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Cardiac macrophages and their functions in homeostasis and injury

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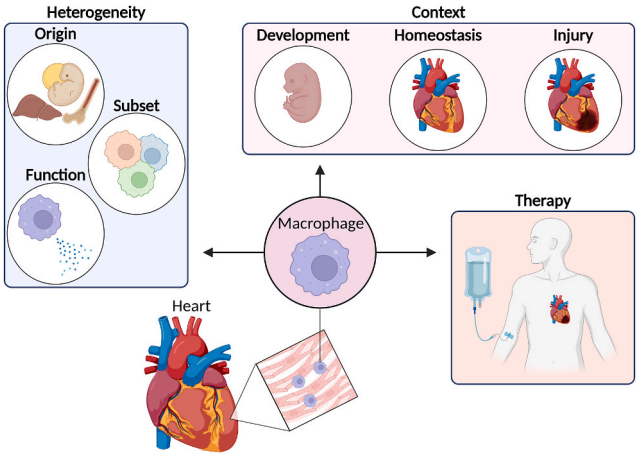
HIGHLIGHTS

- New technologies at single-cell level reveal large diversity of heart macrophages with diverse roles in health and disease.
- Tissue-resident cardiac macrophages contribute to heart development and regulate adult heart physiology.
- Macrophages actively participate in all stages of the cardiac injury response, from initial damage sensing to repair.
- Future research should address whether macrophages may provide therapeutic targets in the context of heart injury.

GRAPHICAL ABSTRACT



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ABSTRACT

Due to their remarkable plasticity, macrophages can adapt to diverse environments and challenges therein, thereby exerting tissue-specific and context-specific functions. Macrophages are the most frequent immune cell population present in the heart and contribute substantially to cardiac homeostasis and function. Moreover, macrophages are key regulators throughout all stages of heart injury, acquiring diverse phenotypes that can either ameliorate or exacerbate cardiac pathology in a context-dependent manner. The contribution of macrophages to both tissue damage as well as to recovery/tissue repair during heart injury provides avenues for therapeutic modulation of their functions to beneficially influence heart injury progression and hence prevent heart failure. However, to effectively fine-tune macrophage function, a deep understanding of their heterogeneity is required. The present review focuses on the phenotypic diversity and different roles of macrophages in cardiac homeostasis as well as in ischemic and non-ischemic heart disease, and discusses macrophages as potential therapeutic targets in the settings of heart injury.

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1. Introduction

Tissue macrophages were originally thought to exclusively originate from the bone marrow (BM) and particularly from blood monocytes that infiltrate peripheral tissues where they differentiate into macrophages [1]. However, in recent years, our understanding regarding the ontogeny, phenotypic heterogeneity and functional diversity of macrophages has completely shifted based on a series of landmark studies that demonstrated that tissue macrophages can have an origin that is distinct from that of circulating adult mononuclear cells in the periphery. Specifically, development of macrophages during embryonic stages gives rise to the majority of adult tissue-resident macrophages that can persist throughout adulthood, as evidenced in various tissues [2–5]. Such embryonically derived adult tissue-resident macrophages are self-maintained through local proliferation at steady state [3,6–9]. In certain tissues, monocyte-derived macrophages can also contribute to the tissue resident macrophage pool or partially replace the embryonically derived cells over time; this process may especially occur in response to tissue injury or inflammation [3,6,10]. Tissue-resident macrophages play key roles in tissue remodeling during development and contribute to tissue homeostasis maintenance [9,11,12]. As opposed to infiltrated macrophages deriving from monocytes that frequently bear pro-inflammatory properties, macrophages of embryonic origin rather display reduced capacity to generate inflammatory responses [11–14].

Macrophages located in the heart [9,10,15] play a crucial role not only in supporting cardiac homeostasis, that is of importance because the heart has limited regenerative capacity [16,17], but also during the response to heart stress due to various conditions, including hemodynamic overload, mechanical strain, metabolic disturbances, inflammatory and neurohormonal activation, infectious agents, and toxic insults, or to injury [18], which can manifest as both ischemic and non-ischemic conditions [18,19]. Ischemic heart injury, primarily caused by atherosclerosis, includes acute ischemic injury, caused by a sudden and severe interruption of blood flow that deprives a segment of the myocardium of oxygen and nutrient supply leading to myocardial infarction; ischemia-reperfusion injury, occurring upon restoration of blood supply due to oxidative stress and consequent inflammation; and chronic ischemic injury, which results from moderate and prolonged reduction in blood supply or unresolved acute ischemic injury [19,20]. Causes of non-ischemic cardiac injury include cardiomyopathies—heterogeneous conditions influenced by risk factors, such as hypertension-driven chronic pressure overload, diabetes, genetic mutations, unhealthy lifestyle and age—and myocarditis, representing inflammation of the myocardium that can be caused by diverse stresses, such as viral infections, autoimmunity or drug toxicity [18]. Independent of their nature, heart injuries are characterized by immune activation and associated inflammation followed by reparative responses, aiming at restoring tissue integrity [19]. Upon ischemic injury, inflammation often occurs before fibrosis, whereas during non-ischemic heart injury, inflammatory and fibrotic processes may temporally coincide [19]. Cardiac injury is often associated with unresolved inflammation and/or excessive fibrosis, thereby resulting in maladaptive tissue repair, adverse remodeling, and ultimately impaired heart function, eventually progressing to heart failure (HF) [20,21]. Despite significant advancements in research and pharmacological therapies, HF remains one of the leading global causes of death, with 50 % of individuals diagnosed with the condition dying within five years of their diagnosis [22]. Due to their diverse phenotypes, heart macrophages play a central role throughout the various stages of the response to injury, where they can contribute to both tissue damage as well as recovery responses [19].

In this review, we discuss the diverse functions of macrophages in the maintenance of heart homeostasis, and in various types and stages of ischemic and non-ischemic heart disease, highlighting their broad plasticity and different phenotypes. We also discuss the novel aspects regarding the possible therapeutic targeting of macrophages in the heart [19].

2. Heterogeneity and functions of cardiac macrophages at steady-state

Cardiac tissue-resident macrophages are present at steady state and are the most abundant immune cells in the adult heart [9,10,13,23–25] accounting for ~5–10 % of the total cells of both the human and murine heart [9,10,23–25]. Cardiac macrophages sequentially arise from embryonic primitive hematopoiesis, which begins in the yolk sac, and then from definitive hematopoiesis, which starts in the fetal liver and later shifts to the bone marrow, the major site of hematopoiesis for the rest of the life [3,6,26].

