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Monocyte and Macrophage Contributions to Cardiac Remodeling

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Abstract

The mammalian heart contains a population of resident macrophages that expands in response to myocardial infarction and hemodynamic stress. This expansion occurs likely through both local macrophage proliferation and monocyte recruitment. Given the role of macrophages in tissue remodeling, their contribution to adaptive processes in the heart is conceivable but currently poorly understood. In this review, we discuss monocyte and macrophage heterogeneity associated with cardiac stress, the cell's potential contribution to the pathogenesis of cardiac fibrosis, and describe different tools to study and characterize these innate immune cells. Finally, we highlight their potential role as therapeutic targets.

Keywords

monocytes; macrophages; myocardial infarction; hemodynamic stress; fibrosis; cardiac remodeling

1. Introduction

The heart is composed of a heterogeneous population of cells including cardiomyocytes, fibroblasts, smooth muscle cells, endothelial cells, and immune cells. It is now clear that intercellular signaling and cross talk between cardiomyocytes and non-cardiomyocytes are critical in the initiation, propagation and development of cardiac remodeling. Left ventricular remodeling has originally been defined as changes in size, shape, structure and physiology of the ventricle [1]. Such remodeling processes follow different types of cardiac stress, like myocardial infarction (MI), myocarditis or chronic hypertension, and when uncontrolled can lead to heart failure or cardiac arrest resulting from pulseless electrical

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Disclosures

None.

activity or arrhythmia. Therefore, great interest lies in the discovery of new therapeutic strategies, which can modulate adverse cardiac remodeling and prevent heart failure.

The discovery and evaluation of new therapeutic targets relies heavily on the use of small animal models. Indeed, rat and mouse heart failure models have been used over the past 40 years to explore the pathophysiology of heart failure and to develop novel therapies [2]. Permanent coronary ligation and transverse aortic constriction are perhaps the most widely used models for MI and pressure overload, respectively. Other models for hypertension-induced heart disease include genetic models, and exogenous administration of angiotensin II or mineralocorticoid (deoxycorticosterone acetate [DOCA] or aldosterone). DOCA-induced cardiac effects include cardiac hypertrophy, fibrosis and diastolic dysfunction in the absence of salt deprivation. These pathophysiological changes are accelerated by supra-normal salt intake and unilateral nephrectomy, and closely mimic the clinical condition of human heart failure with preserved ejection fraction [3,4]. Despite recent advantages in developing rodent heart failure models, translation of findings obtained in rodents is often not straight forward, as pathophysiological processes in humans are complex. Indeed, human heart failure frequently develops as a cluster of interrelated comorbidities rather than a single pathophysiological event. In the future, mammalian systems other than mouse may be needed to model complex neural, immune, endocrine and metabolic interactions during hypertension, obesity and dyslipidemia, all contributing to human heart failure. On the other hand, lower costs, faster timelines and the availability of a great number of transgenic and knockout strains are important benefits of using mice to model heart failure. Moreover, the ability to assess cardiovascular physiology using multiple modalities, including echocardiography, magnetic resonance imaging and micromanometer conductance catheters has removed a significant barrier to their use in heart failure research and makes the mouse a relevant model to retrieve significant mechanistic insights into human disease.

In this review, we summarize the current understanding of the contribution of immune cells, in particular monocytes and macrophages, to the pathogenesis of cardiac remodeling with a focus on the fibrotic response. We highlight the cross talk between these immune cells and parenchymal cells in the heart. Furthermore, we describe tools to study monocytes and macrophages in the heart and explore their potential role as therapeutic targets.

