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MACROPHAGES IN ACUTE MYOCARDIAL INFARCTION: HETEROGENEITY AND TARGETED THERAPIES

HaoDi Fu, YiHuan Chen*
Department of Cardiovascular Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu, China.
**Corresponding Author: YiHuan Chen*

Abstract: Cardiac repair after acute myocardial infarction depends on the precise regulation of the immune microenvironment. Macrophages are now understood beyond the M1/M2 dichotomy, with dual origins and a continuous functional spectrum. This review summarizes the spatiotemporal roles of cardiac resident and monocyte-derived macrophages, as well as their coordination in the resolution of inflammation, tissue repair, and scar maturation. It also outlines new therapeutic strategies targeting the recruitment of macrophages, their phenotypic transition, and metabolic reprogramming to improve post-infarction cardiac remodeling.
Keywords: Myocardial infarction; Macrophages; Ventricular remodeling; Immunotherapy

1 INTRODUCTIONS

Acute myocardial infarction (AMI) is one of the leading causes of death and disability worldwide[1]. Its pathological process begins with acute coronary artery occlusion, which leads to sustained myocardial ischemia and cardiomyocyte necrosis. Large numbers of necrotic cells subsequently release damage-associated molecular patterns, rapidly activating the innate immune response and triggering a strong and complex inflammatory cascade. While this response is essential for the clearance of necrotic tissue, it also causes collateral injury to surviving cardiomyocytes[2]. At the same time, the endogenous renewal capacity of adult human cardiomyocytes is extremely limited. Using ^{14}C isotope dating, Bergmann et al. clearly demonstrated that the annual turnover rate of cardiomyocytes is less than 1%, rendering effective regeneration of injured myocardium unlikely[3]. This finding provides a strong scientific rationale for the development of therapeutic strategies that target inflammatory regulation.

Currently, the main clinical strategies for AMI focus on early reperfusion of ischemic myocardium and suppression of excessive neuroendocrine activation[4]. However, despite standardized in-hospital management, nearly one quarter of AMI patients without a prior history of heart failure develop new-onset heart failure within three months after discharge. Moreover, mortality is significantly higher in patients with new-onset heart failure than in those who do not develop heart failure[5]. A key reason for this unfavorable outcome is that the regulatory mechanisms governing post-infarction cardiac inflammation and repair remain incompletely understood, and existing interventions fail to precisely target the critical balance between inflammation and repair. Therefore, elucidating the key cellular and molecular mechanisms that control cardiac repair after AMI has become a major priority for improving patient prognosis.

Macrophages are the most abundant innate immune cells in the heart[6] and exert dual roles under both physiological and pathological conditions. Under homeostatic conditions, they participate in the clearance of metabolic waste from cardiomyocytes, maintenance of endothelial function, and immune surveillance. Under pathological conditions, macrophages regulate the initiation and resolution of inflammation through dynamic phenotypic transitions, remove necrotic tissue and cellular debris, and promote tissue repair, angiogenesis, and collagen deposition. Dysregulated macrophage responses and persistent inflammation have been clearly identified as key pathological contributors to heart failure following myocardial infarction[7]. Traditionally, macrophages have been classified into pro-inflammatory (M1) and anti-inflammatory or reparative (M2) phenotypes[8,9]. However, with the application of single-cell RNA sequencing (scRNA-seq) and cell lineage tracing, it has become evident that cardiac macrophages after AMI comprise multiple functional subsets that extend beyond the M1/M2 paradigm[10,11]. Importantly, macrophages of different origins and subsets show distinct temporal dynamics and spatial localization in the infarcted heart[11]. Together, these macrophage populations, differing in origin, phenotype, and spatiotemporal distribution, collectively shape the outcome of cardiac repair and remodeling after AMI[12]. Based on these insights, this review systematically summarizes the roles of macrophages in AMI from three perspectives: cellular origin, phenotypic heterogeneity and functional diversity, and emerging macrophage-targeted therapeutic strategies.

