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Review

Emerging roles of macrophages in heart failure and associated treatment approaches

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***Abstract*:** Heart failure is typically caused by different cardiovascular conditions and has a poor prognosis. Despite the advances in treatment in recent decades, heart failure has remained a major cause of morbidity and mortality worldwide. As revealed by *in vivo* and *in vitro* experiments, inflammation plays a crucial role in adverse cardiac remodeling, ultimately leading to heart failure. Macrophages are central to the innate immune system, and they are the most indispensable cell type for all cardiac injuries and remodeling stages. The immediate microenvironment regulates their polarization and secretion. In this review, we summarize the phenotypic heterogeneity and governing roles of macrophages in the infarcted, inflamed, and aging heart and assess their significance as potential therapeutic targets in heart failure. We also highlight the current missing links and major challenges in the field that remain to be addressed before macrophages can be exploited for therapeutic applications.

Keywords: heart failure, inflammation, macrophage, myocardial infarction, myocarditis, stem cell therapy

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Introduction

Heart failure (HF) is a heterogeneous clinical syndrome caused by cardiac overload and injury, impacting an individual's quality of life and longevity.[1,2] It is estimated that about 1% to 2% of the adult population experiences HF.[3] In addition to pharmacological therapy, interventional and surgical treatments offer new opportunities for the treatment of HF. To optimize and establish these therapeutic approaches as well as discover new ones, an understanding of the underlying mechanisms of HF is critical. According to recent studies, inflammation plays an important role in HF pathogenesis. Macrophages, a major cell type of the innate immune system, which are responsible for phagocytosis and immune activation, govern inflammatory processes in injured tissues.[4] These cells contribute to a localized rise in the levels of inflammation cytokines, which activate numerous pro- or anti-inflammatory transcription factors. Many lines of evidence from *in vivo* and *in vitro* studies indicate the importance of macrophages in HF. Here, we specifically discuss the emerging roles of macrophages and their therapeutic potential in HF.

HF and inflammation

HF is a multifactorial systemic disease caused by a structural or functional cardiac abnormality.[3,5] Following cardiac injury, a network of structural, neurohumoral, cellular, and molecular mechanisms are engaged in sustaining the physiological function of the heart.[6] Inflammation and HF are strongly interconnected and mutually reinforce each other.[4] During HF, the immune system is activated, which usually increases in local inflammatory cytokines and proinflammatory transcription factors that trigger subclinical systemic inflammation.[7] Many studies indicate a correlation between the elevation of proinflammatory cytokine levels and poor prognosis and emphasize the role of inflammation and anti-inflammatory agents in acute cardiac injury. However, the underlying molecular mechanisms remain unclear.

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Inflammation is the main element of the cardiac remodeling process in HF and other cardiovascular diseases (CVD). It may also indicate a worsening functional capacity of the heart and a poor prognosis for end-stage cardiac diseases.[8,9] Resolving inflammation is now considered as an active biochemical strategy to restore homeostasis in inflamed tissue.[10] It is accomplished upon prompt resolution of the acute inflammatory response to prevent tissue injury, cessation of leukocyte infiltration, and removal of foreign agents (such as bacteria) and necrotic debris from the inflammation site.[8] These processes are largely governed by macrophages, which play a vital role in mounting and resolution of inflammation, and subsequent tissue repair, due to their high versatility and plasticity.[11,12] In addition, various diseases are associated with chronic nonresolved inflammation, such as cancer, arthritis, and atherosclerosis, wherein the underlying persists for a longer period.[13] For instance, cells in atherosclerotic lesions (macrophages, dendritic cells, and T cells) promote the expression of proinflammatory cytokines and eicosanoids that maintain the proinflammatory state, in response to the activation of both innate immunity and adaptive immunity in the host.[14,15]

Macrophages

Macrophages are an essential part of the innate immune system and reside in virtually all vertebrate tissues.[16] They serve an important role in maintaining the body's homeostasis by disposing internal waste material and engaging in tissue repair.[17] Heterogeneity of the macrophage lineage has been recognized for a long time. It is partly associated with the inability to identify and characterize defined subsets of the monocyte/macrophage lineage[18] because of the differences in replication and turnover rates of macrophages from different tissues.[19] Variations in the physiological microenvironment and the surrounding stimuli have diverse effects on the macrophage phenotype and, hence, impact the macrophage function. Mills *et al.*[20] categorized macrophages into M1 and M2 classes, representing classically activated and alternatively activated macrophages, respectively, based on the T-helper (Th) 1/Th2 T-cell polarization paradigm and their function. It is known that M1 macrophages promote inflammation, while M2 macrophages are responsible for healing and tissue repair.[18] While the M1/M2 nomenclature is useful, it is widely recognized as an oversimplified approach for categorizing multiple polarization phenotypes of macrophages found in various tissues and regulated by multiple microenvironmental signals. However, although a new macrophage classification system is needed to help inpatient clinical diagnosis and treatment, the M1 and M2 nomenclature remains indispensable for the delineation of macrophage phenotypes.

