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REVIEW

Macrophage Polarization in Myocardial Ischemia–Reperfusion Injury: Pathophysiology and Therapeutic Targets

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Abstract: Myocardial infarction is a significant contributor to both morbidity and mortality worldwide. An effective therapeutic strategy for myocardial infarction is myocardial reperfusion via percutaneous coronary intervention and thrombolytic therapy. However, reperfusion may cause another inflammatory injury to surviving cardiomyocytes, inducing further cardiomyocyte death, increasing infarct size and even leading to heart failure. Current clinical interventions mostly target a single pathology and fail to effectively regulate the repair process in the later stages of injury, resulting in limited therapeutic efficacy. Recent studies have shown that macrophages play a dual role in ischemia–reperfusion injury: dynamic changes in their phenotype directly determine the balance between the inflammatory response and tissue repair. In addition, macrophages play a key intersection role in multiple pathological mechanisms, including but not limited to, the regulation of oxidative stress, the drive of programmed cell death, and the remodeling of the microenvironment. This review summarizes the mechanisms of macrophage injury in myocardial ischemia–reperfusion and potential strategies for macrophage-centric targeted therapy. Currently, most studies on potential therapeutic targets are still at the animal experimental stage. Owing to simplified disease models, macrophage therapy is still not well studied in terms of target mechanisms and microenvironmental metabolic reprogramming. In addition, the clinical feasibility of targeted therapies remains to be verified owing to their low delivery efficiency and off-target effects, and further clinical studies are needed to confirm the safety and efficacy of these therapies. In the future, macrophage-related drug research is expected to lead to breakthroughs in the treatment of reperfusion injury.

Keywords: myocardial ischemia–reperfusion injury, macrophage polarization, inflammatory response, treatment

Introduction

Myocardial infarction (MI) is the major cause of death worldwide and a common cause of heart failure. Myocardial infarction is usually instigated by erosion or rupture of atherosclerotic plaques and thrombosis, leading to chronic ischemia and progressive cardiomyocyte death, and the heart's pumping function deteriorates as the infarction progresses.[1] These changes can lead to heart failure and potentially life-threatening arrhythmias.[2] Several studies have confirmed that the most effective strategy for reducing infarct size and improving clinical outcomes, including thrombolytic therapy and direct percutaneous coronary intervention (PCI), is restoring myocardial reperfusion early and in a timely manner.[3–6] The mortality rate of MI has decreased substantially as direct PCI has developed and become popular.[7–9] However, reperfusion after ischemia causes another inflammatory injury to surviving cardiomyocytes, inducing further myocyte death, increasing infarct size, or even leading to heart failure.[10] The impairment of myocardial ischemia–reperfusion (I/R) has severely hampered the treatment of MI and interfered with postinfarction myocardial repair.

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There have been many mechanistic studies of myocardial I/R injury, including various forms of cardiomyocyte death, coronary microcirculation disorder, oxidative stress, calcium overload, and overactivated inflammatory response. Current clinical interventions (eg, antioxidants and anti-inflammatory drugs) mostly target a single pathology and fail to effectively regulate the repair process in the later stages of injury, resulting in limited therapeutic efficacy. Recent studies have shown that macrophages play a dual role in I/R injury: dynamic changes in their phenotype directly determine the balance between the inflammatory response and tissue repair.[11] In addition, macrophages play a key intersection role in multiple pathological mechanisms, including but not limited to, the regulation of oxidative stress, the drive of programmed cell death, and the remodeling of the microenvironment. The functional state of the macrophage has a direct effect on the synergistic or antagonistic effects of these mechanisms, thus making it a central regulatory node linking the inflammatory response, oxidative damage processes and tissue repair mechanisms. However, the spatiotemporal-specific regulatory mechanism of macrophage phenotype switching has not been clarified, and existing strategies have difficulty accurately coordinating their proinflammatory/anti-inflammatory functions, which may be a key factor limiting the efficacy of I/R injury. Therefore, analyzing macrophage heterogeneity and its microenvironmental regulatory network and developing interventions targeting macrophage phenotype switching are expected to overcome the limitations of conventional therapies and provide new directions for improving the prognosis of cardiac function.

This article provides an overview of the complex mechanisms involved in macrophage I/R injury, including inflammatory response-mediated injury, aberrant activation of oxidative stress, disruption of programmed cell death pathways, aberrant regulation of late angiogenesis, and impaired healing and repair processes. Moreover, this study provides insights into the current research progress in the development of therapeutic strategies for myocardial I/R injury, with the aim of identifying additional potential therapeutic options. An in-depth understanding and precise intervention of specific pathways involved in these mechanisms may open new pathways for the treatment of myocardial I/R injury and provide new strategies for myocardial protection.

Overview of the Classification and Function of Macrophages

Macrophages can be found in various tissues, and these tissue-resident macrophages can be classified into two categories depending on their source: macrophages from the yolk sac during embryogenesis and macrophages from bone marrow precursors.[12] Macrophages have remarkable plasticity, and fully differentiated macrophages can transform into polarized phenotypes with specific functional characteristics in response to diverse microenvironmental stimuli.[13] Macrophages can be classified into different subtypes, including proinflammatory M1 macrophages and anti-inflammatory M2 macrophages.[14]

M1 macrophages, alternatively referred to as classically activated macrophages, can be activated by toll-like receptor ligands such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ). M1 macrophages are characterized by high antigen presentation, vigorous bactericidal and tumor-killing activity and high expression of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), interleukin(IL)-1, IL-6, IL-12, IL-23, and matrix metalloproteinase proteases (MMPs), which promote the inflammatory response.[15–17]

In contrast, M2 macrophages are activated by anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, and display characteristic anti-inflammatory gene expression and repair phenotypes. M2 macrophages can be further subdivided into 4 functional subtypes according to their induction mechanism and biological functions as follows: (1) M2a macrophages are activated by IL-4/IL-13 through the STAT6 signaling pathway and are involved mainly in the antiparasitic immune response, tissue repair, and the fibrotic process. It promotes collagen synthesis through the secretion of TGF-β and highly expresses arginase 1 (ARG1) and mannose receptor (CD206), which play central roles in the clearance of parasitic infection and wound healing. (2) M2b subtype: This subtype is synergistically induced by immune complexes in combination with TLR/IL-1R ligands (eg, LPS) and regulates immune complex clearance and inflammatory homeostasis through an IRF4-dependent mechanism. This subtype has both proinflammatory (IL-6 secretion) and anti-inflammatory (IL-10 secretion) properties and is involved in the remodeling of the immunoregulatory network in autoimmune diseases, such as systemic lupus erythematosus. (3) M2c subtype: M2c macrophages are polarized by IL-10, glucocorticoids, or TGF-β through the STAT3/SOCS3 pathway, with immunosuppression and remodeling of tissue as the main functions. High expression of the scavenger receptors CD163 and MerTK promotes vascular homeostasis by

removing apoptotic cells and secreting vascular endothelial growth factor (VEGF), forming an immune escape barrier in the TME. (4) M2d subtype: This subtype is synergistically induced by LPS, an adenosine A2 receptor (A2R) agonist and IL-6 through the NF-κB/HIF-1α pathway and possesses significant proangiogenic and immunosuppressive properties. This subtype secretes S100A8/A9 proteins and the chemokine CXCL1, which play key roles in the formation of the premetastatic microenvironment and chemotherapy resistance.[18–20]

Macrophages and Myocardial I/R Injury

The pathophysiological mechanisms of myocardial I/R injury include various forms of cardiomyocyte death, endothelial inflammation, coronary microcirculatory disorders, calcium overload, oxidative stress, and mitochondrial dysfunction, which jointly cause myocardial remodeling and heart failure.[21] In myocardial tissue, tissue-resident macrophages (TRMs) constitute 7–8% of all nonmyocytes in the heart. TRMs are present in the myocardium during homeostasis, functioning as a defense against infection and eliminating senescent or damaged cells.[22] TRM is rapidly depleted after myocardial injury. After injury, macrophages are derived mainly from the recruitment and proliferation of circulating monocytes, and macrophages also exhibit significant phenotypic changes at different stages of myocardial I/R.[23] Massive polarization of proinflammatory M1 macrophages is observed in the early stage of myocardial I/R. Oxidative stress induced by M1 macrophages and the onset and exacerbation of the inflammatory response are essential mechanisms of reperfusion injury. In addition, programmed cell death associated with macrophages is an important mechanism of myocardial reperfusion injury. In contrast, in the late stage of reperfusion, the polarization of M2 macrophages promotes the abrogation of the inflammatory response, at the same time, facilitates fibrous repair and remodeling of myocardial tissues to attenuate reperfusion injury (Figure 1).