2 ORIGIN OF CARDIAC MACROPHAGES

Multiple studies using fate-mapping approaches, bone marrow chimera models, and single-cell RNA sequencing have demonstrated that cardiac macrophages after AMI exhibit a dual origin, comprising both embryonic and adult-derived populations. Embryonically derived resident macrophages maintain cardiac immune homeostasis through self-renewal and play a dominant role during the early phase after myocardial infarction. In contrast, monocytes derived from the adult bone marrow are extensively recruited from the peripheral circulation during the inflammatory and reparative

phases, infiltrating the infarcted region and its border zone, where they undergo phenotypic differentiation and further participate in inflammatory responses and tissue remodeling[13,14].
Although these two macrophage populations differ in their origin, renewal capacity, and functional specialization, they act in a coordinated manner to maintain the dynamic balance of the inflammatory immune microenvironment following myocardial infarction.

2.1 Cardiac Resident Macrophages (CRMs)

Cardiac resident macrophages (CRMs) are a key component of the intrinsic immune system of the heart. Their origin, maintenance, and functional roles have been extensively characterized over the past decade. Lineage-tracing and bone marrow chimera studies first demonstrated that, under steady-state conditions, the majority of cardiac macrophages are not continuously replenished by circulating monocytes. Instead, they originate from embryonic yolk sac-derived primitive macrophages and fetal liver-derived monocytes, which seed the heart during embryonic development. After birth, these cells are mainly maintained through local self-renewal, exhibiting a renewal pattern that is largely independent of bone marrow hematopoiesis[13,15].
In human cardiac tissue, a similar dual-lineage organization has been confirmed by multi-omics analyses. $CCR2^{-}$ macrophages, which are predominantly embryonically derived, and $CCR2^{+}$ macrophages, which are largely bone marrow-derived, coexist long term and display marked differences in metabolic profiles, phagocytic capacity, and immunoregulatory functions[10]. Notably, under homeostatic conditions, CRMs perform essential roles in the clearance of metabolic waste and the maintenance of extracellular matrix and vascular homeostasis. After myocardial infarction, however, their numbers decline to varying degrees[13]. Importantly, studies have shown that delaying CRM depletion can attenuate adverse post-infarction remodeling, whereas premature loss of CRMs exacerbates cardiac injury[12].

2.2 Monocyte-Derived Macrophages (MDMs)

Although CRMs represent the predominant macrophage population in the heart under steady-state conditions, monocyte-derived macrophages (MDMs) become the major compensatory population when CRMs are depleted under stress conditions such as myocardial infarction or ischemia-reperfusion injury. This compensatory response marks a fundamental shift in the macrophage landscape from homeostatic maintenance toward injury-driven repair. Following myocardial infarction, large numbers of necrotic cardiomyocytes rapidly release damage-associated molecular patterns (DAMPs), including HMGB1 and S100A9. These molecules activate CRMs through receptors such as Toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE), thereby initiating a local pro-inflammatory response[16,17].
Activated CRMs and cardiac stromal cells secrete a range of chemokines, including CCL2, CCL7, CXCL1, and CXCL2, which establish a strong inflammatory chemotactic gradient. This gradient drives the massive mobilization of monocytes from the bone marrow and spleen into the circulation[18-20]. In parallel, sympathetic nervous system activation and angiotensin II signaling further promote the release of monocytes from the splenic marginal zone[21,22]. Once in the peripheral blood, $Ly6C^{high}$ monocytes roll and adhere to the vascular endothelium via adhesion molecules such as VCAM-1 and ICAM-1, and subsequently infiltrate the infarcted myocardium and border zones in a CCR2- and CX3CR1-dependent manner[18,23].
Within the local inflammatory microenvironment, these recruited monocytes differentiate into pro-inflammatory macrophages, amplify the early inflammatory response, participate in the clearance of necrotic tissue, and regulate subsequent repair processes[18,24]. Compared with CRMs, the role of MDMs after myocardial infarction is more stage-dependent. During the early phase, they facilitate debris clearance and modulate inflammation, whereas in later stages, they contribute to fibrosis, angiogenesis, and scar formation. However, excessive recruitment or dysfunctional activation of MDMs can lead to uncontrolled inflammation and exaggerated fibrosis, ultimately aggravating ventricular remodeling and impairing functional recovery[25]. As repair progresses, the proportion of MDMs gradually declines due to differentiation and cellular turnover, and the heart eventually re-establishes an immune steady state dominated by CRMs[26]. Therefore, clarifying the functional division of labor and dynamic balance between CRMs and MDMs is essential for achieving precise immune modulation after AMI.

