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REVIEW ARTICLE

Post-myocardial Infarct Inflammation and the Potential Role of Cell Therapy

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Abstract Myocardial infarction triggers reparative inflammatory processes programmed to repair damaged tissue. However, often additional injury to the myocardium occurs through the course of this inflammatory process, which ultimately can lead to heart failure. The potential beneficial effects of cell therapy in treating cardiac ischemic disease, the number one cause of death worldwide, are being studied extensively, both in clinical trials using adult stem cells as well as in fundamental research on cardiac stem cells and regenerative biology. This review summarizes the current knowledge on molecular and cellular processes implicated in post-infarction inflammation and discusses the potential beneficial role cell therapy might play in this process. Due to its immunomodulatory properties, the mesenchymal stromal cell is a candidate to reverse the disease progression of the infarcted heart towards heart failure, and therefore is emphasized in this review.

Keywords Myocardial infarction · Inflammatory response · Cell therapy · Mesenchymal stromal cell

Introduction

Ischemic heart disease including myocardial infarction (MI) is the number one cause of death worldwide [1]. MI typically results from a (thrombotic) occlusion of a coronary artery leading to myocardial ischemia [2]. Typically, after diagnosis of MI primary percutaneous coronary intervention (PCI) of the infarct related coronary artery is performed to achieve reperfusion, limit tissue necrosis and improve the clinical outcome. Additionally, reperfusion triggers the immune system to initiate an essentially regenerative signaling cascade programmed to repair the damaged tissue after removal of dead cells and matrix debris [3]. However, this immune-mediated response needs to be tightly regulated to prevent additional myocardial tissue damage which may invoke congestive heart failure [4, 5]. Although PCI limits tissue damage inflicted by myocardial ischemia, this intervention typically does not halt or even reverse the loss of functional myocardium [6].

To limit (additional) damage to the myocardium after MI, novel therapeutic interventions involving cell-based therapies have emerged in order to increase our arsenal for treating ischemic heart disease [7]. In this review we systematically summarize the current state of knowledge on the inflammatory response involved in post-myocardial infarct inflammation and discuss how cell therapy may attenuate certain deleterious aspects of this response and may improve cardiac function after MI.

The Post-infarction Inflammatory Response

Myocardial ischemia results in cell death, initiating an inflammatory response ultimately resulting in scar formation [8]. This process of myocardial infarct healing occurs through three successive phases: the inflammatory phase, the proliferative phase and finally the maturation phase [9, 10].

The Inflammatory Phase

The immune system comprises an innate and adaptive system. The innate immune system regulates the non-specific

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immediate response against invading pathogens and injury, whereas the adaptive immune system involves specific recognition of foreign antigens and progresses with a delay as it requires prior activation by innate immune cells. As a consequence, the first phase of the reparative process after MI is mediated by the innate immune system [10].

Initially, platelets are activated upon myocardial injury to prevent bleeding. Platelets aggregate locally to form a fibrin-rich matrix and release important growth factors such as platelet-derived growth factor (PDGF) and Platelet-Factor 4 that aid the repair process [11]. In parallel, platelets produce platelet activating factor thereby stimulating the influx and adhesion of neutrophilic granulocytes to the site of injury [12]. Neutrophils are among the first innate immune cells to enter the myocardium, which occurs within hours after the ischemic event. Their recruitment is stimulated by Reactive Oxygen Species (ROS) produced by activated cardiac myocytes and vascular endothelial cells [10]. ROS (including hydrogen peroxides, superoxide anions and hydroxy radicals) are formed by the incomplete reduction of molecular oxygen and activate the chemotactic cytokine interleukin (IL)-8 / chemokine (CXC motif) ligand 8 as well as the endothelial surface molecule intercellular adhesion molecule-1 (ICAM-1), together coordinating neutrophil recruitment.

Upon arrival, neutrophils secrete proteolytic enzymes that clear the infarct from dead cells and debris [10, 13]. However, the activated neutrophils also contribute to the production of ROS which react directly with cellular lipids, proteins and DNA released from the damaged cells. In this context ROS act as signaling intermediates that activate the transcription factor Nuclear Factor-κB (NF-κB) resulting in the production of pro-inflammatory cytokines and chemokines, but also of growth factors important for tissue repair such as Transforming Growth factor-beta (TGF-β) [10, 14, 15]. Tissue damage inflicted by ROS needs to be limited as early as possible as demonstrated in a study of MI in dogs using free radical scavenging catalase and the anti-oxidant enzyme superoxide dismutase-1. In this study it was shown that infarct size was reduced only when the treatment was given prior to coronary occlusion [16].

It is however difficult to denote the exact role of neutrophils in myocardial repair. Smaller infarcts were observed upon myocardial reperfusion in experimental animals depleted of neutrophils, suggesting that neutrophils have a deleterious effect in myocardial injury followed by reperfusion [17]. However, infarct sizes were not altered when neutrophil recruitment was prohibited in mice deficient for ICAM-1 and P-selectin, despite a reduction in neutrophil trafficking [18]. Initial neutrophil influx is followed by the recruitment of monocytes, which is mainly mediated by the chemokine monocyte chemo attractant protein-1 (MCP-1)/ chemokine (C-C motif) ligand 2. In a study in MCP-1 deficient mice, it was shown that the absence of MCP-1 did not alter infarct size, but attenuated ventricular remodeling, reduced and delayed monocyte/macrophage recruitment and delayed replacement of cardiomyocytes with granulation tissue and diminished myofibroblast accumulation [19]. Phenotypically monocytes can be distinguished in different subsets and numerous studies have tried to attribute different roles to distinct subsets as monocytes appear to be involved in both pathogenic as well as reparative inflammatory responses. In mice, monocytes that express high levels of the molecule lymphocyte antigen 6c (Ly-6C) are regarded as pro-inflammatory monocytes. In mouse MI studies these pro-inflammatory Ly-6C^{high} monocytes are recruited from the bone marrow to the infarcted heart expressing the C-C chemokine receptor 2 (CCR2), where they remain in high numbers until 3 days after MI, scavenging debris and secreting inflammatory cytokines and matrix degrading proteases [20, 21].

