

## Theme Issue Article

# The inflammatory response as a target to reduce myocardial ischaemia and reperfusion injury

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## Summary

Acute myocardial infarction is the leading cause of morbidity and mortality in the adult population of developed and developing nations. Although the prompt restoration of antegrade blood flow in the infarct-related coronary artery is the main therapy for improving survival, reperfusion itself may cause damage to ischaemic myocardial tissue. This event is well known as “reperfu-

sion injury”. Crucial mediators for cardiac damage in the reperfusion phases are oxidative stress, inflammation and leukocyte infiltration. Already approved and novel therapies might directly reduce these inflammatory processes. Treatments modulating chemokine secretion and activity should be considered as very promising approaches to reduce myocardial reperfusion injury.

## Keywords

Acute myocardial infarction, chemokines, inflammation

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## Introduction

The most effective therapy after an acute myocardial infarction is the rapid restoration of blood flow by mechanical or pharmacological intervention (1–3). The early reperfusion is critical for reducing the size of myocardial infarct and improving the clinical outcome. However, reperfusion itself is responsible for myocardial injury which is induced by the preceding ischaemic episode, resulting in cardiomyocyte death and increase in infarct size (4). Potential mediators of reperfusion injury involve oxidative stress, intracellular and mitochondrial  $Ca^{2+}$  overload, complement activation, and the accumulation of inflammatory cells in the infarcted myocardial tissue (4–6). Inflammatory processes including leukocyte recruitment play a major role in the extension of myocardial damages after ischaemia and reperfusion (7, 8). Rapidly after the restoration of blood flow, leukocytes infiltrate into the myocardium in response to complement activation and massive release of reactive oxygen species (ROS) (9, 10). Neutrophils, monocytes and lymphocytes are the principal immune cells implicated in this process (11–13). Once recruited into the tissue, inflammatory cells release proteolytic enzymes and ROS that contribute to the development of injuries (4, 6).

Studies in animal models have improved our current understanding on the underlying mechanisms of reperfusion injury, and several experimental studies suggest a beneficial effect for

targeting reperfusion injury with anti-inflammatory treatments. In particular, targeting cellular recruitment (i.e. by blocking chemokines) at the onset of reperfusion could represent a potent therapeutic strategy to reduce myocardial reperfusion injury (6, 14). Further experimental studies investigating not only the therapeutic effects on acute reperfusion injury, but also the long term effects on cardiac function are warranted before translating potential beneficial effects into the clinical setting. Indeed, inflammatory mediators such as chemokines may have complex roles not only in acute reperfusion injury, but also in cardiac repair (14).

## Mechanisms of disease

Myocardial ischaemia is characterised as a state of insufficient oxygen supply resulting in a decrease of free energy from ATP hydrolysis, leading to failure of maintaining ion channels. Consequently, this leads to irreversible tissue damage within 20 to 30 minutes of sustained ischaemia. The most common complication is the occurrence of left ventricular dysfunction and heart failure. Despite its clear benefits, myocardial reperfusion after an episode of ischaemia exacerbates cellular injury (4, 6, 14). This concept is supported by several experimental studies, using different strategies to reduce the infarct size in animal models of ischaemia and reperfusion (15–17).