In the adult mouse heart, the classification of resident cardiac macrophage subsets relies on a range of both overlapping and distinct cell-surface markers, as identified by different experimental approaches [3,6,10,27,28]. A recent study [6] identified three different cardiac macrophage subsets by single-cell RNA sequencing (scRNA-seq). Each subset has unique origin and turnover dynamics, as documented by inducible fate-mapping approaches, and receives a differential input from blood-derived monocytes, as assessed through parabiosis experiments [6] (Fig. 1A). The most abundant population (named TLF$^+$) expresses the markers TIMD4, LYVE1, and FOLR2 while lacking CCR2 expression and displays low levels of MHC-II [6] (Fig. 1A–Table 1). TLF$^+$ macrophages originate from yolk-sac macrophages as well as fetal liver monocytes; they represent a long-lived subset that is maintained almost completely by self-renewal with minimal input from blood-derived monocytes during adulthood [6] (Fig. 1A). A second population is defined by the absence of expression of the aforementioned three markers, TIMD4, LYVE1, FOLR2 (TLF$^-$), but expresses CCR2 in addition to high levels of MHC-II [6] (Fig. 1A–Table 1). These CCR2$^+$ macrophages originate from fetal liver monocytes, are short-lived and are almost completely replaced by blood monocytes in the adult heart [6] (Fig. 1A). A third population is TLF$^-$ and CCR2$^-$ and displays high expression of MHC-II (MHC-II^{hi} cells) [6] (Fig. 1A–Table 1). This latter subset, similar to the TLF$^+$ cells, originates from the yolk sac and from fetal liver cells and exhibits self-renewal capacity; however, there is also a modest contribution of blood monocytes to this population during life [6] (Fig. 1A). Another study [27] identified a population in the adult murine heart as LYVE1^{hi}MHC-II^{low} cells (Table 1); this population is analogous to the TLF$^+$ macrophages, described by Dick et al. [6]. However, unlike the TLF$^+$ population [6], this study demonstrated a significantly higher contribution of blood-derived monocytes to the LYVE1^{hi}MHC-II^{low} population that further increases with age [27]. In addition, according to the data reported by Epelman et al. [3], the CCR2$^+$ macrophage population is replaced to a less extent by blood monocytes, as compared to the findings of Dick et al. [6]. These discrepancies are likely due to differences in the methodological approaches used for the identification of the different macrophage subsets, as well as variations in the methods employed to assess the monocyte contribution to the macrophage populations.

During steady-state, the contribution of monocytes to the TLF$^+$ and MHC-II^{hi} macrophage population is limited and does not increase with age in adult mice [6]. Of note, the heart microenvironment guides the differentiation of recruited monocyte-derived macrophages into specific resident macrophage subsets, thereby warranting that the overall composition of cardiac macrophage populations remains constant in homeostasis [6,16]. At steady-state, monocyte-derived macrophages initially display distinct transcriptional profiles as compared to that of pre-existing tissue-resident subsets; however, as they mature in the tissue, their transcriptome gradually changes, eventually converging with that of the original subsets [6]. Pathway analysis of scRNA-seq data revealed that TLF$^+$ macrophages are likely involved in homeostatic functions, including cellular transport and endocytosis [6,16]. The transcriptome of MHC-II^{hi} macrophages, in turn, was associated with cell migration functions and inflammatory responses while the transcriptome of CCR2$^+$ macrophages was linked to cellular activation, degranulation, and immune effector processes [6]. Importantly,

pathway analysis of transcriptomic data from other studies supports the pro-inflammatory phenotype of CCR2$^+$ macrophages [3,10]. The TLF$^+$ macrophage subset is conserved between mouse and human hearts [26]. As observed in mouse models, human myocardial tissue also contains CCR2$^-$ macrophages, CCR2$^+$ macrophages, and CCR2$^+$ monocytes (Table 2) [29]. Both human CCR2$^+$ and CCR2$^-$ macrophage populations display high expression of HLA-DR (human MHC class II, Table 2) [29]. Additionally, distinct *LYVE1*$^+$ resident macrophage subsets have been identified in human myocardial tissue by transcriptomic analysis, including monocyte-derived macrophages [23]. However, unlike their murine counterparts, these human *LYVE1*$^+$ macrophages lack *TIMD4* expression [23]. Moreover, a *LYVE1*$^-$ macrophage subset enriched in antigen-presenting molecules has been described [23].

A body of evidence from mouse studies highlights that cardiac resident macrophages engage in a wide array of tissue-specific functions, not strictly related to immunity, that are essential to both cardiac development and the regulation of heart homeostasis at steady-state [30–35] (Fig. 1B). For instance, in the murine developing heart, CCR2$^-$ yolk-sac-derived tissue resident macrophages spatially associate with the endothelial cells of the perfused coronary vasculature where they regulate vascular patterning, an essential step for the functional

Table 1
Different murine macrophage subsets discussed in this review and their surface markers.

Macrophage subset	Surface markers	Reference
TLF$^+$	CD45$^+$ CD11b$^+$ CD64$^+$ TIMD4$^+$ LYVE1$^+$ FOLR2$^+$ MHC-II^{low} CCR2$^-$	6
MHC-II^{hi}	CD45$^+$ CD11b$^+$ CD64$^+$ TIMD4$^-$ LYVE1$^-$ FOLR2$^-$ MHC-II^{hi} CCR2$^-$	
CCR2$^+$	CD45$^+$ CD11b$^+$ CD64$^+$ TIMD4$^-$ LYVE1$^-$ FOLR2$^-$ MHC-II^{hi} CCR2$^+$	
LYVE1^{hi}MHC-II^{low}	LY6C– F4/80$^+$ MERTK$^+$ CD64$^+$ LYVE1^{hi} MHC-II^{low} CX3CR1^{low}	27