The recruitment of neutrophils and monocytes is thus crucial for the initiation of the repair process, but their contribution is determined by the actual signaling cascades that are activated. Intracellular components released from necrotic cardiomyocytes are sensed by innate immune cells that become activated upon tissue entry [22]. The most prominent pathways by which the innate immune system initiates a post-infarction inflammatory response are: 1) the Toll-like receptor (TLR)-mediated pathway; 2) the complement cascade and; 3) the earlier mentioned ROS. These three pathways all converge to activate NF-κB, a transcription factor that drives the expression of numerous genes. In a resting cell the NF-κB dimer is sequestered in the cytoplasm as an inactive protein bound by the inhibitor of κB, IκB. Upon activation of the NF-κB pathway, the IκB protein is degraded, releasing the NF-κB dimer which then translocates to the nucleus where it regulates gene expression by binding specific promoter sequences. Since NF-κB regulates so many different genes ranging from pro-inflammatory cytokines, chemokines, matrix metalloproteinase (MMP) as well as genes involved in cell survival and proliferation, [23, 24] it is considered as one of the most important players throughout the whole process of tissue repair. A recent review summarizes several studies highlighting the participation of NF-κB in post-MI inflammation [24]. A reduction of myocardial infarct size was observed after ischemia/reperfusion in an experimental model where NF-κB activity was blocked by prohibiting DNA-binding using decoy oligodeoxynucleotides, whereas a recent report by Hamid et al. reported that prolonged activity of NF-κB in myocardial tissue results in a chronic inflammatory state with detrimental consequences for infarct healing [25]. Both studies underscore the role of NF-κB in post-MI inflammation [26].

TLRs are a family of heterodimeric transmembrane pattern recognition receptors that recognize and bind antigens derived from pathogens or damaged tissues, the so called damage-associated molecular patterns (DAMPs). Upon ligand binding

most TLRs activate NF-κB leading to the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), pro IL-1β and interferons. Among the ten human TLRs identified, TLR1, 2, 4–6 and 11 are expressed on the cell surface, whilst TLR3 and 7–9 are expressed in intracellular vesicles, mostly endosomes. TLRs are pre-assembled as low-affinity dimers which undergo a conformational change upon ligand binding. Although initially described as receptors that recognize pathogen-derived molecules, several non-pathogenic endogenous molecules have been identified to bind and activate TLRs. For instance TLR4 binds not only to lipopolysaccharide but also to certain heat shock proteins and extracellular matrix remnants such as hyaluronan and fibronectin [27] suggesting a broad role for TLR4 in tissue injury and repair. It has been observed that TLR4 is upregulated in injured myocardium of both humans and mice [28]. Also, in TLR4 deficient mice, MI induced hearts were characterized by reduced left ventricular remodeling with preserved systolic function, but without affecting the infarct size. The infarcted area showed increased collagen density with fewer macrophages and reduced cytokine levels and MMP activity, identifying TLR4 as an important component of the post-MI remodeling process [29]. Next to TLR activation, the release of DAMPs also triggers the complement cascade.

The complement system is a network of soluble and surface bound proteins able of recognizing, tagging and eliminating microbial intruders and foreign cells via initiation of the immune response. The complement cascade consists of three main pathways which are all involved in immunopathological diseases [30]. In a rat model of MI it was shown that ischemic myocardial injury activates the complement cascade, and mRNA and proteins of the complement pathway are upregulated in areas of MI [31–34]. The importance of complement pathway activation in mononuclear cell recruitment was shown in a canine model of cardiac ischemia in which upon cardiac reperfusion, the complement pathway induced migration of monocytes into the myocardium [35]. Studies have been performed in which certain elements of the complement cascade have been inhibited using cobra venom or soluble human complement receptor to antagonize complement signaling. These studies showed a reduction in myocardial necrosis and a decrease in infarct size suggesting a role for the complement pathways in myocardial injury [36, 37].

In conclusion, all actions combined result in recruitment of leucocytes to the infarcted area, the clearance of dead cells and debris and the activation of signaling cascades leading to the production of a variety of essential growth factors for repair of the infarcted area, and the transition towards the proliferative phase [38].

