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Review

Macrophage roles following myocardial infarction

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Abstract

Following myocardial infarction (MI), circulating blood monocytes respond to chemotactic factors, migrate into the infarcted myocardium, and differentiate into macrophages. At the injury site, macrophages remove necrotic cardiac myocytes and apoptotic neutrophils; secrete cytokines, chemokines, and growth factors; and modulate phases of the angiogenic response. As such, the macrophage is a primary responder cell type that is involved in the regulation of post-MI wound healing at multiple levels. This review summarizes what is currently known about macrophage functions post-MI and borrows literature from other injury and inflammatory models to speculate on additional roles. Basic science and clinical avenues that remain to be explored are also discussed.

Keywords: Macrophage; Myocardial infarction; Matrix metalloproteinases; Left ventricular remodeling; Angiogenesis; Fibrosis

1. Introduction

A myocardial infarction (MI) occurs when a coronary artery becomes occluded, resulting in an insufficient oxygen supply to the downstream myocardium [1]. The myocardium reacts to an ischemic challenge with an intricate series of changes in cellular and extracellular components, characterized at the tissue level by altered wall structure, chamber geometry, and pump function, a process termed left ventricular remodeling [2–4]. The lack of oxygen supply induces necrosis in the cardiac myocytes, which stimulates the complement cascade and initiates an inflammatory response [5]. The inflammatory component is primarily composed of neutrophil and macrophage infiltration. Macrophages influence several wound healing events, including fibroblast activation necessary for scar formation and endothelial cell activation necessary for angiogenesis [6]. The timing and rate of macrophage infiltration is orchestrated by a wide range of cytokines and chemokines [6,7].

Due to improvements in emergency percutaneous coronary interventions (reperfusion) and pharmacologic interventions such as inhibitors of the renin–angiotensin–aldosterone system, the 30-day survival rate in post-MI patients is >90% [4,8–11]. However, a significant number of MI patients (3–40%, depending on the study) will undergo adverse remodeling of the left ventricle (LV), leading to LV dilation and compromised LV function that drives the constellation of signs and symptoms indicative of congestive heart failure (CHF) [8]. In a subgroup of 412 post-MI patients from the Survival and Ventricular Enlargement (SAVE) trial [12] (with ejection fractions <40%), 17% developed CHF by the 2 year follow-up [13]. Lavine et al demonstrated a 29% incidence of late onset CHF in post-MI patients diagnosed in 1988–1992, when reperfusion strategies were in use [14]. For MI patients evaluated in 1979–1998, CHF incidence was 41% within 6.6±5.0 years and median survival was 4 years after onset [15,16]. Of 3860 stable MI patients from the

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Cholesterol and Recurrent Events (CARE) study, 6.3% developed CHF within 5 years, at a linear rate of 1.3% per year [17]. Because only the most stable post-MI patients were included, this is the most conservative rate reported. While the number of patients who progress to CHF declined over the past 25 years (current rates are approximately 3%), survival in patients diagnosed with CHF has not changed. Regardless of variable incidence rates among studies, MI predisposes patients to CHF, a significant long-term complication and leading cause of mortality in post-MI patients [3]. Identifying vulnerable patients early in the pathogenesis, therefore, will allow better risk stratification post-MI [18–20]. The macrophage regulates multiple aspects of the post-MI wound healing response, and as such is a likely candidate for investigation and intervention. Accordingly, this review summarizes the role of macrophages in the post-MI wound healing process and discusses outstanding issues that need to be addressed in the field. Ultimately, altering macrophage function may lead to the development of novel therapeutic approaches for LV remodeling.

2. Macrophage activation

Macrophages belong to the mononuclear phagocyte system [21], and are derived from CD34+ bone marrow progenitors [22]. Monocytes within the peripheral blood include a heterogeneous mixture of different cell subpopulations [23]. Commitment to the macrophage lineage gives rise to macrophage colony-forming cells, which are succeeded by monoblasts, the first characteristic phagocytic cells [21]. Monocytes then enter the blood stream and extravasate into injured tissues in response to chemotactic signals [21,22,24].