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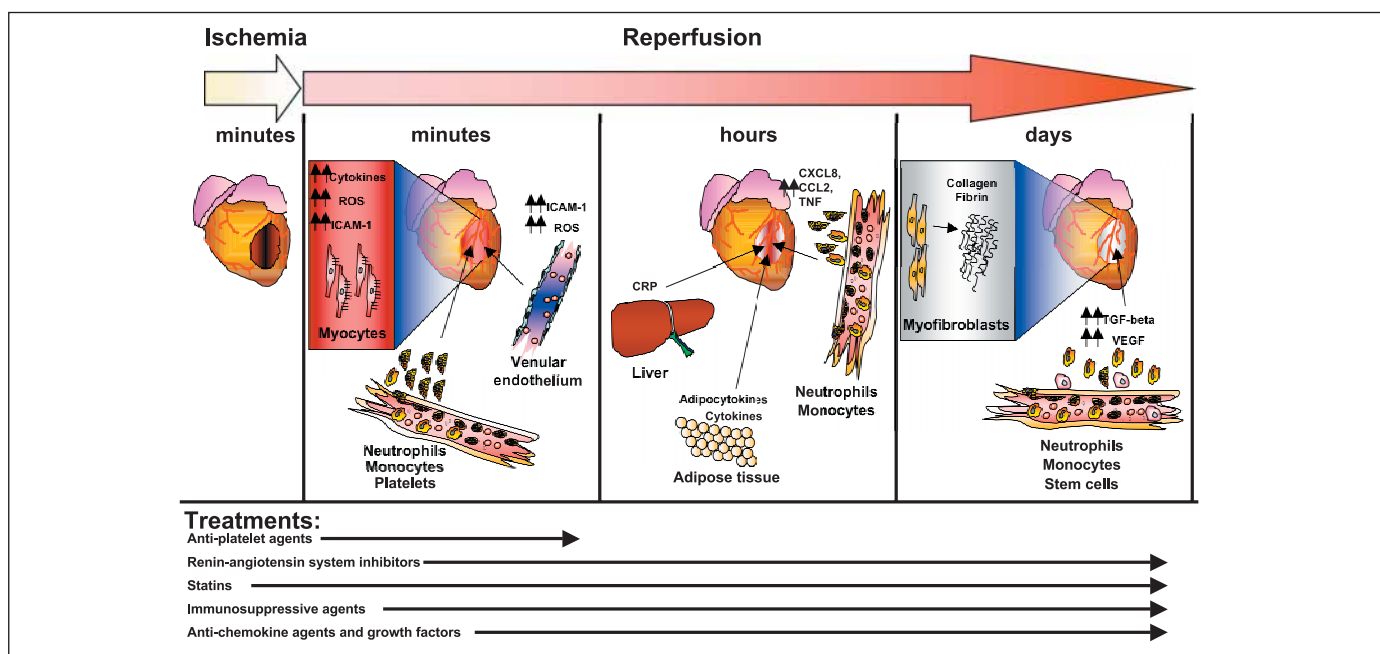
## Inflammatory responses in reperfusion injury

The early reperfusion phase is characterised by enhanced release of ROS from endothelial cells and cardiomyocytes, as well as enhanced expression of cytokines and adhesion molecules (Fig. 1). Among ROS, mainly superoxide contributes to myocardial infarct extent by inducing cellular changes such as mitochondrial permeability enzyme denaturation and DNA damage, but also by triggering neutrophil infiltration (4, 6). Neutrophils and monocytes/macrophages, which are recruited from the blood stream into the infarcted tissues, increase cardiac damage by further releasing ROS, inflammatory mediators and proteases (4, 6).

The enhanced expression of chemokines during the first hours of reperfusion triggers the further recruitment of neutrophils and monocytes into the infarcted myocardium (Fig. 1) (14). Chemokines (chemotactic cytokines) belong to a large superfamily of low molecular weight proteins with a highly homologous three-dimensional structure (18). They are divided into four families (CC, CXC, CX3C, XC) based on the configuration of the first two cysteines. Chemokines are known to induce leukocyte migration, growth, and activation through seven transmembrane domain G protein-coupled cell-surface receptors on target cells. Their receptors constitute a superfamily of 20 members, which possess seven transmembrane loops, coupled with heterotrimeric G proteins (18). The CXC chemokine inter-