The Proliferative Phase

At this stage neutrophils, mononuclear cells, endothelial cells and pericytes all work together to resolve the initial inflammatory reaction and direct it towards a healing process. Short–lived neutrophils become apoptotic and release mediators such as annexin A1 and lactoferrin that suppress further neutrophil recruitment [39]. The Ly-6C^{high} monocytes express the orphan nuclear hormone receptor, nuclear receptor subfamily 4, group a, member 1 (Nr4a1) which reduces the CCR2 dependent recruitment of Ly-6C^{high} monocytes towards the infarct. In addition, Ly-6C^{high} monocytes differentiate into Ly-6C^{low} macrophages in the local cardiac tissue. Ly-6C^{low} macrophages clear the apoptotic neutrophils and are associated with an increased presence of the anti-inflammatory factors IL-10, TGF-β and vascular endothelial growth factor (VEGF) countering the inflammatory response by recruitment of myofibroblasts for scar tissue formation and thereby contributing to infarct healing [20, 40]. A recent study performed by Hilgendorf et al. indicated another important anti-inflammatory role for Nr4a1, as cardiac macrophages in Nr4a1-deficient mice showed a more inflammatory profile and as a result these animals had a decreased cardiac function and increased cardiac remodeling in contrast to wildtype controls following MI [40]. Whilst Ly-6C^{high} monocyte levels decrease, Ly-6C^{low} monocytes, resident in the cardiac tissue, peak 7 days after MI and afterwards also decrease. Ly-6C^{low} monocytes are also Nr4a1 dependent, as Nr4a1-deficient animals had no Ly-6C^{low} monocytes in either the cardiac tissue or the peripheral circulation. The role of Ly6C^{low} monocytes is still under investigation, but they are important in the inflammatory process by the clearance of endothelial necrotic cells via TLR-7 activation [41]. A recent study showed a similar monocyte pattern in post-mortem tissue of human MI patients as mainly CD14^{+}CD16^{-} monocytes were present in the cardiac infarct tissue in the inflammatory phase after MI, while in the proliferative phase both CD14^{+}CD16^{-} and CD14^{+}CD16^{+} monocytes were observed [42]. Since CD14^{+}CD16^{-} monocytes in humans are comparable to Ly6C^{high} monocytes in mice [21, 43], this indicates the monocyte response is comparable between species.

The uptake of apoptotic cells by macrophages induces the release of anti-inflammatory factors such as IL-10 and TGF-β, and lipid mediators such as lipoxins and resolvins which further stimulate the removal of inflammatory leukocytes [23, 44].

After MI, IL-10 becomes highly expressed, mainly by activated T lymphocytes and monocytes as described above. As IL-10 inhibits the secretion of IL-1α, IL-1β, TNF-α, IL-6 and IL-8, it suppresses the ongoing inflammation process [5, 23]. In addition, IL-10 induces the production of a group of peptidases involved in extracellular matrix (ECM) degradation called tissue inhibitor of metalloproteinases (TIMPs),

thereby promoting ECM remodeling [10, 45, 46]. IL-10 deficient mice showed an increased mortality concomitant with an enhanced immune response during myocardial ischemia followed by reperfusion, as measured by a higher neutrophil recruitment, elevated plasma TNF-α and a higher expression of ICAM-1 [47]. In a similar study elevated mRNA levels of TNF-α and MCP-1 were also observed in the infarcted heart of IL-10 deficient mice. However, in this study mortality rates were similar to wild type mice due to the variable effects of IL-10, affecting the production of numerous cytokines such as IL-1 and IL-6 [48]. Both IL-1α and IL-1β are upregulated in experimental models of MI and promote the inflammatory reaction by the induction of cytokine and chemokine production [10]. In contrast, IL-6 appears to have a beneficial role in tissue repair [11]. IL-6 protects cardiomyocytes against apoptosis and induces cardiomyocyte hypertrophy. IL-6 expression is induced in the healing infarct, and can be produced by mononuclear cells, cardiomyocytes and fibroblasts within the ischemic myocardium [10, 49, 50].

TGF-β is upregulated in experimental models of MI and initiates the transition from inflammation to fibrosis by pro-inflammatory cytokine suppression [38]. The secretion of TGF-β will initiate fibroblast growth as well as angiogenesis, whereas MMPs and TIMPs produced by the activated macrophages aid in the extracellular remodeling of the regenerating cardiac tissue [5, 10]. Angiogenesis is crucial to provide oxygen to the injured tissue and maintain cell metabolism [10]. One of the most important angiogenic factors during the proliferative phase is hypoxia-inducible factor 1, expressed early after myocardial ischemia, which upregulates the chemokine stromal cell-derived factor 1-α (SDF-1) and its receptors CXCR4 and CXCR7 [51] and activates the release of VEGF, one of the key growth factors in neoangiogenesis [52]. After SDF-1 is expressed, hematopoietic stem cells and endothelial progenitor cells are recruited to the ischemic myocardium where they improve angiogenesis as has been demonstrated by several studies [51, 53–57]. PDGF signaling induces maturation of the neovessels via the formation of a mural coat of pericytes surrounding the vessel. Withdrawal of PDGF from this process leads to apoptosis of the endothelial cells [58].

Inhibition of TGF-β during the early inflammatory phase after myocardial injury results in a significant increase in mortality and an exacerbated left ventricular dilatation via enhanced cytokine synthesis in mice [59] Moreover, TGF-β inhibits immune cell proliferation and stimulates fibroblasts to produce ECM proteins such as collagens, fibronectin, tenascin and proteoglycans and ultimately suppresses matrix degradation via inhibition of proteinases such as plasminogen activators and collagenases while stimulating production of proteinase inhibitors such as plasminogen activator inhibitor-1 and TIMPs [60–62]. Resident cardiac fibroblasts entering the infarcted tissue differentiate to myofibroblasts that express contractile proteins such as α-smooth muscle actin. Myofibroblast differentiation is induced by mechanical stress, TGFβ/Smad3 signaling and alterations in the composition of the ECM such as up regulation of ED-A fibronectin [63, 64]. These myofibroblasts are predominantly present in the infarct border zone and have a high proliferative capacity [10, 65]. They are the main source of ECM proteins needed to generate a collagen scar [66]. Induction of the pro-inflammatory cytokine TNF-α diminishes ECM collagen synthesis followed by an increase of the MMP activity of cardiac fibroblasts [10, 67]. However, TNF-α deficient mice are protected from cardiac rupture and chronic dysfunction following infarction [68], indicating the pleiotropic role of the cytokine.