M1 Macrophage-Induced Inflammatory Injury

Reperfusion of the ischemic myocardium allows the original hypoxic cells to rapidly obtain large amounts of oxygen, generating large amounts of oxygen free radicals and activating more inflammatory pathways. With the increase in inflammatory responses and the increase in free radicals, the myocardium is more severely damaged. Oxidative stress induced by reperfusion is an essential mechanism of I/R injury. In the early stage of I/R, when massive amounts of damage-associated pattern molecules (DAMPs) are released from damaged cardiomyocytes, many M1 macrophages are activated and subsequently recruited to the infarct area. Activated M1 macrophages produce large amounts of reactive oxygen species (ROS) through multiple pathways, such as activating NADPH oxidase (NOX) and causing electron leakage from the electron transport chain (ETC) in mitochondria dysfunction.[24] As the most critical molecule mediating oxidative stress, ROS in the local microenvironment have cytotoxic effects on cardiomyocytes, leading to more severe myocardial damage and aggravating I/R injury.[25] ROS are volatile oxygen molecules with unpaired electrons that can cause tissue damage by oxidizing biomolecules such as DNA, proteins, and lipids. ROS react with lipids on cardiomyocyte membranes as well as organelle membranes to trigger lipid peroxidation, increasing electron leakage in mitochondria and cell membranes and ultimately causing cell swelling and death.[26,27] ROS also trigger oxidative DNA damage, enzyme denaturation, and intracellular calcium overload, eventually causing cardiomyocyte apoptosis.[25] Moreover, ROS can initiate more cascaded inflammatory signaling pathways, such as the NF-kB pathway, further amplifying local inflammation. In addition to directly triggering cell death, ROS can also induce pyroptosis by activating the NLRP3 inflammasome and promoting ferroptosis via lipid peroxidation.

M1 macrophages release diverse proinflammatory factors, including TNF-α, IFN-γ, IL-1β, IL-6, IL-10, IL-12, IL-13, IL-23, and VEGF.[28] Among them, the crucial proinflammatory factor TNF-α has multiple functions: it can trigger the excessive generation of ROS and the chemokine epithelial neutrophil activation protein-78 (ENA-78); TNF-α can also activate endothelial cells and upregulate the expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and P selectin, which facilitate neutrophil adhesion to endothelial cells and migration to damaged tissues, leading to cellular injury.[29] M1 macrophages produce various inflammatory mediators that recruit other immune cells, exacerbating the early inflammatory response and participating in I/R injury.

In addition, M1 macrophages secrete TGF-β1 and induce myocardial fibrosis. The production of TGF-β1 facilitates tissue fibrosis and myocardial remodeling by mediating Smad3 signaling, leading to the generation of MMPs and

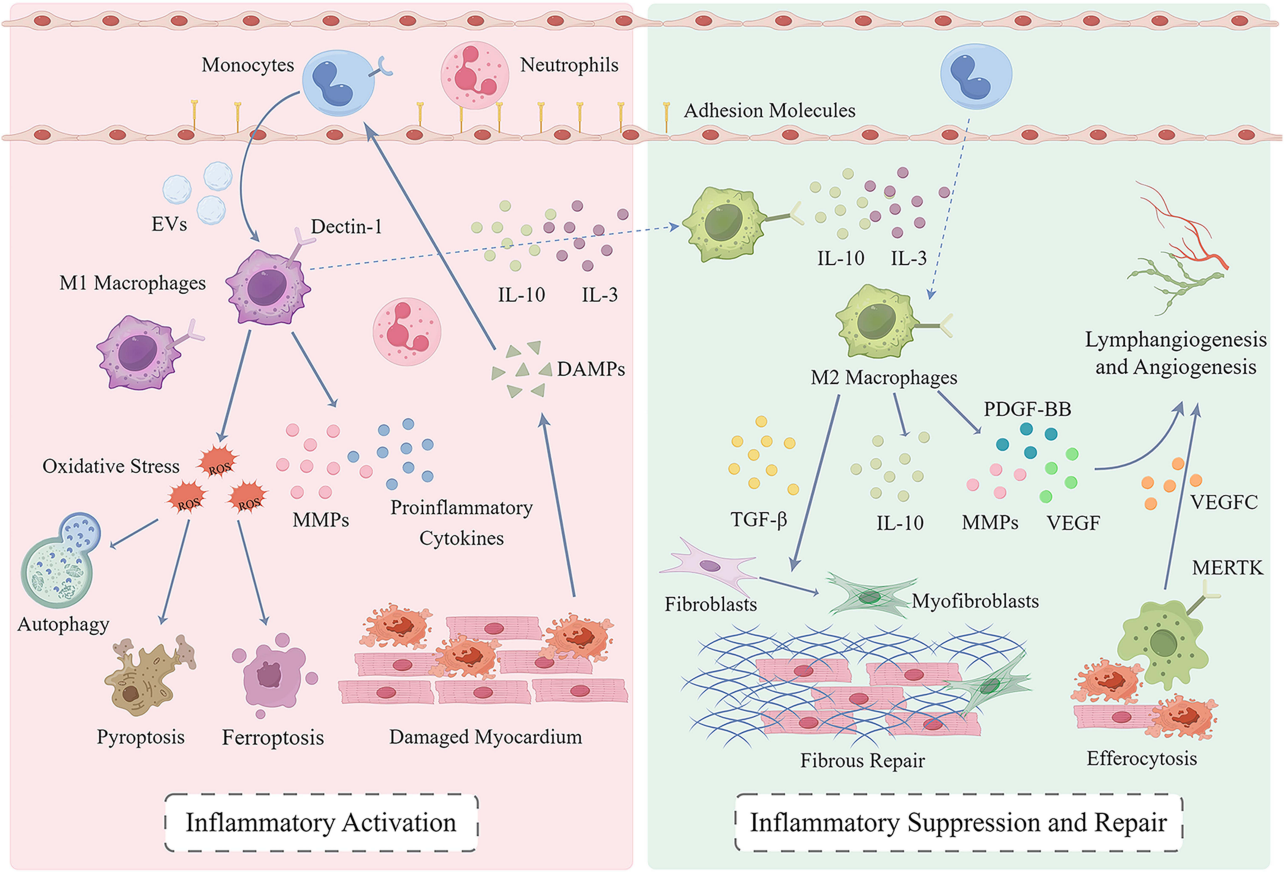

Figure 1 Macrophages and myocardial ischemia–reperfusion injury. In the early reperfusion stage, DAMPs released by damaged cardiomyocytes promote the polarization of circulating monocytes into proinflammatory M1 macrophages. On the one hand, M1 macrophages recruit immune cells and promote the formation of a local inflammatory microenvironment by producing many proinflammatory factors. On the other hand, M1 macrophages produce many types of ROS, which induce oxidative stress, pyroptosis, autophagy, and ferroptosis, aggravating myocardial injury. In the late reperfusion stage, M1 macrophages are replaced by anti-inflammatory M2 macrophages, which promote the regression of inflammation and fibrous repair after injury through a series of anti-inflammatory cytokines and the production of angiogenic cytokines to promote vascular regeneration. In addition, M2 macrophages phagocytose dead cells and debris through efferocytosis, promoting the resolution of the inflammatory response and lymphatic vessel regeneration. M2 polarization of macrophages is an essential mechanism of injury reduction, revascularization, and myocardial remodeling after reperfusion. By Figdraw.

collagen and promoting extracellular matrix (ECM) release from cardiac fibroblasts.[9] Despite the early induction of myocardial fibrosis by M1 macrophages, overactivated inflammatory responses and oxidative stress cause more severe damage to the injured myocardium, inducing more cardiomyocyte death and increasing the infarct size.