3 PHENOTYPIC HETEROGENEITY AND FUNCTIONAL DIVERSITY OF CARDIAC MACROPHAGES

Phenotypic plasticity is a key mechanism that enables macrophages to adapt to the changing demands of different pathological stages. Although the traditional M1/M2 dichotomous model provides a basic conceptual framework, it fails to capture the high degree of heterogeneity and dynamic changes of macrophages after AMI. With the application of single-cell transcriptomic sequencing (scRNA-seq) and cytometry by time-of-flight (CyTOF), multiple macrophage subsets with distinct functional properties have been identified in the infarcted heart. The emergence and interconversion of these subsets are tightly regulated by diverse signaling pathways and metabolic programs.

3.1 Polarization Characteristics and Regulatory Mechanisms in the Classical M1/M2 Paradigm

The M1/M2 classification of macrophages was first proposed by Mills and colleagues, by analogy to Th1/Th2 immune responses, to describe two opposing functional states in inflammatory regulation[27]. This dichotomous framework has provided an important basis for understanding macrophage roles in tissue injury and repair.

Classical M1 macrophage polarization is driven by the coordinated activation of the IFN-γ/JAK-STAT1 and TLR4/NF-κB signaling pathways. IFN-γ induces STAT1 phosphorylation and initiates the transcription of pro-inflammatory genes such as inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β)[28,29]. In parallel, lipopolysaccharide (LPS) activates NF-κB[30-32] and hypoxia-inducible factor-1α (HIF-1α), thereby enhancing the production of pro-inflammatory cytokines and reactive oxygen species (ROS)[33]. The transcription factor interferon regulatory factor 5 (IRF5) also plays a critical role in promoting the M1 phenotype[34,35]. Metabolically, M1 macrophages display enhanced glycolysis, accompanied by a partial "break" in the tricarboxylic acid cycle and accumulation of succinate. Succinate stabilizes HIF-1α and further promotes IL-1β expression. Typical markers of the M1 phenotype include iNOS, CD86, and high expression of major histocompatibility complex class II (MHC II^{high})[36,37]. Functionally, M1 macrophages rapidly initiate inflammatory responses and clear pathogens and cellular debris; however, the excessive release of pro-inflammatory mediators and ROS may cause secondary injury to surrounding viable cardiomyocytes[18,38]. Therefore, during the early phase of AMI, M1 polarization must be tightly regulated in a spatiotemporal manner, as sustained or excessive M1 activation can exacerbate tissue damage and adverse remodeling.

In contrast, M2 macrophage polarization is primarily mediated by the IL-4/IL-13-JAK-STAT6 signaling pathway. Upon activation, STAT6 cooperates with transcription factors such as IRF4, peroxisome proliferator-activated receptor-γ (PPARγ), and Krüppel-like factor 4 (KLF4) to induce the expression of repair-associated genes, including arginase-1 (Arg-1), CD206, and CD163[39-41]. Interleukin-10 (IL-10) further promotes anti-inflammatory programs through STAT3 activation and upregulation of negative feedback regulators such as suppressor of cytokine signaling 3 (SOCS3), which inhibit NF-κB-mediated pro-inflammatory signaling[42,43]. Metabolically, M2 macrophages preferentially rely on oxidative phosphorylation and fatty acid oxidation. Arg-1 converts arginine into ornithine, which can be further metabolized into polyamines that support cell proliferation or proline that contributes to collagen synthesis. Through these pathways, M2 macrophages facilitate fibroblast proliferation, extracellular matrix deposition, and scar formation[44,45]. In addition, M2 macrophages secrete pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), thereby promoting angiogenesis and tissue repair[46-48].

Macrophages play a central role in the inflammatory and reparative processes following acute myocardial infarction. Traditionally, their functional diversity has been described using the polarization paradigm of classical activation (M1) and alternative activation (M2). With deeper investigation, both phenotypes have been further subdivided into functionally distinct subtypes, the detailed characteristics of which are summarized in the table below. In recent years, under conditions of intense stress such as ischemia-reperfusion injury, a mixed M3 phenotype displaying features of both M1 and M2 macrophages has also been identified. Together, these subsets constitute a complex and dynamic functional spectrum, and their precise temporal regulation is a key determinant of the reparative outcome after myocardial injury.