One of the important ECM constituents is hyaluronan, a high molecular weight polymer under physiologic conditions, which becomes degraded upon tissue injury. Hyaluronan fragments stimulate endothelial cells and macrophages to secrete pro-inflammatory cytokines and chemokines and clearance of these fragments precedes the resolution of the inflammatory phase [10, 69, 70]. Finally, there is an accumulation of mast cells during cell proliferation and fibrosis [71]. The exact role of mast cells in the process of cardiac inflammation and repair is still under investigation, but one function of mast cells might be the regulation of fibrosis by the secretion of MMPs [72], inducing tissue remodeling. The summation of these processes finally leads to the formation of highly vascularized granulation tissue and abolition of the pro-inflammatory environment enabling repair.

The Maturation Phase

The formation of the scar, initiated during the proliferative phase, is followed by its maturation when endothelial cells have proliferated to form an extensive microvascular network. Only a part of these vessels mature through the mural wall formation by pericytes and myofibroblasts. These mature vessels aid scar stabilization by providing oxygen and nutrients [23]. However, the remainder of neovessels do not mature and undergo apoptosis together with the remaining myofibroblasts [63]. The highly-vascularized granulation tissue formed during the inflammatory phase, is finally replaced by a collagen-rich scar, completing the process of infarct healing [10]. The site of coronary occlusion, duration of ischemia and timing of reperfusion all influence the inflammatory process and therefore the time course of infarct healing will vary between individuals.

After completion of the reparative response, some fibroblasts remain in the non-infarcted myocardium and may become activated via increased wall stress where they contribute to ventricular remodeling and ventricular dysfunction by producing matrix proteins and proteases [63]. Increasing the number of myofibroblasts as well as the number of capillaries by blocking frizzled signaling via Wnt3a and Wnt5a

antagonizing peptides reduced infarct size and increased infarct thickness in a mouse model of MI, suggesting that preservation of cardiac function after MI can (amongst others) be influenced by modulation of myofibroblasts [73].

In conclusion, inflammatory processes play a crucial role initially clearing the debris of apoptotic cells but also regulating essential repair mechanisms to form mature scar tissue. However, an elaborate immune response clearing as much damaged cellular tissue as possible also induces undesirable collateral damage to surrounding healthy tissue.

Therapeutic Approaches Targeting Cardiac Inflammation and Ischemia–Reperfusion Injury After Myocardial Ischemia

The progress made in understanding cardiac inflammation initiated experimental studies aiming to modulate the unwanted cardiac tissue injury induced by post-MI inflammation and reperfusion therapy. Initial studies targeting pathways of oxidation, inflammation, sodium-hydrogen exchange, nitric oxide metabolism and metabolic pathways showed positive results on clinical parameters such as reduction of infarct size; however these results need confirmation in large trials [74, 75]. The purine analogue acadesine, which increases adenosine levels in energy-deprived tissues, has been studied as a pharmalogical intervention in an ischemia-reperfusion setting [76]. A meta-analysis summarizing all studies that have tested acadesine in 4043 patients undergoing coronary artery bypass grafting (CABG) surgery, suggested a 27 % reduction of the perioperative occurrence of MI (3.6 vs 4.9 %, P=0.02) and a 26 % decrease in the combined outcome of stroke/MI/cardiac death (7.6 vs 4.6 %, P=0.04) [77]. However, the largest trial performed called the Reduction in cardiovascular Events by acaDesine trial in subjects undergoing CABG surgery (REDCABG), was stopped after 3080 of the originally projected 7500 study participants were randomized because of a low expectancy to obtain statistically significant differences. This underscores that beneficial effects are variable.

One of the earliest results of pharmacological intervention to inhibit the inflammatory response after MI was described by Roberts et al. who infused multiple doses of the anti-inflammatory drug methylprednisolone in patients with MI and reported an augmentation of the infarct size and accentuation of malignant arrhythmias. These catastrophic results of the methylprednisolone study made clear that an absolute suppression of the immune system after MI is not desirable for it also interferes with the reparative aspects of the immune response [23, 78].

A growing number of alternative promising therapeutic interventions targeting the cardiac inflammation process, including ischemic pre- or post-ischemic conditioning, has been proposed and in part already investigated in patients or is about to be examined in clinical trials [79–81]. Recently, Padfield et al. determined the effects of etanercept, a TNF-α antagonist, in patients after MI. Whereas they observed a modest anti-inflammatory effect possibly through a decrease in neutrophil recruitment and IL-6 concentrations, TNF-α levels were increased as were platelet activators and aggregators, making it less suitable as a therapeutic candidate to treat MI [82]. In another study, patients were treated with intravenous immunoglobulin after PCI, however without any beneficial effect on either cardiac function or remodeling [83]. A large trial investigating the effects of pexelizumab, an antibody binding the C5 component of complement, did not influence mortality or development of heart failure in cardiac patients [84].

Other promising therapeutic interventions showed contrasting results. The immunosuppressive drug cyclosporine that inhibits the opening of mitochondrial permeability-transition pores caused smaller infarct sizes and attenuated left ventricular remodeling in initial clinical trials when administered after primary PCI [85, 86]. However this was not reproduced in a more recent trial where cyclosporine was injected before thromobolytic treatment [87]. Blockade of the IL-1 receptor by anakinra attenuated cardiac remodeling in a first small pilot study in MI patients [88]. A second study however, did not confirm these results [89].

So far, the effects of different anti-inflammatory therapies are incongruent and their clinical applicability remains unclear. More importantly, this therapeutic approach will only attenuate the results of the inflammation process itself, among which the remodeling process. Here lies a role for the still emerging field of cell-based therapy, as this may influence the post-MI inflammation process, but also potentially regenerate the infarcted tissue [90].

