dimer composed of PDGF-A and PDGF-B is activated intracellularly while for PDGF-C and PDGF-D, the dimer is secreted extracellularly as a latent form and later turns into an active state via the process of some proteases or special activators [36]. Activated PDGFs bind to parallel PDGF-receptor (PDGFR) which contains two kinds of monomer (PDGFR-α and PDGFR-β) (see Fig. 2), prompting PDGFR tyrosine kinase to phosphorylate substrates [37] and initiating downstream signaling pathways that involve in diverse fibrogenic proceedings such as myofibroblast differentiation and fibroblast proliferation [38, 39].

The severity of cardiac fibrosis depends on the expression of PDGF subtypes and their related receptors. In transgenic mice, overexpression of PDGF-A leads to the most severe cardiac fibrosis and subsequent fatal heart failure with the mechanism where cardiac interstitial cells (mainly cardiac fibroblasts) express PDGFR-α and are stimulated to produce extracellular matrix, as PDGF-A interacts to PDGFR-α with the highest affinity [40]. PDGF-B and PDGF-D are implicated to exacerbate cardiac fibrosis whereas the ameliorated cardiac fibrosis occurs in overexpression of PDGF-C [41]. The urokinase plasminogen activator produced by macrophages can activate adipocyte-derived PDGF-D by promoting its homologous dimerization, exacerbating cardiac fibrosis and harmful cardiac remodeling [42]. It is speculated that this pathway is more pronounced in overweight or obese heart disease patients. In a model of dilated cardiomyopathy caused by Lamin A/C mutations constructed

in vitro, transcriptomic analysis revealed that the PDGF signaling pathway was elevated, and inhibiting this pathway could improve adverse cell phenotypes [43]. Moreover, a study suggests that the PDGF signaling pathway participates in and promotes the differentiation of cardiac mesenchymal stem cells into myofibroblasts, aggravating cardiac remodeling and fibrosis in the late stage of myocardial infarction models [44]. Blockade of PDGFR activity in vivo can reduce the severity of myocardial fibrosis and hypertrophy in ischemic heart failure models [44]. In early recovery from injury, PDGFR-α promotes the migration and proliferation of fibroblasts by serum response factor to response intranuclearly. While at the late stage of injury recovery, PDGFR-α is suppressed by TGF-β signaling pathway and the downregulation of PDGFR-α promotes the differentiation of fibroblasts into myofibroblasts, revealing that PDGFR-α may play a seemingly opposite role in different stages of injury recovery [45]. However, PDGF-AB effectively represses the differentiation of fibroblasts into myofibroblasts after pig myocardial infarction and this result also appears in human cardiac tissue administrated with PDGF-AB [46]. Therefore, there may be more mechanisms resembling PDGF-AB in the PDGF signaling pathway that inhibit fibrosis formation.

Wnt signaling pathway

Mounting research has demonstrated the Wnt signaling pathway is prominent in the pathological development of cardiac fibrosis. Based on subsequent receptor types and downstream intracellular effector molecules, Wnt signaling is divided into two categories, namely the β-catenin-dependent signaling (canonical) and the β-independent signaling (non-canonical) [47, 48]. After Wnt protein binds to corresponding receptor (complex receptor comprised of frizzled and lipoprotein receptor-related protein 5/6 in canonical versus comprised of frizzled and receptor tyrosine kinase-like orphan receptor1/2 in non-canonical), the β-catenin-dependent signaling, just as its name implies, promotes expression of profibrotic genes via accumulated β-catenin translocating into nucleus as transcription cofactor [47], whereas the β-independent signaling includes two major avenues, planar cell polarity pathway and Ca^{2+}-dependent pathway, which involve the activation of small guanosine triphosphateases, such as ras-related C3 botulinum toxin substrate 1 and ras homolog gene family member A, phospholipase C, and protein kinase C [49].