Dectin-1 is a pattern-recognition receptor and is expressed primarily in cardiac macrophages. Dectin-1 expression increases in the early stages of I/R injury, determining the polarization of macrophages toward the M1 phenotype.[30] Qin et al demonstrated that in the early phase of I/R injury, upregulated Dectin-1 expression was observed in bone marrow-derived cardiomyocyte macrophages.[31] As a C-type lectin receptor family member, Dectin-1 aggravates myocardial damage associated with M1 proinflammatory macrophage polarization by producing large amounts of proinflammatory cytokines and indirectly mediating the infiltration of neutrophils. Dectin-1 knockout or inhibition alleviates the polarization of M1 macrophages and significantly improves cardiac function. Therefore, a therapeutic strategy targeting the restriction of Dectin-1 activation will provide more options for the management of myocardial I/R.[25]

Macrophage heterogeneity may be highly dependent on the microenvironment, and the myocardium's extracellular vesicles (EVs) play an essential role in macrophage phenotype induction. EVs are cell-derived nanovesicles with bilayer lipid membranes and can carry proteins, lipids, and miRNAs.[6] I/R induces increased release of EVs and promotes the progression of inflammation. EVs can induce the polarization of macrophages toward the M1 phenotype and exacerbate local inflammation. The results of flow cytometry confirmed that EVs increased the percentage of CD86 (M1 marker) macrophages and decreased the percentage of CD206 (M2 marker) macrophages in myocardial tissue subjected to I/R

injury. EV release was increased during reperfusion, and EVs promoted M1 polarization-associated gene expression and decreased M2 polarization-associated gene expression. The protein levels of classical proinflammatory factors, including IL-1β, IL-6, and TNF-α, were also consistent with the increased expression of proinflammatory cytokines. EVs aggravate local inflammatory responses in the myocardium and even trigger systemic inflammation in distant organs. miR-155-5p enriched in EVs promotes M1 polarization in macrophages by inducing JAK2/STAT1 activation, enhancing the proinflammatory, chemotactic, and phagocytic functions of macrophages and exacerbating I/R-induced cardiac injury and dysfunction.[7,25]

Macrophages in Programmed Death-Mediated I/R Injury

Pyroptosis-Mediated I/R Injury

Cell pyroptosis mediated by NLRP3 inflammasome activation in macrophages is also strongly related to myocardial I/R injury.[32–36] As an inflammatory form of programmed cell death, pyroptosis is characterized by persistent cell swelling; it causes the release of cellular contents from ruptured cell membranes and an intense inflammatory response, resulting in a variety of pathophysiological states.[37] Cell pyroptosis occurs mainly in specialized phagocytic cells, including dendritic cells, monocytes, and macrophages.[38] I/R induces NLRP3 inflammasome activation and mediates the pyroptosis of macrophages and nonmacrophages.[25] The NLRP3 inflammasome is composed of NLRP3, caspase-1, and ASC. Of these, NLRP3 is an essential component of the inflammasome. LPS activates NLRP3, DAMPs, ROS, or proinflammatory factors to bind ASCs and recruit procaspase-1.[39] In the context of NLRP3 inflammasome activation, pro-caspase-1 is activated and cleaved to form caspase-1, resulting in the conversion of pro-IL-1β to mature IL-1β and triggering a series of inflammatory responses.[40] The activation of the NLRP3 inflammasome in macrophages triggers macrophage pyroptosis, which is also a key signal for inducing cardiac microvascular endothelial cell (CMEC) damage, and pyroptosis of CMECs leads to microvascular damage and impaired microcirculation.[41]

The process of pyroptosis is induced by the inflammasome and gasdermin-D (GSDMD). ROS play a vital role in the activation of the NLRP3 inflammasome, which can activate the NLRP3 inflammasome and thus cause Caspase-1-dependent pyroptosis.[37] GSDMD is a common final mediator of cellular death and is a major effector of this process.[42,43] GSDMD is expressed mainly in macrophages that infiltrate the infarct zone and can be cleaved by macrophages and nonmacrophages to induce pyroptosis. Upon activation of the NLRP3 inflammasome, procaspase-1 is recruited and autocatalytically cleaved to form caspase-1, and activated cysteine asparaginase cleaves the GSDMD protein, dissociating its N-terminal domain. This structural domain combines with membrane lipids and perforates the cell membrane until it ruptures, forming membrane pores; on the one hand, it causes the release of cellular contents that exacerbate cell death, and on the other hand, the release of proinflammatory cytokines through membrane pores further contributes to inflammatory injury.

GSDMD-targeted regulation has potential therapeutic effects on myocardial I/R injury. GSDMD deficiency alleviates I/R injury and reduces infarct size by attenuating neutrophil infiltration and inflammatory cytokine release.[25] Moreover, caspase-1 activated by the NLRP3 inflammasome also mediates the transition of pro-IL-1β to mature IL-1β, significantly enhancing the local inflammatory response.[44,45] In addition to triggering cell death, ROS-induced macrophage and endothelial cell pyroptosis amplify the inflammatory response because of membrane rupture, the release of cellular contents, and the prosecretory effects of IL-1β, further exacerbating I/R injury.

Neuronal precursor cell-expressed developmentally downregulated 4 (NEDD4) serves as an E3 ubiquitin ligase and plays a critical negative regulatory role in inflammasome activation and pyroptosis. NEDD4 inhibits the activation of the NLRP3 inflammasome and promotes proteasomal degradation of NLRP3.[46] NEDD4 can benefit patients with myocardial I/R injury by reducing cell death and endothelial cell injury after reperfusion.[41] In addition, inhibitors of the NLRP inflammasome have shown therapeutic potential in counteracting ROS and attenuating oxidative stress in cardiomyocytes.[25] M2 macrophage-derived exosomes can effectively inhibit NLRP3 activation and have potent anti-pyroptotic effects.[43] Zhang et al revealed that stachyose inhibited NLRP3-mediated macrophage pyroptosis by suppressing the expression of crucial molecules, including GSDMD, NLRP3, and cleaved caspase-1, thereby decreasing the secretion of the proinflammatory cytokines IL-1β and IL-18.[47] Farrerol may have the potential to precisely target NLRP3 activation in macrophages to attenuate myocardial I/R injury. Farrerol impacts the interaction between NEK7 and NLRP3

to block the assembly of the NLRP3 inflammasome, thereby inhibiting the activation of the NLRP3 inflammasome, which highlights that farrerol can be used as a potential cardioprotective agent.[48] A prospective, randomized, open-label, single-center clinical trial involving 120 patients with MI suggested that coenzyme Q10 may play a role in promoting early recovery of cardiac function after MI by inhibiting the recruitment of CCR2 macrophages and the activation of the NLRP3/IL-1β pathway in macrophages.[49]

Autophagy-Mediated I/R Injury

Autophagy is a vital degradation process in the restoration of cardiac homeostasis, and its detrimental effects alleviate IR injury by eliminating damaged cellular organelles and dead cells. Beclin1 acts as a crucial autophagy mediator in autophagosome formation and processing. During reperfusion, increased Beclin1 expression induced by ROS is an essential mechanism for autophagy activation.[50,51] TFEB is a central autophagy and lysosomal function regulator that can alleviate lipotoxic responses in macrophages and increase IL-1β production.[52] TFEB promotes autophagy by inducing the biogenesis and fusion of autophagosomes and lysosomes, thereby effectively degrading damaged cells and organelles.[53] TFEB is predominantly found in the cytoplasm of macrophages, with minimal expression in the nucleus, and elevated nuclear TFEB levels are found in myocardial I/R injury mice.[54] Selective upregulation of TFEB in macrophages stimulates the autophagy–lysosome pathway, attenuating myocardial dysfunction after I/R and reducing IL-1β secretion. Moreover, autophagy may hinder inflammasome activity and, subsequently, macrophage pyroptosis by degrading inflammasome components. With the activation of autophagy mediated by TFEB, the autophagosome limits NLRP3 inflammasome activation and IL-1β secretion by directly phagocytosing ASCs to attenuate their polymerization or by degrading the NLRP3 protein.[55] The pathophysiology of autophagy and inflammasomes is closely related, but complexly, the NLRP3 inflammasome may subsequently modulate autophagy. When LPS stimulates cells, the NLRP3 inflammasome are activated and induce the nuclear translocation of intracellular TFEB, which promotes autophagy and suppresses cellular damage, thereby protecting against inflammatory injury. Notably, the induction of TFEB in macrophages may be a potential target for alleviating myocardial injury and IL-1β production after I/R.[52] Autophagy certainly has two sides, but the details are still unknown. The degree of autophagy that benefits the myocardium is moderate because excessive autophagy may cause myocardial cell apoptosis and aggravate inflammation in I/R.