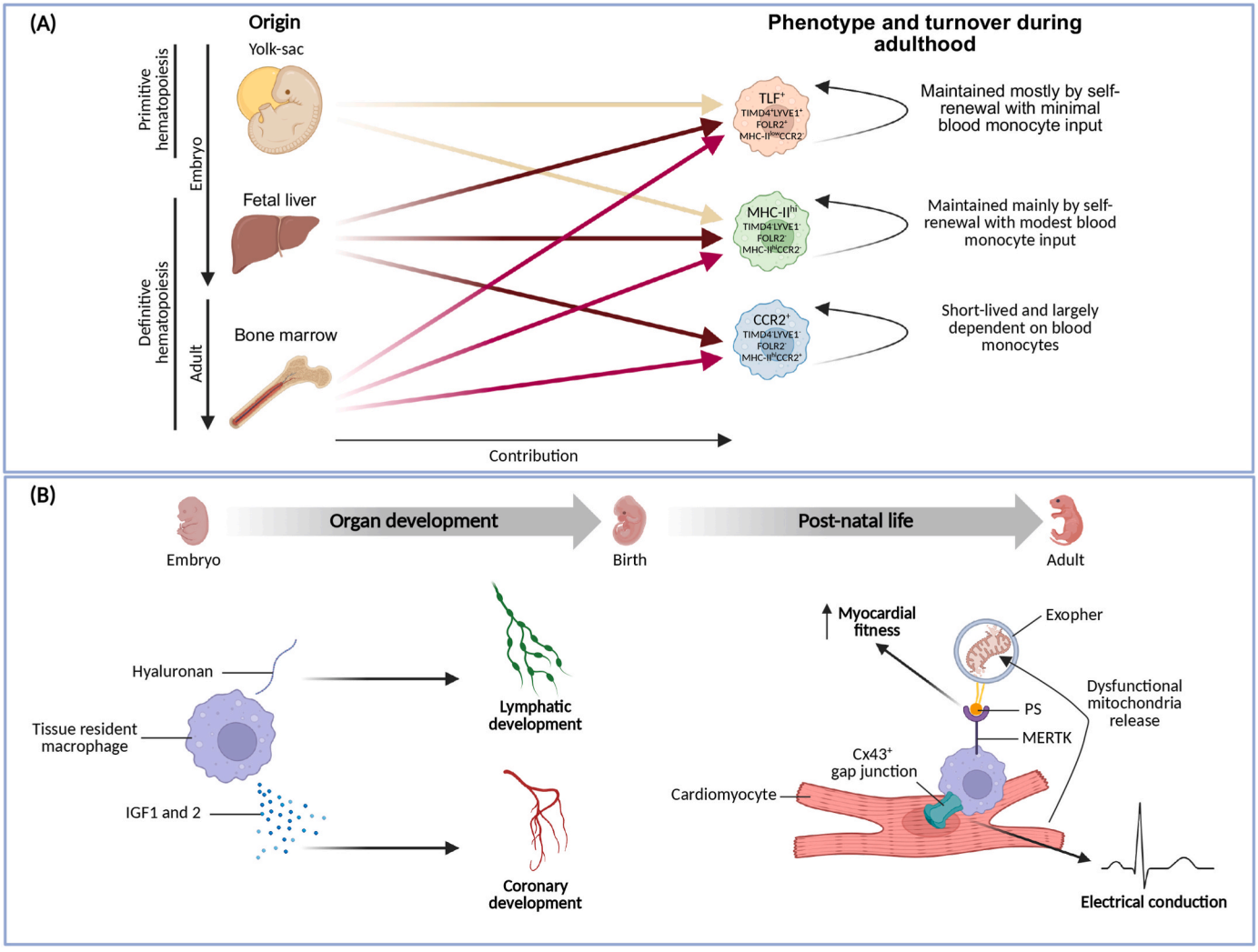

Fig. 1. Origin and heterogeneity of murine tissue-resident cardiac macrophages and their role during heart development and homeostasis. **(A)** Adult tissue-resident cardiac macrophages include three populations namely TLF$^+$, MHC-II^{hi} and CCR2$^+$ [6]. These populations are established at various stages of development and have different lifecycles during adulthood [6]. Yolk-sac macrophages and fetal liver monocytes are the primary source for both TLF$^+$ and MHC-II^{hi} cells [6]. Both populations exhibit self-renewal capacity; however, TLF$^+$ macrophages are maintained with minimal input from blood-derived monocytes during adulthood, whereas MHC-II^{hi} macrophages receive a modest contribution from blood monocytes over time [6]. CCR2$^+$ macrophages mainly derive from fetal liver monocytes, are short-lived and are almost entirely replaced by blood monocytes in the adult heart [6]. **(B)** In mice, tissue-resident macrophages orchestrate the development of the cardiac lymphatic [31,32] and coronary vasculature [30–33] via the production of hyaluronan [31] and insulin-like growth factor (IGF) 1 and 2 [30], respectively. In adult hearts, connexin-43 (Cx43)-expressing tissue-resident macrophages interact with cardiomyocytes to facilitate electrical conduction [34]. Macrophages also support cardiomyocyte fitness by MER tyrosine kinase (MERTK)-dependent phagocytosis of phosphatidylserine (PS)-marked exophers containing dysfunctional mitochondria extruded by cardiomyocytes [35].

Table 2
Different human macrophage subsets discussed in this review and their surface markers.

Macrophage subset	Surface markers	Reference
CCR2$^-$ HLA-DR^{hi}	CD14$^+$ CD45$^+$ CD64$^+$ CCR2$^-$ HLA-DR^{hi} MERTK$^{+/-}$ CD33$^+$ CD163$^+$ CD3$^-$ CD19$^-$ CD56$^-$	29
CCR2$^+$ HLA-DR^{hi}	CD14$^+$ CD45$^+$ CD64$^+$ CCR2$^+$ HLA-DR^{hi} MERTK$^{+/-}$ CD33$^+$ CD163$^+$ CD3$^-$ CD19$^-$ CD56$^-$	