Studies have implicated that extensive molecule regulation deteriorates cardiac remodeling and fibrosis by overactivating the Wnt / β-catenin signaling pathway in diverse animal models and experimental data of human cells [50–54]. Besides, in mice with cardiac stress overload resulting from trans-aortic constriction, the loss of β-catenin function in tissue-resident cardiac fibroblasts can significantly improve cardiac function and alleviate cardiac fibrosis, but it does not affect the number of activated fibroblasts [55]. Researchers detect that the circulating Wnt5a protein is markedly positively correlated with poor right ventricular function and fibrosis in human dilated cardiomyopathy patients, which has been confirmed in mouse models with the mechanism of the activation of nuclear factor of activated T cells related to non-canonical pathways [56]. Wnt signaling aggravates cardiac fibrosis and remodeling by stimulating Yes-associated protein [57]. However, Deletion of Wls, a targeted gene of Yes-associated protein regulating the communication between cardiomyocytes and cardiac fibroblasts, reduces the regeneration of neonatal heart by inhibiting non-canonical Wnt signaling, leading to deterioration of cardiac function and fibrosis, accompanied by activation of cardiac fibroblasts [58]. The above studies indicate Wnt non-canonical signaling is involved in adverse cardiac remodeling and the formation of cardiac fibrosis, and plays different roles in different growth or repair stages, promoting myocardial proliferation in the neonatal stage and hastening profibrotic response of fibroblasts in the mature stage. In the pathogenesis of cardiac fibrosis, Wnt signaling is affected by TGF-β signaling, the well-known signaling participating in detrimental fibrosis [59, 60]. Recently, with the function of modulating gene expression at the post-transcription level, miRNAs are obtaining increasing attention in the process of cardiac fibrosis. By de-repressing the Wnt signaling, miRNA-29 exacerbates pathological hypertrophy and fibrosis of cardiac cells in a mouse model experienced cardiac pressure overload due to constriction of the thoracic aorta [61]. Furthermore, miRNA-384-5p and miRNA-145 target regulatory factors of certain genes and can significantly inhibit the activation of cardiac fibroblasts and attenuate cardiac fibrosis [62, 63]. Wnt receptors are widely believed to exist in interstitial cells, such as fibroblasts. Under pressure overload conditions, as one of the key receptors of the Wnt signaling, lipoprotein receptor-related protein 6 derived from cardiomyocytes is overexpressed, significantly suppressing the expression of β-catenin, through its interplay with cathepsin D (a protein) that reduces the quantity of Wnt5a and Wnt11, ultimately enhancing cardiac function and alleviating cardiac fibrosis [64]. This study suggests there may be an autocrine or paracrine pathway in the myocardial cell population that regulates the chronic repair process of impaired heart via regulating the Wnt signaling.

Others

Follistatin-like protein 1 (FSTL1) is a secreted glycoprotein widely expressed in various tissues and has been found to be closely related to the occurrence and development of cardiac fibrosis in recent years [65, 66]. The role of FSTL1 in cardiac fibrosis is dual. On one hand, FSTL1 promotes cardiac fibrosis by activating the TGF-β/SMAD3 signaling pathway [67]. Research has demonstrated that the absence of FSTL1 derived from endothelial cells led to abnormal activation of SMAD3, which in turn caused fibrosis in the atrium, venous walls, and heart valves [68]. On the other hand, FSTL1 also contributes positively to myocardial cell proliferation and repair. Some studies have shown that promoting the expression of FSTL1 protected against cardiac remodeling and reduced fibrosis [69, 70]. Moreover, specific knockout of FSTL1 augmented pro-inflammatory response with elevated macrophages and pro-inflammatory cytokines/chemokines [71].

MMPs are a group of zinc-dependent endopeptidases that play a crucial role in the degradation and remodeling of the ECM. Based on their substrate specificity, MMPs can be classified into several categories: collagenases, gelatinases, matrix lysins, and membrane-type MMPs [72]. The activity of MMPs is regulated by tissue inhibitors of MMPs [73]. In cardiac fibrosis, the activities of MMP-2 and MMP-9 are significantly increased, leading to the degradation of basement membrane components, promoting fibroblast activation, and increasing collagen deposition [74, 75]. Therefore, emerging investigations have focused on MMP inhibitors, which effectively attenuated adverse cardiac remodeling [76, 77]. Addressing ECM degradation and inhibiting cardiac fibrosis is essential for preserving cardiac function and reducing adverse remodeling.

Immune cells involved in cardiac fibrosis

In addition to the well-known function of eliminating harmful substances via the immune system, the immune cells also participate in the progression of cardiac fibrosis by promoting the activation of various signaling pathways (see Fig. 3). Abundant experimental evidence delineates that immune cells harbor the ability to mediate cytokine secretion from diverse cell types involved in chronic inflammation in impaired cardiac areas, to facilitate the transition to myofibroblasts, and to regulate the phenotypic transformation of crucial cells related to cardiac fibrosis. Taken together, immune cells play a significant role in cardiac homeostasis where the disruption of balance between injury and reparative process may lead to adverse fibrosis and an increasing number of studies unveils advanced insights describing in-depth mechanisms.