Table1 Classification and Characteristics of Classical Macrophages[49-54]

Phenotype	Inducers	Markers	Main Functions
M1(Classically Activated)	IFN-γ, LPS	iNOS, CD86, MHC II	Pro-inflammatory, phagocytosis, oxidative stress
M1a	IFN-γ	STAT1, IRF5	Immune response
M1b	LPS, DAMPs	NF-κB, HIF-1α	Pro-inflammatory, pathogen and necrotic tissue clearance
M1c	TNF	TNF-α, ROS	Pro-inflammatory, oxidative stress
M2(Alternatively Activated)	IL-4,IL-13,IL-10	Arg-1, CD206, CD163	Anti-inflammatory, tissue repair, fibrosis, angiogenesis
M2a	IL-4, IL-13	Arg-1, CD206	Matrix remodeling, pro-fibrotic
M2b	Immune complexes	IL-10, TNF	Immune regulation
M2c	IL-10, TGF-β	MerTK	Anti-inflammatory, matrix degradation
M2d	TLR antagonists, IL-6	VEGF	Pro-angiogenic
M3(Mixed Phenotype)	Strong stress (e.g., I/R)	iNOS, Arg-1	Dual effects, highly metabolically active

It should be noted that the traditional M1/M2 classification is merely a simplified model to describe macrophage functional polarization. Multi-omics studies have revealed the existence of numerous novel macrophage subsets after myocardial infarction, often exhibiting overlapping markers and functions. These findings indicate that macrophages form a highly complex and dynamic network in terms of spatiotemporal distribution, metabolic characteristics, and epigenetic regulation.

3.2 Novel Macrophage Phenotypes and Functional Subsets

After clarifying the differences between CRMs and MDMs, it is particularly important to further understand macrophage heterogeneity based on cellular origin, as macrophages of different origins exhibit markedly distinct

responses in inflammation, repair, and metabolic states after myocardial infarction. This perspective has prompted researchers to identify novel macrophage subsets with specific lineage features and functional orientations, beyond the classical M1/M2 functional framework.

Single-cell transcriptomic analyses have revealed substantial heterogeneity among CRMs. Although CRMs share the common feature of being $CCR2^{-}$, they can be further subdivided based on embryonic lineage markers and functional characteristics. The $TIMD4^{+}/LYVE1^{+}/FOLR2^{+}$ subset, derived from yolk sac and fetal liver, represents the classical embryonic phenotype, exhibiting high efficiency in homeostatic maintenance and phagocytic clearance; these cells are often referred to as "barrier macrophages"[12,55,56]. A smaller MHC II^{high} subset possesses strong antigen-presenting capabilities, contributing to immune surveillance and certain pro-inflammatory functions[11].

scRNA-seq has also identified a $CCR2^{low}/ISG^{+}$ interferon-responsive CRM population, characterized by high expression of antiviral genes such as ISG15, MX1, and IFIT1. These macrophages are primarily responsible for cardiac antiviral surveillance and systemic inflammatory stress responses, and they are rapidly activated in conditions such as myocardial infarction and viral myocarditis[57]. Additionally, a small population of conduction system-specific CRMs has been identified, mainly localized to the atrioventricular node, expressing molecules such as CX3CR1 and performing a unique role in maintaining electrical conduction stability. Ablation of this population leads to atrioventricular conduction block, highlighting their critical importance in cardiac electrophysiological homeostasis[58].

In the context of myocardial injury, these CRM subsets exhibit pronounced spatiotemporal dynamics. Within hours after AMI, CRMs recognize DAMPs, ATP, and mitochondrial DNA released by necrotic cells and are rapidly activated to participate in the early inflammatory response. However, as tissue damage progresses and inflammation spreads, the majority of CRMs are depleted, and the remaining cells shift toward reparative programs. During the repair phase, a subset of CRMs expresses high levels of MerTK, markedly enhancing their phagocytic capacity for apoptotic cells[12].

At the same time, $CCR2^{-}$ CRMs secrete insulin-like growth factor 1 (IGF-1) to promote tissue repair[59,60] and vascular endothelial growth factor (VEGF) to facilitate angiogenesis and reperfusion in the ischemic region[61]. Together, these factors drive the transition from inflammation to repair, limiting adverse ventricular remodeling. Importantly, studies have shown that preserving or enhancing the self-renewal capacity of CRMs significantly improves post-infarction cardiac function, whereas CRM depletion or dysfunction leads to delayed clearance of necrotic debris and apoptotic cells, sustained inflammation, and exacerbated remodeling[12].