M1 macrophages

M1 macrophages (classically activated macrophages) are proinflammatory cells activated by pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides and intracellular pathogens. They are also activated by Th1 cytokines like interferon-γ (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF). The activation ultimately leads to the production of proinflammatory cytokines, including interleukin (IL)-1α, IL-1β, and IL-6, in addition to tumor necrosis factor-α (TNF-α) and cyclooxygenase-2 (COX-2).[12] Damage-associated molecular patterns (DAMPs), secreted or exposed by living cells experiencing stress or by dead cells, are also linked to inflammation and tissue repair.[21] Functionally, during infection, it is thought that pathogens are eliminated by M1 macrophages *via* activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and generation of reactive oxygen species (ROS), nitric oxide (NO), cytokines, and prostaglandins.[22,23] In conclusion, M1 macrophages exhibit Th1-oriented proinflammatory effector properties, as well as robust antibacterial and antitumor activity, which promote ROS-induced tissue damage.

Typically, pattern recognition receptors (PRRs), the surveillance molecules on the cell surface or in the cytoplasm of macrophages, dendritic cells, and a variety of nonprofessional immune cells, are the targets of PAMPs and DAMPs.[24,25] Toll-like receptors (TLRs) are among the best-characterized PRR subfamilies associated with macrophage activation. TLR signaling is roughly categorized into two pathways, the myeloid differentiation primary response gene 88 (MYD88)- and the toll-receptor-associated activator of interferon (TRIF)-dependent pathways, based on the involvement of distinct adaptor molecules,

and ultimately results in transcriptional upregulation of the downstream genes.[25] In M1 macrophages, TLR agonists rely on the MYD88-dependent signaling pathway, translocation of free nuclear factor kappa-B (NF-κB) to the nucleus, and activation of proinflammatory cytokine genes. As a result of this, numerous proinflammatory cytokines and chemokines are released.[26,27] M1 macrophages sense the invading pathogens and initiate local stimuli through this pathway during the innate immune response. M1 macrophages are also stimulated by Th1 cytokines, including IFN-γ. IFN-γ is primarily produced during the innate immune response by natural killer (NK) and natural killer T (NKT) cells.[28,29] Müller *et al.*[30] found that IFN-γ and TLR agonists both enhance the tumoricidal activity of M1 macrophages and the production of NO and proinflammatory cytokines, while IFN-γ suppresses macrophage production of IL-10, which is affected by TLR agonists. There is evidence that combining IFN-γ and TLR agonist therapy may open up new options for macrophage-associated treatment.[30] On the contrary, it has recently been demonstrated that M1-like macrophages produce a large number of proinflammatory exosomes (M1-Exos) after myocardial infarction (MI). M1-Exos express high levels of proinflammatory miRNAs that exert an antiangiogenic effect and accelerate MI injury by downregulating target genes.[31] The current understanding of this process highlights critical roles for M1 macrophages and M1-Exos in cardiac repair. It, thus, paves the way for the development of a new therapeutic approach in MI prevention and treatment.

M2 macrophages

M2, known as 'alternatively activated macrophages', are immunomodulatory macrophages that are activated by various cytokines: CSF-1, transforming growth factor-β (TGF-β), IL-4, IL-10, and IL-13. They primarily function in releasing immune modulators, phagocytosing apoptotic cells, facilitating collagen synthesis, and maintaining tissue integrity, with proliferative and wound-healing properties.[32,33] M2 macrophages are phenotypically heterogeneous and are classified accordingly. M2a macrophages highly express CD206, CD200R, and CD209 after activation by IL-4 and IL-13. M2b macrophages are obtained upon Fc-receptors, immune complexes (ICs), and TLR stimulation and secrete both proinflammatory cytokines (IL-1β, IL-6, and TNF-α) and anti-inflammatory cytokines (IL-10). M2a and M2b macrophages are involved in immune regulation and can trigger M2-type immune responses. Meanwhile, M2c macrophages can be stimulated by glucocorticoids, IL-10, and TGF-β and show strong anti-inflammatory activity against apoptotic cells. Finally, adenosine receptors are responsible for the induction of M2d macrophages by TLR agonists. The M2d subset can mediate proangiogenic effects by producing anti-inflammatory cytokines (IL-10^{high} IL-12^{low}) and vascular endothelial growth factor (VEGF).

