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REVIEW

Immune Mechanisms in Myocardial Remodeling Following Myocardial Infarction: Focusing on Regulatory Networks of T Cell Responses

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Abstract: The pathological course of myocardial infarction (MI) entails a complex interplay between innate and adaptive immunity. Although innate immunity plays a dominant role in the tissue damage and clearance during the acute phase, recent studies have shown that T cells also play an important role in myocardial injury and remodeling. Advances in detection technologies have enabled the identification of several autoantigens and clarified the mechanistic roles of distinct T-cell subsets (such as regulatory T cells, helper T cells, cytotoxic T cells, and γδ T cells) during the remodeling phase. These T cell subsets are widely involved in myocardial inflammation, apoptosis and myocardial fibrosis, and play an important role in myocardial remodeling. This review synthesizes current progress on the repertoire of autoantigens recognized after MI, the mechanistic underpinnings of T-cell responses in myocardial remodeling, and emerging immunotherapeutic strategies aimed at mitigating adverse remodeling. Together, these insights provide a conceptual framework to guide future research and therapeutic development in this field.

Keywords: myocardial infarction, T lymphocytes, myocardial remodeling, autoantigen, myocardial inflammation

Introduction

Following the onset of myocardial infarction (MI), T lymphocytes contribute significantly to the repair of damaged cardiac tissue.[1] Following MI, dendritic cells (DCs) infiltrate the myocardium, take up cardiac self-antigens, and migrate to cardiac draining lymph nodes. There, they activate naive $CD4^+$ T cells via major histocompatibility complex class II (MHCII) and induce their differentiation toward regulatory T cells (Tregs) or T helper 17 cells (Th17).[2] Additionally, DCs can activate $CD8^+$ T cells via major histocompatibility complex class I (MHCI), thereby enhancing their cytotoxic effects and exacerbating myocardial immune injury.[3] Beyond DCs, monocytes/macrophages accumulating in the infarct region can also phagocytose cardiac self-antigens and present them to $CD4^+$ T cells to promote their activation.[4] Simultaneously, monocytes/macrophages secrete multiple cytokines, such as IL-6 and TNF-α, thereby modulating the local inflammatory microenvironment to influence T cell differentiation.[5] Neutrophils are the earliest innate immune cells recruited to ischemic myocardium after MI. They primarily drive local inflammation by releasing chemokines, matrix metalloproteinases, and various inflammatory mediators. Furthermore, some studies indicate that under specific conditions, neutrophils can also perform antigen-presentation-like functions, thereby enhancing T cell activation and differentiation.[6] Under the coordinated regulation of these innate immune cells, T cells differentiate into distinct functional subsets, each playing unique roles in regulating cardiac inflammation and facilitating tissue repair following MI.

Among them, Regulatory T cells (Tregs) play a pivotal role by directing regeneration programs that are specific to the heart.[7,8] Tregs are recruited to the infarcted area and inhibit inflammatory responses by promoting the secretion of anti-inflammatory factors such as interleukin-10 (IL-10) and transforming growth factor β (TGF-β), altering the phenotype of

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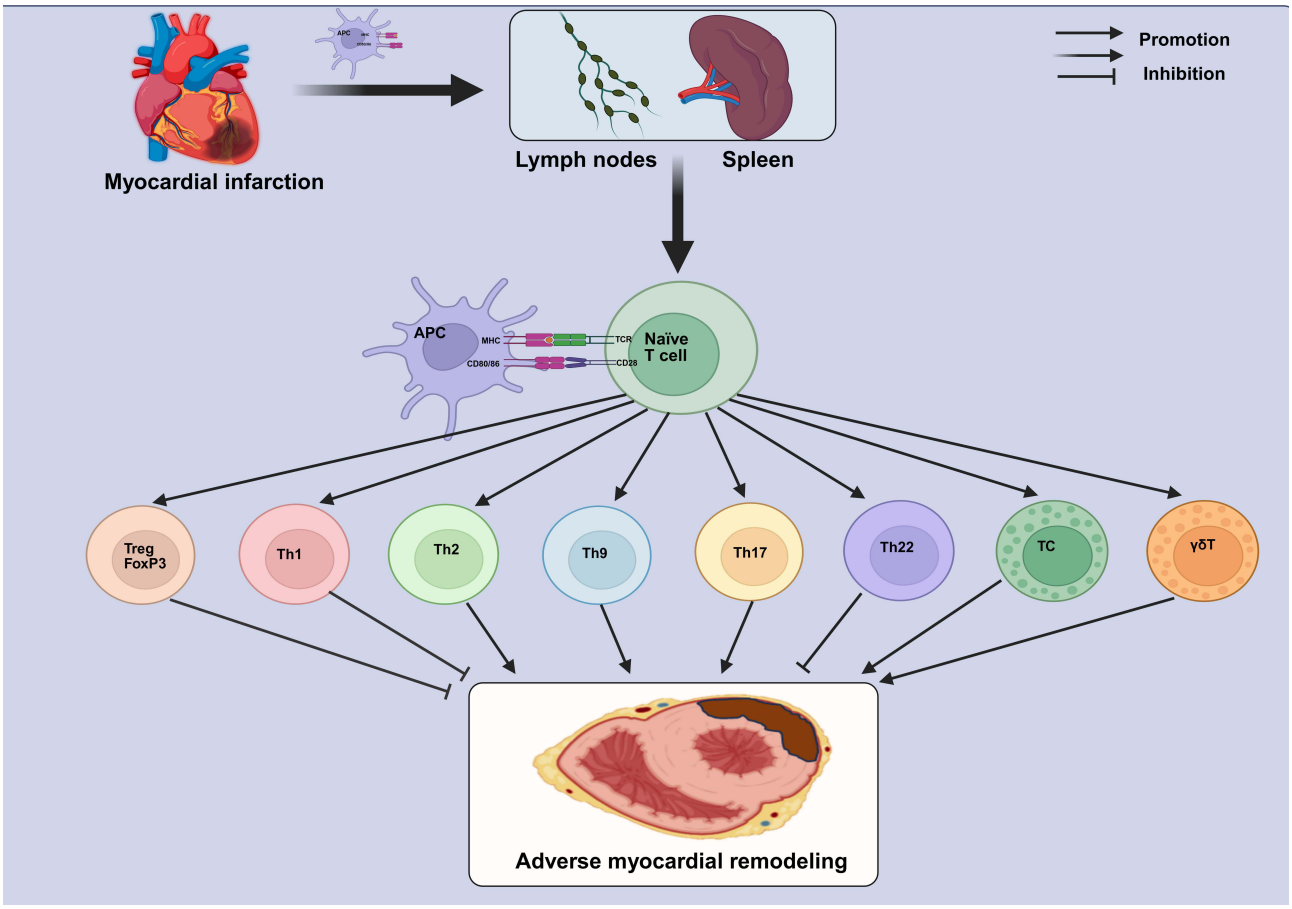
Graphical Abstract



macrophages, and alleviating myocardial fibrosis, thereby suppressing adverse ventricular remodeling and improving cardiac function.[9] Loss of Tregs exacerbates myocardial inflammation, collagen deposition, and ventricular dilatation, whereas adoptive Treg transfer ameliorates these pathological changes.[10] An appropriate T-cell response can drive the reparative fibrosis of the organ after mitosis, prompting the timely formation of dense and stable collagen scars in the infarcted area, while the non-infarcted area only shows mild compensatory hypertrophy. This maintains the stability of the left ventricular volume or promotes its contraction, thereby maintaining or restoring the ejection fraction. This is known as reparative remodeling.[11] If the T-cell activity remains persistently hyperactive, it may induce chronic inflammation in the non-infarcted area, cardiomyocyte hypertrophy and apoptosis, and excessive collagen deposition, leading to adverse remodeling and significantly increasing the risk of heart failure (HF).[12,13] For instance, it is observed that persistent Th cells (such as Th1, Th2, Th17) and Tregs infiltration are associated with HF after MI.[14] Moreover, cytotoxic $CD8^+$ T cells aggravate post-MI fibrosis by releasing granzyme B, which enhances myocardial inflammation and apoptosis.[15] Clinical studies have also demonstrated that reduced peripheral blood Treg ratios in HF patients correlate positively with increased all-cause mortality[16] and may serve as an independent predictor of rehospitalization.[17] Therefore, immunotherapies targeting adverse myocardial remodeling after MI, such as adoptive Treg transfer and chimeric antigen receptor T-cell (CAR-T) therapy, may help restore T-cell balance and promote cardiac repair following MI.

Although the current research results indicate that the imbalance of T-cell response may affect the severity of MI. However, previous summaries have failed to clearly delineate the role of T-cell responses in cardiac remodeling or to

identify the self-antigens that drive these immune reactions.[18] Therefore, a more comprehensive understanding of the self-associated antigens and T-cell epitopes after MI, the activation mechanism of T cells, and the role of T-cell responses in myocardial healing and remodeling is crucial for the development of targeted therapies aimed at regulating T-cell responses. This review highlights recent advances and aims to integrate and refine current knowledge on T lymphocytes–mediated immune responses after MI, their implications for cardiac remodeling, and their therapeutic potential.