Monocyte adherence to extracellular matrix initiates the conversion to a macrophage, in part by inducing the expression of cytokines such as macrophage colony stimulating factor (M-CSF), tumor necrosis factor α (TNFα), platelet derived endothelial cell growth factor, transforming growth factors α and β (TGFα and β), interleukin-1 (IL-1), and insulin-like growth factor [25]. M-CSF is a cytokine necessary for macrophage survival [26], TNFα is a potent inflammatory cytokine [27], and platelet derived growth factor serves as a potent chemoattractant and mitogen for fibroblasts [25]. $TGF\beta_1$ release from macrophages also contributes to fibrosis, by stimulating extracellular matrix release (primarily collagen) in myocardial fibroblasts [28]. Caspases, aspartate-specific cysteine proteases, are also important for the differentiation of blood monocytes into macrophages [29]. In mice, the conditional deletion of caspase-8 in myelomonocytic precursors blocked the formation of macrophages but did not affect the differentiation of dendritic cells or granulocytes [29].

Macrophage activation can be a heterogeneous process, resulting in the generation of different classes of cells that exhibit diverse immunological functions [30]. There are two major macrophage activation patterns: classical (M1) and alternative (M2), which show distinct cell marker expression (Table 1). There is currently no literature available to assign post-MI macrophages to either pathway, and, because stimuli for both activation pathways are present at varying times post-MI, likely a heterotypic representation occurs. Porcheray and colleagues have shown that macrophage activation occurs first through the M1 pathway, and then shifts to the M2 pathway. Further shifts between pathways are reversible [31].

Table 1
Markers of classical (M1) and alternative (M2) activation

Classical (M1)	Alternative (M2)
Pro-inflammatory	Anti-inflammatory
	Arginase I/II
	CD 163
Fas ligand high	Fas ligand low
	Basic fibroblast growth factor
Interferon γ high	IFNγ low
Interleukin-1β high	Interleukin-4 receptor I
Interleukin-6 high	IL-6 low
Interleukin-8 high	
Interleukin-10 low	IL-10 high
Interleukin-12 high	IL-12 low
Interleukin-23 high	IL-23 low
Matrix metalloproteinases	MS-1-high molecular weight protein
Inducible nitric oxide synthase	Transforming growth factor β
Nitric oxide	Vascular endothelial growth factor
Tumor necrosis factor α high	TNFα low
Extracellular matrix destruction	Extracellular matrix reconstruction

Differential macrophage activation affects cytokine secretion and downstream signaling. M1 macrophage activation is induced by lipopolysaccharide, Th1-related cytokines, or C–C chemokines [32–36]. M1 macrophages promote inflammation and ECM destruction [37–41]. IL-1β secretion in the M1 phase induces matrix metalloproteinase-9 (MMP-9), which activates TGFβ and stimulates fibroblast proliferation. M2 activation is induced by glucocorticoids or Th2-related cytokines [32–35]. M2 macrophages facilitate ECM reconstruction, cell proliferation, and angiogenesis [42–44]. Macrophage phagocytosis of apoptotic cells triggers TGFβ production, suggesting that phagocytosis may stimulate the conversion to the M2 phenotype [45]. IL-10 inhibits production of IL-1β, IL-6, IL-12, IL-18, and TNF-α to downregulate M1 activation, while TGFβ feeds back to decrease MMP-9 activty by inducing tissue inhibitor of metalloproteinase-1 (TIMP-1). Inducible nitric oxide synthase and MMPs are considered specific for MI activated macrophages; and MS-1 high-molecular-weight protein (MS-1-HMWP) [46] and CD163 are specific for M2 activated macrophages [47]. The transition and dynamic balance between the two activation phases will determine the net LV remodeling process. However, this dynamic interaction loop has not been clearly defined, and the quantitative relationships among regulation factors have not been described. Because we now have true and reliable markers of macrophage activation (Table 1), studies that characterize activation patterns post-MI will be forthcoming [48].

Macrophage activation upregulates phagocytic, chemotactic, secretory, and angiogenic functions, depending on the

Table 2
Primary macrophage functions

	Role post-MI
Phagocytosis	Remove necrotic myocytes and apoptotic neutrophils
Chemotaxis	Recruit additional macrophages to injury site to amplify response
Secretion	Regulate scar formation by secreting growth factors, angiogenic factors, and MMPs
Angiogenesis	Restore blood flow