leukin (IL)-8 appears to have a fundamental role in regulating neutrophil localisation in ischaemic myocardium (6). As demonstrated in an in-vivo dog model, IL-8 mRNA synthesis was markedly upregulated in ischaemic tissue after 1 hour of coronary occlusion and consistently induced during the following reperfusion phase for up to 24 hours (19). Treatment with a blocking anti-IL8 antibody, impairing neutrophil recruitment, was shown to reduce myocardial I/R injury in rabbits (20). In mice, CXCL2, the homologue of human IL-8, is upregulated in reperfusion myocardial ischaemia (21). Other potent mouse neutrophil chemoattractants such as CXCL1 (also named KC), and CCL3 are also upregulated in mouse hearts subjected to I/R after few hours of reperfusion (21, 22). The chemokine response in ischaemic tissues may be induced by various factors including ROS, cytokines such as tumour necrosis factor (TNF)- $\alpha$ , complement and nuclear factor kappa B (NF- $\kappa$ B) activation (14). In addition, non-chemokine chemoattractants, including cytokines, the complement component C5a, leukotrienes and platelet activating factor have important roles in ischaemic leukocyte recruitment by their own chemoattractant properties (6).

During the post-ischaemic phase, the release of intracellular contents by cardiomyocyte necrosis initiates an intense inflammatory response by activating innate immune mechanisms. Innate immune responses such as those mediated via toll-like receptors (TLRs) represent a defensive mechanism against micro-



**Figure 1: Inflammatory processes during “reperfusion” are differently regulated by therapeutic agents against acute myocardial infarction.** Few minutes after reperfusion, cardiomyocytes, vascular cells and inflammatory cells resident within the myocardium start to release inflammatory mediators (such as cytokines and reactive oxygen species [ROS]) and increase adhesion molecule expression to favour the recruitment of neutrophils and monocytes from the blood flow. These soluble mediators also influence platelet functions. After few hours, novel inflammatory mediators (such as CXCL8, CCL2 and tumour necrosis factor [TNF]- $\alpha$ ) are produced in the infarcted tissue and also released into the blood stream. These cytokines and chemokines

start an inflammatory vicious circle that involves the liver (CRP) and adipose tissue (adipocytokines and cytokines). They further contribute to immune cell recruitment into the infarcted heart. After few days, the reparation of cardiac necrosis with both collagen and fibrin deposition is regulated by anti-inflammatory mediators such as tumour growth factor (TGF)- $\beta$ . Stem cell recruitment into the infarcted zone might be crucial to modulate the healing process and reduce collagen substitution of cardiac tissue. Anti-platelet treatment might reduce platelet aggregation in the early minutes of reperfusion. On the other hand, renin-angiotensin inhibitors, statins, immunosuppressive drugs, anti-chemokine agents and growth factors interfere with all phases of reperfusion.

bial infection, but may also play a role in non-infectious tissue injury. The heart expresses at least three receptors involved in TLR signalling, namely CD14, TLR2 and TLR4 (23–25). In experimental ischaemia/reperfusion injury, it has been shown that TLR4-deficient mice had reduced infarct size and neutrophil infiltration as compared to wild-type mice (26). On the other hand, TLR2-deficient mice showed reduced myocardial fibrosis with improved left ventricular function, but no changes on infarct size and post-ischaemic myocardial inflammation were found (27). Another key player in innate immune responses is the TLR adaptor protein MyD88. MyD88 deficiency in mice was associated with attenuated neutrophil recruitment, reduced infarct size and improved left ventricular contractile function after ischaemia reperfusion injury (22).

### Role of systemic inflammatory mediators

Several clinical studies have demonstrated that adiponectin levels are inversely correlated with the risk of myocardial infarction (28, 29). Adiponectin is an adipose tissue-derived plasma protein with potential antiatherogenic properties (30). Reduced plasma levels of adiponectin, which are found in obese patients, are closely associated with obesity-related diseases, including atherosclerotic cardiovascular diseases, type II diabetes mellitus, hypertension and dyslipidaemia (30). Recent experimental studies with adiponectin deficient mice support the cardioprotective role of adiponectin in ischaemia reperfusion injury (17, 31). Underlying mechanisms are likely to involve a reduction of oxidative and nitrative stress (17).

Prospective epidemiologic studies have shown that serum C-reactive protein (CRP) levels are strong predictors of the occurrence of cardiovascular events such as myocardial infarction (32–34). In addition, several studies revealed the independent association of high plasma CRP levels with an adverse prognosis in patients with acute myocardial infarction. Plasma levels of CRP may be a predictor of impaired reperfusion in patients with acute myocardial infarction (35–37). In an experimental rat model of myocardial infarction, preconditioning was found to inhibit the postischaemic increase of CRP levels (38).