Autoantigens and Epitopes Triggering T Cell Responses After MI

Disease-associated antigens refer to self-molecules that are aberrantly expressed under certain pathological conditions—such as autoimmunity, infection, chronic inflammation, or cancer—or that cross-react with self-proteins.[19] Epitopes are specific short peptides or structural motifs on antigens that are recognized and bound by the T cell receptor (TCR).[20] MI triggers the release of diverse self-antigens from necrotic cardiomyocytes. Local antigen-presenting cells (APCs), with DCs (mainly cDC1) being the most prominent, internalize and process these proteins. This processing leads to the surface display of antigenic peptides complexed with MHCII, enabling the activation of $CD4^+$ T cells through interactions with various resident and recruited immune cells, including DCs, macrophages, and B cells. This interaction drives their differentiation into distinct subsets, including Th1, Th17, or Treg, thereby eliciting divergent immune responses.[2] In addition to TCR recognition of self-antigen presented by MHCI, the complete activation and differentiation of $CD8^+$ T cells into cytotoxic lymphocytes (Tc) depend on co-stimulatory interactions (eg, CD80/86 with CD28) and local inflammatory cytokines such as Interleukin-2 (IL-2) and Interferon-gamma (IFN-γ), which collectively propel their functional maturation.[13] Collectively, this section delineates the myocardial self-antigens and epitopes that trigger T cell responses after MI, providing important clues for understanding the underlying immune mechanisms.

Although T cell responses are fundamentally antigen-specific, the exact cardiac targets that elicit these responses in MI patients are poorly defined. Research in this area remains remarkably scarce (Table 1 has summarized current findings). Evidence suggests that two peptides derived from the β_1-adrenergic receptor ($ADRB1_{167–181}$ and $ADRB1_{168–182}$) can be presented in the context of the MHCII allele HLA-DRB1*13, thereby eliciting IFN-γ–producing Th cell responses in MI patients.[21] Specifically, these peptide fragments, after being taken up by APCs, bind to TCR-β to trigger a cardiac-directed Th cell response in myocardial infarction patients. Furthermore, in animal models, α-myosin heavy chain (MYHCA) has been identified as the primary cardiac autoantigen implicated in post-MI $CD4^+$ T cell responses. The specific epitope $MYHCA_{614–629}$ activates Th cells, which then selectively home to the injured heart tissue. Intriguingly, over half of these cells express FOXP3, indicating potential in situ conversion into Tregs. These localized Th cells facilitate infarct healing by producing a spectrum of reparative molecules, including Csf1, Angptl2, Grn, Tgfb3, and Fgf2.[1] Further studies demonstrated that $CD4^+$ T cells specific for $MYHCA_{614–629}$ not only facilitate Treg expansion and migration but also suppress Th17-derived interleukin-17 (IL-17) production, thereby alleviating post-MI myocardial inflammation.[22] By contrast, when proinflammatory $Ly6C^{hi}$ monocytes dominate antigen presentation, myosin-specific $CD4^+$ T cells initiate pathological autoimmunity against the heart, leading to adverse ventricular remodeling and HF. Conversely, $Ly6C^{lo}$ monocytes direct $CD4^+$ T cells toward reparative functions within the infarct.[4] After MI occurs, cDC2 drives the proliferation and differentiation of autoreactive T cells into effector cells, while cDC1 drives the proliferation of cardiospecific MYHCA-Treg cells.[23]

In addition, MYHCA has also been identified as a target of Th1 cells. Sustained recognition of this antigen can provoke chronic lymphocytic infiltration and impair proper tissue repair within the infarcted myocardium.[24] Although

Table 1 Autoantigens and Epitopes Recognized by $CD4^+$ Cells After MI

Species	Disease	Autoantigen	Epitope (Peptide Segment)	The Types of T Cells	Ref.
Human	MI	ADRB1	$ADRB1_{167–182}$	$CD4^+$ T cell	[21]
Mice	MI	MYHCA	$MYHCA_{614–629}$	$CD4^+$ T cell	[1,22]
Mice	MI	α-MHC	–	$CD4^+$ T cell	[4]
Mice	MI	αMyHC	–	$CD4^+$ T cell	[2]
Mice	MI	αMyHC	–	$CD4^+$ T cell	[24]

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numerous studies have shown that $CD8^+$ T cells promote myocardial inflammation, adverse ventricular remodeling, and HF following MI,[15,25] the precise myocardial antigens and MHC-restricted epitopes recognized by these cells remain undefined. Recent investigations have identified MHC-restricted epitopes and associated cardiac antigens recognized by $CD8^+$ TCRs in myocarditis (MC), offering potential insights into the epitopes targeted following MI. α-Myosin has emerged as a key cardiac autoantigen in mice MC models, functioning as both an MHCI and MHCII restricted antigen. TCRs were shown to recognize $MYH6_{191–198}$ and $MYH6_{418–425}$ peptides,[26] while $MYHCA_{334–352}$ could be recognized by both $CD8^+$ and $CD4^+$ T cells.[27] A study of individuals with fulminant immune checkpoint inhibitor–induced myocarditis (ICI-MC) identified $MYH6_{443–451}$ as a TCR epitope.[26] Recently, a novel α-myosin–derived peptide, $MYHCA_{724–732}$, was characterized as an MHCI restricted $CD8^+$ T cell epitope. In C57BL/6 mice, this peptide effectively elicited a cardiac-specific immune response and induced IFN-γ secretion by $CD8^+$ T cells.[28] Complementary analyses of public datasets revealed conserved TCR motifs strongly associated with MI, HF, and ICI-MC. Significant myocardial inflammation also exists in the infarcted area after MI. Here, it is speculated that the epitopes recognized by CD8+T cells may also originate from MYHCA, and the peptides recognized by it may partially overlap with those of $CD4^+$ T cells. Figure 1 illustrates the role of $CD4^+$ and $CD8^+$ T cells in adverse myocardial remodeling following MI through the recognition of cardiac autoantigens.

While MYHCA and ADRB1 have been experimentally confirmed as $CD4^+$ T-cell autoantigens post-MI, with their epitopes presented via MHCII, their relevance to $CD8^+$ T cells remain unclear. Although MYHCA is a known target for cytotoxic T cells in myocarditis, its role in MI requires further validation. Thus, despite the established involvement of both T cell subsets in post-infarction immunity, delineating their precise antigenic targets continues to pose a significant