Naringenin (NAR), which belongs to the flavonoid family, exhibits promising cardioprotective ability. NAR treatment enhanced the nuclear transcription of TFEB and promoted macrophage autophagy while suppressing NLRP3 inflammasome activation, inhibited M1 macrophage infiltration, and promoted the M2 polarization of macrophages. In animal experiments, NAR protected against myocardial I/R injury in mice via the TFEB-autophagy-NLRP3 inflammasome pathway.[54] NAR induced the proliferation of autophagosomes in cells by promoting the nuclear translocation of TFEB, activating macrophage autophagy, and inhibiting inflammasome activation.[56] NAR reduced tissue damage and infarction in myocardial I/R injury model mice, inhibited macrophage M1 polarization, promoted M2 polarization, reduced the levels of proinflammatory cytokines, and increased the levels of anti-inflammatory cytokines. Ubiquitin-specific protease 19 (USP19) increases autophagic flux and decreases mitochondrial ROS production, thereby inhibiting NLRP3 inflammasome activation and promoting M2 macrophage polarization. USP19 can convert the proinflammatory to anti-inflammatory functions of NLRP3, demonstrating the therapeutic potential of USP19 in inflammatory intervention.[57]

Ferroptosis-Mediated I/R Injury

Ferroptosis represents a newly discovered iron-dependent pattern of cell death resulting from an imbalance in cellular metabolism and redox balance. Ferroptosis is characterized by unrestricted lipid peroxidation caused by the accumulation of iron. In the myocardium after I/R, macrophages are heavily activated and recruited to the infarct area by various forms of dead myocardiocytes, as well as ferroptosis. These macrophages generate large amounts of ROS. ROS not only induce pyroptosis and oxidative stress, thereby harming the myocardium but also facilitate ferroptosis via ROS-mediated oxidative stress.[38]

The process of phagocytosing damaged cells and debris may lead to the accumulation of excess iron within macrophages, subsequently triggering the Fenton reaction between Fe^{2+} and Fe^{3+}, directly resulting in the production of ROS.[58] In turn, iron overload in macrophages induces macrophage polarization toward the M1 phenotype by

enhancing glycolysis and producing proinflammatory cytokines and ROS.[59] Moreover, mitochondria are involved in regulating ferroptosis by producing signaling molecules such as ROS. ROS promote ferroptosis by activating several transcription factors and protein kinases that induce ferroptosis and inhibiting signaling molecules that are resistant to ferroptosis.[60] ROS drive the onset of ferroptosis by inducing phospholipid peroxidation to damage myocardiocytes, and cell death further exacerbates I/R injury. Li et al revealed that ferroptosis enhances the adhesion of neutrophils to CMECs, thereby mediating neutrophil migration to the infarct area.[61] Inhibition of ferroptosis can decrease infarct size and the severity of myocardial I/R injury and improve cardiac function. Xu et al reported that IL-37 may suppress macrophage ferroptosis and attenuate atherosclerosis progression by activating the Nrf2 pathway.[62] Lu et al reported that IL-23p19 deficiency also reduces macrophage ferroptosis, thus alleviating M1 macrophage polarization.[63] These pathways are resistant to ferroptosis and have therapeutic potential in the context of myocardial I/R injury.

M2 Macrophages Attenuate the Inflammatory Damage Caused by Reperfusion and Promote Injury Repair and Remodeling in Myocardial Tissue

During the inflammatory infiltration period of M1 macrophages, Treg cells, essential regulators of macrophage phenotype and function, release anti-inflammatory cytokines after phagocytizing debris and dead cells to inhibit inflammatory injury and alleviate adverse cardiac remodeling. During the repair process, the predominant subgroup of macrophages is converted from M1 to M2, with the upregulation of exogenous signaling molecules such as IL-10 and the downregulation of IL-6, MMP9, and TNF-α and macrophage polarization to the repair-mediated M2 type. The anti-inflammatory M2 macrophages induced by IL-4/IL-13/IL-10 play an essential role in inflammation abrogation. M2 macrophages stimulate fibroblasts to mediate ECM production, cicatrization, cell proliferation, and angiogenesis by producing cytokines such as TGF-β, IL-10, and VEGF, facilitating tissue repair and reconstruction.[23,25] M2 macrophages and fibroblasts contribute to fibrous repair and adaptive myocardium remodeling. Inflammatory factors, including TGF-β, IL-10, and CCL17 secreted by macrophages, promote the differentiation and migration of myofibroblasts and regulate collagen distribution within the myocardial wall effectively, improving ventricular compliance and enhancing cardiac function. TGF-β promotes the conversion of fibroblasts to myofibroblasts, which produce collagen and fibronectin and facilitate the formation of the ECM. The formation of the ECM facilitates the repair and remodeling of damaged cardiac tissue and promotes scar formation and the progression of myocardial fibrosis.[64] Macrophages participate in fibrosis after MI in direct or indirect ways. Recent research has demonstrated that macrophages may generate ECM proteins to directly participate in scar formation and myocardial fibrosis. Additionally, macrophages can increase the expression of fibroblast-specific ECM genes and convert them into fibroblast-like cells in the early stage after MI.[6] The TGF-β/p-smad3 signaling pathway acts as a crucial mechanism that induces macrophage-to-myofibroblast transformation (MMT), which promotes fibrosis.[65]

In addition, M2 macrophages perform a significant function in the phagocytosis of dead cells and inflammatory products, which is essential for inflammation resolution after myocardial injury. The phagocytic removal of dead cells by macrophages is called efferocytosis, which is performed mainly by M2 macrophages.[66] Efferocytosis is characterized by the removal of dead cells in an "immune-silencing" manner, which suppresses inflammatory cytokine production.[67] Expressed explicitly in reparative M2 macrophages, the MERTK receptor plays a crucial role in the process of removing dead cardiomyocytes after MI, facilitating inflammation resolution. In contrast, MERTK deficiency in macrophages results in specific impairment of their phagocytic function, affecting the subsequent process of myocardial repair.[6] On the one hand, M2 macrophages attenuate the inflammatory response by removing necrotic cells and damaging debris via efferocytosis. On the other hand, macrophages in the infarcted myocardium release various cytokines and growth factors during efferocytosis, significantly promoting angiogenesis.

Reparative M2 macrophages participate in the release of proangiogenic factors such as MMPs, VEGF, and platelet-derived growth factor-BB (PDGF-BB) by expressing the membrane-associated proteins alpha-1, TGF-β, and prostaglandin E2.[25] Among these factors, myeloid vascular endothelial growth factor C (VEGFC) is required to alleviate the progression of heart failure after MI. Efferocytosis has been proven to induce macrophages to produce VEGFC, which inhibits inflammatory responses and promotes lymph angiogenesis. Cardiac M2b macrophages promote repair after MI by producing VEGFC to inhibit inflammatory cytokines and promote myocardial lymph angiogenesis.[68,69] By binding to

its receptor, VEGFC participates in lymphangiogenesis and remodeling, and neoplastic lymphatics improve the myocardial fluid balance and promote edema reduction after infarction[70] A study showed that experimental depletion of macrophages at either stage impaired postinfarction capillary formation in mice.[71] On the one hand, VEGFC binds to the corresponding receptor VEGFR3 on lymphatic endothelial cells through paracrine secretion[72] and mediates lymphangiogenesis, contributing to postischemic cardiac repair and cardiac function improvement.[32] On the other hand, VEGFC acts in an autocrine manner to prevent macrophages from producing proinflammatory cytokines.[73] Moreover, VEGFC produced by macrophages effectively inhibits the activation of proinflammatory macrophages. Therefore, reparative M2 macrophages clear dead cardiomyocytes and debris through efferocytosis and, at the same time, secrete large amounts of anti-inflammatory cytokines in the late stage of I/R, thereby attenuating the inflammatory damage caused by reperfusion, promoting angiogenesis and lymphangiogenesis, and inducing injury repair and remodeling of myocardial tissue, which performs crucial functions in the process of injury repair.

Macrophages and Angiogenesis

During the repair of infarcted myocardium, vascular system reconstruction is necessary for myocardial remodeling. An intense angiogenic response accompanies tissue healing and cardiac remodeling after infarction; angiogenesis plays a vital role in the repair and remodeling of the injured myocardium, and impaired angiogenesis inhibits cardiac repair and functional recovery. In a cohort of studies on macrophages and myocardial I/R injury, a recent study demonstrated that M1 macrophages primarily promote vascular sprouting, whereas M2 macrophages mainly promote maturation and stabilization of sprouted vessels.[74] However, extended exposure to M1 macrophages leads to the degradation of already formed vessels. These findings indicate that facilitating the timely conversion of proinflammatory macrophages to a repair phenotype following I/R injury is crucial for angiogenesis.[8,75] Vascular networks are established through the processes of sprouting, anastomosis, and maturation.[76] In the context of angiogenic stimuli such as the angiogenic factor VEGF, endothelial cells differentiate into tip and stalk cells, thereby guiding and supporting nascent sprouting vessels, respectively. Concurrently, proteases such as MMP9 play essential roles in the sprouting process. Subsequently, nascent sprouted vessels not only fuse with other ships in anastomosis but also recruit supporting pericytes through PDGF-BB, thus leading to the stabilization of the sprouts and progression toward maturation into fully developed vessels.

M1 macrophages express genes related to angiogenesis initiation, including the endothelial cell chemotaxis genes VEGF, essential fibroblast growth factor (FGF2), and IL-8.[77] M1 macrophages produce the inflammatory cytokines TNF-α, IL-1β, and VEGF. Among these, VEGFA, which is secreted by M1 macrophages, is a potent initiator of angiogenesis.[78] These cytokines can trigger the sprouting of endothelial cells through the induction of the tip cell phenotype and provide support for pericytes through the enhancement of the recruitment process of endothelial cells.[79] Hence, these findings imply that M1 macrophages play a vital role as initiators of angiogenesis.