After myocardial infarction, MDMs play a central regulatory role in cardiac injury repair. Single-cell sequencing studies consistently show that post-infarction MDMs undergo a multi-stage differentiation process—"pro-inflammatory response, anti-inflammatory transition, fibrotic repair"—forming multiple functional subsets within defined temporal windows.

In the early phase of infarction, circulating $CCR2^{+}Ly6C^{high}$ monocytes are robustly recruited to the infarct core by DAMPs and CCL2[62], where they differentiate into pro-inflammatory $CCR2^{+}$ MDMs[63]. Driven strongly by IRF5 and NLRP3 inflammasome signaling, these cells express high levels of IL-1β, TNF-α, S100A8/A9, and other pro-inflammatory genes[64-66], localizing to the infarct core to clear necrotic tissue and amplify inflammation. Concurrently, a subset of macrophages at the border zone differentiates into antigen-presenting MHC II^{+} MDMs under the regulation of the IFN-γ-IRF1-CIITA axis, expressing H2-Aa, CD74, and other factors to coordinate local T cell immunity, effectively compensating for the depletion of MHC II^{+} CRMs[13,63].

Subsequently, pro-inflammatory MDMs begin to transition toward an anti-inflammatory phenotype, co-expressing markers such as SPP1 and ARG1. This transition is mediated through IL-10/STAT3, TGF-β/SMAD3, and transcription factors including KLF4 and PPARγ, which collectively suppress excessive inflammation while initiating early reparative functions[39,40,67].

Finally, as inflammatory cytokines decline and necrotic debris is cleared, reparative $TREM2^{+}$ MDMs become the dominant subset[11,56,68]. These cells accumulate in maturing fibrotic regions and, under the regulation of metabolic and phagocytosis-related pathways such as PPARγ, LXR, and TFEB, express high levels of TREM2, CD9, and LGALS3. They perform lipid clearance, apoptotic cell removal, and extracellular matrix remodeling, thereby promoting scar stabilization[56,67,69,70].

In summary, macrophage functions during the immune response following AMI exhibit precise spatiotemporal dynamics and high heterogeneity, with phenotypic lineages far exceeding the traditional M1/M2 dichotomy. In the early inflammatory phase, CRMs are rapidly activated by DAMPs and, together with newly recruited $CCR2^{+}$ MDMs, coordinate the response. The $CCR2^{+}$ MDMs highly express IL-1β and TNF-α, performing necrotic tissue clearance and inflammation amplification functions similar to classical M1 macrophages, yet single-cell analyses reveal distinct internal states within this population.

As necrotic debris decreases, macrophages enter a transitional phase, exemplified by $SPP1^{+}ARG1^{+}$ MDMs, in which their function shifts from pro-inflammatory to reparative. This transition is regulated by pathways such as IL-10/STAT3, initiating early repair programs. During the repair and remodeling phase, $TREM2^{+}$ MDMs become the dominant subset, expressing high levels of genes associated with lipid metabolism and phagocytosis. They execute functions akin to M2 macrophages in fibrosis regulation and scar stabilization, but with a more precise molecular definition.

Meanwhile, specific CRM subsets, such as $MerTK^{+}$ cells, continue to clear apoptotic cells and secrete reparative factors, collectively promoting inflammation resolution, angiogenesis, and organized extracellular matrix remodeling. Therefore, cardiac repair after AMI is orchestrated by multiple macrophage subsets of distinct origin, clearly defined molecular identity, and continuous functional spectrum, precisely coordinated over time. Systematic analysis of this continuous lineage provides a new perspective for targeted therapeutic interventions.

Table2 Spatiotemporal Heterogeneity and Functional Specialization of CRMs and MDMs Post-AMI