Lymphocyte

It is well established that lymphocytes are the key members of the adaptive immune system. However, recent research has highlighted their important impact on fibrosis response following heart injury. Lymphocytes consist of T lymphocytes and B lymphocytes and T lymphocytes are divided into CD4+populations and CD8+populations. In the aged heart, T cells secrete interferon-γ (IFN-γ) to accelerate cardiac fibrosis and the decline in cardiac function [78], which can be blunted by IFN-γ neutralizing antibodies [79]. Theresa Dolejsi, Thomas Schuetz, et al. identified that T cell-produced IFN-γ mediates inflammation and activation of immune cells to impair the regenerative process after myocardial infarction through adoptive transfer of adult T cells into neonatal heart [80]. The heart regenerative capacity is regulated by substantial backgrounds and complex mechanisms, which can not be explained clearly by a single T cell-related mechanism. Achieving complete heart regeneration may be difficult, but it is prospective to promote beneficial fibrosis and enhance heart function by regulating T cell differentiation phenotype, immune activity, and inflammatory response [81]. Moreover, as a typical proinflammatory cytokine, tumor necrosis factor-α (TNF-α) alleviates deleterious cardiac inflammation and fibrosis by inducing the death of effector CD4+T cells in myocarditis models [82]. Tregs are considered as key immunosuppressive mediators and protectors of heart repair and fibrosis for their function of inhibiting immoderate inflammatory reaction, dampening immune cell infiltration, and stimulating transformation into protective phenotype [83–85]. In the neonatal heart, genes that promote tissue regeneration and regulate innate immune cells such as *Apoe*, *Cxcl4*, and *Atf3* are upregulated in Tregs, promoting the cardiac regeneration process [84, 86]. Inhibiting interleukin (IL)−35 (a class of immune regulating cytokines mainly secreted by Tregs cells) will impair the heart reparative function after myocardial infarction, increase mortality caused by heart rupture, and exacerbate heart function by reducing the proliferation of $Ly6C^{low}$ $MHCII^{low}$ CCR2-macrophages, repressing the expression of fibrosis-related genes, such as TGF-β activation genes and collagen synthesis genes [87]. Cardiac fibrosis itself is a process of damage repair that plays a protective role, so excessive inhibition of profibrotic process may lead to detrimental outcomes. A study found that inhibition of C–C chemokine ligand (CCL)17 could alleviate cardiac injury and adverse ventricular remodeling by increasing Tregs metastasis and recruitment [88]. Nevertheless, the increased Foxp3+Tregs in ischemic cardiomyopathy exert pro-inflammatory function and worsen cardiac remodeling and fibrosis while losing their immunosuppressive effect by a blurred mechanism [89].