M2 macrophages facilitate the progression of angiogenesis through multiple mechanisms, including vessel remodeling, sprouting, stabilization, and maturation. The different phenotypes of M2 macrophages function in various ways, but all these phenotypes are associated with the expression of genes related to the differentiation of pericyte cells. M2a macrophages produce high levels of PDGF-BB, recruiting pericytes and mediating EC-pericyte interactions to support endothelial cells (ECs), thereby promoting vascular stabilization and anastomosis of sprouting ECs. M2c macrophages may promote sprouting by secreting high levels of MMP9, which supports vascular remodeling. M2c macrophages can also secrete osteopontin, which facilitates EC proliferation, migration, and tube formation by increasing the expression of VEGF in ECs. M2 macrophages modulate vascular stabilization and maturation.[75] Different phenotypes of macrophages promote angiogenesis by inducing the sprouting, anastomosis, stabilization, and maturation of vascular ECs. Macrophages play an essential role in angiogenesis and significantly contribute to myocardial repair and remodeling. The induction of macrophage polarization facilitates postinfarction myocardial repair, attenuates reperfusion injury, and promotes revascularization and myocardial remodeling.

Potential Therapeutic Strategies Targeting Macrophages

The polarization of macrophages is closely associated with myocardial I/R injury, and the inflammatory mechanisms involved in I/R injury have drawn increasing attention in recent years. The oxidative stress and inflammatory response

mediated by M1 macrophage polarization aggravate I/R injury. In contrast, late M2 macrophage infiltration promotes a reduction in the inflammatory response and angiogenesis, which plays crucial roles in fibrous repair of tissue and myocardial remodeling. Despite the triggering of an early inflammatory response being essential for conversion to a late repair stage, excessive infiltration of proinflammatory macrophages exacerbates inflammatory injury and postinfarction remodeling. Therefore, tight control of inflammatory macrophage recruitment and timely modulation of their conversion to the repair macrophage (M2) phenotype are vital to ensure tissue repair, prevent excessive inflammatory responses, and vert the onset of adverse remodeling and contractile dysfunction.[25] Therefore, after MI occurs, both the inhibition of M1 macrophage polarization and the induction of conversion to M2 macrophages may be potential therapeutic strategies for I/R injury, providing additional entry points for mitigating reperfusion injury and improving the efficacy of reperfusion after acute MI. Inflammatory modulation focusing on the macrophage phenotype is promising for promoting better cardiac healing after myocardial I/R injury. Table 1 lists detailed therapeutic strategies for targeting macrophages in myocardial I/R injury. However, macrophage-associated programmed cell death also plays an essential role in myocardial

Table 1 Potential Therapeutic Approaches Targeting Macrophages in Myocardial Ischemia–Reperfusion Injury

Drug/Reagent	Type	Target	Mechanism	Research Level	References
16673-34-0	Compound	NLRP3	Inhibit NLRP3 inflammasome activation	Animals	[80]
Curcumin	Compound	TLR2	Inhibit oxidative stress and inflammatory response	Animals	[81]
Diannexin	Compound	NF-κB	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[82]
Iminostilbene	Compound	PKM2	Inhibit inflammatory response	Animals	[83]
INF195	Compound	NLRP3	Inhibit NLRP3 inflammasome activation	Animals	[84]
Kirenol	Compound	NOX1, NOX4	Inhibit macrophage pyroptosis	Animals	[85]
Lebetin 2	Compound		Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[86]
N-Propargyl Caffeamide	Compound	NF-κB	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[87]
P-Coumaric acid	Compound	IL-4, IDO	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[88]
Phenytoin	Compound	VGSC	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[89]
Pioglitazone	Compound	MCP-1, ICAM-1	Inhibit macrophage infiltration	Animals	[90]
Pubescenoside C	Compound	HSP90/ITA/PKM2	Promote polarization of macrophages from M1 to M2	Animals	[91]
Remimazolam	Compound	NF-κB	Inhibit M1 macrophage polarization	Animals	[92]
Salvianolic Acid B	Compound	mTORC1	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[93]
SGLT2i	Compound	STAT3	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[94]
Shenlian	Compound	JAK/STAT	Inhibit M1 macrophage polarization	Animals	[95]
Stachyose	Compound	NLRP3	Inhibit macrophage pyroptosis	Animals	[47]
Triptolide	Compound	Nrf2/HO-1	Inhibit macrophage infiltration	Animals	[96]
hUC-MSC-Evs	EVs	Nrf2/HO-1	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[97]

(*Continued*)

Table 1 (Continued).

Drug/Reagent	Type	Target	Mechanism	Research Level	References
KLF2-EVs	EVs	miR-24-3p	Inhibit macrophage infiltration	Animals	[98]
M2-Evs	Evs	miR-181b-5p	Promote polarization of macrophages from M1 to M2 and angiogenesis	Animals	[99]
P-EVs	EVs		Promote polarization of macrophages from M1 to M2	Animals	[100]
BMSC-Exos	Exos	JAK/STAT	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[101]
M2-Exos	Exos	NF-κB, NLRP3	Inhibit cell pyroptosis	Animals	[43,102]
FAP CAR-Ms	Genetically engineering		Reduce myocardial fibrosis	Animals	[103]
FGF4-Gene-Transfected Macrophages	Genetically engineering		Promote angiogenesis	Animals	[104]
$MAC^{CCR2+MerTK\ CR}$-$Lipo^{PEP-20}$	Genetically engineering	CCR2, MerTK, CD47	Enhance the phagocytosis of macrophages	Animals	[105]
ABT263-PLGA	Nano-carrier		Promote polarization of macrophages from M1 to M2	Animals	[106]
Biomimetic baicalin nanocrystalline	Nano-carrier		Promote polarization of macrophages from M1 to M2 and angiogenesis	Animals	[107]
BSPC@HM NC	Nano-carrier	Sav1	Reparative reprogramming of M1 macrophages	Animals	[108]
CsA@PPTK	Nano-carrier		Promote polarization of macrophages from M1 to M2	Animals	[109]
DSS/PB@BSP	Nano-carrier		Reparative reprogramming of macrophages	Animals	[110]
M/PCOD@PLGA	Nano-carrier		Inhibit inflammatory response	Animals	[111]
Pioglitazone-NPs	Nano-carrier	PPARγ	Promote polarization of macrophages from M1 to M2	Animals	[112]
PL720 (L-arginine, FTY720)	Nano-carrier	STAT	Reparative reprogramming of macrophages	Animals	[113]
Platelet-like fusogenic liposome	Nano-carrier	miR-21	Reparative reprogramming of macrophages	Animals	[8]
PLP-RvD1	Nano-carrier		Enhance the phagocytosis of macrophages	Animals	[114]
TAK-242-NP	Nano-carrier	TLR4	Inhibit inflammatory response	Animals	[115]
CDCs	Stem Cell		Promote polarization of macrophages from M1 to M2	Animals	[116]
MSCs	Stem Cell	miR-21-5p, miR-182	Promote polarization of macrophages from M1 to M2	Animals	[117,118]
Baicalin	TCM	JAK/STAT	Promote polarization of macrophages from M1 to M2	Animals	[119]
Electroacupuncture	TCM	NLRP3	Promote polarization of macrophages from M1 to M2 and Inhibit NLRP3 inflammasome activation	Animals	[120]
Galangin	TCM	PI3K/AKT	Inhibit inflammatory response and autophagy	Animals	[121]
Naoxicantong	TCM	NLRP3	Inhibit macrophage infiltration and Inhibit NLRP3 inflammasome activation	Animals	[122]

(*Continued*)

Table 1 (Continued).