### The role of inflammation in cardiac repair

Ischaemic tissue damage results in the replacement of contractile myocardium by non-functional scar tissue. Cell death and scar formation occurs not only in the direct infarct zone, but also in the surrounding myocardium which is less severely affected but remains hypoxic. Efficient methods to limit the loss of myocardium may be to trigger angiogenesis, which aims at restoring blood flow to ischaemic tissue before it leads to necrosis. This may be achieved therapeutically by delivering specific growth factors that control blood vessel growth (39). Angiogenic factors such as vascular endothelial growth factor (VEGF) and IL-8 are rapidly released in response to myocardial infarction. It is likely that angiogenic therapy is more beneficial in infarcted hearts submitted to prolonged coronary occlusion, since early reperfusion is associated with an induction of the potent angiostatic factor IP-10 (40). It has been hypothesised that the expression of angiostatic factors in the early reperfusion phase may inhibit the

onset of angiogenesis until the injured myocardium has been cleared from dead cells and debris by infiltrating phagocytes and a fibrin-based matrix necessary to support angiogenesis is formed (40). VEGF may represent an interesting candidate in the field of therapeutic angiogenesis; however, specific microenvironmental levels are crucial for functional vessel growth in ischaemic tissue (41, 42).

The chemokine stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) has recently been identified as a potent tissue-protective and regenerative factor in a mouse model of ischaemia and reperfusion (43). The therapeutic effect was associated with decreased cell death and increased angiogenesis, resulting in reduced scar formation and thus improved cardiac function. The role of SDF-1 $\alpha$  in the recruitment of bone marrow-derived stem cells to the post-ischaemic heart and their transdifferentiation into cardiomyocytes, however, is controversial (44–47).

Finally, inflammation also has a crucial implication in cardiac repair processes. Indeed, inflammatory mediators such as chemokines may have complex roles not only in acute reperfusion injury, but also in cardiac repair. On the other hand, the inflammatory response may also contribute to adverse remodeling of the ventricle by triggering degradation of the extracellular matrix. In this context, mice lacking the chemokine receptor CCL2 showed attenuated left ventricular remodelling after myocardial infarction (48). Recent evidence further suggests divergent functions of monocyte subsets in myocardial infarction and healing. As reported by Nahrendorf et al., the chemokine expression profile in infarcted mouse hearts is modulated over time, which leads to sequential recruitment of inflammatory (Ly-6C(hi)) and resident (Ly-6C(lo)) monocytes via CCR2 and CX3CR1, respectively (49). Inflammatory monocytes dominate the early recruitment phase and exhibit phagocytic, proteolytic, and inflammatory functions. Resident monocytes dominate the later phase, have attenuated inflammatory properties, and promote healing via myofibroblast accumulation, angiogenesis, and deposition of collagen.

In conclusion, targeting inflammation in ischaemic reperfusion injury must be carefully outbalanced between putative beneficial effects in acute injury and possible adverse effects in subsequent repair.

### Anti-inflammatory treatments in reperfusion injury

The mechanical or pharmacological restoration of antegrade flow in the injured-related coronary artery is the main therapy for improving both survival and left ventricular systolic function during the subsequent hours after the acute myocardial infarction (2, 3). Coronary angioplasty or stenting through percutaneous coronary intervention (PCI) or the administration of thrombolytic and anti-platelet agents have been shown to improve survival several days, weeks, or even months after the acute myocardial infarction (50, 51). In recent American College of Cardiology Foundation / American Heart Association (ACC/AHA) guidelines update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), an early invasive strategy is indicated in initially sta-

bilized unstable angina/NSTEMI patients who have an increased risk for clinical events (I-A), and in patients with refractory angina or haemodynamic or electrical instability (I-B) (52). However, growing evidence shows that coronary reperfusion itself causes damage to ischaemic myocardial tissue (4, 6). The “reperfusion injury syndrome” implicates inflammatory processes, endothelial microvascular dysfunction, necrosis and apoptosis of cardiomyocytes. Several experimental studies suggest a beneficial effect for targeting reperfusion injury with anti-inflammatory treatments. In the following, we will discuss on the most promising therapeutic approaches to reduce inflammatory processes in all phases of reperfusion injury.