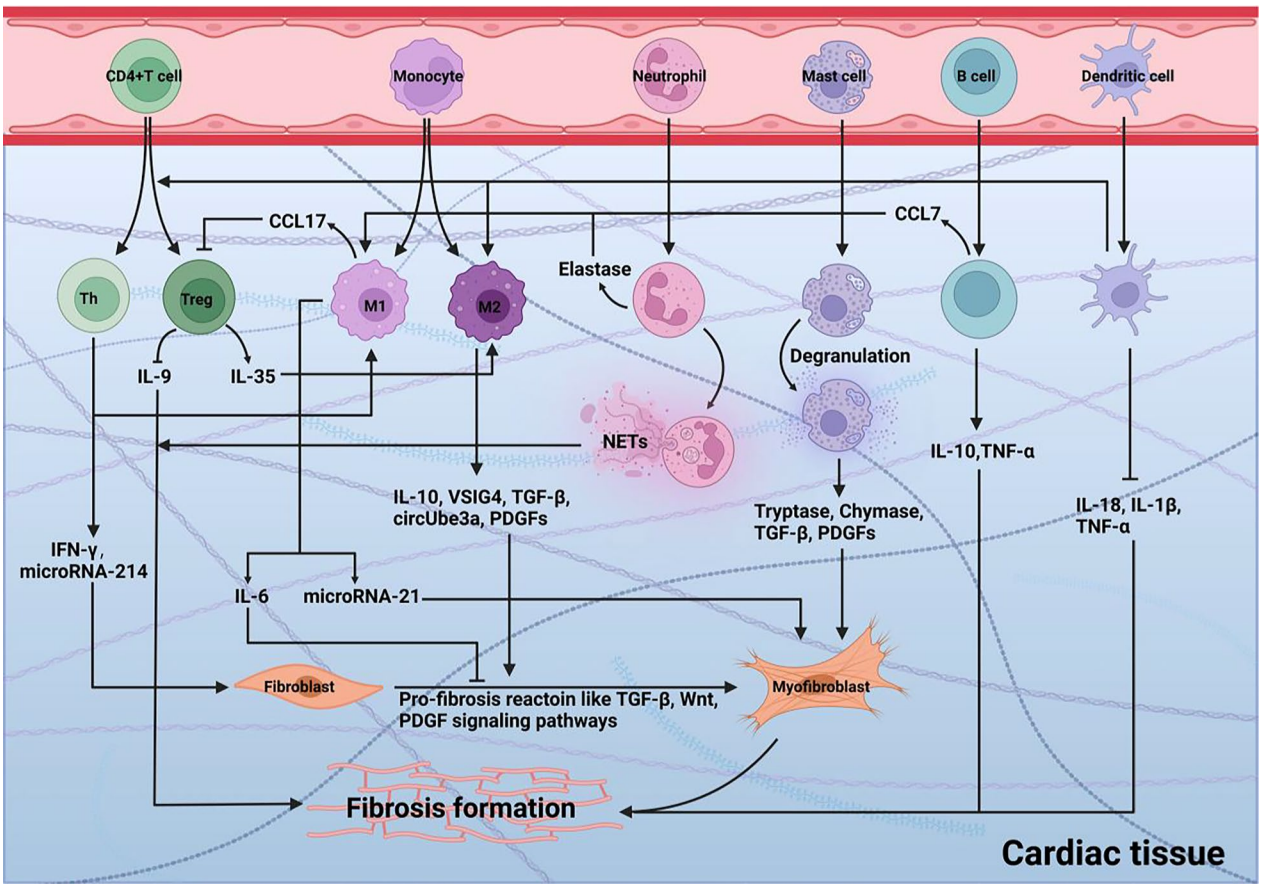

Fig. 3 Involvement of immune cells in cardiac fibrosis. After heart injuries, immune cells are recruited to damaged cardiac tissue by chemokines. Activated and transformed immune cells secrete numerous chemokines, cytokines, growth factors and enzymes to intricately regulate fibroblast activation and fibrosis formation. *Th* helper T cell, *Treg* regulatory T cell, *M1* pro-inflammatory macrophage, *M2* anti-inflammatory macrophage, *CCL* c–c motif chemokine ligand, *NETs* neutrophil extracellular traps, *TGF-β* transforming growth factor-β

The aforementioned study indicates that Tregs exhibit varying functions depending on the specific context in which they are found. Further investigation is needed on the specific pathways through which Tregs promote heart tissue repair and the distinct functions of manifold subtypes. In Ang II-induced cardiac fibrosis, miRNA-214, IL-9 and Kruppel like factor 10 are validated as vital regulators of fibrosis responses [90, 91]. Intriguingly, the perturbation of gut dysbiosis induced by cardiac pressure overload affects T cell activation and leukocyte infiltration, leading to cardiac remodeling and fibrosis [92]. Th cells have been identified to promote the transformation into aggravated cardiomyopathy [93, 94] and participate in cardiac fibrosis, which is associated with fibrosis signaling pathways, such as TGF-β/SMADs [95–97].

Producing antibody is the hallmark of B cells which could enhance cardiac injury and subsequent fibrosis via an antibody-dependent pathway [98, 99]. In an Ig-deficient model, cardiac impairment induced by myocardial infarction is markedly blunted accompanied by improved heart function [100]. Besides, several studies accentuated the role of the complement system activated by antibodies in cardiac homeostasis including profibrotic procedure [101, 102]. Depletion of B cells inhibits myocardial cell proliferation and cardiac regeneration in neonatal mice after apical resection, promoting the formation of cardiac fibrosis and cardiac dysfunction whereas the left anterior descending coronary ligated adult mice with the same administration produce almost opposite results, namely reduced inflammatory response, attenuated fibrosis and improved cardiac function, which may be related to the reduction of B cells that overexpress S100 calcium binding protein A6 and S100 calcium binding protein A4 [103]. This study indicates that the immune system has undergone significant changes during its development and investigation of how these changes occur may suggest the reasons why heart loses regeneration ability in adulthood. Researchers improved cardiac function and reduced cardiac fibrosis by adaptive transfer of Breg following myocardial infarction where $Ly6C^{hi}$ monocytes

were significantly reduced in the infarcted area [104]. Reduction of C–C motif chemokine receptor (CCR)2 in monocytes regulated by Breg inhibits the activation and recruitment of pro-inflammatory cells. In another study utilizing an MI model, B cells produce CCL7 and induce Ly6C^{hi} monocyte mobilization to recruit to damaged heart site, increasing cardiac injury and fibrosis as demonstrated by the experiments of specific deletion of CCL7 in B cells [105]. The study does not elucidate the specific mechanism through which B cells recruit Ly6C^{hi} monocytes and their precise subtypes, and the role of CCL7 deserves further investigation. Activated B cells also have the capability to secrete various cytokines such as IL-10 and TNF-α which may be involved in cell differentiation, modulation of gene expression, and sustained activation of inflammation, resulting in cardiac fibrosis [106–108]. Targeted elimination of CD20 + B cells using Rituximab can significantly ameliorate cardiac fibrosis [109].