Cell-Based therapy

While the amount of therapeutic strategies to treat ischemic events has increased dramatically the past decade, patients are often still prone to develop heart failure, since there are no therapeutic options available to reverse the loss of functional myocardium. Therapeutic cell therapy has the advantage that it can be delivered locally into infarcted tissue, either as a cell suspension or on a supportive scaffold. Additionally, genetic modification allows for cells to be custom-tailored to improve results.

Moreover, certain stem cell populations such as mesenchymal stromal cells (MSCs) have the additional advantage of diminishing the deleterious effects of the inflammatory response that accompanies repair by secretion of different paracrine factors acting on several immune cell populations [91, 92]. However, the potential of cell therapy to influence post-MI inflammation has not been studied extensively yet, leaving for the moment a gap in our knowledge about the effect and

Table 1 Pre-clinical studies of cell therapy in myocardial infarction

	Year	Cell type infused	Host animal	Follow-up	Functional outcome	Assessment inflammatory parameters
Mangi et al. [149]	2003	BM-MSCs	Sprague-Dawley Rats	2 weeks	-Reduction infarct volume -Improved LV systolic performance measured in the perfused Langendorff model -Reduced collagen deposition and ventricular enlargement	-Reduction of myocardial CD45+ infiltration
Zhang et al. [150]	2006	BM-MSCs BM-MNCs PBMCs	Sprague-Dawley Rats	90 days	-Improved echocardiographic function measured by: EF, FS -Reduced LV remodeling and a lower collagen density in LV	- Cardiac MPO levels were similar between groups -No significant lymphocyte or neutrophil counts in (peri)-infarct area
Guo et al. [115]	2007	BM-MSCs	Sprague-Dawley Rats	4 weeks	-Reduced Collagen type I and III deposition, and reduced MMP-1 and TIMP-1 protein en RNA levels -Attenuated LV cavitary dilation and transmural infarct thinning -Increased EF, FS, LVESP and dP/dtmax measured by echocardiography -Decreased LVDd, LVEDV, and LVEDP measured by echocardiography	-Decreased TNF-α, IL-1β, and IL-6 protein and RNA levels
Henning et al. [151]	2008	HUCBCs	Sprague-Dawley Rats	72 h and 2 months	-Reduced LVIS -Improved LVEF measured by echocardiography	-Increase of TNF-α, MCP, Fractalkine, CNF, MIP, IFN-γ, IL-1β and IL-4 in the non-treated infarcted hearts - Reduced neutrophil, CD3, CD4, and macrophage percentages in the cell-treated group
Ciulla et al. [152]	2008	BMMNC only, ACE-I treatment	Fisher-F344 rats	14 days	-Reduced pro-CK response in both cell treated and ACE-I groups	-Reduced IL-1β, IL-6 and TNF-α in the blood, in both the cell treated and ACE-I groups versus the control group
Yang et al. [117]	2008	BM-MSCs only, BM-MSC combined with Atorvastatin	Chinese mini pigs	6 weeks	-Improved cardiac performance and contractility measured by SPECT and MRI when MSC treatment is combined with Atorvastatin	-An inhibition of IL-1β, IL-6 and TNF-α in the infarcted heart with Atorvastatin and with the combination of MSC and Atorvastatin therapy
Kim et al. [121]	2009	BM-MSCs only, BM-MSCs treated with TNF- α	Sprague-Dawley Rats	2 weeks	-A higher EF in the MSC and TNF- α MSC groups versus control measured by echocardiography	-Improved in vivo retention of TNF-α MSC in ischemic myocardium compared to MSC

Table 1 (continued)

	Year	Cell type infused	Host animal	Follow-up	Functional outcome	Assessment inflammatory parameters
					-Lower ESV and EDV in the TNF-α MSC groups versus control measured by echocardiography -Reduced collagen deposition in both the MSC and TNF-α MSC group compared to control	
Lee et al. [122]	2009	BM-MSCs	C57/Bl6 mice	3 weeks	-Reduction of IS by MSC infusion compared to control -Improvements on LVFS and LVEF in the MSC groups versus control measured by echocardiography	-MSC infusion in the permanent cardiac ischemia model induced production of the anti-inflammatory protein TSG-6 -MSC infusion decreased proinflammatory proteases Plasmin, and (pro)MMP9 in mice with MI
Yang et al. [118]	2009	BM-MSCs only, BM-MSCs combined with Statin	Chinese miniswine	6 weeks	-Decreased number of dyskinetic segments and a decreased IS in the Simvastatin group measured by MRI -Improvement of cardiac function measured by MRI and a decrease of the perfusion deficit measured by SPECT in the Simvastatin-MSC group only compared to control	-Reduction of the pro-inflammatory cytokines IL-1B, IL-6 and TNF-α in the statin only, MSC only and the combination groups
Xu et al. [153]	2009	BM-MNCs	Chinese miniswine	3 or 6 weeks	-Improved ventricular functions compared to control measured via the MPA multichannel signal analytical system	-Reduced serum levels of TNF-α and IL-8 compared to control but elevated IL-10
Vicente- Tavares et al. [154]	2010	BM-MNCs	Wistar rats	48 h	-No improvement in EF in the cell treated groups compared to control measured via echocardiography	-A reduction of cardiac TNF- α and IL-6 in the cell treated group compared to control after MI
Premaratne et al. [155]	2011	SVF BM-MNCs	Lewis rats	8 weeks	-Reduced LV diastolic- and systolic dimension and an increase in FS measured via echocardiography in both the BM-MNCs as the SVF treated groups compared to control	-Reduced cardiac TNF-α, IL-6 mRNA in the SVF treated group versus control
Dayan et al. [129]	2011	BM-MSCs UCPVs	NOD-*Scid* gamma null mice	72 h	-Enhanced FS measured by echocardiography in 2 weeks but this parameter was similar to control in after 16 weeks	-Reduced overall macrophage/monocytes levels -An increase of alternatively activated M2 macrophages in the circulation and the heart -Decrease in IL-1β and IL-6 e xpression and an increase in IL-10 expression in the infarct area