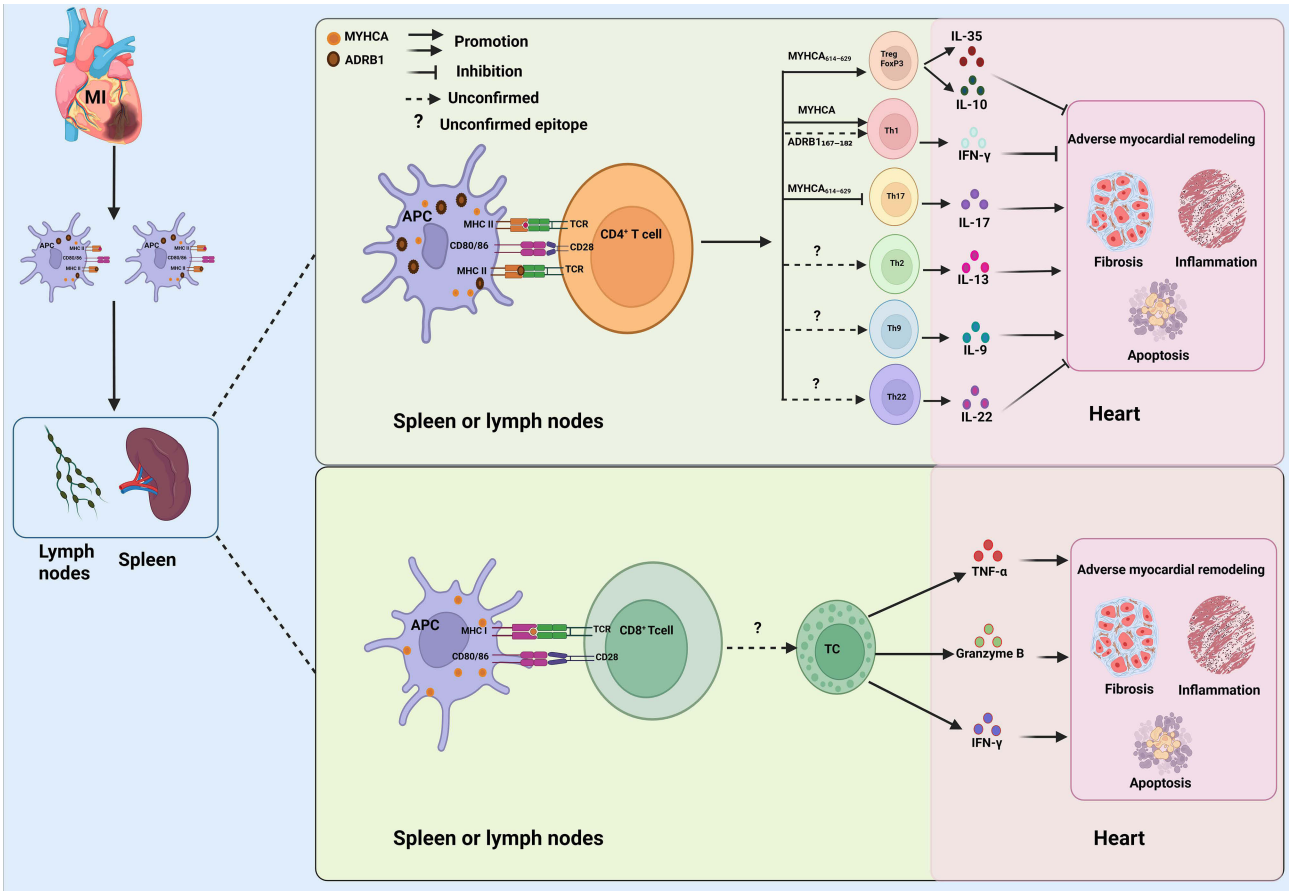

Figure 1 Autoantigen-driven T-cell responses and adverse myocardial remodeling after MI. Following MI, cardiac autoantigens are released and transported by APCs to peripheral lymph nodes and the spleen, where they are presented to $CD4^+$ and $CD8^+$ T cells. This process drives their differentiation into multiple subsets that participate in cardiac remodeling. The figure was constructed with BioRender (https://biorender.com).

challenge. Moving forward, elucidating the autoimmune landscape in MI will likely depend on combining cutting-edge methodologies—such as immunopeptidomics,[29] proteomic analyses,[30] and single-cell TCR sequencing[31,32] —with functional assays to definitively validate epitope specificity. Such efforts will be essential to delineate the complete repertoire of autoantigens and the dynamic process of T-cell epitope recognition, thereby advancing the development of targeted therapeutic strategies.

T Cell–Mediated Adaptive Immunity Contributes to Cardiac Remodeling After MI

Following MI, the resolution of local inflammation typically initiates a wound healing program that facilitates structural and functional recovery of the heart. Conversely, an extensive infarct or a dysfunctional repair process can trigger adverse remodeling, often culminating in HF.[33,34] The immunomodulatory roles of T-cell subsets in this context are complex. Although many reports attribute a protective function to $CD4^+$ T cells and a pathogenic one to $CD8^+$ T cells, contradictory evidence exists.[35] Consequently, clarifying the nuanced functions of individual T lymphocyte populations during post-infarction remodeling represents a critical research imperative.

Classification of T Cells

T cells originate in the bone marrow and subsequently migrate via the bloodstream to the thymus, where they undergo differentiation and maturation. Functionally, they are primarily classified into Th cells, Tregs, Tc and specialized subsets such as gammadelta (γδ) T cells and natural killer T (NKT) cells.[36–38] Th cells recognize antigens presented by MHCII molecules and initiate adaptive immune responses, orchestrating both cellular and humoral immunity.[39] After pathogens are cleared, a portion of T helper cells give rise to long-lived memory populations, which mount accelerated responses upon subsequent antigen encounter.[40] Meanwhile, Tregs dampen excessive immunity through cell-contact-dependent suppression, release of IL-10 and TGF-β, and IL-2 deprivation, which collectively uphold immune homeostasis and protect against autoimmune pathology.[41] Tc cells mediate precise cytotoxicity against target cells: upon recognition and binding of antigens presented by MHCI molecules on target cells, they release perforin, granzymes, and cytokines, which not only directly eliminate target cells but also activate and coordinate other immune effectors.[42] Some other special types of T cells, such as γδ T cells and NKT cells, are also involved in immune regulation.[43] T lymphocytes are broadly categorized into $CD4^+$ and $CD8^+$ subpopulations based on their surface marker expression. The $CD4^+$ lineage comprises Th cells, while $CD8^+$ identifies Tc cells. A critical $CD4^+$ subset is the Treg, which is defined by the expression of CD25 and the transcription factor Foxp3.[44–46] Additionally, certain specialized subsets, including γδ T cells and NKT cells, lack CD4 and CD8 expression. Following MI, the activation of different T cell subpopulations exhibits marked heterogeneity, finely regulated by damage-associated molecular patterns, the local cytokine milieu, and antigen presentation pathways. Elucidating the activation mechanisms of these T cell subsets in post-MI adaptive immunity is critical for understanding the immune regulatory network underlying cardiac remodeling.

The Role of Th Cells in Myocardial Remodeling After MI

$CD4^+$ T cell activation requires two primary signals from antigen-presenting cells: TCR recognition of MHCII-presented antigen and concurrent CD28 co-stimulation.[18] This activation licenses the T cells to then interpret polarizing cytokines (eg, IL-4, IL-12, IFN-γ), which dictate their functional specialization into distinct Th lineages. This "antigen–co-stimulation–cytokine" triad represents the fundamental mechanism directing Th cell lineage commitment.

Th1 Cell

Th1 cells represent a principal effector lineage within the $CD4^+$ T cell family, whose differentiation is instructed by antigens and polarizing cytokines like IL-12 and IFN-γ. Post-MI, both animal and human studies document a marked increase in systemic IL-12 levels.[47,48] This cytokine, chiefly secreted by activated macrophages and DCs, programs Th1 cells to produce a characteristic set of soluble mediators, including IFN-γ, TNF-α, and IL-2.[49,50] The sustained presence of this inflammatory milieu can exacerbate tissue damage. Mechanistically, IL-12 and IFN-γ initiate signaling cascades through STAT4 and STAT1, respectively, which converge to upregulate the lineage-defining transcription factor T-bet. As

the master regulator of Th1 commitment, T-bet reinforces the production of hallmark cytokines like IFN-γ while simultaneously repressing the genetic programs that guide Th2 and Th17 cell development.[49] Figure 2 illustrates the mechanism of action of Th cells in myocardial remodeling after MI.

Cardiac repair following MI is a complex process, in which Th1 cells predominantly participate during the inflammatory phase by clearing dead cells and extracellular matrix (ECM) debris. In mice, Th1 cells are the predominant infiltrating subset in the heart seven days post-MI.[51] This Th1-dominated infiltration is also seen in human subjects presenting with ischemic HF or acute myocardial infarction (AMI),[32] alongside heightened levels of the pro-inflammatory mediators IFN-γ and TNF-α.[52,53] Chemokines CXCL10 and CXCL12 promote Th1 recruitment via interaction with CXCR3, contributing to myocardial fibrosis in both MI and pressure overload–induced cardiac dysfunction.[54,55] IFN-γ–secreting Th1 cells play a key role in post-MI/reperfusion (MI/R) myocardial inflammation, apoptosis, and necrosis.[35] In mice MI models, cardiac IFN-γ levels remain elevated for up to one month post-infarction,[52] though reperfusion can reduce this duration.[53] Th1 polarization is driven by IL-12 signaling mediated via the macrophage surface pattern-recognition receptor Dectin-2, leading to robust IFN-γ release. By antagonizing the TGF-β–driven fibrotic program in cardiac fibroblasts (CF)—specifically the expression of α-smooth muscle actin (α-SMA), type I collagen (Col I), and type III collagen (Col III)—IFN-γ impedes their differentiation into myofibroblasts. This thereby blunts myofibroblast proliferation and migration in the injured area, increasing the likelihood of ventricular rupture.[56] Conversely, interleukin-23 (IL-23) can suppress Th1-derived IFN-γ, alleviating excessive post-MI inflammation.[57] IFN-γ also skews macrophages to an M1 state, potentially worsening cardiac inflammation and damage, with indirect consequences for remodeling.[58] Despite this, the direct involvement of Th1 cells in post-infarction maladaptation is not