2. Monocytes and Macrophages

Monocytes and macrophages are part of the vertebrates' innate immune system, and pursue distinct functions in the steady-state and during disease. It is now widely accepted that the innate immune system plays an important role both during the initial insult and the chronic phase of cardiac injury. In humans, three monocyte subsets have been identified based on the expression of CD14 and CD16: classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$) and nonclassical ($CD14^{+}CD16^{++}$) monocytes [5]. Heart failure in humans has also been associated with increased peripheral inflammation, monocytosis and distinct monocyte subset profiles [6–11]. On the other hand, mature murine monocytes have been classified into two subsets according to their expression of Ly-6C. Ly-$6C^{high}$ chemokine (C-C motif) receptor-2 $(CCR2)^{high}$ chemokine (C-X3-C motif) receptor-1 $(CX_3CR1)^{low}$ monocytes preferentially accumulate in inflammatory sites, including acute MI, where they give rise to

macrophages, and nonclassical Ly-6C^{low}CCR2^{low}CX$_3$CR1^{high} monocytes, which patrol the endothelium to maintain homeostasis [12]. Furthermore, the nonclassical Ly-6C^{low} monocytes in mouse blood are homologous to human nonclassical CD14^{+}CD16^{++} monocytes as shown by cell-depletion studies and transcriptional profiling [13,14]. The use of CD43 has been proposed to further subdivide murine Ly-6C^{high} monocytes into classical Ly-6C^{high}CD43^{low} and intermediate Ly-6C^{high}CD43^{high} monocytes resembling the 3 subsets described for human monocytes [5]. Ly-6C^{high} monocytes are produced in the bone marrow by hematopoietic progenitors that derive from hematopoietic stem cells (HSCs). The most restricted monocyte progenitor is the common monocyte progenitor, which is developmentally downstream of monocyte-macrophage dendritic cell progenitors [15]. Ly-6C^{high} monocytes produced in the bone marrow are released into the blood depending on CCR2 signaling, and travel to inflammatory sites where they participate in the host's initial immune response [16]. Ly-6C^{low} monocytes arise from Ly-6C^{high} monocytes through conversion, relying on a nuclear receptor subfamily-4-dependent transcriptional program [17]. HSCs can also intravasate into the blood and give rise to monocytes outside the bone marrow, which is called extracellular monocytopoeiesis [18,19]. This phenomenon is rare in the steady-state, but increases during inflammation. Furthermore, monocytes can also reside in the spleen, which functions as a reservoir for storage and rapid deployment of monocytes during inflammation [20]. The heart itself contains very few, if any, monocytes during steady-state conditions.

In contrast, macrophages are the primary immune cells that reside in the heart under physiological conditions. They appear as spindle-like cells and are found within the interstitial space or in close proximity of endothelial cells [21–23]. For the past half century, macrophages were thought to arise solely from circulating blood monocytes. However, recent studies using genetic fate mapping, parabiosis and adoptive transfer techniques show that tissue-resident macrophages in the brain, liver, lung, and skin do not derive from circulating monocytes but are replenished through local proliferation [24–27]. In contrast, intestinal or dermal macrophages, which have a high turnover rate, are constantly replaced by Ly-6C^{high} blood monocytes [28,29]. In the steady-state heart, tissue-resident cardiac macrophages comprise discrete subsets, defined by their expression levels of histocompatibility-2 and CCR2 [30]. These macrophage subsets arise primarily from embryonic yolk-sac progenitors and self-maintain independent of bone marrow-derived monocytes through *in situ* proliferation. On the other hand, when the steady-state is perturbed during sterile injury or hemodynamic stress, the majority of cardiac macrophages are derived from blood monocytes [23,30]. Interestingly, a recent study by Molawi *et al.* claims declining self-renewal of embryo-derived cardiac macrophages with age, and their progressive substitution by monocyte-derived macrophages even in the absence of inflammation [31].