Drug/Reagent	Type	Target	Mechanism	Research Level	References
Naringenin	TCM	NLRP3	Promote M2 macrophage polarization and Inhibit NLRP4 inflammasome activation	Animals	[54]
Nuanxinkang	TCM	NF-κB	Inhibit M1 macrophage polarization and promote M2 macrophage polarization	Animals	[123]
QiShenYiQi Pills	TCM	TGFβ1/Smads	Inhibit macrophage infiltration	Animals	[124]

Abbreviations: SGLT2i, sodium-glucose cotransporter 2 inhibitors; EV, extracellular vesicle; hUC-MSC-EVs, extracellular vesicles from human umbilical cord mesenchymal stem cells; KLF2-EVs, extracellular vesicles from Krüppel-Like Factor 2-overexpressing endothelial cells; M2-EVs, M2 macrophage-derived extracellular vesicles; P-EVs, platelet membrane modified extracellular vesicles; Exos, exosomes; MSC-EXOs, mesenchymal stem cell-derived exosomes; M2-exos, M2 macrophage-derived exosomes; FAP CAR-Ms, chimeric antigen receptor-macrophages targeting fibroblast activation protein; FGF4, fibroblast growth factor-4; $MAC^{CCR2+MerTK\ CR}$-$Lipo^{PEP-20}$, macrophages co-overexpressing C-C chemokine receptor type 2 and cleavage-resistant myeloid-epithelial-reproductive tyrosine kinase, as well as surface clicking with liposomal PEP-20; ABT263-PLGA, Navitoclax loaded in poly (lactic-co-glycolic acid) nanoparticles; BSPC@HM NC, nanocomplexes reversibly camouflaged with a platelet–macrophage hybrid membrane carrying helical polypeptide and poly(l-lysine)-cis-aconitic acid; CsA@PPTK, Tregs biomimetic nanoparticle using Cyclosporine A(CsA) encapsulated by Poly (5,5-dimethyl-4,6-dithio-propylene glycol azelate) (PTK) as core and platelet membrane as shell; DSS/PB@BSP, nanoparticles with Prussian blue nanoparticles (PB) as carriers to encapsulate betamethasone sodium phosphate (BSP) and further modified with dextran sulfate sodium (DSS); M/PCOD@PLGA, macrophage cell membrane-coated poly (lactic-co-glycolic acid) (PLGA) nanoparticles and PCOD585; NP, nanoparticle; PL720 (L-arginine, FTY720), platelet membrane-encapsulated L-arginine and FTY720 (fingolimod) biomimetic nanocarrier; PLP-RvD1, platelet-bionic, ROS-responsive Resolvin D1; TAK-242-NP, poly-(lactic-co-glycolic acid) nanoparticles containing TAK-242; CDCs, cardiosphere-derived cells; TCM, traditional Chinese medicine.

I/R injury. Potential therapeutic strategies targeting macrophage injury mechanisms are limited to theoretical studies and animal experiments, which have been proven to be promising for alleviating cardiac inflammation and promoting repair in animal models. The feasibility of their clinical and bedside application is still being determined. Currently, extensive clinical trial outcomes validating both the safety and the efficacy of treatment are lacking. In the future, more comprehensive clinical studies and trials with the aim of developing more efficacious and practicable treatments for I/R injury are needed.

Drug Delivery Systems

In macrophage-associated reperfusion injury mechanisms, possible therapeutic targets are expected to attenuate reperfusion injury and promote myocardial remodeling. Nevertheless, the transport vehicle is also essential for transporting the drug to the injured myocardium or macrophages precisely. EVs, which have the capacity to carry miRNAs, lipids, and proteins, are essential for intercellular communication and can be used as drug delivery systems for cardiovascular and oncological applications. The modification of extracellular vesicles can address the problems of low retention and transient efficacy, and modified EVs, including platelet membrane-modified EVs (P-EVs) based on membrane fusion methods, simulated monocyte-modified EVs, and EVs incorporated into alginate hydrogels, improve the transportation efficacy of EVs toward specific cells and provide therapeutic benefits.[100] In addition, specially modified nanocarriers, including liposomes, polymeric nanoparticles, and complexes, can also improve the transportation efficacy of therapeutic agents. Extracellular vesicles, along with nanomaterial drug delivery systems, are expected to serve as potent tools for future targeted macrophage modulation after MI.[125] Altering macrophage polarization through the transport of therapeutic molecules to the injured myocardium precisely benefits the reperfused myocardium and attenuates injury.[100]

Myocardial I/R can induce substantial generation of cardiac EVs. These EVs not only increase local inflammation within the damaged myocardium but also trigger systemic inflammation with circulatory shunting.[7] As mentioned previously, miR-155-5p, which is enriched in EVs, enhances M1 macrophage polarization by upregulating the expression of genes related to M1 macrophages, exacerbating local myocardial inflammatory injury. Inhibiting proinflammatory M1 macrophage activation by targeting EVs can attenuate early reperfusion injury and improve cardiac function in the clinical setting. GW4869 is a commonly utilized chemical inhibitor of exosome generation, and its ability to inhibit EVs represents a potential therapeutic approach for I/R injury. Ge et al confirmed that GW4869 could inhibit EV release and attenuate M1 polarization in a mouse model of myocardial I/R injury, thereby reducing I/R injury.[126]

Small Molecule Inhibitors/Agonists Target Key Signaling Pathways

NF-κB Pathway Inhibitors

NF-κB, as a core regulatory hub of the inflammatory response, significantly promotes the release of proinflammatory factors such as TNF-α, IL-6, and IL-1β, which play key roles in signaling and guiding macrophages to polarize toward the M1 type once activated, thus exacerbating the inflammatory response.[127,128] In contrast, interventions such as blocking the nuclear translocation of NF-κB or inhibiting its upstream signaling molecule IKKβ can effectively reduce the release of inflammatory mediators, which not only inhibits macrophage polarization toward the M1 type but also significantly attenuates the extent of myocardial fibrosis.[129] In particular, Bay 11–7082 effectively blocked the activation pathway of NF-κB by precisely inhibiting the phosphorylation process of IKKβ, which in turn significantly reduced the activation ratio of M1-type macrophages and significantly inhibited cardiomyocyte apoptosis.[130–132]

STAT1/STAT3 Inhibitors

STAT1 plays a key role in promoting M1 polarization (ie, proinflammatory effects) in the inflammatory response, whereas STAT3 drives M2 polarization with anti-inflammatory and protissue repair functions.[133] Studies have shown that fludarabine, a potent inhibitor, blocks the phosphorylation of STAT1, thereby inhibiting M1 polarization induced by IFN-γ.[134] In a MI model, the application of fludarabine significantly reduced the proportion of M1-type macrophages in the heart and effectively reduced the infarct size, which provides a new therapeutic strategy for myocardial protection and functional recovery.[135]

Regulation of the CHOP Pathway

CHOP is a key transcription factor triggered by endoplasmic reticulum stress (ERS), which promotes the polarization of M1-type macrophages and accelerates the release of inflammatory factors, such as IL-6 and TNF-α, under ERS conditions.[136,137] Integrative stress response inhibitor (ISRIB), a potent regulator, effectively blocks the M1 polarization process by inhibiting the activation of CHOP downstream of ERS.[138] In diabetic cardiomyopathy models, the application of ISRIB significantly reduces the expression level of CHOP in cardiac macrophages, which in turn reduces the secretion of IL-6 and TNF-α and helps attenuate the inflammatory response.[139,140]

AMPK/Sirt1 Pathway Activators

AMPK/Sirt1, as a key energy metabolism sensor, plays a dual role once activated: on the one hand, it inhibits NF-κB activity, and on the other hand, it promotes the activation of the antioxidant pathway, thus finely regulating the polarization state of macrophages.[141–143] Resveratrol, a natural active ingredient, was shown to effectively activate Sirt1 in a model of myocarditis, and this activation process in turn inhibited the activities of NF-κB and STAT1, significantly reducing the infiltration of M1-type macrophages in the heart.[144,145] This effect not only helps reduce the inflammatory response but also promotes improvements in cardiac function, providing a new strategy for the treatment of myocarditis and related heart diseases.

JAK/STAT Pathway Inhibitors

The JAK/STAT pathway is a key signaling axis that regulates macrophage polarization, especially M1-type polarization.[119] When cytokines such as IL-6 and IFN-γ bind to receptors on the macrophage surface (eg, IL-6R and IFN-γR), they induce dimerization of the receptors. This change in turn activates receptor-associated JAK kinases (eg, JAK1 and JAK2), leading to the phosphorylation of these kinases.[146] The phosphorylated JAK kinases then activate downstream STAT proteins (eg, STAT1 and STAT3). These phosphorylated STAT proteins form dimers and enter the nucleus to initiate the transcription of a range of genes associated with M1 polarization, including TNF-α, iNOS, and IL-1β.[147,148] By inhibiting the JAK/STAT pathway, the signaling of proinflammatory cytokines (eg, IL-6 and IFN-γ) can be effectively blocked, thereby reducing inflammatory injury.

The main mechanism of action of tofacitinib, an oral small-molecule JAK inhibitor, is to target JAK1 and JAK3, and it also has some inhibitory effects on JAK2;[149,150] it blocks the activity of the JAK kinase by competitively binding to ATP-binding sites, thereby effectively inhibiting the phosphorylation and activation of downstream STAT proteins (eg, STAT1 and STAT3).[151] This inhibition significantly reduced M1 polarization in macrophages.[152] Tofacitinib inhibited the

infiltration of M1-type macrophages within plaques and reduced the area of the necrotic core of plaques (by approximately 40%) in an ApoE-/- mouse model, thereby slowing the progression of the disease.[153] These findings not only further confirm the critical role of the JAK/STAT pathway in macrophage polarization but also demonstrate the remarkable efficacy of tofacitinib as a potential therapeutic tool for reducing inflammatory damage, improving cardiac function and delaying disease progression.