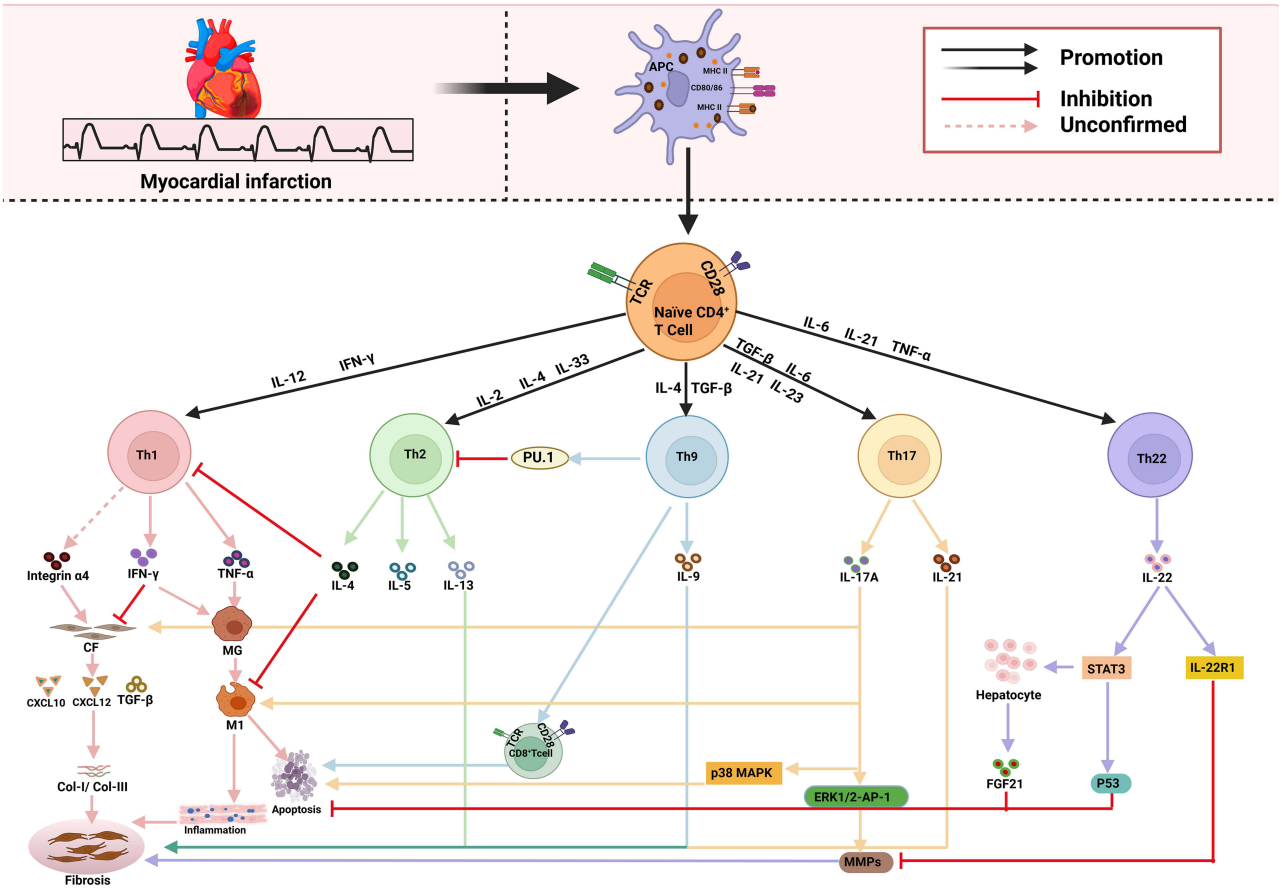

Figure 2 The mechanism of action of Th cells in myocardial remodeling after MI. Following MI, naïve $CD4^+$ T cells recognize cardiac-specific antigens presented by APCs and differentiate into distinct Th cell subsets under cytokine stimulation. These subsets participate in regulating myocardial remodeling by promoting or suppressing myocardial inflammation, apoptosis, and fibrosis. The figure was constructed with BioRender (https://biorender.com).

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well established. Research in a transverse aortic constriction (TAC)-induced HF model revealed that Th1 cells interact with cardiac fibroblasts through α4 integrin, enhancing TGF-β–mediated synthesis of profibrotic proteins (α-SMA, Col I, Col III) and driving fibrosis.[59] Co-culture of Th1 cells with primary CFs similarly revealed a pro-fibrotic effect.[60]

These findings suggest that post-MI Th1 cells may restrict ECM deposition within the infarct zone, limiting fibrosis. However, they also exacerbate cardiac inflammation and cardiomyocyte apoptosis, and excessive Th1 infiltration may contribute to functional deterioration and adverse remodeling. Future efforts should focus on delineating the precise role and operative mechanisms of Th1 cells in maladaptive cardiac remodeling following MI.

Th2 Cell

After the naïve $CD4^+$ T cells undergo the three signals of "antigen-co-stimulation-cytokine", if the microenvironment is dominated by IL-4 and factors such as IL-12 and IFN-γ are absent, they will differentiate towards Th2. IL-2 and IL-4 establish a feed-forward loop in which IL-2 upregulates the interleukin-4 receptor α chain via STAT5, and IL-4 induces GATA-binding protein 3 (GATA3) through STAT6, ultimately stabilizing the Th2 phenotype.[61] GATA3 drives Th2 differentiation by promoting the expression of Th2 signature cytokines, recruiting growth factor independent 1, and antagonizing the Th1 transcriptional program through interaction with T-bet.[49] Th2 cells exert their anti-inflammatory and reparative effects largely through cytokines like IL-4 and interleukin-13 (IL-13). This activity suppresses Th1 cells and pro-inflammatory macrophages, thereby limiting detrimental cytokine release and facilitating healing following an infarction.[62,63]

Notably, Th2-derived IL-13 acts as a key profibrotic mediator, implicated in fibrosis across multiple organs including the liver, lungs, and kidneys.[38] IL-33 can activate DCs and adipocytes in mice, promoting naïve T cell polarization toward a Th2 phenotype and directly enhancing IL-13 secretion by Th2 cells.[64,65] In a mice MI model, left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) significantly decreased 28 days post-infarction. A therapeutic strategy using chimeric stem cells for IL-33 delivery demonstrated efficacy in curbing inflammatory damage and shifting the cardiac macrophage equilibrium towards an M2-reparative state, concomitant with functional improvement.[66] This approach is complemented by evidence that targeted increase of IL-13 and IL-4 within the heart post-MI fosters a pro-repair environment, potentially via enhanced collagen deposition.[67] Additionally, Th2-derived IL-5 reinforces this reparative axis by expanding $CD206^+$ macrophages through IL-4/STAT6 pathway activation, which correlates with reduced infarct size.[68] Supporting this mechanism, a 15-year longitudinal study of 700 participants found that elevated Th2 cell frequency independently predicted a lower incidence of AMI in women, and IL-4 levels were inversely correlated with cardiovascular disease risk.[69] Together, this evidence establishes a cardioprotective function for Th2 cells and their cytokine products in the context of post-infarct healing.

However, excessive Th2 responses may also contribute to pathological scarring and fibrosis. In a murine MI model, seven days post-infarction, neither the key Th2 transcription factor GATA3 nor IL-4–secreting $CD4^+$ T cells were significantly elevated in the left ventricle.[70] By eight weeks of ischemia, mice developed HF characterized by predominant Th2 and Th17 infiltration, a decreased Th1/Th2 ratio, and concurrent increases in IL-4, IL-13, IL-5, IL-33, and TGF-β levels.[12] Sustained Th2 expansion may exacerbate local injury through excessive release of profibrotic mediators.[71] A 15-year follow-up study previously showed that an increase in the count of Th2 cells in peripheral blood was associated with a reduced risk of cardiovascular events, and an increase in the number of Th2 cells was also independently associated with a decreased risk of acute MI in women.[69] In conclusion, although Th2 inhibits inflammation and promotes fibrous scar formation in the acute phase to prevent cardiac rupture, its long-term excessive activation may be involved in HF and adverse remodeling. In the future, it is necessary to further clarify the spatiotemporal dynamics and action boundaries of the Th2 response in ventricular remodeling after MI in order to better understand its pathological mechanism.

Th9 Cell

Th9 cells represent a distinct Th subset, characterized by high expression of the transcription factors PU.1 and Foxo1 and by robust secretion of interleukin-9 (IL-9).[72] Interestingly, PU.1 both inhibits GATA3 to suppress Th2-type cytokine production and drives Th2 cells toward Th9 transdifferentiation, inducing IL-9 production and amplifying immune responses via IL-9–mediated effects.[73,74] Th9 differentiation is co-regulated by IL-4 and TGF-β, and this subset has been

implicated in various immune-related disorders, including systemic lupus erythematosus and allergic inflammation.[75] However, its role in MI remains poorly understood. Clinical studies indicate that patients with AMI exhibit elevated proportions of peripheral Th9 cells, increased plasma IL-9 levels, and higher PU.1 mRNA expression, while IL-9 enhances $CD8^+$ T cell cytotoxicity.[76,77] In murine models of MI/reperfusion (MI/R), cardiac IL-9 expression is significantly upregulated on days 7 and 14 post-infarction before gradually declining.[53] In patients with ischemic cardiomyopathy (ICM) and non-ischemic chronic HF, the plasma IL-9 level is also elevated, and the IL-9 level in ICM patients is negatively correlated with LVEF.[78] In the mice model of HF induced by isoproterenol, the levels of IL-9 in serum and myocardial tissue increased simultaneously. Exogenous administration of recombinant IL-9 could significantly aggravate the deterioration of cardiac function, myocardial hypertrophy and collagen deposition; conversely, the application of anti-IL-9 neutralizing antibodies could significantly improve cardiac dysfunction and alleviate myocardial hypertrophy and fibrosis.[79] Collectively, these findings support a potential pathogenic role of IL-9 in post-MI cardiac remodeling, although the precise cellular source remains to be elucidated. Future studies are needed to dissect the signaling pathways mediating IL-9 effects in cardiac remodeling and to evaluate its therapeutic potential.