stimulus (Table 2). The macrophage undergoes reciprocal activation, such that an increase in one function is often accompanied by a decrease in another function [31]. Using an *in vitro* rat bone marrow-derived macrophage model, for example, Erwig and colleagues demonstrated that initial cytokine exposure influences final macrophage function [49]. They determined that macrophage activation by one cytokine can affect the response to a subsequent cytokine. Interferon-γ stimulated nitric oxide secretion was blocked if the macrophage was pretreated with IL-4, TGFβ, or TNFα. TNFα stimulated the uptake of apoptotic neutrophils, and this stimulation was blocked if the macrophage was pretreated with Interferon-γ, IL-4, or IL-10. TGFβ stimulated the expression of β glucuronidase, and this stimulation was blocked if the macrophage was pretreated with Interferon-γ. Thus, because the local environment determines which functions will be upregulated, the exact combination of cytokines, chemokines, adhesion molecules, and growth factors surrounding the cell will determine the precise activation phenotype for that particular macrophage. This provides a potential mechanism to explain how heterotypic macrophage differentiation can occur in the same LV.

Activated macrophages also produce angiotensin converting enzyme (ACE), which induces local angiotensin II (Ang II) expression without activating the systemic renin–angiotensin–aldosterone system [50]. While the exact role of macrophage-derived ACE on post-MI remodeling has not been studied, high-density ACE binding is found at the site of infarction from day 4 post-MI, and ACE activity is increased in the aneurysmal infarct [51–54]. In addition, ACE inhibitors have been shown to reduce the risk of recurrent MI in patients with LV dysfunction [55]. ACE inhibitors specifically reduce LV mass and decrease fibrosis in the viable myocardium, which indicate a direct connection between macrophages, macrophage-derived ACE, myofibroblast stimulation, and LV remodeling [56].

3. Macrophage roles in the inflammatory response in wound healing and post-MI LV remodeling

The three major components of the MI response are inflammation, scar formation, and scar remodeling, with overlapping time frames between individual components. Macrophages play roles in all three components. Similar to other tissues (e.g. atherosclerotic plaque, skin, lung, and tumors), macrophage infiltration into the LV regulates multiple wound healing functions, including phagocytosis and wound debridement, angiogenesis, fibroblast activation and proliferation, and collagen metabolism [57]. Macrophage activation has been extensively studied in animal models of the development and progression of coronary atherosclerosis, and macrophage roles in atherosclerosis have been previously reviewed [58,59]. Because macrophage-depleted animals exhibit defective wound repair, macrophages are likely a primary source of growth factors necessary for scar formation [25,60–66].

The primary role of the macrophage in the post-MI LV is to facilitate wound healing through phagocytosis of necrotic cells and secretion of growth factors and angiogenic molecules. Macrophage migration is directed by signals from the injured myocardium, including signals from resident cells (myocytes) and acute inflammatory cells (neutrophils). The local synthesis of chemoattractants, adhesion molecules, and other proteins recruits and confines macrophages to the site of injury and nearby border zone [67]. Activated macrophages, in turn, produce many cytokines, chemokines, and proteases such as MMPs [68,69].

Following MI, the inflammatory reaction is a prerequisite for healing and scar formation (Fig. 1). A principle inflammatory cell type that modulates the inflammatory response to MI is the macrophage [70]. The inflammatory response is both accelerated and augmented if the ischemic tissue is reperfused. Paradoxically, this enhancement of the inflammatory response actually improves tissue repair. Indeed, early clinical trials inhibiting the inflammatory component with methylprednisolone drastically increased mortality due to LV rupture [7,71,72]. Several laboratories have recently shown that M-CSF treatment increases macrophage infiltration post-MI, resulting in improved function and accelerated infarct repair, while macrophage depletion using clodronate-containing liposomes impaired wound healing in a cryoinjury mouse model [73–75]. Inflammation, therefore, is a necessary component of the healing response. Recently, Leor and colleagues showed that injecting activated macrophages into the ischemic myocardium, immediately after coronary artery ligation, improved myocardial healing, attenuated LV remodeling, and preserved LV function [76]. This experiment mimicked reperfusion, except that neutrophils were not included in the equation. This experiment suggests that a major beneficial role of reperfusion is to increase the kinetics of macrophage infiltration [77].