3. Monocytes and Macrophages in Cardiac Remodeling

3.1. Expansion of Macrophages

During various cardiac stresses, expansion of macrophage populations occurs through both local proliferation and monocyte recruitment (Fig. 1) [22,23,30,32]. Ly-6C^{high} monocytes

are the primary subset recruited to the heart [27,30,32–34]. In response to signals induced by ischemic cardiac injury, sequential recruitment of monocytes regulates the inflammatory and reparative response following MI [22]. During the early inflammatory phase of infarct healing, Ly-6C^{high} monocytes infiltrate the infarcted myocardium in response to the marked upregulation of monocyte-chemoattractant protein-1 (MCP-1) [35]. In a second phase, low numbers of Ly-6C^{low} monocytes are recruited via CX_3CR1 [22]. Secondary to angiotensin II-induced hemodynamic stress, monocyte-derived CCR2$^+$ macrophages require monocyte input prior to proliferative expansion in the tissue [30]. The CCR2$^+$ macrophage subset is thought to be involved mainly in promoting and regulating inflammation; however, the intensity of the chronic inflammatory reaction is orders of magnitude lower after pressure overload and hypertensive cardiac stress than what is observed after acute ischemic injury [36,37]. This discrepancy is probably related to the difference in local insult stimulus, which is drastic in the setting of MI. Indeed, ischemic injury results in acutely dying myocytes leading to rapid accumulation of inflammatory cells [38]. The basis for initiation of the inflammatory reaction in pressure overloaded myocardium remains poorly understood and may involve activation of innate immune signals due to cardiomyocyte death, reactive oxygen generation, or angiotensin-mediated pro-inflammatory actions [39]. CCR2$^+$ macrophages are capable of producing and secreting large amounts of pro-inflammatory cytokines, including those associated with the NLPR3 inflammasome, which is required to process and deliver interleukin (IL)-1β to the heart during cardiac stress [30]. Indeed, angiotensin II–induced inflammasome activation and IL-1β production are blocked in mice with CCR2 deficiency [40–42]. Furthermore, CCR2 knockout in bone marrow cells or inhibition of MCP-1 with neutralizing antibodies markedly reduces vascular inflammation and myocardial fibrosis without affecting hypertrophy during angiotensin II infusion and pressure overload [43,44]. Blocking this chemotactic pathway appears to have a pronounced impact on fibrotic remodeling and might have a more direct role in regulating fibroblast function. Also, inhibition of intercellular adhesion molecule-1 with neutralizing antibodies reduces infiltrating monocytes and suppresses cardiac fibrosis during pressure overload [45]. In conclusion, monocyte recruitment, followed by differentiation to macrophages and macrophage proliferation, contribute to the expansion of cardiac macrophages following ischemic and hemodynamic stress.

3.2. Macrophage Subpopulations

Functional binary categorization of macrophages, such as the M1/M2 classification, is used as an easy, but probably too simplistic way to address the macrophage heterogeneity associated with cardiac stress. We propose using the terms inflammatory/reparative macrophages instead, as we frequently observed that the typical M1/M2 markers used in *in vitro* studies are not necessarily helpful to describe macrophage phenotypes *in vivo*. During cardiac injury, the resolution of neutrophil recruitment by phagocytic macrophages is critical for limiting tissue injury and promoting the transition to tissue healing. Macrophages that have ingested apoptotic cells are believed to initiate this process by decreasing their production of pro-inflammatory cytokines, such as IL-1β and tumor necrosis factor-α (TNFα), and increasing their production of anti-inflammatory and pro-fibrotic cytokines, such as IL-10 and transforming growth factor-β (TGFβ) [46,47]. Indeed, macrophage depletion during the early inflammatory phase after MI results in increased necrotic debris

and neutrophil presence [22,30,48]. The transition from inflammatory to reparative macrophages occurs after ischemia, resembling *in vitro* polarization from the so-called "M1" to "M2" macrophage phenotype. However, the concept of M1/M2 macrophage polarization is derived from *in vitro* studies and do not reflect the more subtle phenotypes observed *in vivo*. Indeed, macrophages do not form stable subsets but respond to a combination of factors present in the tissue resulting in complex, even mixed, phenotypes. Recent technological and analytical advances in epigenetic, gene expression, and functional studies revealed a spectrum of macrophage activation states extending the current M1 versus M2-polarization model [49]. This resource can serve as a framework for future research into regulation of macrophage activation in health and disease.