IL-4 and IL-13 are the most important M2-polarizing cytokines that can cause fibrogenesis by regulating the expression of fibronectin-1 (FN-1) and β2-integrins.[34] Abnormal expression of these two cytokines is correlated with fibrosis in multiple tissues and diseases. IL-10 can also drive M2 polarization by regulating the signal transducer and activator of transcription 3 (STAT3) pathway *via* the IL-10 receptor (IL-10R).[35] A recent study in a mouse model of MI confirmed that the administration of long-acting IL-4 complex increases the population of M2-like macrophages (CD206+ F4/80+), primarily in the damaged myocardium.[36] IL-4 complex administration improved cardiac function, which was linked to reducing infarct size, enhancing tissue repair, improving connective tissue development and microvascular formation, and decreasing hypertrophy of cardiomyocytes. The therapeutic effect was reduced when IL-4 complex was administered 28 days after MI. These experiments validated the efficacy of IL-4 and M2 macrophages as a treatment for acute MI.[36] Meanwhile, according to recent studies, Klotho, an anti-aging protein, alleviates indoxyl sulfate-induced HF and kidney damage *via* NF-kB signaling inactivation and promotes M2 macrophage polarization.[37]

Notably, the polarization of macrophages determines the fate of organs and tissues after inflammation or infection. In the case of severe inflammation, macrophages first manifest the M1 phenotype to secrete proinflammatory cytokines. If the M1 phase continues for a long time, this causes extensive damage because of the prolonged exposure to proinflammatory molecules, which explains why some inflammatory diseases get exacerbated. Investigation of how polarized M1

macrophages mature and transform into M2 repair macrophages may be the key to developing new therapeutic approaches.

Other macrophage subtypes

Other macrophage subtypes such as M4, Mox, and M (Hb) or Mhem are induced by CXCL4, oxidized low-density lipoprotein (LDL), and hemoglobin, respectively, in an intraplaque hemorrhage setting.[38,39] However, the current understanding of their unique functions is poor. Further exploration of these subtypes may provide new insights into macrophages and macrophage-associated diseases to enable more effective and novel therapeutic strategies for treating HF.

Cardiac-resident macrophages

Tissue-resident macrophages have been identified as a heterogeneous immune cell population with tissue-specific functions.[40,41] They present in different organs, such as the liver, brain, lung, skin, and heart, maintaining homeostasis and enabling tissue regeneration.[42,43] Furthermore, a self-renewing and self-proliferating population of tissue-resident macrophages that is not monocyte-derived and decreases with age has been detected during adulthood.[40,42]

The tissue microenvironment is a major determinant of macrophage phenotype and influences the expression of numerous genes. In the adult heart, resident macrophages constitute the largest subpopulation of cardiac macrophages.[44] While circulating monocyte-derived macrophages express high levels of C-C motif chemokine receptor 2 (CCR2) and are vital in promoting and coordinating inflammation and migration, CCR2− resident cardiac macrophages promote angiogenesis and cardiomyocyte proliferation in a steady state.[45,46] Recently, Dick *et al.*[47] demonstrated the existence of four macrophage populations in a healthy adult myocardium: TIMD4 + LYVE1 + MHC-II^{low}CCR2− (independent of blood monocytes), TIMD4−LYVE1−MHC-II^{high}CCR2− (partially replaced by monocytes), and two subsets of TIMD4−LYVE1−MHC-II^{high}CCR2+ (fully replaced by monocytes). They also found that ischemia damage reduces the number of TIMD4+ and TIMD4− resident macrophages, while CCR2+ monocyte-derived macrophages take on other roles inside the infarcted tissue. According to the study, using a CX3CR1-based system, depleting resident cardiac macrophages led to impaired cardiac function and exacerbated peri-infarct remodeling. Another study showed that depleting resident cardiac CCR2 macrophages in an MI murine model increased the infarct area and exacerbated left ventricular remodeling.[48] These results indicate that resident cardiac macrophages provide cardioprotection. Lavine *et al.*[49] captured this characteristic feature and assessed the potential therapeutic impact of resident cardiac macrophages by selective administration of a CCR2 inhibitor in a cardiac injury mouse model. They found that the mRNA expression of proinflammatory cytokines in the heart of the injured mouse treated with the CCR2 inhibitor was lower than that in the control. These treated mice showed only minimal adverse remodeling after cardiac injury and, ultimately, revealed restored cardiac function.