Regulation of IL-38

IL-38 may shift the polarization state of macrophages from M1 to M2, inhibit NLRP3 inflammasome activation, and increase the production of anti-inflammatory factors, including TNF-β and IL-10, thereby alleviating myocardial I/R injury. Moreover, IL-38 contributes to modulating the polarization of macrophages through the regulation of dendritic cell-induced regulatory T cells, improving myocardial remodeling after MI.[42] Thus, these results indicate that IL-38 may serve as a prospective therapeutic target for myocardial I/R injury.

Regulation of Heme Oxygenase-1 (HO-1)

HO-1 serves as a rate-limiting enzyme that facilitates the cleavage of heme, leading to the generation of biliverdin, free iron, and carbon monoxide.[154] Notably, HO-1 has antioxidant and anti-inflammatory functions, and myeloid HO-1 expression can ameliorate I/R injury by promoting macrophage M2 polarization. However, the molecular mechanisms by which it supports phenotypic transformation have not yet been investigated. In addition, HO-1 plays an essential role in pinocytosis programs and anti-inflammatory responses.[154] Subjects with higher levels of HO-1 exhibit decreased expression of M1 markers and increased expression of M2 markers.[155,156] Macrophage polarization toward the M2 phenotype induced by increased expression of HO-1, including genetic or chemical modulation of HO-1 expression, can be an effective therapeutic strategy;[157] its therapeutic potential has been demonstrated in I/R injury of the heart, lung, liver, kidney, and other organs.[158] Sha et al demonstrated that astragalus polysaccharide (APS) could stimulate macrophage M2 polarization by enhancing the HO-1 signaling pathway in vitro.[159] Adiponectin, curcumin, and heme can promote macrophage M2 polarization by inducing HO-1 expression. In mice and humans with HO-1 deficiency, the anti-inflammatory and immunoregulatory effects of HO-1 have been demonstrated, suggesting the therapeutic potential of HO-1 induction in myocardial I/R injury.[156]

miR-155 Antagonists

Exosomes released by M1-type macrophages are highly enriched in miR-155, and overexpression of this microRNA impairs endothelial cell function and inhibits neoangiogenesis by blocking the RAC1/Sirt1 signaling pathway, thereby exacerbating the degree of fibrosis and deteriorating cardiac function after myocardial I/R injury.[160] In this context, inhibiting the function of miR-155 or increasing the expression level of its target genes is expected to be a strategy to reverse the adverse effects of M1 polarization on cardiac repair. In a mouse model of MI, miR-155 was translocated to ECs, which reduced the angiogenic capacity of ECs, exacerbated myocardial injury, and inhibited cardiac healing by inhibiting the Sirt1/AMPKα2-endothelial nitric oxide synthase and RAC1-PAK2 signaling pathways.[161]

PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway, as a core intracellular regulatory network, plays a key role in macrophage functional remodeling. When PI3K is activated by extracellular signals such as growth factors and cytokines, it catalyzes the generation of PIP3 from PIP2, which then recruits Akt to the cell membrane and triggers two-site phosphorylation activation.[162] Activated Akt remodels the macrophage phenotype through multidimensional regulation: on the one hand, it blocks the M1-type inflammatory response by inhibiting the NF-κB pathway and NLRP3 inflammatory vesicles, and at the same time, it activates M2-type polarization by activating STAT6, CREB and other transcription factors.[163–165] On the other hand, Akt signaling strengthens macrophage burial, promotes the construction of a microenvironment for tissue clearance and repair, and forms a dynamic regulatory axis of the metabolic state-epigenetic-functional phenotype, which profoundly affects the process of inflammation reduction and tissue remodeling.[166]

Gene and Cell Therapy

Chimeric Antigen Receptor Macrophages Targeting Fibroblast Activation Protein (FAP CAR-Ms)

Lentiviral or CRISPR-Cas9 technologies introduce chimeric antigen receptors (CARs) into macrophages that specifically recognize and target junctional fibroblast activation proteins (FAPs).[167] FAPs are highly expressed on the surface of activated myofibroblasts in myocardial fibrosis and are key markers of fibrosis progression.[168] The CAR structure contains a combination of a FAP-binding domain and a macrophage-specific recognition domain and a macrophage activation signaling domain (eg, CD3zeta or FcγR), and the modified FAP CAR-Ms combine antigen-specific recognition and enhanced phagocytosis/killing functions.[167] In a mouse I/R injury model, FAP CAR-Ms were intravenously injected into mice 3 days after I/R. FAP CAR-Ms significantly improved cardiac function and reduced myocardial fibrosis in mice after I/R.[103] The inherent migratory properties of macrophages make them more likely to infiltrate fibrotic lesions. Compared with traditional broad-spectrum antifibrotic drugs (eg, pirfenidone), FAP CAR-Ms selectively eliminate myofibroblasts in the pathological state, preserving normal cardiomyocyte function.[169] However, owing to the problem of off-target toxicity caused by macrophage overactivation, such as mistakenly attacking normal fibroblasts with low FAP expression, future studies still need to be devoted to finding the optimal regimen for balancing inflammatory clearance and tissue repair.

Stem Cell Therapy

Stem cell therapy has significant potential for treating I/R injury involving macrophages, and its core mechanism involves the modulation of macrophage polarization, the inflammatory response, and tissue repair processes. However, the current dosage, infusion timing and route of stem cell therapy have not been standardized, and protocols need to be optimized through large-scale clinical trials. The molecular mechanisms by which stem cells regulate macrophage polarization (eg, the interaction of miRNAs with signaling pathways) need to be further clarified to avoid delayed repair due to excessive inhibition of inflammation.

Stem Cells Regulate Macrophage Polarization Through Paracrine Effects

Exosome-derived MSC-Exos produced from mesenchymal stem cells (MSCs) can effectively shift the polarization state of macrophages from the M1 phenotype to the M2 phenotype.[117] It has been shown that miR-182, which is highly abundant in MSC-Exos, modulates TLR4/NF-κB (inhibitory effect) and PI3K/Akt (activating effect) signaling cascades to promote the conversion of M1 to M2 macrophages. Inhibition of TLR4 by exosomal miR-182 underlies the immunoregulatory and cardioprotective effects of MSC-Exos.[117] In addition, MSC-Exo-induced macrophage M2 polarization exerts anti-inflammatory effects on organs such as the brain, lung, liver, kidney, and intestine.[170] Even macrophage-secreted EVs help to regulate the progression of inflammatory restoration in the damaged myocardium via intercellular cross-talk; M2 macrophage-derived EVs further polarize macrophages to the M2 type by delivering miR-181b-5p.[99] Many animal experiments have demonstrated that MSC-Exos have excellent therapeutic potential in myocardial reperfusion injury by reprogramming macrophages to regulate immunity and activating M2 macrophages to reduce inflammation. Cardiac repair serves as a rate-limiting enzyme that facilitates the cleavage of hemes, leading to the generation of biliverdin, free iron ions, and carbon monoxide.

Stem Cells Modulate the Inflammatory Microenvironment Involving Macrophages

MSCs maintain the dynamic balance between inflammation and repair by inhibiting the excessive infiltration of neutrophils and monocyte macrophages, reducing the release of proinflammatory factors (eg, TNF-α and IL-1β) while promoting the production of anti-inflammatory factors (eg, IL-10).[171] In addition, stem cells inhibit M1 polarization and enhance angiogenesis by regulating macrophage metabolic pathways, thereby improving tissue repair after IRI.[172–174]

Traditional Chinese Medicine (TCM) Intervention Strategies

Curcumin pretreatment effectively attenuates myocardial injury after I/R and improves cardiac function by inhibiting inflammation and lipid peroxidation. Curcumin exerts potent anti-inflammatory effects by reducing macrophage infiltration and modulating the expression and activity of proinflammatory factors to attenuate inflammatory injury. Curcumin

suppresses the expression of ischemic cardiac early growth response-1, preventing the production of pro-inflammatory factors such as TNF-α and IL-6 that protect the heart.[175] In addition, curcumin has antioxidant activity, protects cells from oxidative damage by scavenging various ROS, resists cardiomyocyte apoptosis, and reduces collagen synthesis and fibrosis. A meta-analysis of several animal experiments revealed the potential of curcumin for treating myocardial I/R injury. In contrast, the results of curcumin interventions in only four clinical studies showed significant variability, which may be related to the therapeutic dose and length of the treatment course, indicating that curcumin may need a prolonged treatment period and a greater dosage to achieve protection of the myocardium.[176] There is still a significant gap in clinical studies on curcumin intervention in myocardial I/R, and more high-quality clinical trial results are needed in the future to support the protective effect of curcumin on the reperfused myocardium.