Th17 Cell

Th17 cells constitute a distinct Th subset whose differentiation, function, and roles in immune responses have been extensively studied. Their development is tightly regulated by multiple signals: TGF-β, interleukin-6 (IL-6), and IL-21 cooperatively initiate differentiation; IL-23 maintains expansion and phenotypic stability; and key transcription factors including STAT3, RORγt, and RORα drive terminal Th17 differentiation.[80] The core effector molecules of Th17 cells—IL-17A, IL-17F, and IL-21—mediate diverse functions in immunity, tissue homeostasis, and pathology.[81] Interestingly, IL-17 acts in an autocrine manner to promote its own T-cell lineage.[82] It can also induce factors such as TNF-α, IL-1β and IL-6 to trigger a strong inflammatory response, thereby exacerbating tissue damage.[83] Th17 cells and IL-17 are closely linked to MI.[84] An immunological shift toward Th17 prominence is observed in AMI patients, characterized by a higher peripheral Th17/Th1 ratio and augmented expression of critical components such as IL-17, IL-6, IL-23, and the lineage-defining transcription factor RORγt.[85,86] Following percutaneous coronary intervention (PCI), the Th17/Treg ratio decreases, and a lower ratio is associated with improved quality of life.[87] In murine models, eight weeks post-MI, HF is observed alongside pronounced Th17 infiltration in the infarct zone, accompanied by a distinct Th17/Treg imbalance.[12] In rats, IL-6, IL-23, TGF-β, and IL-17A expression in the infarcted myocardium are concomitantly upregulated one week post-MI,[88] suggesting early activation of this inflammatory axis.

In TAC rat models, adoptively transferred Th17 cells activate the IL-17/ERK1/2-AP-1 signaling pathway, upregulate lysyl oxidase expression, enhance MMP-2/9 activity, and increase collagen I/III deposition, thereby exacerbating myocardial fibrosis.[89] IL-17 not only induces pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α to amplify inflammation,[90] but also promotes TGF-β1 secretion, driving CF differentiation into myofibroblasts and further aggravating adverse myocardial remodeling.[91] In MI mice, exogenous IL-17A induces elevated MMP-2 expression, cardiac fibrosis, and functional decline, all of which are mitigated by IL-17A knockout. Mechanistically, IL-17A initiates cardiomyocyte apoptosis through the p38 MAPK–p53–Bax pathway, a key driver of adverse remodeling.[92] Concurrently, it perpetuates a pro-inflammatory state by facilitating macrophage infiltration and the release of soluble mediators, leading to further worsening of ventricular architecture.[93] In conclusion, these findings indicate that IL-17 accelerates ventricular remodeling by amplifying inflammation, inducing cardiomyocyte apoptosis, and promoting myocardial fibrosis.

IL-21 may also contribute to myocardial fibrosis, ventricular remodeling, and HF progression.[94,95] However, IL-21 is not exclusively secreted by Th17 cells; NKT cells, $CD8^+$ T cells, and γδ T cells can also produce this cytokine. Following MI, these cells may infiltrate the infarcted myocardium, complicating identification of the predominant local IL-21 source. Future studies are required to elucidate the cellular origin and precise functional roles of IL-21 in cardiac remodeling.

Th22 Cells

Th22 cells are mainly characterized by secreting interleukin-22 (IL-22) but not IL-17 and IFN-γ.[96] Their differentiation is orchestrated by cytokines such as IL-6, TNF-α, and IL-21, in concert with transcription factors including the aryl

hydrocarbon receptor. Upon binding to IL-22 receptor subunit 1 (IL-22R1) expressed on epithelial cells, IL-22 maintains barrier integrity, suppresses inflammation, and promotes tissue repair.[97] Clinical studies indicated that patients with acute coronary syndrome displayed elevated proportions of circulating Th22 cells, higher AHR expression, and increased IL-22 levels compared with individuals with stable angina.[77] After receiving PCI treatment, the levels of IL-22 in AMI patients decreased significantly.[98] Insights from a murine MI model reveal that subcutaneous delivery of IL-22 over 7 days effectively limited infarct size, decreased peri-infarct collagen deposition, and promoted functional recovery. This protective effect was mediated by hepatocyte-driven STAT3 activation and subsequent induction of fibroblast growth factor 21.[99] In vitro, IL-22 was shown to counteract angiotensin II (AngII)-induced fibroblast-to-myofibroblast transition by downregulating α-SMA, type I/III collagen, and the glycolytic enzyme PKM2, thereby reducing lactate production. Activation of the JNK/PKM2 pathway further suppressed aerobic glycolysis and mitigated fibrosis.[100]

In MI rat models, IL-22/IL-22R1 signaling inhibited MMP-9 expression, attenuated left ventricular collagen accumulation, reduced cardiomyocyte apoptosis, and lowered inflammatory cytokine levels (IL-1β, IL-6, IFN-γ, TNF-α) within the infarcted myocardium. Hypoxia-inducible factor 1α was found to amplify reparative signaling through the IL-22/IL-22R1/Bmi1 axis, leading to stromal cell-derived factor-1 upregulation.[101] In mice MI/R model, IL-22 directly bound to IL-22R1 on cardiomyocytes and activated STAT3, which suppressed p53 expression and conferred cytoprotection. Moreover, IL-22 enhanced superoxide dismutase activity, stabilized mitochondrial membrane potential, and inhibited ROS generation and cytochrome c release, thereby attenuating I/R injury.[102] Clinical data further demonstrate that PCI is associated with increased Ang II and concomitant reduction of IL-22 levels,[103] suggesting that exogenous IL-22 supplementation may hold therapeutic promise. Collectively, Th22-derived IL-22 exerts cardioprotective effects against adverse remodeling after MI, yet its safety and efficacy in clinical contexts warrant further investigation.

The Role of Tregs in Myocardial Remodeling After MI

Tregs are pivotal mediators of immune homeostasis and peripheral tolerance.[104] Treg differentiation is driven by environmental cues (including TCR/CD28 signaling and antigen exposure), pivotal transcription factors like Foxp3 and STAT5, and cytokines such as TGF-β and IL-2.[41,105] In the post-MI context, Tregs suppress inflammatory responses and aid in repair and remodeling, with IL-10, IL-35, and TGF-β identified as their primary functional mediators.[106,107]

Accumulating evidence highlights Tregs as central contributors to myocardial protection and fibrosis regulation after MI.[108–110] So how can it be recruited and play a protective role? Studies have shown that C-C chemokine ligand 17 (CCL17) and CCL22can activate G protein-coupled C-C chemokine receptor type 4 (CCR4) to influence the recruitment of Tregs.[111–113] In murine I/R models, CCL17 selectively triggered Ca^{2+} signaling, whereas CCL22 engaged beta-arrestin (ARRB) and cooperated with Ca^{2+} signals to enhance chemotaxis. Competitive inhibition of ARRB signaling by CCL17 impaired Treg recruitment, attenuated macrophage-driven inflammation, and ameliorated adverse left ventricular remodeling.[108] Following MI, cardiac Tregs peaked at day 7 and persisted for at least 28 days, while in I/R settings their numbers peaked at day 3 and declined by day 7. Parabiosis experiments demonstrated that cardiac Tregs are predominantly recruited from the circulation, with IL-33/ST2 signaling promoting their expansion. CFs secreted a large amount of IL-33, which drove proliferation of $Ki67^{+}CD4^{+}Foxp3^{+}$ and $ST2^{+}CD4^{+}Foxp3^{+}$Tregs and enhanced expression of secreted protein acidic and rich in cysteine (SPARC), thereby accelerating collagen maturation and scar stabilization. IL-33 treatment upregulated SPARC in cardiac Tregs, reinforced collagen deposition, and prevented myocardial rupture.[114] Furthermore, The TGF-β secreted by Treg also promotes collagen deposition, which is beneficial for myocardial fibrosis and scar formation.[115] This suggests a bifurcated function for Treg cells in the orchestration of myocardial fibrosis.