Collectively, although the role of resident cardiac macrophages in cardiac injury has not yet been characterized, an increasing number of studies suggest that these cells might have cardioprotective properties in MI. Resident cardiac macrophages continue to proliferate and self-renew upon disruption of homeostasis.[50] They may be involved in the initiation and resolution of ischemic heart disease, contrary to the role of monocyte-derived macrophages. Their potential functions in cardiomyocyte metabolism, contraction, and survival remain to be established.

Macrophages and early MI

The immune responses in myocardial ischemia can be divided into three distinct but overlapping phases: very early, early, and late, representing a time of zero–hours, hours–days, and weeks–months, respectively.[51] After ischemic myocardium necrosis, the intracellular contents are released into the surrounding tissue environment. Cardiac macrophages, fibroblasts, endothelial cells, and other cardiac cells become immediately activated. In the infarcted heart, macrophages constitute the majority of the immune cells.[48] A mount of bone marrow and splenic monocytes is attracted to ischemic heart tissue as monocyte-derived macrophages in response to the ischemic injury. These macrophages replace the resident cardiac macrophages and support the inflammatory process.[52,53] It has been reported that, within

30 min of MI, ROS are generated and the MCP-1/CCR2 axis mediates recruitment of Ly6C^{high} monocytes from the bone marrow and spleen.[54,55] Ly6C^{high} monocytes become the predominant and first cell populations arriving at the infarct lesion to produce proinflammatory cytokines, including IL-6, IL-1α, and TNF-α.[12,56] As phagocytosis occurs extensively, there may be myocardial tissue damage due to the release of proteolytic enzymes and attraction of immune cells to the heart during inflammatory episodes.[57] On the contrary, Ly6C^{high} monocytes phagocytize cell debris and mediate proteolysis at an early stage of acute inflammatory response,[58] presenting a cardioprotective function. Ly6C^{high} monocytes peak approximately 3 days after MI.[56] From days 1–3, monocytes accumulate and constantly differentiate into classically activated macrophages. Consequently, M1 macrophages are the dominant cells in the infarcted zone. They produce proinflammatory cytokines and enhance the proinflammatory response, contributing to the breakdown of collagen and extracellular matrix (ECM). These proinflammatory macrophages pave the way for the ensuing reparative phase by clearing apoptotic cells, cell debris, and ECM components.[59] Approximately 5–7 days after injury, macrophage populations within the infarct area peak, with a transition to the postinfarction proliferative phase following the resolution of inflammation.[60]

Macrophages and postinfarction cardiac remodeling

Cardiac remodeling following MI is a response to either functional or structural cardiac stress, as well as the loss of viable myocardium, and plays a pivotal role in the progress of the disease.[61] During this stage, inflammatory cells (Ly6C^{high} monocytes and M1 macrophages) are gradually replaced by anti-inflammatory cells (Ly6C^{low} monocytes and M2 macrophages). As the inflammatory phase subsides, macrophages regain control of the wound-healing process. Alternatively, activated macrophages produce anti-inflammatory (IL-10), proangiogenic [VEGF, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF 1)], and pro-fibrotic (TGF-β1, fibronectin) factors to help reconstruct vascular supply and repair the necrotic tissue.[62,63] This remodeling initially supports improved cardiac performance; however, with time, it may lead to detrimental pathological consequences such as cardiomyocyte death, compromised ventricular wall integrity, impaired ventricular function, and cardiac fibrosis, eventually contributing to HF[61] (Figure 1).

Despite increasing evidence showing that macrophages are abundant in infarcted hearts and are capable of regulating inflammation, our understanding of macrophage-mediated interactions in suppressing inflammatory signals and resolving leukocyte infiltration is limited. Reports reveal that inflamed heart tissue postinfarction contain a wide range of macrophage subpopulations with distinct functional characteristics, such as regulatory macrophages and reparative macrophages.[64] It has been indicated that the phenotype of a macrophage population can change over time, after infarction. However, it remains unknown whether this alteration of new subpopulations of macrophages into the infarcted zone replaces the original macrophages or is a result of the original cells transforming into different states.