## Anticoagulation and antiplatelet therapies

The 2007 ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI recommends anticoagulation therapy (such as unfractionated heparin) in patients at intermediate or high acute coronary syndrome risk (52). The beneficial effect of anticoagulation therapy in myocardial infarction is mainly due to the inhibition of the coagulatory cascade and thrombotic events. Heparin may also exhibit direct anti-inflammatory effects by activating TLR receptors, however, experimental studies are warranted to further support this hypothesis (53).

Antiplatelet therapy with acetylsalicylic acid (or alternatively clopidogrel in allergic patients) is indicated in patients with acute coronary syndrome, and also before PCI (52). In patients undergoing early invasive strategy, small molecule glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa) are recommended alone or in combination with clopidogrel. The main mechanisms influenced by antiplatelet agents are the inhibition of platelet functions (acetylsalicylic acid) or activation (clopidogrel) and aggregation of already activated platelets (GPIIb/IIIa) (54–56). However, strong evidence from both clinical and basic research studies suggests that antiplatelet therapies might directly influence proinflammatory mediators and cell types involved in the reperfusion injury (57, 58). Acetylsalicylic acid administration has been shown to reduce the activation of the transcription factor NF $\kappa$ B as well as levels of CRP and soluble CD40 ligand. Treatment with clopidogrel reduced serum levels of CD40 ligand, CRP, P-selectin, and platelet-leukocyte aggregate formation (58). The possible immunomodulatory role of GPIIb/IIIa is subject of ongoing research. Although further experimental evidences are needed, the prompt administration of antiplatelet therapy should be considered as a very promising approach to reduce both platelet and immune cell-mediated inflammatory processes in early phases of the reperfusion injury (Fig. 1).

## Beta-blocker therapy

The 2007 ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI further recommends the administration of oral beta-blocker therapy (in the absence of contraindications) within the 24 hours of care for the non-ST-segment-elevation acute coronary syndrome patients (52). The use of beta blockers is supported by their anti-ischaemic properties (reduction of myocardial oxygen demand and increase of diastole duration). In addition, there is evidence for beta-blocker-me-

diated immunomodulatory effects on leukocytes (59–61). However, the possible influence of beta blockers in the regulation of inflammatory processes should not be considered as a main mechanism to reduce reperfusion injury. Further studies are warranted in the context of myocardial ischaemia reperfusion injury to better investigate this aspect.

## Angiotensin converting enzyme (ACE) inhibitor and statin therapy

Treatment with ACE inhibitors has been shown to improve post-infarction left ventricle remodelling and function in both animals and humans (62–64). The most relevant mechanisms underlying this beneficial effect imply the inhibition of angiotensin II-mediated activities on cardiomyocytes, fibroblasts, vascular cells and leukocytes (65–68) and the improvement of revascularisation after stenting and neoangiogenesis (69, 70). ACE inhibition reduced myocardial collagen deposition and improved survival in a rat model of acute myocardial infarction (71, 72). This beneficial effect was confirmed by further investigations suggesting that ACE inhibition directly modulate tumour growth factor (TGF)- $\beta$ -induced activities. In particular, captopril or fosinopril (two different ACE inhibitors) suppressed the acute induction of TGF- $\beta$ 1 mRNA expression in rat infarcted hearts (73, 74). Furthermore, ACE inhibition also blocked TGF- $\beta$  signalling pathway and the associated deleterious cardiac remodelling after infarction (75). Benazepril treatment reduced Smad 2 and Smad 3 protein expression in myocardial infarcted rats (76). Accordingly, transgenic rats overexpressing cardiac ACE developed an increased myocardial collagen deposition in association with higher Smad2/3 phosphorylation (77). These studies strongly support the crucial role of ACE inhibition to prevent post-ischaemic ventricular remodelling.