Tregs also shape macrophage polarization: at day 7 post-MI in mice, Tregs promoted monocyte-to-M2 transition, upregulated Arg1, TGF-β1, IL-13, and IL-10, and facilitated myofibroblast activation. After the depletion of Tregs, the MI area in mice increased, cardiac function deteriorated, and mononuclear macrophages transformed to the M1 phenotype, but it did not directly affect collagen renewal and scar formation.[115] Adoptive transfer of Tregs ameliorated cardiomyocyte death and fibrosis, likely through suppression of proinflammatory $Ly6C^{Hi}$ $CCR2^{+}$ monocytes/macrophages and induction of nidogen-1 and IL-10, which in turn promoted M2 macrophage expansion.[110] Notably, amphiregulin (AREG)-expressing Tregs infiltrated infarcted myocardium at day 7, and AREG overexpression enhanced neovascularization via FoxM1

activation.[116] Seven days post-MI in mice, cardiac-infiltrating Tregs exhibited high surface expression of CD73 ($CD4^+CD73^+Foxp3^+$). These $CD73^+$ Tregs physically engaged $CD4^+Foxp3^-$ effector T cells (Teff), thereby suppressing Teff secretion of IL-1β, TNF-α, IFN-γ and IL-17 and markedly attenuating inflammatory injury.[117] In MI patients, CD69 expression marked cardioprotective Tregs and correlated with reduced HF readmission risk; mechanistically, $CD69^+$ Tregs limited γδ T cell–derived IL-17 via a CD39-dependent pathway.[118] Additionally, Tregs curb adverse ventricular remodeling by blocking neutrophil infiltration, attenuating pro-inflammatory cytokine release, and blunting Tc.[10] They also indirectly modulate cardiac remodeling via activation of the ERK/Akt signaling axis, thereby inhibiting cardiomyocyte apoptosis.[119] After the adoptive transfer of transgenic T-cell receptors-induced Treg, it can inhibit the inflammatory signals mediated by IL-17 and alleviate the inflammatory infiltration and damage in the hearts of mice with MI.[22]

Collectively, Tregs exert multifaceted protection against adverse remodeling by limiting inflammation, apoptosis, and fibrosis, while promoting angiogenesis. However, the fine balance between its fibrogenic and anti-fibrotic actions remains to be fully elucidated; future studies must further clarify this mechanism so as to provide molecular targets for novel anti-remodeling strategies. Figure 3 illustrates the mechanism of action of Tregs in myocardial remodeling after MI.

Other Types of T Cell Subsets

A distinct subset of T lymphocytes, γδ T cells express a TCR formed by γ and δ polypeptide chains. They can directly recognize various non-peptide antigens without relying on MHC molecules.[120] In mice MI, γδ T cells infiltrated the myocardium on the 7th day. Meanwhile, IL-17A in the circulating blood significantly increased, and IL-17A mainly originated from γδ T rather than Th17 cells.[118] These γδ T cells promote cardiomyocyte apoptosis through the NKG2D/

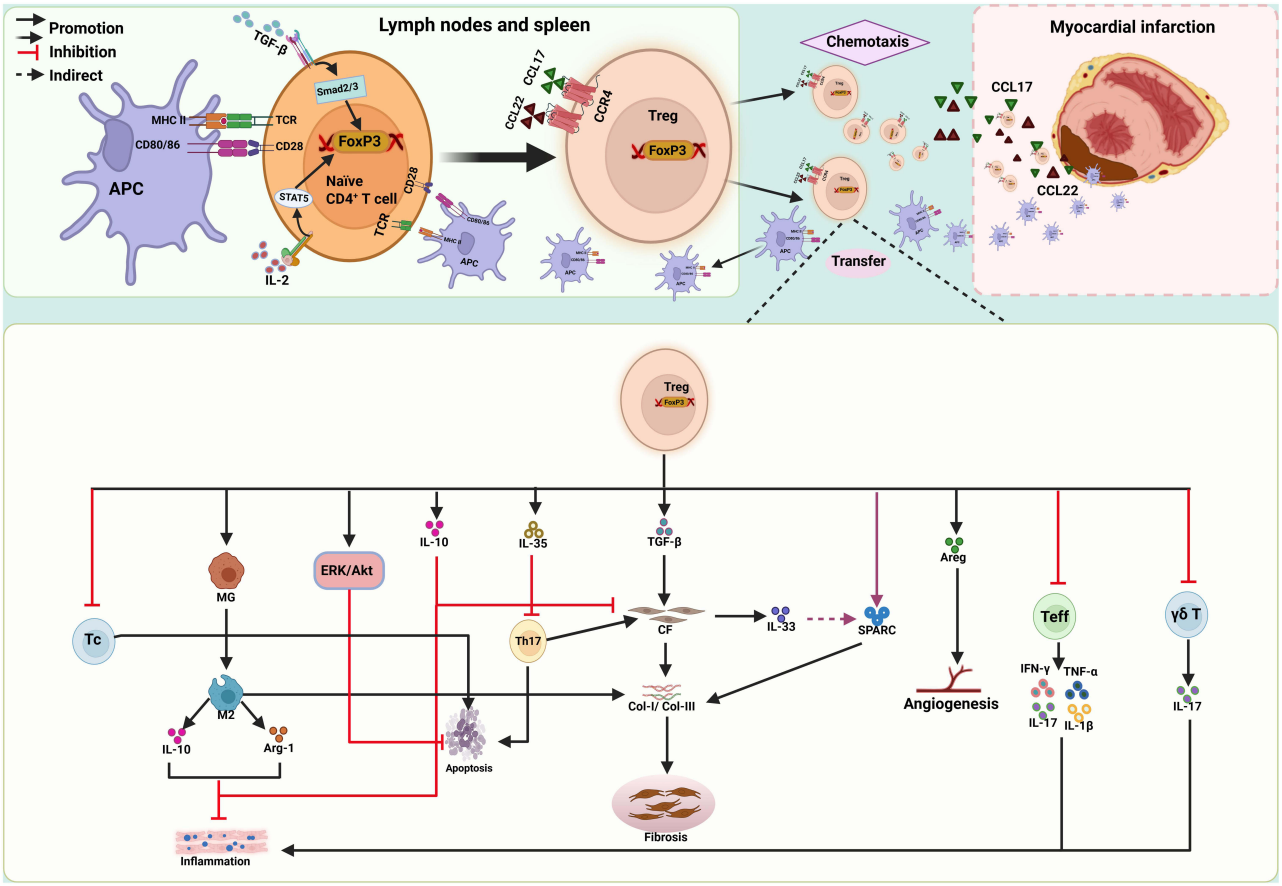

Figure 3 The mechanism of action of Tregs in myocardial remodeling after MI. Following MI, naïve $CD4^+$ T cells recognize cardiac-specific antigens presented by APCs and differentiate into Tregs ($FoxP3^+$) under cytokine stimulation. These Tregs are recruited to the infarcted region, where they modulate cardiac remodeling by suppressing myocardial inflammation and apoptosis while promoting fibrosis and neovascularization. The figure was constructed with BioRender (https://biorender.com).

NKG2DL pathway,[121] and by secreting IL-17A, they recruit neutrophils and monocytes, amplify proinflammatory cytokine production, and drive fibroblast proliferation and profibrotic gene expression.[93] Thus, γδ T cells appear to aggravate adverse remodeling following MI.

NKT cells are a unique subpopulation of T cells, characterized by the co-expression of NK receptors and unaltered TCR. Significant activation of NKT cells was found in the peripheral blood of AMI patients.[122] In mice, NKT cell numbers increased by day 3 post-MI, peaked at day 7, and showed distinct kinetics under I/R conditions, with an earlier day-3 peak followed by rapid decline.[70] Pharmacological activation of NKT cells by α-galactosylceramide attenuated left ventricular dilatation and reduced mortality in I/R models,[123] with IL-10 implicated as a key mediator of this protective effect.[124] Nevertheless, the contribution of NKT cells to the remodeling process following MI is yet to be fully elucidated, warranting further mechanistic investigation.

The Role of Tc Cells in Myocardial Remodeling After MI

Tc cells are defined by expression of CD3, CD8, and CD44, and mediate cytolysis of antigen-bearing target cells via perforin, granzymes, and Fas signaling. In murine MI, $CD8^+$ T cells infiltrated the myocardium within 24 h, persisted for two weeks, and peaked at day 7.[70] Consistently, AMI patients showed an expansion of circulating $CD8^+$ T cells, which demonstrated heightened production of IFN-γ, TNF-α, perforin, and granzyme B, reflecting enhanced cytotoxic potential.[76] This enhanced activity may involve MMP-2–mediated shedding of mCD100 from $CD8^+$ T cells.[125] After stimulating MI mice with LPS, it was found that Tc cells labeled with CD3, CD8, CD44 and CD27 were the main CD8 +T cell subsets in the heart.[126] The observation that $CD8^+$ T cell numbers drop precipitously within 90 minutes of PCI in AMI patients provided clinical evidence suggesting a significant involvement of this lymphocyte subset in post-infarction myocardial remodeling.[127] Mechanistic studies underscore the pathogenic role of Tc cells: in mice, $CD8^+$ T cell infiltration at day 1 post-MI peaked by day 3, coinciding with granzyme B upregulation. Depletion of $CD8^+$ T cells dampened pro-inflammatory cytokine and MMP-9 production, improved left ventricular contractility, attenuated collagen synthesis, and limited fibrosis.[15] Similar results were validated in porcine and human studies, implicating granzyme B–dependent $CD8^+$ T cell activity in driving inflammation, fibrosis, and pathological remodeling. Importantly, $CD8^+$ T cell depletion improved cardiac function and prognosis.[15] By contrast, one study reported that $CD8^+$ T cells did not exacerbate I/R injury in mice,[35] although permanent MI models were not evaluated. Taken together, Tc cells emerge as key mediators of adverse remodeling after MI, and their inhibition may represent a promising therapeutic strategy. Further research is required to delineate their precise contributions across different MI models. Figure 4 illustrates the mechanism of action of Tc cells in myocardial remodeling after MI.