Subtype	Spatiotemporal Distribution	Markers	Key Pathways	Core Functions
CRMs				
Barrier type	Throughout the heart at steady state	TIMD4^{+}, LYVE1^{+}, FOLR2^{+}, CCR2^{-}	—	Phagocytosis of senescent cell debris; maintenance of cardiac homeostasis
Antigen-presenting type	Throughout the heart at steady state	MHC II^{high} (H2-Aa, CD74)	—	Antigen presentation and immune surveillance
Interferon-responsive type	Activated under stress	ISG15^{+},MX1^{+}, IFIT1^{+}, CCR2^{low}	—	Antiviral defense; early response to systemic inflammatory signals
Conduction-specific type	Atrioventricular node	CX3CR1^{+}	—	Maintenance of normal AV node electrical conduction
Reparative/activated type	Infarct and border zones	MerTK	Apoptosis-related pathways	Clearance of apoptotic cells
MDMs				
Pro-inflammatory	Days 1-3 post-MI, infarct core	CCR2^{+},IL-1β, TNF-α, S100A8/A9	CCL2/CCR2, IRF5, NLRP3	Clearance of necrotic tissue; amplification of inflammatory response
Antigen-presenting	Days 2-5 post-MI, infarct border	MHC II ^{high} (H2-Aa, CD74)	IFN-γ/IRF1/CIITA	Antigen presentation; modulation of local immune response
Transitional	Days 3-6 post-MI, infarct border	SPP1^{+}, ARG1^{+}	IL-10/STAT3, TGF-β/SMAD3, KLF4, PPARγ	Suppression of excessive inflammation; promotion of tissue repair
Reparative	Days 5-14 post-MI, fibrotic regions	TREM2^{+},CD9^{+}, LGALS3^{+},FABP5^{+}	PPARγ, LXR, TFEB, APOE/TREM2	Phagocytosis of residual debris; extracellular matrix remodeling; scar formation

4 NOVEL THERAPEUTIC STRATEGIES TARGETING MACROPHAGES

The inflammatory response following myocardial infarction is double-edged: early inflammation is essential for clearing necrotic tissue, but excessive or persistent inflammation can lead to adverse remodeling and heart failure. Traditional systemic broad-spectrum anti-inflammatory approaches, such as glucocorticoids, can significantly suppress inflammation but may also delay the clearance of necrotic tissue, interfere with scar formation, and ultimately exacerbate adverse remodeling[71,72]. Therefore, broad anti-inflammatory interventions are not beneficial across all temporal windows, making the timing and specificity of intervention critical.

In recent years, accumulating preclinical evidence has highlighted the central role of macrophages in bridging inflammation and repair[73]. As a result, research focus has shifted from non-specific, systemic suppression of inflammation toward precision immunomodulation centered on monocyte/macrophage lineages. Some of these strategies have already progressed to preclinical or early-phase clinical trials, offering promising new avenues to improve outcomes in patients with AMI.

4.1 Targeting Monocyte Recruitment and Infiltration

The key to regulating monocyte recruitment is targeting chemokine-receptor axes. After myocardial infarction, CCR2^{+} monocytes from the bone marrow and spleen are extensively mobilized and migrate into the heart, exacerbating early inflammation. Experimental studies have shown that angiotensin-converting enzyme inhibitors (ACEIs) can suppress the expression of chemokines and adhesion molecules induced by Ang II, thereby reducing the release of peripheral monocytes and their recruitment to the infarcted region[22]. In mouse MI models, nanoparticles delivering CCR2-targeted siRNA significantly reduced Ly6C^{high} monocyte infiltration into the infarct zone and improved ejection fraction[23].

However, other studies indicate that in CCR2-deficient mice, collagen deposition and tissue stiffness in the infarct scar are markedly reduced[74], suggesting that insufficient or mistimed monocyte/macrophage recruitment may delay the formation of collagen and elastin in the scar, ultimately impairing long-term functional recovery.

4.2 Targeting Macrophage Phenotypic Polarization

In the early phase of AMI, pro-inflammatory macrophages are essential for clearing necrotic tissue, but their prolonged presence can exacerbate tissue damage. In contrast, timely differentiation into reparative macrophages promotes

angiogenesis, collagen deposition, and tissue remodeling through the secretion of factors such as IGF-1, TGF-β, and VEGF. Therefore, modulating the local inflammatory microenvironment to facilitate the temporal transition of macrophages from a pro-inflammatory to a reparative phenotype has become one of the most active areas in immunomodulatory research.

Several pharmacological agents have been shown to directly regulate macrophage polarization. For example, the SGLT2 inhibitor dapagliflozin can activate JAK-STAT3 signaling to promote M2 polarization, potentially improving ventricular remodeling by reducing post-MI fibroblast infiltration[75]. Resveratrol similarly induces M2 polarization via STAT3 phosphorylation, thereby improving cardiac function after MI [76]. Moreover, PPARγ agonists such as rosiglitazone, originally used for diabetes treatment, have been shown to induce M2 polarization through STAT6 phosphorylation[76]. Moreover, PPARγ agonists such as rosiglitazone, originally used for diabetes treatment, have been shown to induce M2 polarization through STAT6 phosphorylation[77,78], and in ischemia-reperfusion models, they reduce pro-inflammatory cytokine expression and decrease myocardial necrosis[79,80].