Macrophage

When the heart gets attacked or undergoes chronic injury, macrophages are one of the first corresponding immune cells. Based on function natures, macrophages are roughly divided into two types, namely M1 (pro-inflammatory) and M2 (anti-inflammatory) [110]. M2 produces and secretes cytokines and circulating RNAs such as IL-10, VSIG4, and circUbe3a, which subsequently alter the biological function of cardiac fibroblasts and initiate fibrotic response [111–113]. This effectively controlled pro-fibrotic process mainly plays a protective role. M1 activates fibroblasts through miRNA-21, mediating pressure overload-induced cardiac fibrosis and cardiac dysfunction [114]. But with the application of more advanced technologies, a cognition is emerging that M1 and M2 classifications are the two extreme states among which the roles of various macrophages are affected by the expression of different receptors and ligands [115, 116]. According to the origin, CCR2 + macrophages derive from bone marrow progenitor cells and achieve replenishment via monocyte recruitment mainly promoting inflammation [117], whereas CCR2- macrophages originate in the embryonic development harboring the capacity of self-renewal with the function in cardiac homeostasis [118]. For example, CCL17 secreted by CCR2 + macrophages inhibits Tregs recruitment by binding to CCR4, exacerbating ventricular remodeling and increasing myocardial fibrosis [88]. The disorder of crosstalk between immune cells contributes to the formation of harmful fibrosis. In cardiac ischemia–reperfusion injury, IL-34 activating the NF-κB pathway induces the expression of CCL2, which in turn promotes the polarization of CCR2 + macrophages, leading to deleterious cardiac fibrosis [119]. However, adoptive transfer of M2-like (CCR2 + CD206 +) macrophages can alleviate cardiac toxicity and fibrosis in a non-infarctive heart failure model induced by doxorubicin [120].

Macrophages can form a phenotype like myofibroblasts, expressing marker genes of fibroblasts, such as *α-SMA (α-smooth muscle actin)*, *FSP1 (fiber last specific protein-1),* and *COL1A1 (Collagen type I alpha 1)* [121]. Recent studies manifest that affected by diverse cytokines CCR2- macrophages activate cardiac fibroblasts to express collagen and ECM via complex pathways such as TGF-β and NADPH oxidase 4 dependent channel [87, 122, 123]. Through hypoxia inducible factor-1α dependent pathway Ly6C^{hi} macrophages recruit to hypoxic impaired areas and secrete oncostatin-m, a member of the IL-6 family, to inhibit TGF-β/ SMAD pathway [124]. Specific deletion of bone marrow cell WWP2 (an E3 ubiquitin ligase) affects the function of Ly6c^{hi} macrophages through the IRF7-Ccl5 axis, inhibits the transdifferentiation of myofibroblasts and ultimately alleviates cardiac fibrosis [125]. The crosstalks between macrophages and fibroblasts depend on various molecules, initiating intracellular fibrosis programs. Targeting these molecules may effectively prevent fibrosis progression. Research found that the deficiency of EGF-like repeats and discoidin I-like domains protein 3 (an endogenous inhibitor of neutrophil adhesion) promoted the recruitment and release of neutrophil extracellular traps (NETs) following myocardial infarction, which facilitated the transition from monocyte to Mertk MHCII^{low} macrophages through Toll-like receptor (TLR)9, reducing collagen production and α-SMA + myofibroblasts [126]. Compared with the conventional concept that collagen is completely secreted by myofibroblasts, a study has found that in mouse and zebrafish heart attack models, macrophages can secrete collagen directly promoting fibrosis [127]. Justin F. Deniset et al. revealed an intriguing discovery that pericardium-resident Gata6 + macrophages migrate to the damaged heart area after myocardial infarction which results in phenotype conversion, attenuates cardiac injury and inhibits fibrosis formation while the ablation of Gata6 + pericardial cavity macrophages (GPCMs) does not apparently influence fibrosis extent following myocardial infarction [128, 129]. It is a possible elucidation that transdifferentiation of other macrophage subtypes into GPCMs counteracts the regulation of ablated cells in cardiac fibrosis. At present, it has been found that cardiac macrophages exhibit multiple phenotypes and play different functions. However, it is not fully understood whether this alteration in phenotype proportion is the cause or result relative to the final fibrosis, and the molecular mechanisms involved also require further investigation.