The inflammatory response to MI is similar to the inflammatory response to wound healing processes in tissue types throughout the body [25]. The primary difference between wound healing in other tissues and the post-MI response is that cardiac myocytes are generally considered to be terminally differentiated cells, which precludes significant tissue regeneration [78,79]. Similarities include a common mechanism of complement activation that mediates the

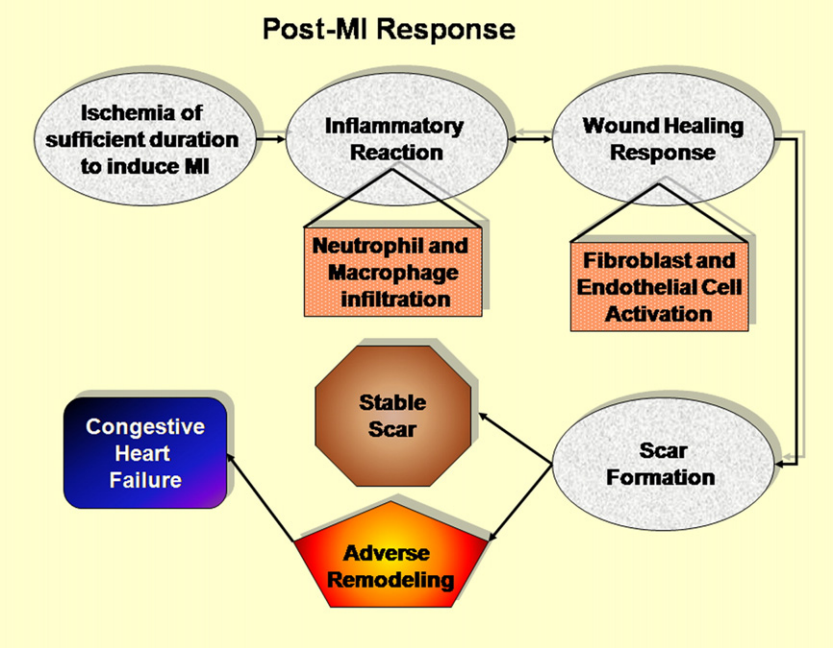

Fig. 1. Ischemia of sufficient duration to induce myocardial infarction stimulates an inflammatory reaction that is characterized by infiltration of neutrophils during the first day and macrophages beginning at day 3. The influx of macrophages coordinates the wound healing response, which involves activation of both endothelial cells and cardiac fibroblasts. The coordination between inflammation and scar formation determines the fate post-MI.

upregulation of a series of cytokines, chemokines, and cell adhesion molecules that trigger the recruitment of leukocytes (predominantly neutrophils and monocytes) into the infarct region [5,80]. Neutrophil roles post-MI have been extensively reviewed previously and will not be considered in detail here [7]. Inhibition of local complement activation improves LV function and increases perfusion of previously ischemic myocardium, indicating a role for acute complement activation in exacerbating reperfusion injury [81]. Induction of chemokines by complement also initiates monocyte recruitment and macrophage activation, further implicating this pathway [36].

No studies have evaluated post-MI macrophage function by directly isolating macrophages from the infarcted myocardium. Instead, peritoneal macrophages or blood monocytes are most frequently isolated and stimulated as surrogate cells to examine the role of cytokines and growth factors on macrophage activation [82–84]. While these models do not entirely recapitulate the *in vivo* environment of the post-MI macrophage, immunohistochemical techniques have been applied to validate *in vitro* results in the *in vivo* setting [83].

Macrophage infiltration into the myocardium post-MI involves upregulation of both β_2 integrins on the blood monocyte and adhesion molecules on the endothelial cell, stimulated by the local generation of chemotactic factors, including apoptotic neutrophils that previously homed to the infarct region [85]. Once activated, macrophages produce many cytokines, chemokines and growth factors. Over 150 secretory proteins have been identified from macrophage cultures, including those listed in Table 3 [24,86–89]. Among the secreted proteins are IL-1 α and β, IL-6, TNFα, and macrophage inflammatory proteins 1α, 1β, 2α, and 2β [90,91]. Cytokines and growth factors secreted at the site of injury regulate the inflammatory component, angiogenesis, and fibroblast proliferation [7]. In particular, monocyte chemotactic protein-1 (MCP-1) is a small molecular weight C–C chemokine that serves as a potent monocyte chemotactic factor in several models of inflammation [92], including MI [70,93]. Produced by vascular endothelial

Table 3
Key proteins secreted by macrophages [28,85,168–170]