Table 1 (continued)

	Year	Cell type infused	Host animal	Follow-up	Functional outcome	Assessment inflammatory parameters
Herrmann et al. [119]	2011	BM-MSCs, BM-MSC with TGF-α	Sprague-Dawley Rats	7 or 28 days	-Reduced ventricular remodeling and IS in the TGF-α- BM-MSC compared to PBS measure by echocardiography	-Reduced myocardial IL-1β, IL-6 and TNF-α protein in both the BM-MSC and the TGF-α- BM-MSC groups compared to control
Poynter et al. [116]	2011	BM-MSCs, STAT3 knockout BM-MSCs	Sprague-Dawley Rats	40 min reperfusion	-Improved LVDP, EDP, dP/dt in BM-MSC group compared to STAT3 knockout BM-MSC and vehicle	-Reduced TNF- α, IL-1β and IL-6 in the BM-MSC group -Reduced caspase 3 levels in the BM-MSC group
Van Dijk et al. [156]	2011	SVF ASCs	Wistar rats	35 days	-Reduced IS in both cell treated groups versus control measured via histology	-No difference in myocardial macrophage infiltration between test groups
Chi et al.[120]	2012	BM-MSCs/SH SH	Rats	8 weeks	-Higher LV wall thickness in the BM-MSC/SH patch group compared to the SH patch only group measured by echocardiography –Improved LVFS in both the BM-MSC/SH group and the SH only compared to control	-Reduced expression of the macrophage marker CD68 in the infarct area in both the BM-MSC/SH patch group and the SH patch only group compared to control
Ben-Mordechai et al. [130]	2013	BM-MSCs, BM-MNCs	Balb/C Mice	7 or 30 days	-Reduced IS after BM-MSC infusion -Attenuation of LV remodeling and dysfunction in the BM-MSC group	-Switch of infarct macrophages into reparative M2 macrophages in the BM-MSC group -Increased secretion of IL-10, IL5 and GM-CSF in the BM-MSC group

ACE angiotensin converting inhibitor, *ASCs* adipose-derived stem cells, *BM-MSCs* bone marrow-derived mesenchymal stromal cells, *BM-MNCs* bone marrow mononuclear cells, *Dd* diastolic diameters, *DP* developed pressure, *dP/dt* maximum rate of pressure rise, *CNF* cytotoxic necrotizing factor, *EF* ejection fraction, *EDP* end diastolic pressure, *EDV* end diastolic volume, *ESP* end systolic pressure, *ESV* end systolic volume, *FS* fractional shortening, *GM-CSF* granulocyte macrophage colony-stimulating factor, *HUCBCs* human umbilical cord mononuclear cells, *INF* interferon, *IL* interleukin, *IS* infarct size, *LV* left ventricle, *MCP* monocyte chemotactic protein, *MIP* macrophage inflammatory protein, *MMP* matrix metalloproteinase, *MRI* magnetic resonance imaging, *PBS* phosphate buffered saline, *SH* silk fibroin/hyaluronic acid patches, *SPECT* single-photon emission computed tomography, *SVF* adipose-derived stromal vascular fraction, *TGF* transforming growth factor, *TIMP* tissue inhibitor of metalloproteinases, *TNF* tumor necrosis factor, *TSG* tumor necrosis factor-inducible gene 6 protein, *UCPVs* umbilical cord perivascular cells

capacity cell therapy might have in modulating post-MI inflammation. The field of stem cell transplantation was accelerated a decade ago by a preclinical study that reported improved cardiac regeneration upon infusion of bone marrow-derived cells into a cardiac ischemic mouse heart [93]. These results initiated a new area of research, exploring the potential of cell therapy to regenerate the diseased heart and clinical trials quickly followed.

The ideal cardiac regenerative therapy involves a cell type that is easily accessible, produces the optimal combination of paracrine factors, is able to engraft in the injured cardiac tissue niche, can possibly even differentiate into a cardiomyocyte or other desired cardiac cell types, and can be delivered via a safe and minimally invasive procedure. In search for this cell type, a variety of cell populations are being studied, all initially aimed toward regenerating cardiac tissues, each having their own advantages and limitations [94].

Transplantation of various cell types such as hematopoietic and non-hematopoietic bone marrow-derived stem cells as well as MSCs and other adult stem cells has been performed in experimental and clinical studies with the purpose to stimulate neoangiogenesis [95]. It is reported that therapeutic cell therapies can regulate tissue inflammation through paracrine mechanisms acting on angiogenesis, apoptosis and scar formation and are able to potentiate recruitment of endogenous stem cells to the site of injury [90, 92]. In addition, there are cell types that have proven to be able to form de novo cardiomyocytes, such as embryonic stem cells, induced pluripotent stem cells and cardiac progenitor cells (CPCs) [96]. The CPCs can be isolated from the adult heart and show spontaneous electrical activity and action potentials upon appropriate in vitro differentiation [97].

In the cardiac field, the effect of cell therapy has been studied in different animal models, but studying inflammation has not been a main focus in these studies (Table 1).