Given their pleiotropic immunomodulatory properties beyond cholesterol-lowering, statins are promising drugs for reducing reperfusion injury. Although the early use of high-dose statins in acute coronary artery disease is controversial (78), these drugs reduced cardiovascular hospitalisation in older patients with systolic heart failure (79). Experimental and clinical evidence suggests a possible cardioprotective role of statins in acute myocardial infarction and reperfusion. Underlying mechanisms may involve the reduction of serum levels of pro-inflammatory mediators such as CRP (80, 81), the inhibition of leukocyte activation (82, 83) and the protection against cardiac fibrosis (84–86). Although further evidence is needed, treatment with ACE inhibitors or statins might be a very promising therapeutic approach in all phases of reperfusion injury (Fig. 1).

## Immunosuppressive and anti-proliferative therapies

Immunosuppressive or anti-proliferative medication-eluting stents have reduced the occurrence of restenosis through the inhibition of local inflammatory processes underlying smooth muscle cell proliferation and leukocyte infiltration (87). Sirolimus and paclitaxel-eluting stents have initially enjoyed great

success; however, adverse effects, such as thrombosis, have recently come to focus (88). A second generation of drug-eluting stent with novel medications is under investigation with some preliminary promising results (88). Alternatively, a systemic immunosuppressive approach for restenosis prevention may be considered (89–91). There is little experimental and clinical evidence for direct cardioprotective effects of immunosuppressive therapies. In a dog model of ischaemia/reperfusion, methotrexate and its derivative (MX-68) reduced the infarct size through an adenosine-dependent mechanism (92). More recently, a small pilot trial in humans has shown that an intravenous bolus of cyclosporine at the reperfusion time slightly reduced infarct size (93). Conversely, several clinical studies showed that intravenous administration of methylprednisolone in the first hours after acute myocardial infarction did not reduce infarct size or regional and global myocardial functions in humans (94–96). Furthermore, the SoluMedrol Sterile Powder AMI Studies Group treated a larger cohort of patients with 30 mg/kg methylprednisolone also later (from 6–12 hours after chest pain) (97). No significant modifications in mortality rate or incidence of myocardial rupture, cardiac aneurism, early malignant ventricular arrhythmias have been observed at 28 days in comparison to placebo. Treatment with methylprednisolone has been shown to reduce only post-acute myocardial infarction symptomatic pericarditis (98). Although corticosteroids failed to reduce acute myocardial infarction in humans, systemic immunosuppressive therapies might be a very promising approach to reduce infarct size and reperfusion injury (Fig. 1). However, data available are still preliminary and require confirmation in larger clinical trials to evaluate the safety and efficacy of systemic immunosuppression.

### Novel anti-inflammatory strategies

The complex cross talk regulating inflammatory, vascular and cardiac cells is orchestrated by soluble mediators such as cytokines, chemokines hormones and growth factors. Treatments targeting the balance between pro- and anti-inflammatory factors have been investigated in models of reperfusion injury. Different therapeutic approaches have been explored, including the neutralization of already secreted pro-inflammatory cytokines, the inhibition of proinflammatory cytokine secretion, the administration of anti-inflammatory cytokines, and factors favouring mesenchymal stem cell (MSC) implantation and mobilization.

A humanised monoclonal antibody that binds the C5 component of complement (Pexelizumab) failed to ameliorate survival in a large controlled randomised trial with patients undergoing PCI (99). On the other hand, Pexelizumab reduced the risk of death in patients undergoing coronary artery bypass grafting (100). Further studies are needed to explain the mechanisms underlying these controversial results. The administration of FR167653, an inhibitor of IL-1 $\beta$  and TNF- $\alpha$  cytokine release, partially abrogated myocardial reperfusion injury in rats (101).