Cytokines and chemokines	Growth factors
Interferon α	Angiotensinogen
Interleukin-1α and β, -6, -8, -10	Basic fibroblast growth factor
Macrophage inflammatory proteins	Endothelial cell inhibitory factor
Monocyte chemotactic protein-1	Granulocyte colony stimulating factor
Tumor necrosis factor α	Granulocyte macrophage colony stimulating factor
Proteases and protease inhibitors	Insulin-like Growth Factor 1
Angiotensin converting enzyme	Macrophage colony stimulating factor
ADAMTS-4, -7, -8, -9	Monocyte chemotactic protein-1
α2-macroglobulin	Substance P
Caspases 2, 3, 8, 9	Thrombospondin-1
Cathepsin B	Transforming growth factors α and β
MMP-1, -3, -7, -8, -9, -12	Vascular endothelial growth factor
Plasmin	
Plasminogen activator inhibitor 1	

cells, smooth muscle cells, and macrophages, MCP-1 heralds macrophage infiltration into the ischemic myocardium [94]. No studies to date have examined whether any of the macrophage secreted factors listed in Table 3 could be used to discriminate between normal wound healing and adverse LV remodeling post-MI.

4. Macrophage roles in post-MI phagocytosis and wound debridement

A primary function of the macrophage is to engulf apoptotic and necrotic cells within an injured tissue [95]. Experiments involving the depletion of macrophages and circulating monocytes resulted in decreased wound debridement, reduced fibroblast activation, and reduced fibrotic response in a rat kidney injury model [96]. Galectin-3 is an animal lectin abundantly expressed in macrophages that has been implicated in regulating phagocytosis. Cells deficient in galectin-3 display reduced phagocytosis of apoptotic cells both *in vitro* and *in vivo* [97]. Phenotypic alterations in macrophage response can be evaluated by monitoring phagocytosis in isolated cells. Marée and colleagues elegantly monitored *in vitro* time-course assays of the number of engulfed apoptotic cells observed within macrophages between a diabetic and non-diabetic group to quantify rates of macrophage phagocytosis in terms of rates and percentage uptake of cells over time. They observed that macrophage defects can be a potential pre-disposition to diseases such as type 1 diabetes [98]. Parameters of macrophage phagocytosis that can be evaluated include percentage phagocytosed, phagocytic index, densities of activated and unactivated macrophages, maximum number of engulfed cells, and several rate variables (Table 4).

5. Macrophage roles in post-MI scar formation

Myocardial fibroblasts actively regulate the post-MI response by influencing structural, biochemical, mechanical, and electrical properties of the myocardium [99]. As such, fibroblasts sense, integrate, and functionally respond to multiple factors by altering ECM turnover [100]. The source of the post-MI myofibroblast, whether from existing resident fibroblasts, bone marrow-derived precursors, or a combination of sources, remains controversial [101–106]. Nonetheless, fibroblast conversion to a myofibroblast phenotype is characterized by increased α smooth muscle actin expression, cell proliferation, and ECM production (collagen I, collagen III, fibronectin, and laminin) [107]. Fibroblasts secrete collagen to form first a provisional scar and later a more advanced scar. Fibroblasts also synthesize many other factors relevant to LV remodeling, including MMPs, TIMPs, IL-1, IL-6, TGFβ, connective tissue growth factor, TNFα, Ang II, and endothelin I [108–116]. Ang II stimulates fibroblast transformation into myofibroblasts and induces ECM production [117–120]. TGFβ released from necrotic myocytes and activated macrophages is also important in the phenotypic transformation of interstitial fibroblast to myofibroblasts, which express receptors to Ang II, TGFβ, and endothelin-1 [116,121].

There are multiple response factors that will amplify fibroblast activation, and the macrophage is a major source for these initiating factors. Interestingly, fibroblast activation also occurs at day 3 post-MI, in parallel with the observed changes in macrophage migration and activation. Yano and colleagues have shown that the level of collagen deposited post-MI is directly correlated with macrophage numbers [74]. The cause and effect link between macrophage infiltration and concomitant fibroblast activation, however, remains to be explored.

Table 4
Parameters that quantify macrophage phagocytosis [98]

- % phagocytosis — the percentage of all macrophages containing at least one engulfed apoptotic cell
- phagocytic index — the number of engulfed apoptotic cells per 100 macrophages
- density of macrophages with engulfed apoptotic cells
- density of unactivated macrophages
- maximum number of engulfed apoptotic cells observed within a single macrophage
- rate at which macrophages engulf apoptotic cells
- initial rise time — rate at which unactivated macrophages engulf apoptotic cells and consequently become activated
- rate at which apoptotic cells are digested

6. Macrophage roles in post-MI angiogenesis

The term *angiogenesis* describes the sprouting of new capillaries from postcapillary venules [122,123]. Angiogenesis stimulated by tissue hypoxia occurs via activation of hypoxia-inducible factor 1α gene expression and usually leads to the development of capillaries [124]. In contrast, *arteriogenesis* refers to the process of maturation or de novo growth of collateral conduits [122,125,126] and typically occurs outside the area of ischemia [122]. Both are important components of inflammatory reactions and subsequent repair processes [21].