Neutrophil

Before the infiltration of other inflammatory cells, neutrophils are recognized as the first responders to various cardiac damages [130, 131]. Following injuries, such as ischemic cardiomyopathy and myocarditis, neutrophils rich in impaired zones not only secrete multiple proteases to eliminate cell debris but also contribute to the resolution of inflammation and tissue repair where macrophages and neutrophils are transited into a reparative phenotype [132–136]. At hemostasis state, neutrophils mainly explore a protective effect to assist with cardiac restoration. Once the hemostasis is disrupted, aberrant neutrophils in a pathological context produce excessive proinflammatory mediators which may cause damage to heart and lead to maladaptive remodeling [137, 138]. Calcium sensing receptor activates nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 inflammasomes in neutrophils, leading to cardiac fibrosis and ventricular remodeling after acute myocardial infarction [139]. Moreover, increased neutrophil elastase promotes the recruitment of neutrophils and M1 macrophages to heart, enhancing inflammatory damage and fibrosis of non-infarcted myocardium [140]. Excessive histidine catalyzes pro-inflammatory effects on neutrophils, as confirmed by increased reactive oxygen species and NETs, as well as activation of cardiac fibroblasts in histidine decarboxylase deficient mice [141]. Through the positive feedback loop between neutrophils and IL-1β, neutrophils play a profibrotic role accompanied by activation of specific signals to fibroblasts including TGF-β signaling [142].

NETs are a kind of chromatin structures embellished by histones, cytoplasmic and granular proteins [143] and participate in fibrosis formation via promoting the migration and infiltration of neutrophils into heart [133, 144]. Extensive experiments evidences suggest that inhibition of NETs potently dampens the pathogenesis of cardiac fibrosis [145], in which suppressing PAD4 (a class of nuclear molecules that promote NETs expression) and tACPA (therapeutic anti-citrullinated protein antibody) have been implicated to play a beneficial role in many cardiopathy models [146–148]. Intriguingly, NETs expand the polarization of Mertk-MHCII^{lo-int} macrophages through the TLR9 pathway, which inhibits myofibroblasts from expressing collagen I/III and α-SMA [126]. The above studies imply that NETs play various roles in fibrosis depending on the distinct responding microenvironments and injury phases.

Mast cell

Mast cells are well-known as mediators of allergic reactions. Nonetheless, years of profound investigations indicate mast cells are vital in cardiac tissue metabolism and fibrosis development characterized by a variety of granules including tryptase, chymase, cytokines, and growth factors [149–151]. The number of mast cells has a pronounced increase in heart following injury [152–154], which triggers degranulation and initiates ensuing inflammation. Enhanced mast cells are found in heart correlated with interstitial fibrosis in hypertensive myocardial damage [155]. A study demonstrated that mast cells accelerated right ventricle remodeling and deteriorated heart function induced by pressure overload [156]. A plethora of experimental evidences suggest that chymase is a crucial regulator of cardiac fibrosis through activating fibroblasts like mediating the activation of TGF-β and Ang II [151, 157], as reduced collagen I/III and ameliorated fibrosis occur in the models with blockade of chymase [158–160]. Mast cell tryptase also plays a similar role in fibroblasts including promoting proliferation and transition into myofibroblast [161, 162]. In addition, TNF-α and IL-1β derived from mast cells during degranulation lead to adverse remodeling and fibrosis by facilitating detrimental inflammatory response and MMP-9-dependent signaling [163–165]. Mast cells have been established to be involved in atrial fibrosis and atrial fibrillation coinciding with elevated PDGF, a pro-fibrotic growth factor [166]. But it is still unclear where the mast cells come from and what the complex mechanism is.

However, mast cells can also exert converse function in specific contexts, in which numerous anti-fibrosis mediators are secreted such as IL-10, IL-13, and CXCL-10, and inhibit ECM deposition and collagen synthesis [151, 167, 168]. Deletion of mast cells in hyperhomocysteinemia-induced cardiac dysfunction results in enhanced perivascular fibrosis with aggravated heart function suggesting a protective role of mast cells [169]. Another study manifests that augmented mast cells found in atrium correspond to mitigated cardiac fibrosis and improved functions [170]. There is also in vivo experimental evidence identifying that transplantation of mast cells into murine ischemic heart significantly improves cardiac function and decreases fibrosis extent [171, 172].

In summary, cardiac mast cells are a double-edged sword and several problems to be solved are proposed from the above contradictory conclusions, partially attributed to the failure to select appropriate animal models [173]. Moreover, the common models of mast cell deficiency require mutations of *c-Kit* which lead to some physiological defects in mast cells. Therefore, achieving a better understanding of how mast cells manipulate cardiac fibrosis process brings valuable insights into promising treatment.