Immunotherapies Targeting Adverse Cardiac Remodeling After MI

Adverse ventricular remodeling is a major determinant of cardiac recovery and long-term prognosis after MI. This process involves a complex interplay of inflammation, apoptosis, fibrosis, and angiogenesis, with T cell responses emerging as pivotal regulators. Beyond orchestrating inflammatory cascades, T cells modulate the activity of macrophages, CFs, and cardiomyocytes, thereby shaping both tissue repair and fibrotic remodeling. In recent years, two therapeutic strategies have attracted particular attention: CAR-T therapy and approaches aimed at promoting Treg differentiation to enhance cardiac repair.[10,128] Table 2 has summarized CAR-T and treatments that promote Treg differentiation.

CAR-T therapy employs genetically engineered T cells capable of specifically recognizing and eliminating target cells, a strategy that has already transformed cancer therapy.[133] Fibrosis represents a central component of post-MI remodeling and a key driver of HF progression. Following MI, immune cells interact with cardiomyocytes, endothelial cells, and CFs to amplify inflammation and activate CFs, promoting extracellular matrix deposition and scar formation. Targeting activated CFs through CAR-T cells directed against fibroblast activation protein (FAP) has been shown to alleviate fibrosis and improve cardiac function.[134] FAP, a cell-surface glycoprotein, is selectively expressed on activated CFs in the infarcted heart, but is absent in healthy myocardium of both humans and mice.[135] Accordingly, FAP-targeted CAR-T cells ameliorate cardiac fibrosis, as demonstrated in a murine hypertension–HF model driven by combined AngII and phenoxyethanol (AngII/PE) infusion.[129] To evaluate the therapeutic potential of FAP-targeting CAR-T cells, a mice model of cardiac fibrosis was first established via AngII/PE infusion. After one week, C57BL/6 mice developed evident

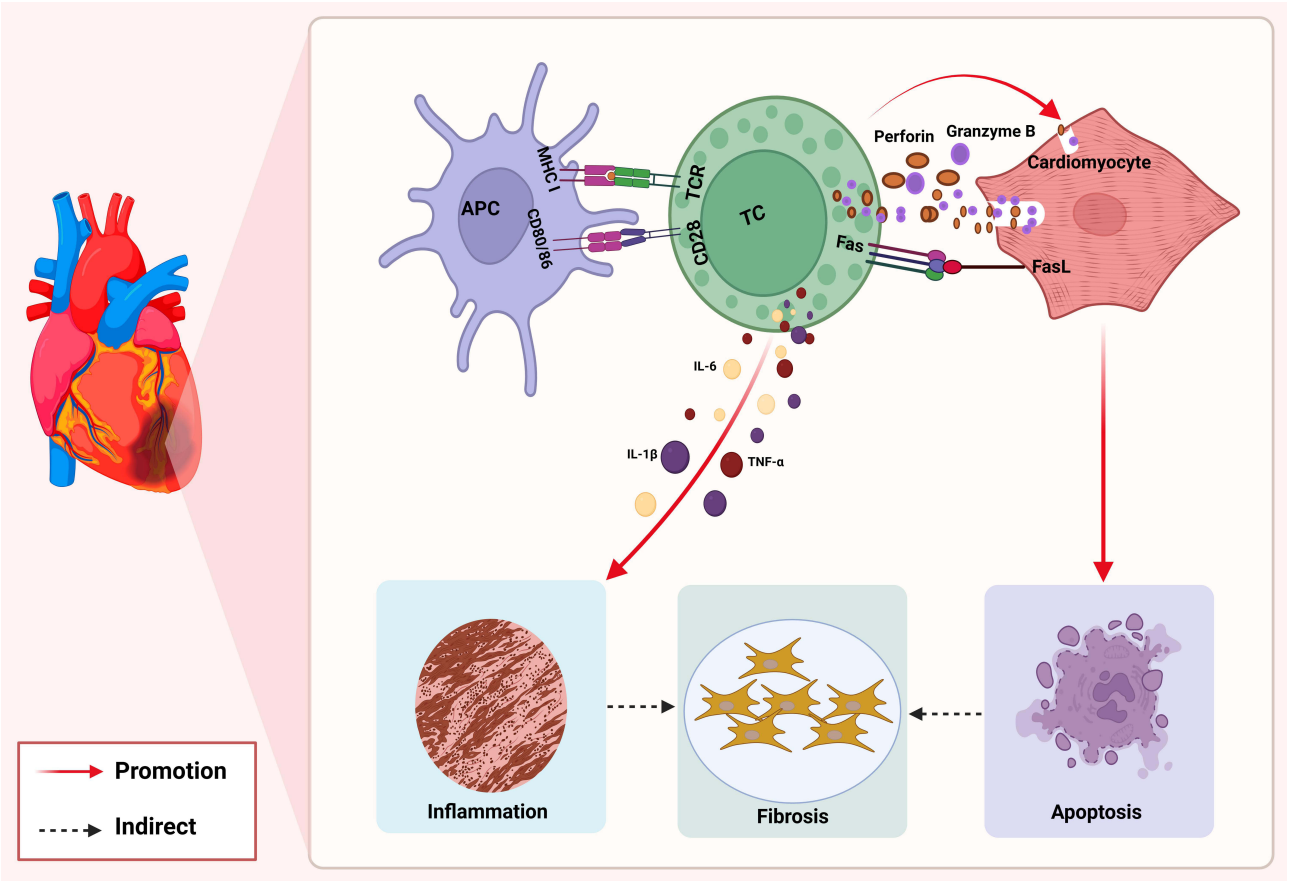

Figure 4 The mechanism of action of Tc cells in myocardial remodeling after MI. Upon recognition of cardiac-specific antigens presented by APCs, Tc cells become activated and subsequently release an array of pro-inflammatory cytokines and cytotoxic granule proteins, thereby amplifying myocardial inflammation, apoptosis, and fibrosis to modulate post-infarct cardiac remodeling. The figure was constructed with BioRender (https://biorender.com).

cardiac fibrosis alongside a marked expansion of FAP^+ CFs. Upon administration, the FAP CAR-T cells rapidly homed to the heart and engaged their targets within 24 hours. This intervention led to a progressive resolution of fibrosis, as quantified by Picro-Sirius Red staining, which showed substantial regression from the 4th to the 8th week. Furthermore, a comprehensive safety assessment at the 12-week mark, which included the evaluation of 84 cardiotoxicity-related and 1659 inflammation/immunity-related genes, revealed no significant evidence of treatment-related toxicity.[129] However, given that CF activation is essential for wound healing across multiple tissues, the long persistence of antifibrotic CAR-T cells—ranging from months to years—raises concerns regarding potential interference with future reparative processes.[136] To address this, Rurik et al developed a transient CAR-T platform using nucleoside-modified mRNA encapsulated in CD5-targeted lipid nanoparticles (CD5/LNP-FAPCAR). Upon systemic administration, this approach generated short-lived $FAPCAR^+$ T cells in vivo, alleviating fibrosis without causing off-target organ damage.[130] Nevertheless, several challenges remain. In oncology, CAR-T therapy has been associated with serious cardiovascular adverse events, including HF, cardiogenic shock, and MI, with increased mortality among affected patients.[137] To date, no dedicated studies have tested CAR-T therapy for post-MI remodeling. While CAR-T–based antifibrotic strategies represent a promising frontier, their clinical translation will require careful optimization and rigorous safety evaluation. Recently, researchers at Nanjing University in China utilized the specific antigen of the $CD248^+$ fibroblast-like subpopulation (F-Act) to construct biologically controllable BBIR-T cells (biotin-binding immunoreceptor T cells). Following tail vein injection on days 14, 17, and 20 post-MI in mice, significant reductions in myocardial collagen area and marked improvements in cardiac function were observed by day 28, with sustained efficacy up to 3 months.[138] While CAR-T strategies show great promise for treating cardiac fibrosis after MI, optimization of delivery regimens and long-term safety require further validation.