Regulators of macrophage polarization such as interferon regulatory factor-5 (IRF5) and myeloid mineralocorticoid receptor (MR) have been shown to be involved in cardiac remodeling. *In vivo* silencing of IRF5 reduces inflammatory macrophages and improves infarct healing [50]. MR activation by mineralocorticoids (e.g. aldosterone) enhances the polarization to inflammatory macrophages, whereas MR deficiency in macrophages mimics the effects of MR antagonists and protects against cardiac hypertrophy and fibrosis [51]. In contrast, scavenger receptor class-A on cardiac macrophages, which is a key modulator of inflammation, exerts a protective effect against MI by contributing to the reparative macrophage phenotype, and anti-inflammatory and anti-fibrotic remodeling [52]. Hypoxia-inducible factor (HIF) is also a critical regulator of macrophage polarization during cardiac remodeling. Myeloid-specific deletion of prolyl hydroxylase domain protein-2, an enzyme that induces degradation of HIF, attenuates macrophage recruitment, inflammatory gene expression, and cardiac remodeling upon infusion of N^G-nitro-L-arginine methyl ester/angiotensin II [53]. Serum- and glucocorticoid-inducible kinase-1 induces cardiac fibrosis after angiotensin II infusion at least in part through signal transducer and activator of transcription-3-dependent macrophage proliferation and activation [54]. In contrast, IL-12 produced by cardiac macrophages activates interferon-γ-producing $CD4^+$ T cells, which shifts macrophages towards the inflammatory phenotype and subsequently prevents excessive angiotensin II-induced cardiac fibrosis [55]. microRNAs (miRs) have also been shown to regulate the myeloid cell phenotype and modulate cardiac remodeling (for in-depth review see also [56]). Knockout of miR-155 for example reduces angiotensin II– and pressure overload–induced polarization to inflammatory macrophages, hypertrophy and cardiac dysfunction [57].

These data suggest that the transition of macrophage phenotypes from inflammatory to reparative could be a potential mechanism of cardioprotection after MI, but prolonged activation of reparative macrophages may eventually contribute to extensive cardiac fibrosis, increased stiffness and diastolic dysfunction. Indeed, a recent study by Kanellakis *et al.* shows that inhibition of IL-4, a potent inducer of reparative macrophages, with neutralizing antibodies attenuates cardiac fibrosis and hypertrophy during pressure overload, suggesting that IL-4 is pro-fibrotic and may exacerbate adverse cardiac remodeling [58].

3.3. Macrophages as Fibrogenic Mediators

The activation of cardiac fibroblasts, transdifferentiation into secretory and contractile cells, termed myofibroblasts, and subsequent extracellular matrix deposition are key cellular events that drive the fibrotic response during cardiac stress (for in-depth review see also [59–61]). Macrophages are almost always found in close proximity with collagen-producing myofibroblasts [62,63]. Due to their functional and phenotypic plasticity, the role of monocytes and macrophages in mediating the fibrotic response is complex and context-dependent (Fig. 2). Macrophages exert a wide range of actions that alter the extracellular matrix: through their phagocytic properties, by producing cytokines, chemokines and growth factors including TGFβ and platelet-derived growth factor, by disrupting normal cardiac structures, and by altering the extracellular matrix turnover through regulating the balance of various matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs [44,64–66]. In addition, the activation of cardiac fibroblasts, non-adaptive fibrosis and subsequently increased myocardial stiffness after angiotensin II infusion requires the induction of MCP-1, which suggests the causal contribution of monocytes to the fibrotic response [67]. Interestingly, cardiac senescence is associated with phenotypic changes in resident macrophages including upregulation of pro-fibrotic genes, which possibly contribute to aging-associated cardiac fibrosis [68]. Westermann *et al.* also showed that TGFβ-producing inflammatory cells contribute to diastolic dysfunction in human heart failure with preserved ejection fraction by triggering the accumulation of extracellular matrix [69]. Most studies on the role of monocytes and macrophages in cardiac fibrosis have focused on their pro-fibrotic actions; however, they could also mediate resolution of fibrosis by removing apoptotic myofibroblasts, by expressing high levels of MMP13 and by suppressing fibroblast activation as has been shown in the setting of hepatic fibrosis [66,70,71].