Recently, progressive adverse cardiac remodeling after MI has been treated by targeting macrophages. Bai *et al.*[65] concluded that environmental eustress (EE) improved cardiac function and ameliorated adverse ventricular remodeling after MI in mice models, possibly contributing to the increased survival of Ly6C^{low} macrophages and their CCR2-MHCII^{low} subsets by the brain-derived neurotrophic factor (BDNF)-mediated ERK1/2 and AKT pathways. It represents a previously unknown strategy for preventing adverse ventricular remodeling postinfarction. Another recent study by Wei *et al.*[66] demonstrated that EGF-like repeats and discoidin domains 3 (EDIL3) deficiency ameliorates adverse cardiac healing by neutrophil extracellular traps (NET)-mediated M1 macrophage polarization. Moreover, Yes-associated protein (YAP)/transcriptional coactivator with Postsynaptic density 95, PSD-85; Discs large, Dlg; Zonula occludens-1, ZO-1 (PDZ)-binding motif (TAZ) deletion impedes IL-6 and promotes Arg1 expression *via* interaction with the histone deacetylase 3 (HDAC3)-nuclear receptor corepressor 1 (NCoR1) repressor complex.[67] These changes in macrophage polarization contribute to improved cardiac function by reducing MI-induced ventricular hypertrophy and fibrosis and increasing angiogenesis. Dysregulation of macrophage polarization into the M1 and M2 phenotypes causes severe inflammation and cardiac injury.