Mesenchymal Stromal Cells

Over the last years many studies have focused on the therapeutic potential of MSCs in different diseases in animals and humans, due to their versatile nature which includes their immunomodulatory capacities. This cell type was first described by Friedenstein et al. in 1968 and has already been studied in clinical trials [98]. The MSC is a rare population of multipotent cells, present in bone marrow and other mesenchymal tissues like adipose tissue. MSCs are poorly defined but ex vivo expanded MSC populations are traditionally characterized by the presence of surface antigens CD90, CD73, CD105 and MHC-I and the absence of characteristic hematopoietic cell surface antigens such as CD45, CD34, CD80 and MHC-II. MSCs are capable of differentiating into multiple mature cell lineages including chondrocytes, osteoblasts and adipocytes. Due to its limited plasticity and restricted lifespan the MSC has a major theoretic advantage regarding safety compared to the ES and IPS cell, with a reduced risk of tumorigenicity, a major concern of therapeutic cell products. Whilst most cell populations are studied for their potential to regenerate damaged tissues, the MSC is additionally capable of dampening deleterious aspects of the immune response that accompanies injury. Inhibition of undesired immune responses by MSC infusion has been observed in experimental animal models for various diseases and underscores the potential of MSCs for clinical immune regulation [99]. The clinical applicability of MSCs for immunological disease was initially shown in patients with graft-versus-host disease (GvHD) after bone marrow transplantation [100] . In a successive phase II study it was found that MSC administration improved the manifestations of GvHD in the majority of patients [101]. These positive results of MSC therapy led to MSCs entering various clinical trials. Notwithstanding the positive effects of MSCs, the cellular and molecular mechanisms responsible are complex, probably multifactorial in nature and poorly understood.

MSCs are immunosuppressive in vitro, evidenced by their ability to suppress the proliferation of T-cells and their effect on cytokine profiles [102–104]. Furthermore, MSCs are able to induce the formation of CD4+CD25+FOXP3+ regulatory T cells [105], and interfere with the differentiation, maturation and function of antigen presenting dendritic cells, thereby directly affecting processes such as immunity and tolerance [106]. Huang et al. showed that neither infusion of allogenic nor syngeneic MSCs after MI in rats elicited a significant immune response, confirming the lack of immunogenic surface antigen expression or expression of antigens in an immunoregulatory fashion on such MSCs. Syngeneic MSC therapy improved cardiac function up to 6 months after infusion when compared to controls, whereas allogeneic MSC therapy improved cardiac function up to 3 months only. However, in vitro treatment before infusion of MSCs with 5-azacytidine, VEGF or TGF-β in an effort to stimulate differentiation towards myogenesis, endothelial cells or smooth muscle cells respectively, altered the immunogenic surface antigen expression profile of these cells, potentially triggering an immune response in vivo after allogeneic MSC infusion [107].

We recently demonstrated that MSCs act on monocyte differentiation, promoting the formation of anti-inflammatory IL-10 producing cells with low antigen presenting capacity [108]. MSCs have also been reported to inhibit the proliferation of B lymphocytes upon anti-Ig antibody, soluble CD40 ligand or cytokine-mediated activation [109] and have been suggested to inhibit IL-2- and IL-15-induced natural killer-cell proliferation [110]. In summary, these studies demonstrate the immunomodulatory capacities of MSCs in vitro, however the biological relevance of these findings in vivo is still largely unknown [111].

The first in vivo results were obtained in an experimental model of GvHD in which systemically infused MSC improved survival of mice transplanted with haplo-identical hematopoietic stem cell grafts [112, 113]. However, in another study injection of a single dose of MSCs did not ameliorate GvHD [114]. In the cardiac field, MSC infusion has been studied in different animal models. MSC transplantation after MI in a rat model showed an attenuation of the decline in cardiac function and the remodeling process, which may be explained by the anti-inflammatory properties of MSCs as the expression of TNF-α, IL-1β and IL-6 was reduced in these animals [115]. Infusion of MSCs in a rat MI model using a Langendorff apparatus also resulted in the highest preservation of cardiac function when compared to controls, most likely by a decrease of the pro-inflammatory cytokines TNF-α, IL-1 and IL-6. In addition, apoptosis was reduced, suggesting a beneficial role for MSC in apoptotic signaling, possibly via a signal transducer and activator of transcription 3 pathway [116]. This decrease in the pro-inflammatory cytokines TNF-α, IL-1 and IL-6 was also observed after injecting MSCs combined with either atorvastatin [117] or simvastatin, in a porcine MI model [118]. Herrmann et al. showed that infusion of MSCs, both naïve cells and cells pretreated with TGF-α decreased infarct size and preserved cardiac function, possibly through lowering of the TNF-α, IL-1β and IL-6 expression and increasing VEGF expression in a rat MI model [119]. The increased expression of VEGF by MSC therapy was also demonstrated after application of MSC/silk fibroin/hyaluronic acid patches in an MI model in rats, in addition to a decreased inflammatory response as demonstrated by reduced CD 68 expression [120]. Kim et al. showed preservation of cardiac function by infusion MSCs as well, with enhanced MSC engraftment and cardiac function preservation after TNF-α stimulation [121]. Lee et al. infused MSCs in an experimental MI mouse model where cells were afterwards cells entrapped in the lungs forming micro-emboli [122]. Subsequently, signals from the injured heart induced MSCs to secrete the anti-inflammatory protein tumor necrosis factor-inducible gene (TSG) 6 protein which suppresses the excessive and thereby deleterious inflammatory response involved in cardiac ischemia. This limited the protease release by macrophages and neutrophils, decreasing the damage to cardiomyocytes. Ultimately, an improvement of cardiac function and a decrease in scar formation of the left ventricle was observed. TSG-6, secreted by MSCs, has been shown to be a key anti-inflammatory factor in many other experimental disease models such as bleomyocin-induced lung injury, sterile cornea injury, and zymosan-induced peritonitis [123–126].