Monocytes and macrophages also contribute to the pathogenesis of cardiac fibrosis by interacting with neurohumoral factors such as angiotensin II and aldosterone. Indeed, macrophages in the injured heart are a source of renin and angiotensin-converting enzyme, which are necessary for the local production of angiotensin II and subsequent activation of cardiac fibroblasts [72]. Angiotensin II also regulates the mobilization of monocytes, i.e. macrophage progenitors, in the spleen [73]. In addition, aldosterone directly influences the cardiac fibrotic response by driving macrophages towards a fibrogenic phenotype [51,74].

Despite recent discoveries describing a causal role of monocytes and macrophages in the fibrotic response after cardiac stress, dissecting the context-depending factors driving macrophages towards a pro-fibrotic or an anti-fibrotic phenotype is an ongoing process, and many cell-cell interactions still remain to be determined (Fig. 2).

4. Tools to Study Monocytes and Macrophages

Monocytes and tissue macrophages are typically studied at cellular resolution by staining for cell surface markers in histology or multicolor flow cytometry. These markers include CD11b, CD45, CD68, CD115, F4/80, Ly-6C and MAC-3 in addition to the core macrophage signature suggested by the Immunological Genome Project, which include FCGR1 and MerTK [75]. The development of transgenic mice such as the $Cx_3cr1^{GFP/+}$ reporter mouse also facilitated the detection of cardiac macrophages and improved the sensitivity of *ex vivo*

histology for detecting macrophages and their dendrite-like protrusions in the myocardial tissue context [21,23]. Additionally, recently developed real-time *in vivo* imaging techniques make it possible to track migration patterns of monocytes in the heart with microscopic resolution [76,77]. Monocytes and macrophages can also be probed with nanoparticles [78] to follow them or determine their specific function at the organ level by noninvasive imaging modalities such as magnetic resonance imaging [79], positron emission tomography [80], fluorescence molecular tomography [81], or hybrid approaches [82].

Furthermore, monocytes and macrophages can be functionally characterized using specific depletion methods such as clodronate liposomes. Clodronate is a small hydrophilic molecule that binds intracellular ATP and inhibits ATP function resulting in cellular apoptosis. Monocytes and, with less efficiency macrophages, can be targeted by encapsulation of clodronate into liposomes. Organ restriction of depletion can be attempted by choosing the appropriate administration route [83]. Depletion of myeloid cells can also be accomplished by using $Cd11b^{DTR}$ transgenic mice. These transgenic mice have a diphtheria toxin inducible system under control of the human *CD11b* promoter that transiently depletes myeloid cells in various tissues [84].

To study and assess the contribution of monocytes to the turnover of cardiac macrophages in the steady-state and during disease, one could use the parabiosis setup, in addition to fate mapping, and adoptive transfer approaches. Parabiosis surgery joins the circulation of two mice, whose circulating blood cells then mix. This setup enables the quantification of recruited macrophages by determining the percentage of macrophages that derived from circulating monocytes made in the donor mouse [23]. Although parabiosis provides a convenient tool to study the recruitment of cells, it may also induce artifacts through pro-inflammatory stimuli. Adoptive transfer of bone marrow HSCs into an irradiated recipient mouse can be used to assess the contribution of recruitment to the macrophage population. A disadvantage of this approach is that radiation may deplete the cardiac resident macrophages, or some relevant fraction thereof. In addition, several inducible fate mapping models including the $Runx1^{MercreMer}$, $Csf1r^{MercreMer}$, Cx_3cr1^{creER}, and $Kit^{MercreMer}$ mice are currently available and are a convenient tool to study the ontogenesis of tissue-resident cardiac macrophages in the steady-state and during disease [24,26,85–87].