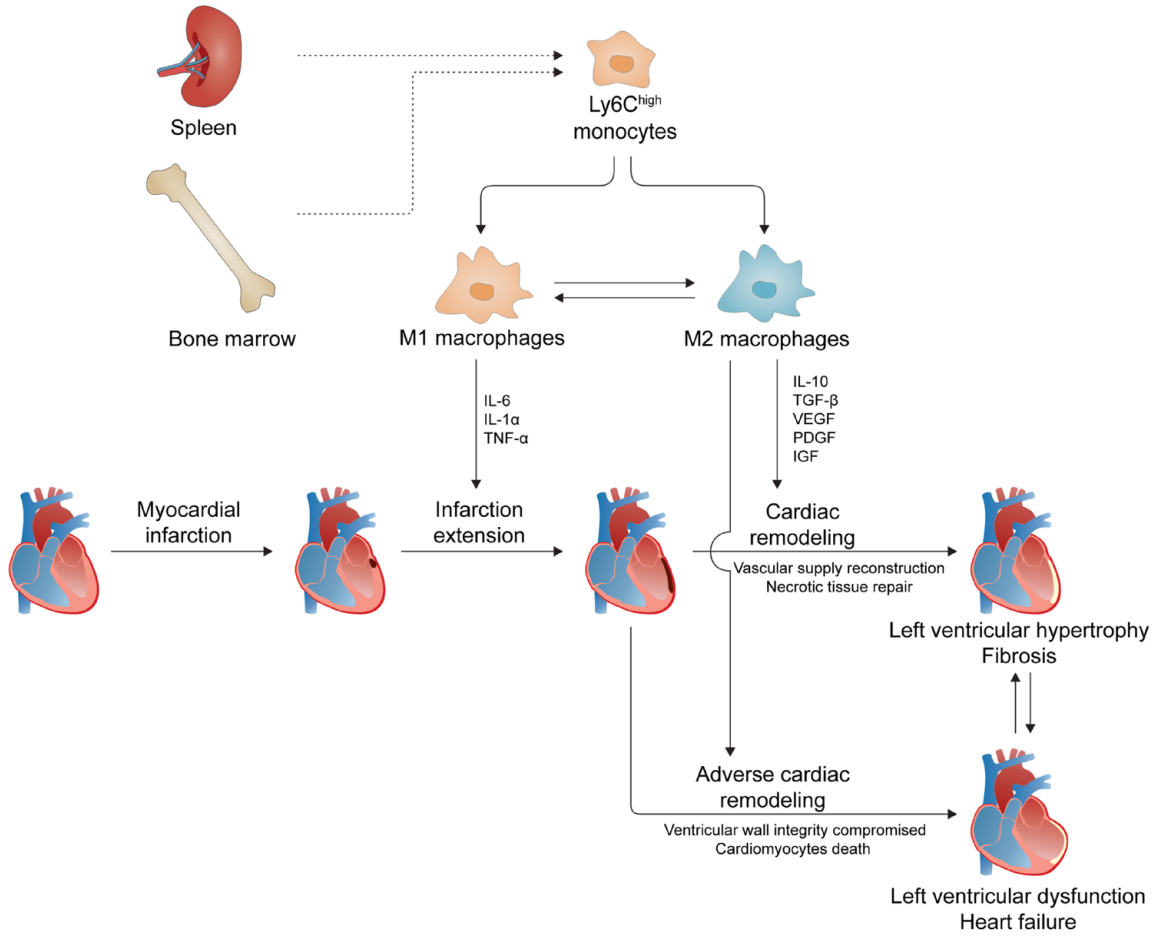

Figure 1. Macrophage involvement in postinfarction cardiac remodeling.
In the early stage of myocardial infarction, the infarct expansion can lead to left ventricular remodeling. The necrosis of cardiomyocytes activates inflammatory pathways. M1 and M2 macrophages arise from Ly6C^{high} monocytes recruited from the spleen and bone marrow to the ischemic heart tissue in response to ischemic injury. M1 macrophages secrete proinflammatory cytokines to enhance the proinflammatory response during the early stage. Anti-inflammatory M2 macrophages participate in chronic inflammatory repair and regeneration during the later reparative phase that involves interstitial fibrosis, left ventricular dilatation, and hypertrophy. Terminal disease trajectory inevitably leads to damage of the ventricular wall integrity and HF.

KDM3A plays an essential role in the biological function of rat bone marrow-derived macrophages (BMDMs) acting *via* epigenetic mechanisms. *KDM3A* deficiency promotes the M1 phenotype but restrains the polarization of the M2 phenotype *in vitro*, as well as aggravates inflammation and exacerbates left ventricular remodeling *in vivo*.[68] On the contrary, as recently demonstrated, M2 macrophage-derived exosomes (M2-exos) carry microRNA-148a (miR-148a) that alleviates myocardial ischemia/reperfusion injury by down-regulating thioredoxin-interacting protein (TXNIP) and inactivates the TLR4/NF-κB/NLRP3 inflammasome signaling pathway.[69] Furthermore, in the same study, *in vivo* treatment with M2-exos reduced infarct size along with mitigated $Ca^{2}+$ overload and cardiac enzyme dysregulation. Glinton *et al.*[70] indicated that cardiac macrophages ameliorate cardiac injury post-MI through the promotion of myocardial lymphangiogenesis by secreting vascular endothelial growth factor C (VEGFC). These important regulators of macrophage-mediated responses may provide new insights for MI treatment.

Macrophages and myocarditis

Myocarditis is an inflammatory mechanism that affects the heart's muscular tissue. It is the main factor behind HF and sudden death.[71,72] If acute

inflammation persists, the disease may progress into subacute and even chronic stages, leading to fibrosis, heart remodeling, and deterioration of the myocardium's architecture and contractility.[71,73] In myocarditis, macrophages and monocytes are the most prominent immune cells involved. Specifically, monocyte-derived macrophages are the earliest myocardium-infiltrating cells in myocarditis and play a role in disease initiation.

The year 2019 saw an outbreak of a new coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2. COVID-19 has led to millions of infections and deaths worldwide and is one of the biggest medical challenges in decades. Although COVID-19 primarily affects the respiratory system, it can also affect other organs, such as the heart, brain, and digestive tract. As regard the cardiovascular system, HF has been reported in approximately 23% of hospitalized individuals with COVID-19, with fulminant myocarditis as one of the most predominant causes.[74] As reported in mouse models of viral myocarditis, the pathology of myocarditis starts with viral-mediated myocyte lysis, which triggers the release of proinflammatory molecules and activates the innate immune response.[75] Considering the major inflammatory cell types in the cardiac injured zone, macrophages migrate and infiltrate the impaired myocardium immediately after viral infection. Depletion of cardiac tissue-resident macrophages and an abundance of inflammatory monocyte-derived macrophages were found in the injured heart tissue of individuals with severe COVID-19 infection.[76]

Altogether, macrophages are the predominant inflammatory cells in myocarditis. They take part in the initiation phase and are also in charge of the progression of the disease. Hence, further studies should focus on the compensatory and regulatory mechanisms of myocarditis therapies targeting these cells.

Macrophages and the aging heart

It is widely recognized that aging increases cardiac-related morbidity and mortality, leading to higher rates of stroke, coronary heart disease, HF, and other CVD.[77] Aging enhances adverse changes in cardiac structure and function, probably by slowing down the cardioprotective molecular mechanisms, thus lowering the CVD threshold.[78] Several pathological changes occur in the aging heart: myocardial sarcopenia, vascular hyperpermeability, hypertrophy, fibrosis, inflammation, and impaired cardiac function. In mouse models of aging, the age groups are defined as young, middle-aged, old, and senescent, corresponding to the ages of <9 months, 12–15 months, 18–24 months, and >26 months, respectively. The old heart (>18 months) harbors more monocyte-derived macrophages and fewer resident cardiac macrophages with self-renewal ability.[79,80] Macrophages, one of the key contributors to the aging process, secrete proinflammatory cytokines, including IL-6, CCL2, TNF-α, and matrix metalloproteinase (MMP)-9. MMPs are zinc-dependent enzymes that regulate ECM, indirectly affecting cardiac structural support and myocardial passive stiffness.[81] Among them, MMP-9 mediates the pathogenesis of cardiac remodeling, and its levels are increased in the plasma and left ventricle of the aging mouse.[82] Chiao *et al.*[81] showed that, in a mouse model, the deletion of MMP-9 reduces age-related diastolic dysfunction partly by lowering the expression of TGF-β signaling-mediated periostin and connective tissue growth factor (CTGF), along with increased MMP-8 levels to adjust myocardial collagen. These abovementioned examples provide growing evidence supporting the therapeutic intervention potential of macrophages in various cardiac diseases.