maturation of the coronary vasculature [30–33] (Fig. 1B). This proangiogenic role is mediated in part by the secretion of insulin like growth factor (IGF) 1 and 2 and is achieved through regulation of endothelial cell proliferation and migration, with subsequent endothelial cell incorporation into areas of active remodeling [30] (Fig. 1B). Macrophages with similar properties are also found in the adult heart where they were shown to play a pro-angiogenic role at steady state [30,33]. Similar to their crucial function in coronary angiogenesis, yolk-sac derived tissue resident macrophages play a role in the lymphatic development of the embryonic murine heart, a process orchestrated by macrophage-derived hyaluronan that facilitates the interaction between macrophages and lymphatic endothelial cells, thereby promoting lymphatic sprouting, branching, and fusion [31,32] (Fig. 1B). These macrophages are typically LYVE1$^+$, reflecting their specialized role in hyaluronan-mediated crosstalk with the developing lymphatic vasculature [36]. In the distal atrioventricular node of the adult mouse heart, tissue resident macrophages are interspersed with cardiomyocytes, with which they interact via connexin-43 (Cx43$^+$)-containing gap junctions facilitating electrical conduction [34] (Fig. 1B). Similar to the murine heart, tissue-resident macrophages expressing Cx43$^+$ gap junctions at their contact points with conducting cardiomyocytes were also detected in the human AV node [34], though a possible role for these cells in the human heart homeostasis remains unclear. Another study demonstrated that ventricular tissue-resident cardiac macrophages support the fitness of surrounding cardiomyocytes by degrading damaged and dysfunctional mitochondria released from cardiomyocytes, a process that is autophagy-dependent and complements autophagic mitochondrial turnover [35] (Fig. 1B). Mechanistically, this process involves the MER tyrosine kinase (MERTK)-dependent recognition of the 'eat-me' signal phosphatidylserine (PS) on the surface of mitochondria-containing subcellular particles (called exophers) extruded from cardiomyocytes, followed by the phagocytosis of these exophers [35] (Fig. 1B). Exopher phagocytosis by macrophages prevents free mitochondria and mtDNA from accumulating in the cardiac extracellular space, thereby avoiding inflammatory activation and ultimately preventing ventricular dysfunction [35]. Exopher-like structures were also found in the human myocardium [35], although their exact role in human heart physiology remains unknown. Taken together, multiple articles in recent years established that cardiac tissue-resident macrophages play essential roles in heart development and homeostasis.

3. Macrophage function in the context of heart injury

Following heart injury, the initial inflammatory phase is followed by a reparative phase (in some cases referred to as proliferative or anti-inflammatory) that involves fibrosis, collagen deposition, granulation tissue formation and angiogenesis following resolution of inflammation [20,37,38] (Fig. 2). During the subsequent maturation phase, the granulation tissue is cleared, angiogenesis is terminated and a cross-linked collagen matrix is formed, leading to scar remodeling [21,38] (Fig. 2). Here we will discuss the function of cardiac macrophages in these different phases of heart injury.

3.1. Inflammatory phase

An ischemic cardiac event results in limited delivery of oxygen and nutrients to the heart, consequently leading to necrosis of cells located in the infarcted area, including cardiomyocytes and resident macrophages [20,21,39] (Fig. 2). This process drives the release of inflammatory factors, particularly damage-associated molecular patterns (DAMPs) that activate parenchymal and stromal cells and tissue-resident macrophages via interaction with pattern recognition receptors (PRRs) [16,19–21,40,41] (Fig. 2). Alarmins, such as extracellular RNA, trigger the DAMP-related inflammatory response [20,42,43]. Activation of PRRs, such as toll-like receptors (TLRs), occurs on fibroblasts and tissue-resident macrophages [16,20,40], and triggers proliferation of the latter [10] and, as demonstrated in models of cardiac transplantation, expression of pro-inflammatory cytokines, such as interleukin (IL)-1b, as well as chemokines, such as CXCL5, which promote recruitment of monocytes and neutrophils, in turn further aggravating the inflammatory response [19,44,45] (Fig. 2). The C–C Motif Chemokine Ligand 2 (CCL2) signaling axis is a central axis involved in monocyte recruitment [44,46–48]. Moreover, disrupting the CCL5-dependent leukocyte-recruitment axis in mice is protective after MI [49]. Bearing a pro-inflammatory profile at baseline, mouse tissue resident CCR2$^+$ macrophages [3,6,10] are the main drivers of initial monocyte recruitment. Indeed, transplantation of hearts from CCR2-diphtheria toxin receptor (DTR) transgenic mice after depletion of the CCR2$^+$ population by diphtheria toxin administration was associated with reduced recipient inflammatory monocyte and macrophage accumulation in the donor heart [44]. CCR2$^+$ tissue-resident macrophages in the human system are also pro-inflammatory and their increase is associated with detrimental remodeling of the left ventricle and consequent systolic dysfunction in patients with HF [29]. Conversely, CCR2$^-$ macrophages rather prevent excessive inflammation and monocyte recruitment to infarcted murine hearts [44].

Activation of acute emergency myelopoiesis in the bone marrow in mice leads to monocyte generation underlying the sustained large-scale recruitment of monocytes to the infarcted area [50] (Fig. 2). Moreover, IL-1 expression upon TLR activation [51] and activation of the sympathetic nervous system [52] induce extramedullary generation of splenic macrophages, which support the sustained demand for macrophages at the injury site (Fig. 2). Infiltrated monocytes differentiate into macrophages, mainly into the CCR2$^+$ population [10,33,44], possibly compensating for the decrease of resident macrophages, which are depleted through cell death and egress [9,10]. An increase in CCR2$^+$ macrophages during myocardial infarction was also described in human patients with the help of molecular imaging [53]. Interestingly, in a cardiomyocyte ablation mouse model, recruited CCR2$^+$ macrophages displayed increased production of pro-inflammatory chemokines and cytokines relative to the tissue-resident CCR2$^+$ macrophages [44]. Moreover, at 11 days post MI in mice, a large proportion of recruited macrophages adopted a gene expression signature that resembled that of resident macrophages with the exception of some genes that confer essential repair functions to resident macrophages, demonstrating that infiltrated macrophages are not capable to completely compensate for the functions of the diminished resident macrophages [10]. In mice, although the remaining resident macrophages proliferate post infarction and the number of recruited macrophages decreases, the ratio of resident to infiltrated macrophages four weeks after infarction does not reach the ratio at steady-state [10].