5. Clinical Translation and Conclusions

The growing body of evidence implicating immune cells in the initiation and propagation of cardiac remodeling lends itself to exploiting this knowledge to explore new therapeutic avenues. Indeed, monocytes and macrophages appear to coordinate cardiomyocyte and non-cardiomyocyte responses during maladaptive remodeling after cardiac stress. Because of their functional and phenotypic versatility, regulating specific macrophage phenotypes rather than depleting them may spare important immune functions, such as repair and defense against infection, while preventing specific deleterious effects contributing to adverse cardiac remodeling.

A valid strategy could be to tackle the inappropriate activation of pro-inflammatory $CCR2^{+}$ cardiac macrophages in the setting of sterile inflammation or to prevent the infiltration of

Ly-6C^{high} monocytes during hypertension-induced cardiac fibrosis [22,44,88,89]. These data suggest that recruited Ly-6C^{high} monocytes have a pathological role, in contrast to tissue-resident cardiac macrophages, in the setting of cardiac injury. Furthermore, it is possible to phenotypically change inflammatory macrophages by nanoparticle-delivered small interfering RNA. The ease of delivering nanomaterials to phagocytic immune cells renders macrophages a prime target for *in vivo* RNAi [90]. Advantages of applying RNAi to target immune reactions include the selectivity for specific gene products (thereby avoiding unwanted side effects of broad immunosuppression) and the ability to reach intracellular decision nodes such as transcription factors involved in macrophage polarization [50]. Inflammatory cardiac macrophages during ischemic injury can also be modulated to a reparative state by phosphatidylserine-presenting liposomes, mimicking the anti-inflammatory effects of apoptotic cells [91]. A recent study by de Couto *et al.* showed that cardiac macrophages can be polarized toward a distinctive cardioprotective phenotype in the ischemic heart by administering cardiosphere-derived cells, which are a stem-like population that is derived *ex vivo* from cardiac biopsies [92]. Together, these studies suggest that manipulation of macrophage phenotypes could be exploited therapeutically to improve outcome after sterile injury. Unfortunately, our current knowledge regarding molecular pathways involved in driving macrophages toward specific phenotypic profiles is still limited and requires further exploration. In addition, it is quite reasonable to assume that cardiac macrophages also pursue salient functions that promote myocardial health, thus indiscriminate targeting strategies could be harmful. Novel, non-biased methods combining experimental data with mathematical modeling may shed light on the complex, spatiotemporal plasticity of cardiac macrophages after cardiac stress [49,93,94]. Finally, most of our current understanding of macrophage phenotype and function is derived from mouse models and still requires clinical translation and validation in human tissue samples.

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Abbreviations

ACE	angiotensin-converting enzyme
CCR2	chemokine (C-C motif) receptor-2
CX$_3$CR1	chemokine (C-X3-C motif) receptor-1
DOCA	deoxycorticosterone acetate
HIF	hypoxia-inducible factor
HSCs	hematopoietic stem cells
IL	interleukin
IRF5	interferon regulatory factor-5
MCP-1	monocyte-chemoattractant protein-1

MI	myocardial infarction
miR	microRNA
MMPs	matrix metalloproteinases
PDGF	platelet-derived growth factor
TGFβ	transforming growth factor-β
TIMPs	tissue inhibitors of MMPs
TNFα	tumor necrosis factor-α

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Highlights

- Macrophages are an intrinsic part of the heart under physiological conditions
- Cardiac macrophages expand in response to stress
- Macrophage expansion through monocyte recruitment associates with cardiac remodeling
- Monocytes and macrophages may exert a wide range of pro- and anti-fibrotic actions