APS, an active macromolecular compound obtained from the Astragalus membranous, has potent immunomodulatory, antitumor, and antioxidant biological activities. APS can inhibit the differentiation of macrophages into the M1 phenotype, thereby suppressing the production and release of proinflammatory factors and ROS.[158] Moreover, macrophages treated with APS promote polarization to M2 macrophages and increase the production of anti-inflammatory factors by enhancing the Nrf2/HO-1 pathway.[159] IL-34 is involved in the polarization of macrophages, the inflammatory response following reperfusion, and cardiac remodeling. IL-34 activates the NF-κB pathway to increase the expression of the chemokine CCL2, thereby facilitating the early recruitment and polarization of M1 macrophages and aggravating myocardial I/R injury. IL-34 may have the potential to alleviate myocardial inflammation and prevent clinical MI and MI cardiac dysfunction in patients with PCI.

Baicalin attenuates the myocardial inflammatory response and inhibits I/R-induced apoptosis by inhibiting JAK/STAT activation. Baicalin exerts an immunoregulatory effect and shifts macrophages from the M1 phenotype to the M2 phenotype after I/R injury. After baicalin administration, decreased expression of M1 markers and increased expression of M2 markers are observed, accompanied by a significant reduction in the number of CD86-expressing (inflammatory macrophages) cells and an increase in the number of CD206-expressing (anti-inflammatory macrophages) cells.[119] In addition, baicalein promoted NO release via the PI3K-AKT-eNOS pathway to protect CMECs after I/R in rats, contributing to the protection of cardiac microvascular circulation.[177]

Nuanxinkang (NXK), through IKKβ/IκBα/NF-κB-mediated macrophage polarization of the regulatory axis, induces cardioprotective effects against I/R injury by modulating the ratios of the proinflammatory (M1) and anti-inflammatory (M2) macrophage populations and alleviating inflammation. In the case of I/R injury-induced heart failure, cardioprotective activity was demonstrated by the regulation of M1 and M2 macrophage populations.[178]

The above study proved that TCM has demonstrated unique advantages in the treatment of myocardial I/R injury in regulating macrophage polarization and inhibiting inflammation and oxidative stress, but the complexity of its compound composition and the unclear material basis of its efficacy still limit clinical translation. Current studies focus on the phenotypic observation of animal models and lack of large-scale RCTs with hard endpoints as the core, and long-term safety and individualized protocols need to be further explored.

In vivo Imaging of Macrophages in Myocardial I/R Injury

After myocardial I/R injury, macrophages, as core immune effector cells, exhibit dynamic functional properties related to inflammatory regulation and tissue repair. The spatial and temporal distribution patterns of their subpopulations are not only sensitive biomarkers for the extent of myocardial injury but also important predictors for risk stratification of ventricular remodeling. In the field of molecular imaging, FAP, as a key target in the myocardial fibrosis microenvironment, initially demonstrated its value in CAR-M-cell therapy.[103] On this basis, the development of radionuclide-labeled FAP-targeted probes (eg, anti-FAP monoclonal antibodies or small-molecule inhibitors), combined with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) technology, is expected to achieve four-dimensional visual monitoring of macrophage–fibroblast interaction networks. This strategy not only reveals the functional status of immune cells in fibrosis progression but also provides quantitative imaging indicators for assessing the effectiveness of antifibrotic therapy. For macrophage-specific tracking, markers such as lysosomal membrane protein (CD68), hemoglobin scavenger receptor (CD163) and mannose receptor (CD206) have been used for probe design.[179,180]

However, it is worth noting that macrophages overlap with immune cells such as neutrophils in terms of surface markers (eg, CD11b/CD18), and their phenotypes can undergo M1/M2 dynamics in response to changes in the microenvironment, necessitating the development of more specific probes.[181] In addition, the migration, polarization, and phenotypic transition of macrophages in inflammation and damage repair are highly spatially and temporally heterogeneous, and accurately capturing the dynamic changes at the cellular level with existing imaging techniques limited by spatial resolution and temporal sampling frequency is difficult. Especially in dynamic inflammation scenarios, the rapid turnover of macrophage subpopulations further exacerbates the difficulty of signal resolution. Moreover, the high expression of metabolic enzymes in macrophages accelerates the metabolism of radiotracers, and myocardium also have a significant effect on the uptake of radiotracers, which further exacerbates the interference of imaging signals by the complex microenvironment in vivo.[182,183] Overall, current clinical studies have focused on the development of immune intervention strategies, but the visualization and monitoring of the dynamic behavior of macrophages in vivo is still in the exploratory stage.

Conclusion

Different phenotypes of macrophages play essential roles in the progression of myocardial I/R. In different pathophysiologies of inflammation, different macrophages are involved in the inflammatory response and anti-inflammatory response after MI, assuming intricate and multifaceted roles throughout I/R injury. In the early stage of reperfusion, proinflammatory M1 macrophages are activated by multiple factors, including LPS, TNF-γ, and DAMPs, releasing various proinflammatory factors, exacerbating cellular damage by inducing oxidative stress, and mediating a cascade of inflammatory responses and several types of cell death. In contrast, converting macrophages to the reparative M2 phenotype promotes the abrogation of the inflammatory response. Activated M2 macrophages display characteristic anti-inflammatory gene expression and reparative effects, alleviate the inflammatory response by secreting anti-inflammatory factors, remove dead cellular debris through efferocytosis, and promote cardiomyocyte repair and regeneration. In addition, M2 macrophages play crucial roles in both angiogenesis and remodeling of the myocardium, facilitating the restoration of damaged myocardial tissue. The massive activation of anti-inflammatory M2 macrophages significantly ameliorated reperfusion injury in myocardial tissue.

Thus, targeting macrophage phenotypic transformation during I/R may have tremendous therapeutic potential. However, most potential therapeutic targets identified thus far are still in the stage of animal experiments. Macrophage therapy faces insufficient research on therapeutic targets and microenvironment-dependent metabolic reprogramming mechanisms due to simplified disease models. In addition, targeted therapies also face insufficient in vivo target delivery efficiency and off-target effects; the feasibility of its clinical application is still unknown, and more clinical studies and trials are needed to ascertain and validate its safety and efficacy. In the future, reperfusion injury will benefit from more drug studies targeting macrophages. However, in the process of clinical translation of targeted macrophage therapeutics, it is urgent to focus on the following key research directions, including but not limited to: applying cutting-edge emerging technologies to deeply analyze the heterogeneity of macrophage subpopulations, and thus achieve accurate monitoring of macrophage subpopulation dynamics; and at the same time, building an effective bridge between preclinical modeling and human pathology research, in order to promote the research results to accelerate the translation to clinical applications. These prospective therapeutic strategies could open novel paths for cardiovascular disease, leading to enhanced clinical efficacy and improved clinical prognosis.

Abbreviation

APS, astragalus polysaccharide; A2R, adenosine A2 receptor; ARG1, arginase 1; CARs, chimeric antigen receptors; CCL17, C-C motif chemokine ligand 17; CMEC, cardiac microvascular endothelial cell; DAMPs, damage-associated pattern molecules; ECM, extracellular matrix; ECs, endothelial cells; ENA-78, epithelial neutrophil activation protein-78; ERS, endoplasmic reticulum stress; ETC, electron transport chain; EVs, extracellular vesicles; FAP CAR-Ms, chimeric antigen receptor macrophages targeting fibroblast activation protein; FAPs, fibroblast activation proteins; FGF2, basic fibroblast growth factor; GSDMD, gasdermin-D; HO-1, heme oxygenase-1; I/R, ischemia–reperfusion; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; ISRIB,

integrative stress response inhibitor; LPS, lipopolysaccharide; MI, myocardial infarction; MMPs, matrix metalloproteinase proteases; MMT, macrophage-to-myofibroblast transformation; MSCs, mesenchymal stromal cells; NAR, naringenin; NEDD4, neuronal precursor cell-expressed developmentally down-regulated 4; NOX, NADPH oxidase; NXK, nuanxinkang; PCI, percutaneous coronary intervention; PDGF-BB, platelet-derived growth factor-BB; PET, positron emission tomography; P-EVs, platelet membrane modified EVs; ROS, reactive oxygen species; SPECT, single-photon emission computed tomography; TCM, traditional Chinese medicine; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TRMs, tissue-resident macrophages; USP19, ubiquitin-specific protease 19; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFC, vascular endothelial growth factor C.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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