Angiogenesis is tightly regulated and occurs within the context of a fine balance between conditions that facilitate (angiogenic) and those that inhibit (angiostatic) vessel formation [86]. A diverse literature implicates macrophages in the angiogenic process, and, indeed, the single most extensively evaluated role for macrophages is with angiogenesis [23]. The occurrence of angiogenesis correlates positively with the number of macrophages in various injury models, including MI, stroke, and skin wound healing [127]. Manoonkitiwongsa and colleagues have proposed a “clean up hypothesis” to explain the relationship between macrophages and angiogenesis in the brain following stroke, in that new blood vessels are formed to promote macrophage infiltration and to remove necrotic cells [127]. During wound healing, DNA synthesis increases in endothelial cells

concomitant with macrophage infiltration, and macrophages isolated from such wound sites induce angiogenesis by *in vitro* assays [128]. Culture media from activated macrophages also stimulates angiogenesis, while unstimulated peritoneal macrophage conditioned media does not [129].

Activated macrophages have the capability to influence each phase of the angiogenic process, including alterations of the local extracellular matrix, induction of endothelial cells to migrate or proliferate, and inhibition of vascular growth with formation of differentiated capillaries (Fig. 2) [21]. Macrophages are key angiogenic effector cells, producing a number of growth stimulators and inhibitors [130], yet also help to turn off angiogenesis by releasing angiostatic factors such as thrombospondin-1 and various cytokines (e.g. interferon α, monocyte-derived endothelial cell inhibitory factor, IL-1, TNFα, and TGFβ) [21].

6.1. Macrophages induce angiogenesis via matrix metalloproteinases (MMPs)

MMPs are a family of zinc-dependent enzymes comprised of more than 25 individual members divided into specific classes based on *in vitro* extracellular matrix substrate assays [131]. Interestingly, MMPs also show specificity for many non-matrix proteins such as cytokines, adhesion molecules, growth factors, and receptors [132]. MMPs are produced by constitutive myocardial cell types (myocytes, fibroblasts, and endothelial cells), as well as by inducible cell types (neutrophils, macrophages, and myofibroblasts) [2]. MMP activation requires cleavage of an approximately 10 kD propeptide in the amino terminus through the cysteine switch mechanism [131]. When the peptide domain is cleaved, the bond between a cysteine in the propeptide domain and the active site zinc is disrupted to expose the active site. MMPs are regulated at every level, including transcription, translation, secretion, and activation. Studies conducted by Shankavaram et al. indicate that agents that block any part of the signal transduction pathway will inhibit MMP synthesis. Although this inhibition mechanism is published, this strategy is not highly selective [2,133].

Induction of angiogenesis and subsequent migration of endothelial cells requires the dissolution of the capillary basement membrane and the local extracellular matrix [21,134–136]. Macrophages are a rich source of MMPs that can degrade extracellular matrix molecules, modulate mechanical architecture, and liberate extracellular matrix-bound growth factors [21]. Thus, MMP and plasmin release by local macrophages may have profound effects on the