Dendritic cell

Because of genomic research, dendritic cells (DCs) are comprised of conventional DCs (cDCs) and plasmacytoid DCs (pDCs) [174]. Explored more, cDCs contain two subsets, cDCs1, and cDCs2, mediating the adaptive immune response of CD8 + T cells and CD4 + T cells respectively [175]. Plasmacytoid DCs have been demonstrated to hold the capacity to secrete substantial type I interferon with the elusive molecular basis [176]. Beyond presenting antigens to specific immune cells to initiate adaptive immune response, DCs are also essentially involved in the pathogenesis of plenty of diseases including heart failure and cardiac fibrosis [177, 178].

CD103 + /CD11b + cDCs amplify inflammatory responses leading to detriment after MI, as demonstrated by improved cardiac function and diminished fibrosis area of deletion of cDCs [179]. In mice with aldosterone/mineralocorticoid receptor-dependent cardiovascular impairment induced by aldosterone and high-salt diet, activated mineralocorticoid receptors facilitate neutrophil gelatinase-associated lipocalin expression in DCs, enhancing cardiac hypertrophy and fibrosis [180]. Moreover, emerging studies have established that activated DCs contribute to the development of autoimmune reaction-dependent heart damage via recruiting and activating T cells including CD4 + T cells and cytotoxic CD8 + T cells in heart [181–184]. However, DCs could exert a beneficial role in the repair phase following MI through modulating inflammatory activity and phenotype shift of immune cells such as tissue-specific Tregs and macrophages, which promotes reparative fibrosis and protects against cardiac rupture [178, 185]. For instance, after myocardial infarction, deletion of DCs exacerbates left ventricular remodeling associated with increased inflammatory mediators like IL-1β, IL-18, and TNF-α, compared to the control group. Meanwhile, macrophage subsets are altered by DCs deletion, namely enhanced pro-inflammatory M1 and reduced anti-inflammatory M2, suggesting an immunomodulatory role of DCs [186]. But the accurate crosstalk between DCs and macrophages during myocardial infarction is still ambiguous. Furthermore, Qian Wang et al. found that the adoptive transfer of tolerogenic DCs significantly raised cardiac function and attenuated fibrosis correlated with a decline of inflammation, probably due to inhibited TLR-4/NF-κB signaling [187]. Given that DCs hold the central regulation of immune system, more investigation should be attached to the interaction between DCs and other immune cells in cardiac diseases.

Treatment of cardiac fibrosis

Recent advances in immunology have highlighted the pivotal role of immune cells, particularly in the development and treatment of cardiac fibrosis. Study have shown that modulating macrophage polarization, such as by enhancing glycogen metabolism using inhibitors, can shift M2 macrophages to an anti-fibrotic M1 phenotype, thereby reducing fibroblast activation and collagen deposition [188]. Invariant natural killer T cells, activated by α-galactosylceramide-pulsed dendritic cells treatment, prevented decline in the left ventricular ejection fraction, accompanied by reduced interstitial fibrosis [189]. In mice with ischemic cardiomyopathy by left coronary artery ligation, selective Tregs ablation alleviated the deterioration of heart function and fibrosis [89], inferring the restoration of normal Tregs function may be a promising avenue of therapeutic immunomodulation.

In addition, IL-1β signaling between CCR2 + macrophages and fibroblasts is a key driver of fibrosis. Inhibiting IL-1β signaling through genetic deletion or monoclonal antibodies has shown promise in reducing fibrosis and improving cardiac function [190].

Cardiac fibrosis presents a significant therapeutic challenge, as current treatments primarily aim to slow disease progression rather than reversing established fibrosis. Traditional therapies, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (see Table 1), target the renin–angiotensin–aldosterone system to reduce fibrosis and ventricular remodeling [191, 192]. However, their effectiveness is often limited in advanced stages of fibrosis, and they may lead to side effects, such as hypotension or hyperkalemia. Emerging therapies are beginning to address these limitations. Chimeric antigen receptor (CAR) -T cell therapy and CAR-macrophage therapy target fibroblast activation protein to eliminate activated fibroblasts, though challenges such as off-target effects and limited tissue infiltration remain [193, 194]. Nanozyme-based therapies use ATP-responsive nanoparticles to deliver antioxidants and siRNA for precise anti-fibrotic effects, although concerns about systemic toxicity exist [195]. Additionally, modulation of the YTHDF3/FLCN/cPLA2 pathway presents a novel approach by regulating lysosomal function and fibrosis through m6A methylation, though its clinical application requires further validation [196].

While traditional therapies remain the cornerstone of treatment, these emerging strategies hold promise for more targeted and effective interventions. Combining these approaches may yield synergistic benefits, but additional research is needed to overcome current limitations and translate these advancements into clinical practice.