In the field of cell therapy, stem cells and their derivatives—particularly mesenchymal stem cell-derived exosomes (MSC-Exo)—are recognized as key modulators of macrophage fate and function, which is considered one of the central mechanisms underlying their cardioprotective effects[81,82]. Studies indicate that mesenchymal stem cells (MSCs) do not repair the heart by directly differentiating into cardiomyocytes; rather, they actively remodel the immune microenvironment of the infarcted region through continuous secretion of exosomes, microvesicles, and soluble factors[83,84].

Firstly, MSC-Exo can deliver critical microRNAs such as miR-21, miR-146a, miR-182, and miR-223, targeting upstream regulators of inflammation. This suppresses classical pro-inflammatory signaling pathways, including TLR4/NF-κB and NLRP3, and significantly reduces the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6[85-87]. Secondly, MSC-Exo activate reparative signaling axes, including PI3K/AKT, STAT6, and S1P/SK1/S1PR1, upregulating genes such as Arg1, CD206, IGF-1, and VEGF. This drives macrophages toward a reparative M2 phenotype, promoting inflammation resolution and tissue remodeling[88-90].

Additionally, some studies suggest that MSCs or their exosomes may indirectly exert anti-inflammatory effects by enhancing macrophage phagocytosis of apoptotic cells or infiltrating neutrophils, thereby further supporting cardiac repair after injury[91,92].

4.3 Targeting Macrophage Metabolic Reprogramming

In recent years, post-MI immunomodulatory strategies have advanced from simply regulating macrophage phenotypic polarization to precise interventions targeting their underlying metabolic programs. Studies have shown that macrophage functional polarization is closely coupled with metabolic state: pro-inflammatory macrophages primarily rely on glycolysis for energy[93,94], and the accumulation of metabolic intermediates such as succinate stabilizes HIF-1α, driving the expression of pro-inflammatory cytokines like IL-1β[36]. In contrast, following the phagocytosis of apoptotic cells, exogenous fatty acids enter macrophage mitochondria for β-oxidation, providing the main energy source for reparative and biosynthetic functions[95].

Based on these metabolic insights, several interventions targeting specific pathways have demonstrated effective immunomodulation. For example, inhibition of pyruvate kinase isozyme M2 (PKM2), a key glycolytic enzyme, alleviates post-ischemic inflammation[96]. Activation of the IRG1-itaconate pathway or exogenous administration of its derivative 4-octyl itaconate reduces macrophage glycolysis through NADPH-dependent mechanisms, exerting anti-inflammatory effects[97-99]. Conversely, upregulation of the PPARγ-PGC1β axis drives fatty acid β-oxidation, promoting macrophage transition toward a reparative phenotype and suppressing excessive inflammation[100].

Collectively, targeting macrophage metabolic reprogramming represents a novel frontier in post-MI immune microenvironment modulation and offers promising strategies to improve cardiac repair outcomes.

5 CONCLUSIONS AND PERSPECTIVES

Macrophages serve as central regulators throughout the course of AMI, with research paradigms evolving from static phenotypic classification to dynamic functional continua and spatiotemporally specific interaction networks. However, current intervention strategies still face major challenges, primarily the difficulty of precisely distinguishing and targeting macrophage subsets with opposing functions. Achieving selective inhibition of harmful subpopulations while preserving protective ones is key to successful translational applications.

To address these challenges, future research could focus on three frontier directions. First, leveraging spatial multi-omics and in situ imaging technologies to map the spatial distribution and intercellular interactions of distinct macrophage subsets at the microscale, laying the foundation for precise targeting. Second, developing spatiotemporally intelligent delivery systems that enable selective release of therapeutics within defined time windows and infarct regions, thereby coordinating inflammation resolution and tissue repair. Third, exploring personalized therapeutic strategies that integrate patient-specific multi-omics data to understand individual variations in immune responses, ultimately enabling a paradigm shift from broad-spectrum anti-inflammation to precision immune remodeling.

In-depth exploration of these mechanisms holds promise for bridging the gap between scientific understanding and clinical translation of post-MI heart failure, providing a solid basis for the development of targeted prevention and treatment strategies.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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