Table 2 CAR-T Cell Therapy and Treg Induction Strategies in Adverse Myocardial Remodeling

Animal Disease Models	Treatment Methods	Target	Main Effect	Adverse Reactions	Ref.
Hypertension with HF (AngII/PE-Induced)	Intravenous injection of FAP CAR-T cells	FAP^+CF	Increase LVFS. Reduce MV E and left ventricular fibrosis.	No cardiac toxicity or abnormal fibrosis in other tissues was observed 4 weeks after FAP CAR-T treatment.	[129]
Hypertension with HF (AngII/PE-Induced)	Intravenous injection of CD5/LNP-FAPCAR	FAP^+CF	Reduce E/e′, left ventricular fibrosis, and left ventricular end-diastolic and end-systolic volumes. Increase LVEF.	No histological changes were observed in non-cardiac organs 2 weeks after CD5/LNP-FAPCAR treatment.	[130]
MI/R	Intravenous injection of CDC-EV-BCYRN1	Treg	Reduce MI area and plasma cTnI levels; Increase Treg numbers in the heart and improve LVEF.	Not described.	[131]
MI (Permanent)	Injection of MTK-TK drug microgel system into the MI area	Treg	Increase the number of Tregs in the heart, LVEF, LVFS, left ventricular wall thickness, and vascular density. Reduce left ventricular fibrosis, LVESV.	Not described.	[132]
MI (Permanent)	Pericardial cavity injection of MSC-exosomes	Treg	Increased the number of Tregs in the heart, left ventricular wall thickness, type III collagen, and LVEF. Reduced MI area, type I collagen, LVESV, and LVEDV.	Not described.	[109]

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Tregs hold well-documented cardioprotective potential in MI Tregs.[139] By suppressing excessive inflammation, increasing anti-inflammatory cytokine release, and promoting monocyte/macrophage polarization toward an M2 phenotype, Tregs reduce cardiomyocyte apoptosis and fibrosis, thereby preserving left ventricular function.[10,110,115] Early studies have demonstrated that enhancing Treg recruitment to the myocardium suppresses inflammatory responses following MI/R in mice, preventing excessive extracellular matrix degradation and mitigating adverse remodeling. For instance, this protective effect can be achieved by enhancing CC chemokine receptor 5 signaling.[140] Subsequent studies further employed exogenous Treg infusion (eg, via tail vein injection), significantly improving myocardial fibrosis and cardiac function after MI.[110,141] However, how to efficiently promote Treg differentiation and enhance their infiltration efficiency in cardiac tissue remains a core issue in current research.

Current research is therefore focused on strategies to enhance Treg differentiation and activity. Several clinically translatable approaches have been reported. Cardiac-derived cell extracellular vesicles (CDC-EVs), enriched in the long noncoding RNA BCYRN1, act as a "miRNA sponge" to promote Treg proliferation, CCR6-dependent migration, and IL-10 production. In ischemia–reperfusion models, CDC-EVs reduced infarct size and improved cardiac function, highlighting EV/lncRNA-based Treg modulation as a feasible therapeutic strategy.[131] Advances in biomaterials and delivery methods also enable fine-tuning of the local immune microenvironment. For example, intramyocardial injection of MTK-TK-loaded drug microgels converted pro-inflammatory Th17 cells into Tregs, while simultaneously scavenging reactive oxygen species and releasing therapeutic agents to suppress early inflammation. This intervention reduced apoptosis and fibrosis while preserving cardiac function.[132] In addition, mesenchymal stem cell-derived exosomes administered intrapericardially activated the APC-Foxo3 signaling pathway in mediastinal lymph nodes, creating a niche favorable for Treg differentiation. This promoted Treg expansion within the heart, facilitated inflammation resolution, and enhanced tissue repair.[109] Recent research confirms that CAR-Treg targeting FAP can precisely homing to the infarct area following a single tail vein injection on day 3 after MI. Through an IL-10-dependent mechanism, they significantly alleviate fibrosis and inflammatory responses,[142] fully demonstrating the immense therapeutic potential of Treg in cardiac repair.

Additionally, administration of low-dose IL-2/anti-IL-2 complexes during the acute phase of mice MI (24 h–7 d) significantly increased myocardial Treg infiltration at 14 days, suppressed M1 macrophage polarization, reduced collagen deposition by approximately 25%, and improved cardiac function.[143] This finding aligns with results showing cardiac protective effects observed 4 weeks after exogenous Treg infusion within 2 hours post-MI.[144] Patients clinically diagnosed with non-ST-segment elevation MI received low-dose IL-2 therapy for 5 consecutive days within 8 days of enrollment. This significantly expanded the proportion of peripheral blood Tregs, which persisted for at least 12 weeks without major adverse events.[145] However, this study did not evaluate cardiac function changes. Animal studies further demonstrated that administering CD8 monoclonal antibodies to deplete $CD8^+$ T cells within 1 hour post-MI reduced myocardial fibrosis and improved cardiac function at 21 days.[15] However, functional $CD8^+$ T cell depletion, while reducing long-term fibrosis, delayed necrotic tissue clearance and increased acute cardiac rupture risk.[25] In summary, increasing Treg during the acute phase of MI has been demonstrated to exert clear cardioprotective effects; whereas the benefits and drawbacks of $CD8^+$ T cell intervention vary depending on the temporal window and pathological stage, requiring systematic evaluation. Future research should further elucidate the precise balanced regulatory strategies and therapeutic value targeting distinct T cell subsets at different time points.

Despite these encouraging results in rodent models, translation to clinical settings remains limited by uncertainties regarding safety, dosing, and delivery routes. Intramyocardial or intrapericardial injection methods, while effective experimentally, are not yet optimized for human use. Future efforts should prioritize the development of clinically viable delivery systems and rigorous testing of long-term safety, laying the foundation for Treg-based immunotherapies in post-MI remodeling.

Conclusion

The immunologic events after MI involve a cascade of tightly coordinated steps: the presentation of cardiac self-antigens, the subsequent activation and functional specialization of various T-cell populations, and the complex interplay of their cytokine and signaling networks. Among cardiac antigens, MYHCA stands out as a central player: it can drive protective Treg responses under certain contexts, yet in other settings, it may provoke pathogenic $CD8^+$ T-cell responses, depending

critically on the local immune microenvironment. $CD4^+$ T cells display dual functions in post-MI remodeling, with Tregs exerting predominantly cardioprotective effects, while Th subsets and cytotoxic $CD8^+$ T cells largely contribute to adverse remodeling.

Despite significant progress in current research, the precise regulatory networks governing T-cell responses after MI, the systematic identification of T-cell epitopes, and how to precisely balance protective and pathogenic immune responses remain core scientific questions that urgently need to be addressed in this field. Currently, several potential immunomodulatory strategies are in preclinical research or early exploratory phases. However, further validation of their safety and efficacy in human MI patients is required to advance their clinical translation.

Future research should leverage multi-omics technologies and advanced experimental models to comprehensively map T-cell epitopes in human MI, delineate the molecular basis of their divergent roles, and design precision immunotherapies that selectively modulate specific T-cell subsets or functions. Rather than bluntly suppressing or amplifying immune activity, the key lies in fine-tuning T-cell responses. Such strategies hold the promise of improving post-MI outcomes and ultimately preventing the progression to HF.

Abbreviations

MI, Myocardial infarction; Treg, Regulatory T cell; HF, Heart failure; TCR, T cell receptor; APCs, Antigen-presenting cells; DCs, Dendritic cells; MHCI, Major histocompatibility complex class I; Tc, T cytotoxic cell; MHCII, Major histocompatibility complex class II; MYHCA, Myosin heavy chain alpha; ADRB1, Beta-1 adrenergic receptor; MC, Myocarditis; NKT, Natural killer T cell; γδ T, Gammadelta (γδ) T cell; CF, Cardiac fibroblast; CXCL10, C-X-C motif chemokine 10; CXCL12, C-X-C motif chemokine 12; Col-I, Type I collagen; Col-III, Type III collagen; MG, Macrophage; PU.1, Purine-rich box 1; MMPs, Matrix Metalloproteinases; ECM, Extracellular matrix; AMI, Acute myocardial infarction; TAC, Transverse aortic constriction; GATA3, GATA-binding protein 3; LVEF, Left ventricular ejection fraction; LVFS, Left ventricular fractional shortening; CCR4, C-C chemokine receptor type 4; CCL17, C-C chemokine ligand 17; SPARC, Secreted protein acidic and rich in cysteine; AREG, Amphiregulin; FoxP3, Forkhead box P3; Teff, Effector T cell; CAR-T, Chimeric antigen receptor T cell; FAP, Fibroblast activation protein; CDC-EVs, Cardiac-derived cell extracellular vesicles; AngII/PE, angiotensin II and phenoxyethanol; MI/R, Myocardial ischemia/reperfusion; BCYRN1, A long non-coding RNA enriched in CDC-EV; MTK-TK-drug microgel system, A microgel system containing ROS-responsive crosslinkers, a ROS-responsive prodrug (Aminoxyacetic acid), and a hydrogen-bonding crosslinker ureacymidone (UPy); MSC, mesenchymal stem cells.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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Author Contributions

WG: Conceptualization, Methodology, Visualization, Writing – original draft. H-xL: Methodology, Visualization, Writing – review & editing. Z-hW: Formal Analysis, Writing – original draft. Z-lW: Formal Analysis, Writing – original draft. A-nL: Conceptualization, Writing – original draft. XW: Visualization, Writing – original draft. QT: Conceptualization, Writing – review & editing. H-yL: Conceptualization, Writing – original draft, Writing – review & editing. All the authors have made significant contributions to the reported work and have participated in the drafting, revision or review of the article. All authors gave final approval of the version to be published. They all consent to the journal in which the article was submitted, and all are responsible for all aspects of the work.

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