Macrophages and ectopic calcification

In the pathogenesis of cardiovascular calcification, two distinct phases can be distinguished.[83] The first phase of this process (initiation) is characterized by lipid deposition as well as inflammation and injury. In this stage, immune cells infiltrate the tissue and become activated upon lipid oxidization. For disease progression, osteogenic differentiation and calcification occur in the second phase (propagation). Further calcification is triggered by calcifying microvesicles released by macrophages, valvular interstitial cells (VICs), and vascular smooth muscle cells (VSMCs).[83,84] Multiple studies indicate that M1 macrophages promote aortic valvular calcification,[85–87] secrete cytokines from proinflammatory macrophages (TNF-α, IL-1β, and IL-6), inhibit the myofibroblast response in VICs, and promote their osteoblast-like phenotype.[88] Based on these findings, inflammatory M1 macrophages may contribute to the myofibroblast-to-osteogenic intermediate

VIC phenotypes. Further investigation on the switch from fibrosis to calcification and macrophage-driven inflammation as therapeutic targets in calcific aortic valve disease is needed.

In human atherosclerotic lesions, vascular calcification occurs when calcium phosphate is improperly deposited, similar to the process of bone formation. Chinetti-Gbaguidi *et al.*[89] emphasized that macrophages surrounding calcium deposits in human atherosclerotic plaques are phenotypically defective and incapable of resorbing calcification. It is, therefore, possible that uniquely attractive pharmacological approaches targeting macrophage subpopulations involved in vascular calcification could alleviate calcium deposition by modulating their activity. Interestingly, single-cell RNA sequencing uncovered that a previously undescribed group of macrophages was enriched in *Trem2* (triggered receptor expressed on myeloid cells 2) in atherosclerotic aortas of LDL receptor-deficient (*Ldlr*−/−) mice.[90] It appears that TREM2^{hi} macrophages possess specialized lipid metabolism and catabolism functions as well as an osteoclast-like gene expression signature. In addition, these macrophage populations were found in advanced atherosclerosis, as well as in *Apoe*−/− aortas, which indicates the importance of TREM2^{hi} macrophages in lesion calcification.[90] More systematic and theoretical studies in the future may elucidate their role in detail.

Macrophages and cardiac stem cell therapy

Despite the major developments in modern medicine, morbidity and mortality due to HF remain high. The HF treatment typically depends on the etiology. The condition rapidly progresses and compromises the quality of life if left untreated. Stem cell therapy is a relatively new technology that is still being developed.[5] In recent decades, an increasing number of studies have shown it to be an attractive therapeutic approach for treating and preventing CVD.[91] Vagnozzi *et al.*[92] demonstrated the integral role of macrophages in cardiac stem cell therapy. The authors showed that, in stem cell therapy, the cardiac function in mice following ischemia-reperfusion injury is enhanced by an acute sterile immune response with induction of CCR2+ and CX3CR1+ macrophages rather than the production of new cardiomyocytes. They also observed that this selective macrophage response improves the cardiac fibroblast activity, reduces ECM content in the border zone, and improves the mechanical properties in the ischemic area. These macrophage types constitute a new cell-mediated cardiac protection mechanism. Additional research is needed to determine the therapeutic implications of these findings.

Macrophages are regulated by stem cells and *vice versa*. In general, bone marrow-derived mesenchymal stem cells (BMMSCs) interact with immune cells in the injured heart, providing novel insights for cardiac regeneration therapy.[93] According to previous studies, coculturing macrophages with BMMSCs shifts macrophage polarization toward the anti-inflammatory phenotype.[94] Lim *et al.*[95] confirmed that priming macrophages with BMMSCs enhances their therapeutic effects. They used a rat model of MI to inject one animal group with BMMSCs and another with a mix of cocultured BMMSCs and BMDMs. The authors found that M2 macrophages were more abundant in the latter group but that improved cardiac function was noted in both groups. Furthermore, angiogenesis was significantly improved, and cardiac fibrosis was reduced in the group injected with the mixed cell population. These findings indicate the therapeutic effects of macrophages and demonstrate the successful application of BMDMs primed with BMMSCs as a complementary therapy for cardiac repair.