During the inflammatory phase, both recruited and remaining resident macrophages can clear dead tissue via efferocytosis, thereby generating an environment that facilitates resolution of inflammation and subsequent tissue repair [19,37,54] (Fig. 2). In mice deficient for REG3β, an important regulator of macrophage trafficking to the damaged heart, the reduction of macrophage abundance resulted in diminished clearance of neutrophils within the ischemic heart environment, thereby leading to elevated matrix degradation, delayed

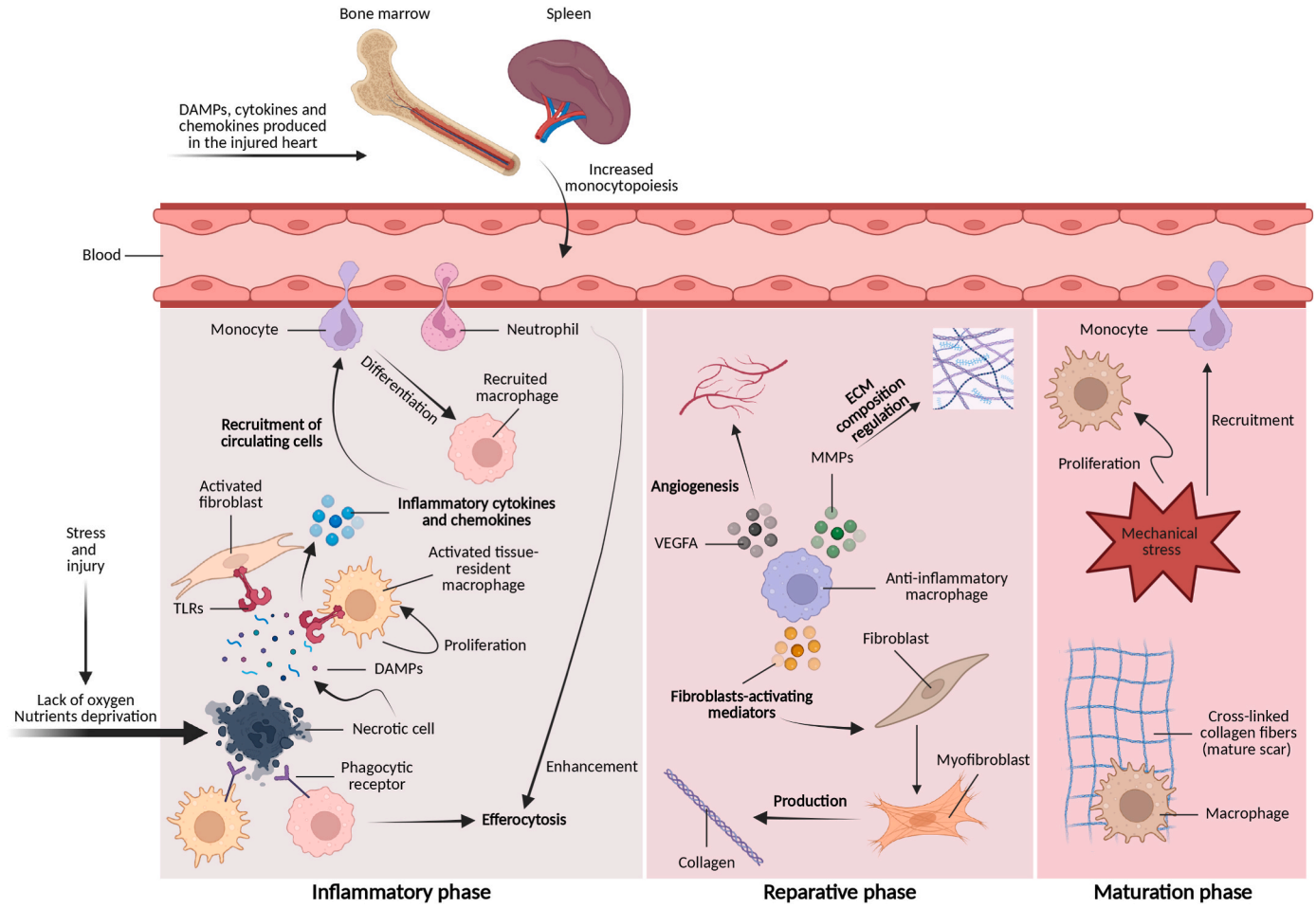

Fig. 2. The processes occurring during the different phases of cardiac injury. Following an ischemic event, necrosis of cardiomyocytes and resident macrophages in the infarcted area leads to the release of damage-associated molecular patterns (DAMPs) that activate pattern recognition receptors (PRRs, e.g., toll-like receptors [TLRs]) on fibroblasts and immune cells [16,20,40]. This process leads to cellular activation and initiates an inflammatory cascade that promotes neutrophil and monocyte recruitment [44,45]. Concurrently, emergency myelopoiesis in the bone marrow and extramedullary hematopoiesis in the spleen further contribute to the infiltrated macrophage pool [50–52]. During the inflammatory phase, both tissue-resident and infiltrated macrophages clear necrotic tissue via efferocytosis, which fosters an environment that supports inflammation resolution and tissue repair [19,37,54]. Neutrophils support the switch of macrophages to a reparative phenotype via neutrophil gelatinase-associated lipocalin, enhancing efferocytosis [61]. During the reparative phase, anti-inflammatory macrophages secrete factors to promote fibroblast-to-myofibroblast transition and collagen synthesis [19,73,74]. Moreover, they promote angiogenesis and regulate extracellular matrix (ECM) composition via the production of vascular endothelial growth factor A (VEGFA) [98–100] and matrix metalloproteinases (MMPs) [91–96], respectively. In the maturation phase, a stable cross-linked collagen scar forms [21,38]. While macrophage density decreases, a persistent population remains in mature scars [102]. Non-infarcted myocardium undergoes hypertrophy and remodeling under chronic load, associated with low-grade inflammation and macrophage accumulation, continuing for weeks post-injury [21,38,52].

collagen deposition, and a higher risk of heart rupture [55]. Macrophage efferocytosis is mediated through the expression of phagocytic receptors such as MERTK or opsonins bridging apoptotic cells to phagocytic macrophage receptors, such as milk fat globule-EGF factor 8 (MFGE8) [38,54,56–58]. The clearance of apoptotic cells drives macrophages toward an anti-inflammatory and reparative phenotype [57,58]. In a mouse model of ischemia-reperfusion injury, expression of constitutively active MERTK, engineered to resist protease cleavage, promotes inflammation resolution, as evidenced by reduced infiltration of neutrophils and monocytes and increased expression of the anti-inflammatory mediators IL-10 and transforming growth factor-β (TGF-β) [38,57]. The cleavage of MERTK in macrophages is regulated by hypoxia inducible factor (HIF)1α, which promotes the expression of the metalloprotease ADAM17 [59]. While deletion of HIF1α in myeloid cells improves efferocytosis and promotes resolution of inflammation, combined deletion of HIF1α and HIF2α in myeloid cells results in macrophage necroptosis and cardiac rupture—highlighting the essential role of basal HIF signaling in maintaining macrophage survival during cardiac injury [59].