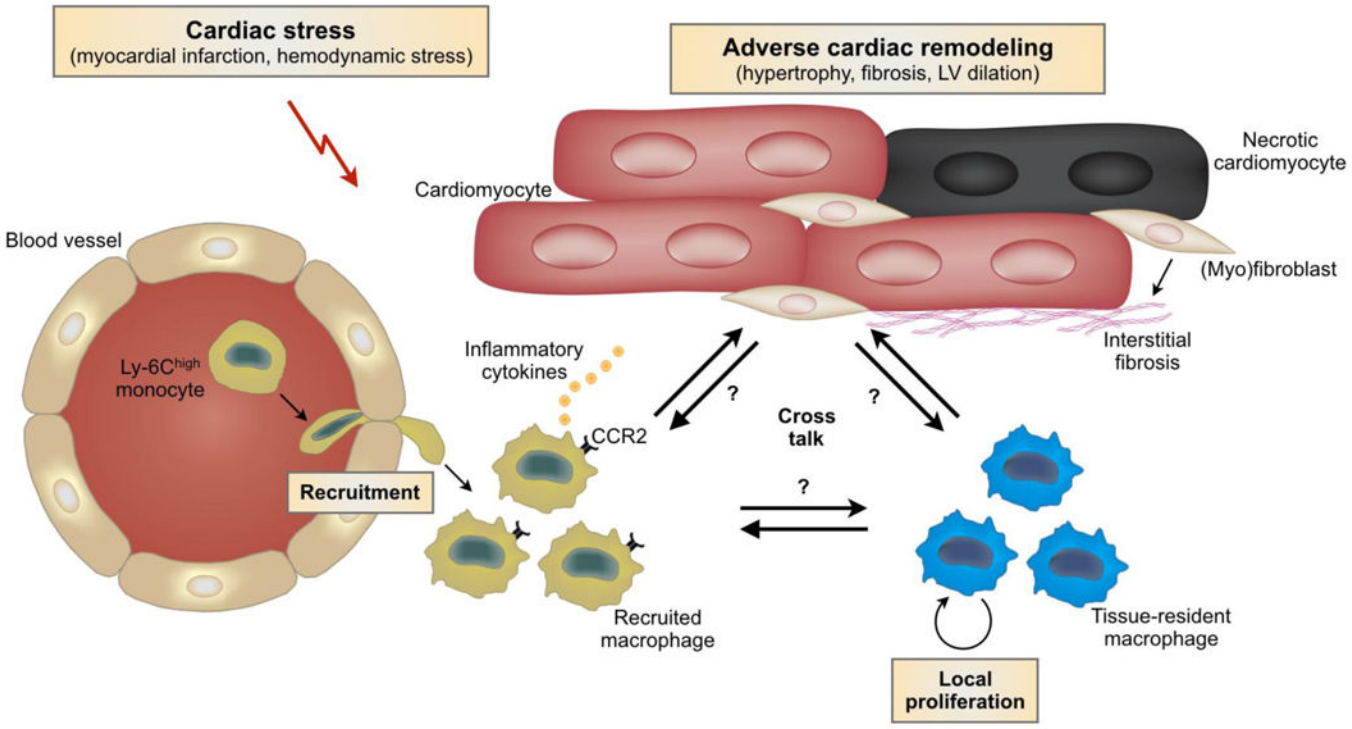

Fig. 1. Expansion of macrophages during cardiac stress

After cardiac stress such as myocardial infarction or hemodynamic stress, there is a marked expansion of the cardiac macrophage population through both local proliferation and monocyte recruitment. $CCR2^{+}$ macrophages are capable of producing and secreting large amounts of pro-inflammatory cytokines, which contribute to adverse cardiac remodeling. However, our current knowledge regarding the cross talk between macrophage subpopulations and parenchymal cells in the heart is still limited and requires further exploration. Abbreviation: LV, left ventricular.