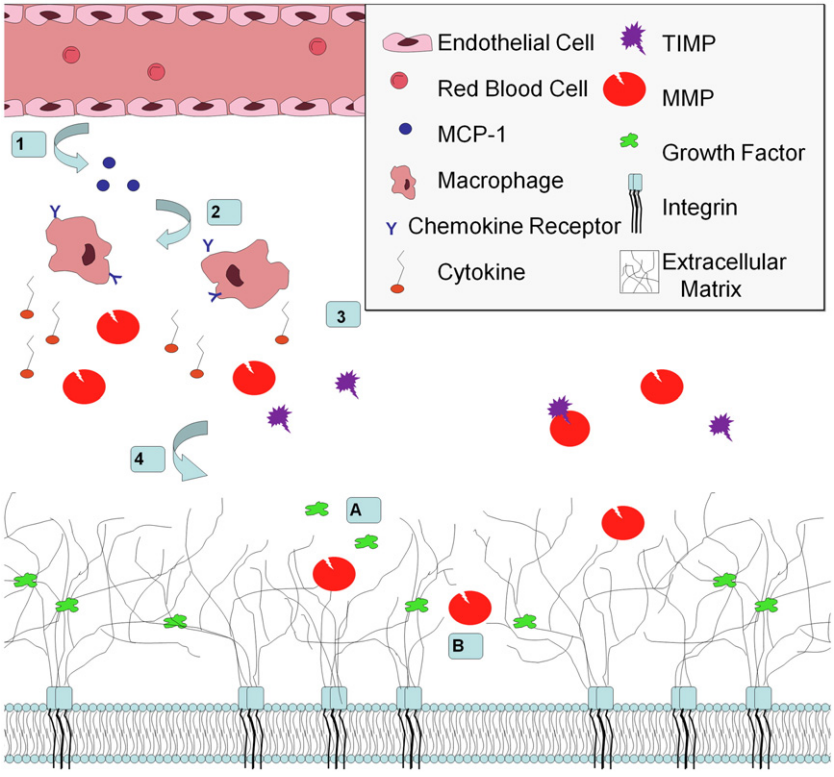

Fig. 2. Macrophage regulation of angiogenesis in ischemic tissue. 1) Vascular endothelial cells release monocyte chemotactic protein-1 (MCP-1) into the extracellular space. 2) MCP-1 attracts macrophages with the MCP-1 receptor, C–C chemokine receptor. 3) Activated macrophages secrete a variety of substances, including cytokines and matrix metalloproteinases (MMPs). 4) MMPs and TIMPs may function in early angiogenesis through interactions with extracellular matrix components. A) Degradation of matrix can release and activate extracellular matrix-bound growth factors and angiogenic molecules. MMPs and TIMPs also stimulate proliferation of endothelial and smooth muscle cells. B) MMP migration through matrix can create a pathway in the extracellular matrix for endothelial or precursor cells for angiogenesis.

formation of new vasculature as cell-matrix interactions are modified [24].

Moldovan and colleagues demonstrated that macrophages also serve a structural role in angiogenesis by actively digging channels in the matrix that become inhabited with endothelial cells to form capillaries [23,24]. The sequence of events for endothelial cells begins with the destruction of the basement membrane and local degradation of the extracellular matrix, a process mediated by macrophage-derived MMPs. This allows endothelial cells to migrate by extending cytoplasmic buds in the direction of chemotactic factors [21]. Initially, macrophages may modify the extracellular matrix by drilling a tunnel, which would thereafter be colonized either by capillary sprouts or by endothelial progenitor cells [86,137]. At the same time, macrophages potentially nurture and/or attract additional cells by secreting differentiation, growth, and angiogenic factors [86]. Macrophage-derived MMPs also produce angiostatic factors. For example, MMP-7, -9, and -12 can generate angiostatin through cleavage of plasminogen [138,139].

6.2. MMP-directed extracellular matrix degradation releases pro-angiogenic factors

Both pro-angiogenic and anti-angiogenic factors are bound to matrix components, and as such are functionally sequestered within the intact extracellular matrix. These factors include basic fibroblast growth factor, TGFβ, and granulocyte-macrophage colony-stimulating factor. Proteolytic modification of the matrix may facilitate their enzymatic release, making them available for endothelial cells [21,24]. Modification of the extracellular matrix also yields fragments of constituent proteins, which have potent effects on the angiogenic process [24]. Matricryptin is the term first coined by Davis et al. to describe peptides generated from the degradation of ECM macromolecules [140–142]. Matricryptins, also known as matrikines or cryptic fragments, are biologically active molecules with relevant biological roles, including effects on vascular myogenic response, angiogenesis or tumor formation [140,141,143–148]. What role matricryptins play in regulating macrophage function, however, has not been explored.

7. Additional roles of macrophage-derived MMPs

Macrophages synthesize several MMP types, including MMP-1, -3, -7, -8, -9, and -12. These particular MMPs may facilitate and direct macrophage migration, amplify the inflammatory response, and mediate signaling processes through proteolysis of both extracellular matrix and non-matrix substrates, ultimately influencing the myocardial response to MI. McGavigan and colleagues monitored serological markers of collagen synthesis and degradation in the plasma of 51 post-MI patients. They estimated there was approximately a 25% net loss of collagen within the first 24 h post-MI, and that patients with the highest degradation rates had the highest remodeling as measured by echocardiographic indices [149]. This experiment suggests that collagen degradation by MMPs is a highly relevant function early post-MI.