Beyond inflammation control, efferocytosis also contributes to tissue repair. Following MI in mice, the MERTK- and MFGE8-dependent efferocytosis facilitates the switch of macrophages towards a reparative phenotype, accompanied by production of vascular endothelial-derived growth factor A (VEGFA), which may promote survival and proliferation of endothelial cells [58]. Additionally, MERTK facilitates the removal of exophers, containing damaged mitochondria, released by stressed cardiomyocytes, thus preserving tissue integrity during heart injury [35]. A similar role in scavenging cardiomyocyte-ejected dysfunctional mitochondria was demonstrated for TREM2^{hi} macrophages in the settings of cardiac septic stress [60]. Interestingly, neutrophil gelatinase-associated lipocalin secreted by neutrophils, which are recruited very early to the site of injury, promotes a reparative macrophage phenotype with elevated efferocytosis capacity [61] (Fig. 2). Depletion of macrophages, or inhibition of their efferocytosis ability, impact also on non-immune functions as the disruption of the clearance of toxic material and dying cells upon MI causes abnormal

electrical conduction, and thus ventricular tachycardia driven by rapidly infiltrating neutrophils [62]. In another context, specifically, in a pressure overload model, macrophages were found to maintain heart electrical conduction and prevent cardiac death [63]. Mechanistically, amphiregulin produced by macrophages leads to Cx43 phosphorylation in cardiomyocytes and promotes the formation of gap junctions thus facilitating intercellular communication between cardiomyocytes during stress, thereby preventing lethal arrhythmias [63].

During the inflammatory phase of MI, macrophages can also produce matrix-metalloproteinases (MMPs), which modulate disease outcome [19]. For instance, decreased MMP-9 expression owing to deficiency of the inflammatory signaling adapter CARD9 was associated with reduced cardiomyocyte apoptosis and beneficial effects post-MI [64]. Altogether, there is ample scientific evidence supporting a central role for both tissue-resident and recruited macrophages in regulating the inflammatory phase upon heart injury.

3.2. Reparative phase

The reprogramming of macrophages from pro-inflammatory to anti-inflammatory cells, along with the proliferation of the latter, underlies the process of resolution of inflammation, which initiates cardiac repair [19,37,38,65] (Fig. 2). Several factors contribute to this phenotypic transition of macrophages in mice [38]. These include the clearance of apoptotic cells by macrophages through efferocytosis [54], already outlined earlier in the text, the production of intrinsic anti-inflammatory signals in macrophages, triggered by pro-inflammatory cytokines within the infarct microenvironment [66], and the induction of various anti-inflammatory cytokines in the injured heart [67]. Anti-inflammatory macrophages express genes encoding reparative factors, such as *Pdgf* (platelet-derived growth factor) *b* and *Igf1* [38,68]. A wide variety of secreted mediators derived from macrophages, such as TGF-β [69], IL-10, IL-4, and IL-13 [67,70], VEGF-C [71] and IGF1 [72], have been associated with anti-inflammatory properties in the infarcted heart. Following termination of inflammation, myofibroblasts work together with macrophages and other cells to shape the scar tissue that will replace the injured region [20,37]. Indeed, among the factors produced by the macrophages in this phase, the anti-inflammatory cytokine IL-10 and the profibrotic TGF-β boost the migration of fibroblasts, their transdifferentiation to myofibroblasts, their proliferation and collagen synthesis [19,73,74] (Fig. 2). Mouse studies implied IL-10 in enhancing fibrosis [75], via mechanisms that include galectin-3- and MERTK-dependent enhanced expression of osteopontin [56,76,77]. Macrophage-derived IL-10 was also shown to stimulate fibroblasts and enhance collagen deposition eventually promoting diastolic dysfunction in mice [78]. However, anti-fibrotic actions of IL-10 have been reported as well [79–81]. Further mediators released by injury-associated macrophages that contribute to fibrosis include Neuregulin 1 [82] and SPARC [83]. Another study showed that TREM2^{+} macrophages—previously associated with anti-inflammatory and reparative functions [60]—have increased production of the metabolite itaconate upon efferocytosis [84]. Itaconate is synthesized from the TCA-cycle intermediate *cis*-aconitate in response to inflammatory stimuli [85]. This leads to reduced cardiomyocyte apoptosis and increased fibroblast proliferation, thereby improving mouse cardiac function [84]. Supporting these findings, spatial transcriptomic analysis revealed that TREM2^{hi} macrophages gradually increase over time in the infarct zone and become abundant in the late phase after MI, associated with tissue remodeling functions and cardiac repair [86]. Moreover, macrophages can reduce fibrosis through the production of exosomes enriched in mir-155 [87]. Interestingly, macrophages are also capable of undergoing mesenchymal transition to adopt a fibroblast-like phenotype [88]. In this context, the absence of IKKε, which is responsible for phosphorylating NF-κB inhibitors, thereby releasing NF-κB into the nucleus for transcription [89], impedes cardiac repair after myocardial infarction in mice by excessive increase of the macrophage-myofibroblast transition [90]. Although macrophages produce little collagen themselves, they are essential for tissue remodeling, regulating extracellular matrix composition through the secretion of proteases and anti-proteases that control extracellular matrix [38]. Indeed, as already mentioned above, they serve as the primary cellular source for various members of the MMP family within the infarct [91–96] (Fig. 2). Some MMPs may have functions that extend beyond extracellular matrix remodeling and endothelial proangiogenic actions [38]; for instance, they can influence the availability of bioactive chemokines [93] or modify proteins essential for cardiomyocyte contraction [97] and electrical signaling [95]. Reparative macrophages also produce vascular endothelial growth factor A (VEGFA) [98–100], which induces angiogenesis and mediates repair of the infarcted heart [58] (Fig. 2). Indeed, the emergence of newly generated vessels is essential for delivering oxygen and nutrients to the actively healing infarct area [38,101]. Altogether, the works discussed here underscore the multifaceted and dynamic role of macrophages in coordinating scar formation, fibrosis, and angiogenesis, ultimately shaping the structural and functional recovery of the infarcted heart.