The importance of the SDF-1 release by MSCs in the process of cardiac repair of MI was recently demonstrated in a model in conditional cardiac myocyte CXCR4 null mice [127]. In the absence of CXCR4, the SDF-1 receptor, preservation of cardiac function by MSCs is no longer observed, possibly due to a decrease in the recruitment of stem cells or an increase in apoptosis. An earlier study injected MSCs that over-expressed SDF-1, which resulted in increased angiogenesis through VEGF expression and subsequently preservation of cardiac function [128].

Dayan et al. showed that MSC therapy after MI in a mouse model decreased the number of monocytes and pro-inflammatory M1 phenotype macrophages. Also, in vitro and in vivo data demonstrated that the amount of M2 phenotype macrophages, which are associated with an anti-inflammatory phenotype, was increased, which was thought to be mediated by MSC secretion of the anti-inflammatory factor IL-10 [129]. This MSC-mediated switch from M1 phenotype to M2 phenotype macrophages was recently confirmed by another group [130]. In vitro experiments proposed that the modulation of macrophages may be dependent on cell-to-cell contact, as the secretion of reparative cytokines was highest in cultures of MSCs mixed with macrophages [130].

While the therapeutic effectiveness of MSCs has been shown in a number of studies as described above, the mechanisms through which MSCs act remain still unknown. Purported beneficial immunomodulatory factors derived from MSCs in addition to TSG-6, include inducible nitric oxide synthase, indoleamine dioxygenase, CCL2, SDF-1, IL-10 and prostaglandin E2. In addition, immunomodulatory effects may rely on pathways acting on specific immune cell populations or via cell-cell contact with dendritic cells, macrophages or other cells of the immune system [90, 91, 111, 130–132]. Clearly this must be studied more intensively and much progress will be made when the in vivo fate of MSCs can be determined to clarify the cellular interactions that are made during the initiation and ongoing process of repair.

Clinical Trials of MSCs

MSC therapy is at present being studied in various clinical trials for their efficacy in inflammatory and degenerative disorders. However, when entering the clinical arena potential risks have to be taken into account: the immunogenicity of the cells, the biosafety of medium components, the risk of ectopic tissue formation and potential in vitro transformation of cells during expansion [133].

The ClinicalTrials.gov web-based resource has summarized a large number of clinical trials that involve MSC therapy targeted against various diseases. One of the key clinical trials performed is a phase II trial in which 55 patients with steroid resistant acute GvHD were treated with MSCs [101]. In the 60 months follow up, infusion of in vitro expanded MSCs was considered a possibly effective therapy for this specific patient group. The mode of action of MSCs in

GvHD seems highly related to their immune modulatory properties.

In the cardiac field MSC therapy has also been evaluated in numerous studies [134]. In 2004, a study of autologous bone-marrow-derived MSC infusion in patients with acute MI was performed [135]. In 69 patients undergoing PCI after acute MI significant improvements in left ventricular function were found, which were assessed by echocardiographic monitoring. The first phase-I, randomized, double blind, placebo-controlled, dose-escalation study of intravenous allogeneic adult MSCs in patients with acute MI was completed in 2009, suggesting it was safe to use allogeneic MSCs in patients after acute MI [136]. The same group reported in 2012 a direct comparison of autologous versus allogeneic bone marrow-derived MSCs in ischemic cardiomyopathy patients showing low rates of treatment-emergent serious adverse events, including immunologic reactions. A recent trial in ischemic cardiomyopathy patients showed no adverse effects of MSC injection and encouraging beneficial results, though the study size was small [137]. Injection of MSCs in chronic ischemic cardiomyopathy patients during CABG surgery showed a promising improvement of cardiac function and decreased scar size, however due to lack of placebo and small study size results are not conclusive [138]. Our group recently reported that intramyocardial injection of autologous MSCs using the NOGA injection system in acute MI patients was safe up to 5 years after injection, and was associated with improved cardiac function as compared to baseline [139]. In aggregate, the MSC injection favorably affected patient functional capacity, quality of life, and ventricular remodeling [140].

The current experimental and clinical data available indicate that MSC therapy is feasible and safe, and neither early toxicity nor later side effects have been found to date. However, long-term follow up studies in larger patient cohorts are warranted to give definitive answers whether long-term adverse events may occur [141]. The latest findings suggest that patients receiving cell therapy mainly experience beneficial results on clinical outcomes instead of objective parameters regarding cardiac function [134]. At present it is not clear whether the beneficial effect of MSCs in cardiac patients is also caused by a beneficial effect on post-MI inflammation or by other mechanisms. More research is needed to address this issue.

Summary and Future Perspectives

This review describes the role of the immune system in the healing processes following an acute ischemic event. The inflammatory response that occurs after MI is a precarious balance, since it is indispensable in the clearance of cell debris and ultimately the formation of a collagen scar but the pathways necessary for a timely initiation, suppression, resolution, and containment of the inflammatory response can also cause additional injury to the heart. When certain aspects of this inflammatory process triggered by cardiac injury are excessive, ultimately infarct expansion and adverse remodeling of the infarcted heart can occur [142, 143]. However, it is not fully known if suppression of the detrimental part of the inflammatory response would prevent the adverse remodeling and concomitant worse outcome in patients with MI and if this therapeutic goal can be reached clinically. Modulating the immune response after myocardial damage is a road less travelled that might be a promising therapeutic option for cardiac disease. Of all cell types, the MSC currently seems a suitable candidate for this specific goal, based on the proven immunomodulatory properties, in addition to the ability to secrete angiogenic factors such as VEGF, important for neoangiogenesis [144, 145]. Infusing MSCs in the ischemic myocardium therefore might not only improve cardiac function by dampening excessive immune responses but also induce growth of new vasculature. Recapitulating the studies on the physiologic function of MSCs in regulating the immune system in the hematopoietic niche and their ability to modulate immunity in cardiac disease might be a feasible option to move forward [146–148].

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