Of the MMPs identified in the macrophage, MMP-9 may be the most relevant to post-MI remodeling. MMP-9 readily digests denatured collagens and gelatins [150], and additionally can process multiple cytokines and adhesion molecules (e.g., endothelin-1, intercellular adhesion molecule-1, IL-1β and IL-8) [151–153]. MMP-9 is prominently expressed during macrophage differentiation and over-expressed post-MI [154]. MMP-9 null mice display attenuated LV remodeling during the early healing process post-MI, suggesting a prominent role for MMP-9 in the post-MI response [155]. MMP-9 may also play a specific role in angiogenesis. Johnson and colleagues demonstrated that MMP-9 was necessary for capillary branching, as MMP-9 null mice showed a blunted angiogenic response following skeletal muscle ischemia [156]. In the myocardium, however, MMP-9 deletion promoted post-MI angiogenesis [157]. Together, the above studies provide rationale for examining MMP inhibitors that target particular MMPs, including MMP-9. Currently, there are no individual MMP type inhibitors, and clinical trials using broad spectrum MMP inhibitors in cancer studies have been plagued with side effects attributed to the non-selective nature of these protease inhibitors [158–161]. Future studies evaluating the use of MMP-9 specific inhibitors may yield promising results. Targeted drug delivery strategies that selectively inhibit MMP-9 in the cardiac tissue, rather than systemic inhibition, may also need to be considered.

In addition to MMPs, macrophages also express TIMPs. Activated MMPs are inhibited by binding of the TIMP C-terminal domain [150]. TIMPs play a role in a variety of disease processes, including post-MI remodeling. Previous studies reveal that endogenous MMP inhibitory control is lost early in the post-MI period, and this loss of TIMP was a major factor in LV remodeling [162,163]. In addition to MMP blocking functions, TIMPs also regulate cell growth and signaling [164]. Little is known about the role of macrophage-derived TIMPs in LV remodeling, and the net balance between macrophage-derived MMP activity and TIMP inhibition remains to be further clarified.

8. Future directions

While many studies correlate macrophage infiltration with changes in LV remodeling parameters, direct causal links between macrophages and many of the above-mentioned processes remains to be experimentally established. The exciting results already seen in the macrophage biology arena reveal avenues for basic science research, in regards to macrophage function in the post-MI setting specifically and the wound-healing environment generally. A sampling of questions that remain to be explored include:

- How do macrophage roles in the LV post-MI compare and contrast with macrophage roles in other tissues? Are macrophages in the post-MI myocardium identical to

macrophages that infiltrate into other injury sites? What are features in common and what are distinct characteristics of myocardial macrophage activation? How do these changes affect macrophage function?

- What are the complete functions of macrophages post-MI? Which components of the macrophage response are beneficial and/or necessary for wound healing, and which components are detrimental? Can detrimental components be selectively inhibited therapeutically?
- What is the complete secretory catalogue of macrophages, both in the basal state and following activation? Using genomic and proteomic techniques to identify the complete catalogue of secretory proteins expressed in macrophages, both in the unactivated and activated states, will help to assign previously unknown roles for macrophages in remodeling.
- Can macrophages be used to target drug therapy to the MI site? Several groups have proposed using macrophages to target drug delivery, and whether this strategy will be effective remains to be determined [6,90,95,165,166].
- How do macrophages regulate the function of other cell types post-MI, particularly endothelial cells and myofibroblasts? What role will influencing macrophage function have on these other cell types?

From a clinical research view, there are also several outstanding issues to be resolved. The recent results of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial indicate that further mechanistic insight is still required [167]. Patients were randomized to receive either placebo or Pexelizumab, a C5a inhibitor, 10 min prior to primary percutaneous transluminal coronary intervention (PCI), and treatment was continued for 24 h. At 30 days follow up, there was no difference in survival between the two groups, indicating that PCI already provided maximal benefit for short-term mortality. Whether Pexelizumab prevented the long-term progression to heart failure was not measured. Future trials evaluating the effects of short-term anti-inflammatory strategies on long-term outcomes is warranted. In addition, improved imaging modalities, including contrast echocardiography and magnetic resonance imaging, now provide improved monitoring opportunities to evaluate infarct scar development and remodeling. In conclusion, inhibition studies using anti-inflammatory strategies have taught us the importance of discerning beneficial and detrimental roles for the macrophage post-MI. The ability to isolate these opposing functions could potentially be used to derive novel therapeutic strategies.

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