3.3. Maturation phase

The final stage of cardiac repair may result in either effective healing or pathological remodeling, which in turn may lead to HF [21,38]. After its peak during the proliferative phase, macrophage density usually decreases during the subsequent transition to the maturation phase, however a substantial macrophage number persists in scars [38,102] (Fig. 2). During infarct healing, the non-infarcted myocardial regions are exposed to increased volume and pressure loads and undergo hypertrophic adaptation, which in turn may trigger prolonged macrophage activation and subsequent stimulation of a fibrogenic program [21,38] (Fig. 2). Mouse studies revealed that, 8 weeks after MI, macrophage numbers rose in distant remodeling heart regions due to both local cell division and incoming monocyte-derived cells [52] (Fig. 2). Activation of macrophages in the remote regions of remodeling myocardium may be triggered as a consequence of increased wall stress in these areas [38,52]. In murine dilated cardiomyopathy, macrophages can recognize mechanical stretch via specific mechanosensitive ion channels, such as the transient receptor potential vanilloid (TRPV) 4, that in turn results in their stimulation and the subsequent production of growth factors [38,103].

4. Role of macrophages during heart regeneration

Adult human hearts have a very limited ability to regenerate after injury [16,17], as mature cardiomyocytes cannot divide and must instead rely on structural remodeling to preserve function. In contrast, neonatal hearts can regenerate damaged myocardium, an ability lost in adulthood [104,105]. Macrophages are potential mediators of cardiac repair in neonatal mice that have inherent regenerative capacity [106]. In response to injury, MHC-II^{low}CCR2^{-} resident macrophages accumulate in the neonatal cardiac tissue [16,33]. Importantly, neonatal macrophages promote heart recovery by triggering endothelial cell proliferation [33,106] and cardiomyocyte proliferation [33,107,108] the latter via secretion of CCL24 [107] and Oncostatin M [108]. Conversely, the adult heart's resident macrophages are mainly replaced by monocyte-derived macrophages, which have no regenerative capacity and rather promote inflammation, which may in turn result in fibrosis [16,33]. Maintaining the reparative potential of resident macrophages thus depends on their ability to respond appropriately to tissue stress. One key factor involved in this adaptation is HIF1α. Resident cardiac macrophages act as local sensors of ischemia, and recent findings show that deletion of HIF1α in these cells by using *Cx3cr1*^{ERT2Cre} *x* *Hif1α*$^{flox/flox}$ mice, disrupts monocyte-to-macrophage differentiation and impairs the resolution of inflammation, ultimately worsening cardiac remodeling [109]. Without HIF1α, *Arginase 1*$^{+}$ macrophages fail to

differentiate into reparative *Trem2*$^{+}$, *Gdf15*$^{+}$, and MHC-II^{hi} subsets [109]. These findings suggest that HIF1α not only regulates resident macrophage-intrinsic pathways but also influences the surrounding microenvironment to guide monocyte differentiation after MI [109].

5. Macrophage-targeted therapeutic approaches

Macrophage-targeting strategies may offer a promising path in the ongoing quest for new effective therapies for heart injury and HF. In several experimental models, inhibition of recruitment of monocyte-derived macrophages to the diseased heart led to blunted inflammation and resulted in beneficial effects, such as reduced myocardial lesions or improved heart function [48,49,110–116]. Strategies to reduce inflammatory cell recruitment include blocking chemokine axes involved in monocyte infiltration [48,49,110–113], suppressing toll-like receptor 4 signaling [114] or inhibiting the angiotensin axis [115,116], consistent with the beneficial effects of angiotensin-converting enzyme inhibitors on the heart [117]. Another preclinical approach is the modulation of the macrophage phenotype by reducing their pro-inflammatory activation that was achieved by silencing the transcription factor interferon regulatory factor 5 (IRF5) [118] or via inhibition of the calcium-sensing receptor (CaSR), involved in the activation of NLRP3 inflammasome in macrophages [119]. Additional strategies attempted the increase of the anti-inflammatory properties of MI-infiltrating macrophages by different approaches, including the administration of the anti-inflammatory cytokines IL-10 [79] and IL-4 [120,121] as well as the silencing of collapsin response mediator protein-2 (CRMP2) [122] and the inhibition of the class I/II histone deacetylases (HDACs) [123]. Furthermore, treatment with IL-35 increases the presence of reparative macrophages in murine infarcted hearts partially by promoting their survival [124].

Interestingly, preclinical studies demonstrated that cell therapies (mainly involving bone marrow, adipose or cardiac stem cells/mesenchymal stromal cells, as well as bone marrow mononuclear cells) may have beneficial effects in ameliorating cardiac fibrosis and maladaptive remodeling, while promoting optimal cardiac healing, primarily through macrophage-mediated mechanisms, including the polarization of the latter toward an anti-inflammatory phenotype and/or intercellular communication and paracrine effects [125–130]. This triggered the approach of directly administering *ex vivo/in vitro* reprogrammed macrophages, such as macrophages preconditioned with hypoxia or incubated with macrophage colony-stimulating factor (M-CSF) and IL-4; these therapies resulted in attenuated adverse tissue remodeling, enhanced myocardial tissue repair or cardiac function in pre-clinical settings [131–133] (Table 3). At the clinical level, Ixmyelocel-T, which is a therapy obtained by expanded patient-derived bone marrow mesenchymal stromal cells and alternatively activated macrophages [134], showed reduction of adverse cardiovascular events in patients with ischemic dilated cardiomyopathy but not in patients with nonischemic dilated cardiomyopathy (NCT00765518, NCT01020968, [16,135]) (Table 3). A clinical trial (NCT01670981) established to treat patients with ischemic HF revealed that treatment with Ixmyelocel-T resulted in a reduction of clinical cardiac events compared to placebo (Table 3) [16,136]. However, another clinical trial (NCT00824005) with administration of patient-derived bone marrow mononuclear cells transendocardially reported that the ischemic HF patients did not show improved heart function relative to the group that received placebo treatment [16,137] (Table 3). Other pre-clinical studies highlighted the potential of administering engineered macrophages to overexpress VEGF [138] or neonatal macrophages [139] in order to promote cardiac repair (Table 3). The use of chimeric antigen receptor (CAR)-expressing macrophages engineered to phagocytose FAP^{+} myofibroblasts alleviated cardiac fibrosis and improved heart function in mice [140] (Table 3). As reprogrammed macrophage administration strategies are hindered by the methodological challenges related to macrophage collection, genetic manipulation and expansion processes, the use of embryonic pluripotent stem cells derived from healthy donors is currently under consideration; this approach may represent a valuable source for reparative macrophages in experimental studies [141,142].