The CC chemokine monocyte chemoattractant protein (MCP)-1/CCL2 is upregulated in myocardial infarction in both experimental models and humans (14, 102). CCL2 induces monocyte, T-lymphocyte and natural killer (NK)-cell recruitment and phenotype pro-inflammatory modifications (14). On the other hand, CCL2 positively regulates myocardial neovascu-

larisation in infarcted hearts (103). In an experimental model of myocardial ischaemia/reperfusion, CCL2-deficient mice had decreased and delayed macrophage infiltration in the healing infarct as compared to wild types, associated with delayed replacement of injured cardiomyocytes with granulation tissue. On the other hand, no differences in the time course and density of neutrophil infiltration were observed (16). The postischaemic expression levels of the cytokines TNF- $\alpha$ , IL-1 $\beta$ , TGF- $\beta$ 2, - $\beta$ 3, and IL-10 were reduced in the CCL2 knockouts, and the removal of apoptotic cardiomyocytes was delayed. Although no difference in infarct size was observed, CCL2-deficient mice showed attenuated left ventricular remodelling. In conclusion, CCL2 is a key player of inflammatory responses critical for cardiac repair that should be considered a controversial target for limiting reperfusion injury.

The injection of antagonists blocking the chemokine RANTES/CCL5 has been shown to reduce myocardial leukocyte infiltration in a mouse model of *T. cruzi*-induced myocarditis (104). This study may suggest a possible therapeutic application for RANTES chemokine blocking approaches aiming at reducing inflammation during the reperfusion period. However, further investigations are warranted to clarify the role of RANTES in post-ischaemic cardiac repair. Furthermore, the intracardiac administration of SDF-1 $\alpha$  prolongs hypoxic myocardium survival and favours angiogenesis (43). Recent evidence also showed that antagonism of IL-1 receptor might be of potential benefit in acute myocardial infarction. The exogenous administration of a recombinant human IL-1 receptor antagonist (anakinra) reduced cardiomyocyte apoptosis and left ventricular remodelling after acute myocardial infarction (105). Although still controversial, these preliminary results support cytokine/chemokine and anti-chemokine/anti-cytokine treatments as a pivotal and promising field to limit myocardial reperfusion injury (Fig. 1).

### Cell therapy

Infarcted myocardium undergoes reparative fibrosis and is replaced by scar tissue mainly because mature cardiomyocytes have a minimal regenerative capacity and fibrotic processes start early during reperfusion (106). Cell-based therapy is a promising option for reducing infarct size and improving cardiac contractile function. It can be used in different ways: stem cell transplantation, stem cell mobilisation, or regulation by growth factors and cytokines. Interestingly, a forth therapeutic approach based on injecting inflammatory cells has been used by Schuh et al. with some promising results in a rat model of acute myocardial infarction (107). On the other hand, published clinical studies investigating stem cell transplantation based on autologous bone marrow mononuclear cells (BMC), mesenchymal stem cells (MSC), haematopoietic or endothelial progenitor cells. The results were controversial. Pilot trials showed that progenitor cell infusion was safe and increased global myocardial contractility in comparison to controls (108–112). Randomised clinical studies investigating BMC infusion only partially confirmed these encouraging results (113, 114). Moreover, two studies did not show any improvement of global myocardial contractility (115, 116). Several mediators (such as granulocyte macrophage

colony stimulating factor [G-CSF], erythropoietin [EPO] and stem cell factor) are involved in stem cell mobilisation and cardiac repair. Whereas in experimental cardiac injury models, their administration improved myocardial function, preliminary trials in humans failed to induce beneficial effects (117). Given these discrepant findings, it is difficult to draw firm conclusions about a possible benefit of stem cell therapy in acute myocardial infarction in humans.

## Conclusions

Inflammatory processes play a crucial role in myocardial reperfusion injury, and experimental studies suggest a beneficial effect for targeting reperfusion injury with anti-inflammatory treatments. However, further experimental studies investigating

not only the therapeutic effects on acute reperfusion injury, but also the long-term effects on cardiac function are needed before translating potential beneficial effects into the clinical setting. Indeed, inflammatory mediators such as chemokines may have complex roles not only in acute reperfusion injury, but also in cardiac repair. A future challenge will be the development of more selective treatments targeting inflammatory mediators and cells to limit acute reperfusion injury, without inhibiting pathophysiological processes crucial for healing myocardial infarcts.

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