Macrophage-targeted therapies in HF

Although the production, differentiation, and recruitment of macrophages have been considerably studied in the last decades, this knowledge is yet to lead to effective clinical therapies. In HF, macrophages are mainly responsible for mediating tissue damage and fibrotic scar formation. Precise targeting of macrophages could be beneficial therapeutically, limiting the deleterious effects of the innate immune system while preserving many of its essential features. Macrophages are phagocytic and, thus, capable of swallowing particles ranging in size from nanometers to micrometers.[96] Accordingly, designing nanoparticles and nano-based drug delivery systems is essential for the implementation of macrophage-targeted therapy. As mentioned above, inflammatory monocytes, which differentiate into classically activated macrophages and promote inflammatory diseases, rely on CCR2 to mark the lesion. Leuschner *et al.*[97] synthesized specific monocyte-targeting siRNA

nanomolecules to silence *CCR2* mRNA in the inflammatory monocytes and selectively inhibit their migration. When administered systemically in mice, these molecules were promptly taken up by monocytes and enriched in the spleen and bone marrow. Surprisingly, the authors observed that the degradation of *CCR2* mRNA in monocytes reduced their accumulation at the inflammatory lesion. This treatment has been tested in mouse models, where it reduced the infarct size after coronary artery occlusion, lowered the number of atherosclerotic plaques, and decreased the tumor-associated macrophages.

One of the main causes of HF in adolescents is myocarditis, highlighting the need for macrophage-targeted therapy for viral infection and autoimmune myocarditis. It has been reported that, in individuals with myocarditis, the expression of CSF-1 is elevated.[98] CSF-1 is produced by cells of the mononuclear phagocyte system, which influences the origination and development of monocytes/macrophages through the CSF-1 receptor tyrosine kinase (CSF-1R).[99] Meyer *et al.*[98] downregulated the CSF-1 axis by using nanoparticle-encapsulated siRNA. They observed that silencing CSF-1 production attenuates acute inflammatory injury to the heart and mitigates the lasting sequela of acute myocardial damage. This was shown to be effective in the treatment of viral and autoimmune myocarditis.

Macrophages have been a specific target for treating cardiovascular disease since the discovery of their importance in inflammatory heart tissue and their phenotypic plasticity during disease progression. Many macrophage-targeted therapies for HF can be expected in the future, such as the ones based on the identification and utilization of macrophage markers to provide tissue-specific therapy. In addition, in recent years, the knowledge of epigenetic programming in fibrosis and HF has rapidly evolved,[100] even in the context of macrophage polarization.[101] Targeting epigenetic modifications in macrophages with genetic or pharmacological interventions is highly promising. Moreover, introduction of permanent genetic changes in cells using the clustered regularly interspaced short palindromic repeats (CRISPR) technology could also be used to alter macrophage polarization and their functional phenotype. After cardiac surgery, the protective role of macrophage migration inhibitory factor has been reported.[102] Although there are few studies focused on macrophages and cardiac surgery at the moment, we believe it will be a promising direction for further investigation in the near future.

Limitations

This review mainly discusses the various roles of macrophages in HF, as understood in recent years. Although we have read the literature extensively, some of the latest research advancements may not be fully covered in this review due to the rapid development of emerging technologies and molecular research in this field.

Conclusion

In this review, we present the recent advances in the understanding of the participation of cardiac macrophages in HF pathology, cardiac repair, and postischemic remodeling. Nonetheless, there is still a mountain to climb in this field. Further studies should utilize new tools to image the dynamic recruitment, apoptosis, and function of macrophages in the ischemic myocardium and injured tissues. Although extensive progress has been made in the understanding of the roles of macrophages in HF, translating these pathophysiological findings into clinical practice requires additional information. As insight beckons effort and innovation, we believe that innate immunity processes are crucial for the HF mechanism and that macrophage-targeted treatment will eventually become an effective and neoteric therapy.

Declarations

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Consent for publication

Not applicable.

Author contributions

Lan Xie: Conceptualization; Investigation; Writing – original draft.

Jinyong Chen: Investigation; Resources; Visualization; Writing – review & editing.

Yidong Wang: Conceptualization; Validation; Writing – review & editing.

Chengjiang Jin: Methodology; Writing – original draft.

Yao Xie: Methodology; Writing – review & editing.

Hong Ma: Conceptualization; Project administration; Supervision; Writing – review & editing.

Meixiang Xiang: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

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