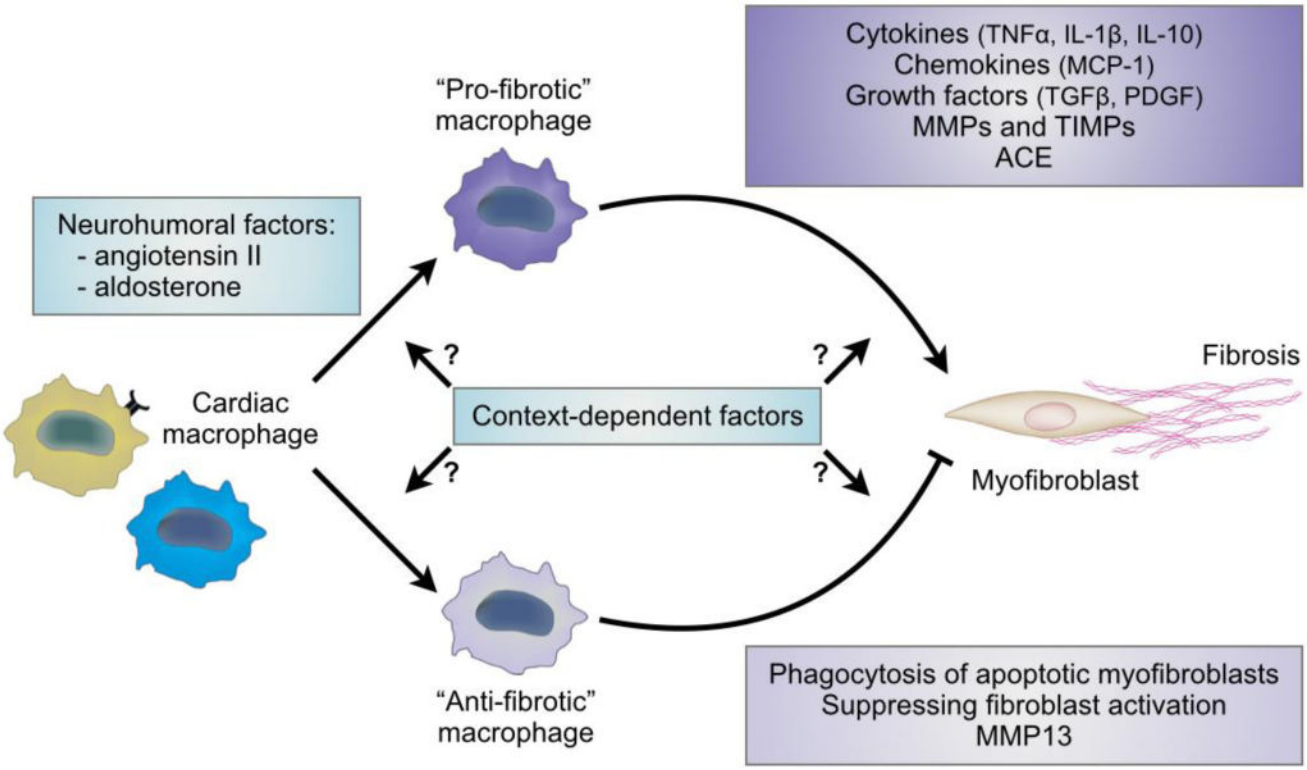

Fig. 2. Cardiac macrophages as regulators of the fibrotic response after cardiac stress

Macrophages are found in close proximity with collagen-producing myofibroblasts and contribute to the fibrotic response after cardiac stress. Neurohumoral factors such as angiotensin II and aldosterone drive macrophages towards a fibrogenic phenotype. Macrophages also exert a wide range of anti-fibrotic actions in addition to their pro-fibrotic effects, but the context-depending factors driving macrophages towards a pro-fibrotic or an anti-fibrotic phenotype are yet-to-be determined. Abbreviation: ACE, angiotensin-converting enzyme; IL, interleukin; MCP-1, monocyte-chemoattractant protein-1; MMPs, matrix metalloproteinases, PDGF, platelet-derived growth factor; TGFβ, transforming growth factor-β; TIMPs, tissue inhibitors of MMPs; TNFα, tumor necrosis factor-α.