Table 1 Current treatment of cardiac fibrosis

Treatment	Mechanism	Limitations	References
Traditional therapies			
ACE inhibitors	Reduces angiotensin II levels, decreasing fibrosis and ventricular remodeling	Limited efficacy in advanced fibrosis; side effects like hypotension	[191]
ARBs	Blocks angiotensin II receptors, reducing fibrosis and inflammation	Similar limitations to ACE inhibitors; may not fully reverse fibrosis	[192]
Mineralocorticoid receptor antagonists	Reduces aldosterone effects, decreasing collagen deposition and fibrosis	Risk of hyperkalemia; limited efficacy in severe fibrosis	[197]
Beta-blockers	Reduces myocardial stress and fibrosis progression	Poor bioavailability; limited impact on established fibrosis	[198]
Emerging therapies			
CAR-immune cell therapy	Targets fibroblast activation protein to eliminate activated fibroblasts	Challenges include off-target effects and limited infiltration into fibrotic tissue	[193, 194]
mRNA therapies	Delivers mRNA to produce anti-fibrotic CAR-T cells or T-regulatory cells	Early-stage research; challenges in targeted delivery and stability	[199]
Nanozyme-based therapies	Uses ATP-responsive nanozymes to deliver antioxidants and siRNA	Requires precise targeting; potential systemic toxicity	[195]
Extracellular vesicles	Delivers miR-664a-3p to inhibit SMAD4, reducing fibrosis	Limited scalability; challenges in large-scale production	[200]
YTHDF3/FLCN/cPLA2 pathway modulation	Regulates lysosomal function and reduces fibrosis via m6A methylation	Complex mechanism; requires further validation in clinical settings	[196]

Conclusions

Fibrosis is a normal and beneficial physiological process following a variety of heart injuries, nevertheless, while the balance between formation and degradation is out of control, fibrosis plays a detrimental role in deteriorating tissue compliance and heart function instead of a protective role. The review accentuates the importance of immune cells and signaling pathways in cardiac fibrosis and recapitulates distinct properties that orchestrate the complicated fibrotic responses. Furthermore, the effect of immunomodulation on cardiac fibrosis deserves special attention. It was demonstrated that heart transplant recipients experienced more severe cardiac fibrosis compared to healthy ones both in human and mouse [201, 202]. Cyclosporin A, an effective immunosuppressive agent, significantly lead to detriment in cardiac structure and increased fibrosis [203]. In immunocompromised mice with streptozotocin-induced diabetic cardiomyopathy, depletion of T cells mitigated cardiac fibrosis [204]. As an urgently needed direction in clinical practice, the importance of immunomodulation on cardiac fibrosis has been highlighted. Future investigations need to concentrate on several aspects to make progress in the fight against cardiac fibrosis. First, an immune cell-mediated inflammatory response could reduce the area of acute cardiac injury, but chronic excessive inflammation leads to fibrosis and reduced cardiac compliance. Therefore, it is meaningful to choose different strategies to target pro-inflammatory signals and to maintain optimal regulation of inflammatory intensity during the acute or chronic phase of injury. Second, despite the progress in fibrosis, which shows that the reversal of organ fibrosis is possible [14], current anti-fibrotic therapies are mostly targeted at early fibrosis with unmet results. Targeted immunotherapy using engineered immune cells is one of the research highlights [193, 205]. However, some limitations cannot be ignored in chimeric antigen receptor-T cells against cardiac fibrosis. For example, off-target killing of normal cells outside the heart, such as fibroblasts, results in severe dysfunction of other physiological activities. Third, given the complex background ranging from the injury phase to aging and pathophysiology, more well-defined subtypes of cardiac fibrosis need to be classified in order to achieve better targeted treatment. Finding or creating relevant biomarkers to measure the classification and severity of cardiac fibrosis is a wise move [32, 206]. Taken together, due to the dramatic impact of multiple immune cells, signaling pathways and their intercommunications, targeted immunotherapy, especially multi-target, offers the exciting prospect of slowing down and even reversing the progression of cardiac fibrosis.

Abbreviations

ACE	Angiotensin converting enzyme
ARBs	Angiotensin receptor blockers
CAR	Chimeric antigen receptor
CCL	C–C chemokine ligand
CCR	C–C motif chemokine receptor
cDCs	Conventional DCs
CVD	Cardiovascular disease
DCs	Dendritic cells
ECM	Excessive extracellular matrix
FSTL1	Follistatin-like protein 1

GARP	Glycoprotein A repetitions predominant
GPCMs	Gata6 + pericardial cavity macrophages
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IFN-γ	Interferon-γ
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
NETs	Neutrophil extracellular traps
pDCs	Plasmacytoid DCs
PDGF	Platelet-derived growth factor
PDGFR	PDGF-receptor
TGF-β	Transforming growth factor-β
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
TβRI	TGF-β type I receptor

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