Given that an important mechanism by which cardiac stem cells and bone marrow mesenchymal stromal cells exert their beneficial effects involves extracellular vesicles (EVs) [143,144] and their cargo, such as microRNAs (miRNAs) and other RNAs [145–147], EVs are considered a promising cell-free therapeutic approach. In several preclinical studies with cardiac injury such EV-based approaches promoted macrophage polarization towards an anti-inflammatory and reparative phenotype, thereby ameliorating inflammation, and leading to beneficial effects, such as reduction of infarct size and fibrosis, or improving heart function

Table 3
Current macrophage-focused therapeutic approaches in pre-clinical models and clinical trials.

Research phase	Organism	Disease model	Therapeutic strategy	Disease outcome	Reference
Pre-clinical	Mouse	MI	Hypoxia-induced Mϕ	↓ Scar size ↑ Capillaries ↑ Heart function ↑ Survival	131
Pre-clinical	Mouse	MI	M-CSF and IL-4-induced Mϕ	↓ Infarct size ↑ Thickness of the infarcted LV ↑ Capillary density ↑ Replacement fibrosis ↓ Interstitial fibrosis ↑ Cardiac function	132
Pre-clinical	Mouse	HF		↓ Interstitial fibrosis ↑ Cardiac function	133
Clinical (phase 2A)	Human	IDCM NIDCM	Ixmyelocel-T	↓ Adverse cardiovascular events No improvement	135
Clinical (phase 2B)	Human	IDCM		↓ Adverse cardiac events	136
Clinical (phase 2)	Human	CIHF	Autologous bone marrow mononuclear cells	No improvement	137
Pre-clinical	Mouse	MI	VEGF-overexpressing Mϕ	↑ Capillary density ↑ Heart function	138
Pre-clinical	Mouse	MI	Murine neonatal cardiac Mϕ	↓ Infarcted area ↑ Cardiomyocyte proliferation ↑ Heart function ↑ Survival	139
Pre-clinical	Mouse	HI	CAR Mϕ engineered to phagocytose FAP^{+} myofibroblasts	↓ Cardiac fibrosis	140

Mϕ; macrophages; MI; myocardial infarction; HF, heart failure; IDCM, ischemic dilated cardiomyopathy; NIDCM, nonischemic dilated cardiomyopathy; CIHF, chronic ischemic heart failure; HI, heart injury; M-CSF, macrophage colony-stimulating factor; IL, interleukin; LV, left ventricle; VEGF, vascular endothelial growth factor; CAR, chimeric antigen receptor.

[143–147]. Importantly, the lipid bilayer structure of EVs can be modified to improve their delivery to infarcted heart tissue [148]. Another cell-free strategy involves the use of small interfering RNAs (siRNAs) as therapeutic agents that may exert different beneficial actions, such as limit leukocyte recruitment, promote macrophage anti-inflammatory phenotypes, reduce heart damage or enhance cardiac function in the setting of murine cardiac injury [52,111,113,149–152]. A promising recent preclinical study developed a nanotherapeutic delivery system that specifically targets $CD86^{+}$ (pro-inflammatory) macrophages in the infarct zone post-MI, using ultrasound-responsive nanoparticles to deliver nitro-oleic acid, a compound known to modulate various pathophysiological processes, e.g. by suppressing inflammation and fibrosis, and a siRNA against STAT1 [152]. This approach reduced ventricular remodeling and preserved cardiac function in animal models, suggesting strong translational potential [152]. Despite advancements in macrophage-related therapies, this approach still has substantial challenges; in this context developing advanced systems is of crucial importance for enabling precise delivery of therapeutic agents to tissue macrophages [16]. Future efforts should hence put their focus on preserving tissue-resident macrophage function while decreasing inflammation from monocyte-derived macrophages in order to enhance cardiac recovery [16,153].

6. Conclusions and perspectives

Heart injury can lead to HF, which, despite decades of research, continues to represent a significant burden on global health and healthcare systems [22]. Our article focused on the continuously expanding understanding of macrophage heterogeneity, and on their plasticity to adapt their phenotype in response to environmental cues following injury. Since macrophages exert crucial roles in the post-injury response, they have emerged as promising targets for therapeutic intervention, which is supported by encouraging basic research and preclinical findings [16]. However, macrophage-targeted therapies are still at the early stage of development, and translating basic research into clinical applications remains a substantial challenge. Additional studies are necessary to assess the efficacy and safety of macrophage-targeted therapies in clinical settings. To leverage the therapeutic potential of targeting macrophages, it is essential to deepen our understanding of macrophage phenotypic and functional diversity, and their interactions with surrounding cells in the heart. Advances in spatial transcriptomics have revealed the diversity and precise localization of macrophage subsets during cardiac remodeling after myocardial infarction [154]. By elucidating gene-regulatory networks, the niche-specific functions of macrophages in cardiac repair can be characterized, including their activation states and interactions with myofibroblasts. These observations underline the dual roles of macrophages in inflammation and fibrosis/scar formation—and underscore their potential as therapeutic targets to improve outcomes after MI [14,155,156].

The impact of aging, sex, and comorbidities such as diabetes and other non-communicable diseases on macrophage function in the human heart is poorly understood. The extent to which monocyte-derived macrophages can adopt tissue-resident-like phenotypes post-injury also requires further investigation.

Importantly, most of our current knowledge on macrophage function in the heart comes from mouse models. Hence, efforts to translate findings from mice to human settings should take into account inter-species differences in macrophage origin [157], and marker expression [158] as well as in transcriptomic and metabolic responses to stimulation [159,160]. Moreover, one should not overlook that mice are housed in sterile, pathogen-free facilities, while humans are continuously exposed to pathogens throughout life, which significantly influences macrophage function [161]. Furthermore, since myocardial diseases are more prevalent in the elderly, studies using young mice may not accurately model the altered immune dynamics characteristic of aged individuals [38]. Together, these differences underscore the importance of cautious interpretation and careful validation of mouse macrophage data before extrapolating them to human biology and clinical application.

Future research should prioritize developing advanced drug delivery systems to selectively target macrophage subsets and modulate their functions beneficially. Validation of such approaches is crucial for the development of effective therapies that can balance protective and detrimental macrophage responses in cardiac tissue, ultimately leading to improved outcomes after heart injury.

Author contributions

G.T. wrote the original draft, which was edited by T.C.; A.E.A. and P. M. reviewed and edited the text.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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