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Review

Post-infarct remodelling: contribution of wound healing and inflammation

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In human and experimental myocardial infarction (MI), cessation of blood supply leads to rapid necrosis of cardiac myocytes in the ischaemic heart. Immediately after injury, various intra- and intercellular pathways contribute to healing the myocardial wound in order to achieve tissue integrity and function. MI and the consequent loss of myocardium are the major aetiology for heart failure. Despite aggressive primary therapy, prognosis remains poor in patients with large infarction and severe left ventricular dysfunction. Thus, it would be highly desirable to improve healing of the cardiac wound to maintain structure and function of the heart. Healing in the heart occurs in overlapping phases. Herein, we review the inflammatory phase as a trigger of tissue formation.

1. Introduction

One major determinant of remodelling post-myocardial infarction (MI) is infarct size.[1] Infarct size depends on the amount of myocardium supplied by the infarct-related coronary artery, the time to effective reperfusion therapy, and myocardial energy consumption during coronary occlusion. Early reperfusion and beta-blockers are therefore standard therapy today. However, slow-flow or no-reflow phenomena are quite frequent post-MI and may contribute to ongoing ischaemia. After reperfusion, 'the infarct' in most instances will consist of highly inhomogeneous tissue which may immediately recover, be stunned, or be apoptotic/necrotic. Sensitivity to ischaemia varies among myocardial cells, vasculature, and connective tissue adding to inhomogeneity of infarct tissue composition.[2] In addition, inflammatory cells and macrophages may invade from circulating blood and start as well as maintain processes of inflammation, clearing debris, and wound healing. Toxic or protective mediators, circulating and locally released by autochthonous or recruited cells, add to the complexity. It may be of major therapeutic value to influence myocardial healing as it opens a new time window and addresses new mechanisms for therapy. However, specific measures have not yet been developed mostly due to a lack of precise knowledge of processes contributing to wound healing. The present review (i) puts forward the hypothesis that a reperfused MI may be considered a healing wound, (ii) compiles evidence for cells and factors controlling the inflammatory phase of wound healing, and (iii) proposes potential anti-inflammatory mechanisms as targets for therapeutic research.

2. Myocardial infarction: a healing wound

The capacity for regeneration and reparation certainly was of selection value in evolution and is highly variable among species. Some species may restore organs or limbs in total; mammals are mostly restricted to reparation; and variability is high among individual organs. Healing of external wounds is a *conditio sine qua non* for survival and therefore secured by multiple redundant mechanisms. Nevertheless, it may vary substantially among individuals. There appear to be differences in wound healing with regard to sex, age, and race, whereas genetics of wound healing have not been clarified. A large body of empirical knowledge has been accumulated on measures to support wound healing. More recently, essential factors for wound healing have been identified, but implications of such 'healing factors' for healing of internal wounds remain unclear. Two types of 'wounds' are particularly frequent and highly clinically relevant in the cardiovascular system: rupture of an atherosclerotic plaque and MI. For the latter,

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if survived, healing is essential for further prognosis. Both of them are modern diseases and thus evolution has not yet developed specific strategies by selection. Thus, general strategies of coping with stress and wound healing take place.

The healing process may first be dominated by inflammation (degradation of extracellular matrix, inhibition of tissue proliferation, and release of inflammatory mediators = 'inflammatory phenotype') and turn then to reparation (increased matrix synthesis, proliferation of fibroblasts and inflammatory cells, and release of fibrosis-promoting cytokines leading to scar formation = 'activated phenotype'). The analysis of these processes may be of major therapeutic importance. Herein, we will focus on the early inflammatory phase as the trigger of tissue formation.

3. The inflammatory phase of wound healing

3.1 Triggers of inflammation after cardiac injury

What is the trigger of an inflammatory reaction after cardiac injury? Indeed, activation of the immune system after cardiac injury follows the pattern of immune activation after infection: most microorganisms encountered daily by a healthy individual are detected and destroyed within hours by defence mechanisms that are not antigen-specific, the so-called innate immune system. In contrast to adaptive immunity, whereby specific antigen receptors are generated by somatic hypermutation and selection, the innate immune system uses germline-encoded proteins that recognize specific patterns shared by groups of pathogens, but not the host. These receptors, called 'pattern recognition receptors', detect largely invariant patterns, for example, lipopolysaccharides (LPS) of bacteria or double-stranded RNA of viruses.[3–5] They are constitutively expressed; thus, defence mechanisms are readily available and need not be upregulated. The heart itself expresses all parts of the innate immune system, including pattern recognition receptors and effector proteins.

Although it is commonly accepted that the innate immune system is activated by microbial patterns, Matzinger and co-workers[6] assume in the 'Danger' model that the presence of potentially infectious patterns does not necessarily trigger an immune response, unless there is evidence of host tissue injury by the so-called 'alarm' signals. In support of this hypothesis, Matzinger and co-workers have demonstrated that, in the absence of any foreign pathogens, resting dendritic cells can be activated by virally infected or necrotic cells, but not by healthy cells or cells undergoing programmed cell death (apoptosis). Potential mediators include reactive oxygen species (ROS), heat shock proteins (HSP), and fibronectin.[7] Thus, this work suggests that certain products of tissue injury, such as ROS and intracellular proteins released from necrotic cells, initiate an inflammatory response, leading to the activation of pattern recognition receptors such as Toll-like receptors (TLRs), the transcription nuclear factor kappa B (NF-κB), and complement.

3.1.1 Toll-like receptors

TLRs have emerged as the primary, non-antigen-specific defence mechanisms that enable innate immune detection of foreign pathogens. Thus, TLRs could be important for the initiation of the inflammatory phase after tissue injury.

To date, 11 human and 13 mouse TLRs have been cloned.[5] The ligands for TLRs are molecular motifs produced by pathogens, but also certain host-derived proteins such as HSP or fibronectin. As recently reviewed by us,[7,8] TLR2, -3, -4, and -6 are expressed in cardiac myocytes, whereas TLR1 and -5 are not.[9,10] TLRs and their signalling components are activated in experimental or clinical heart failure. TLR4 expression is increased in the myocardium of patients with advanced heart failure.[10,11] In addition, there is a change in the TLR expression pattern: whereas in normal murine and human myocardium the TLR4 expression is diffuse and predominantly confined to cardiac myocytes, myocardium from patients with advanced heart failure displays focal areas of intense TLR4 staining[10] (*Figure 1*).

The data on myocardial wound healing and TLRs are very limited. After coronary artery ligation, mortality and left ventricular dilatation were significantly reduced, and left ventricular function was preserved in $TLR2^{-/-}$ and $TLR4^{-/-}$ mice.[12,13] In ischaemia/reperfusion experiments, the invasion of inflammatory cells as well as infarct size were significantly reduced in TLR4 KO animals.[14] Conclusively, the data suggest a role of TLRs for the activation of inflammatory cells after cardiac injury.

3.1.2 Nuclear factor kappa B (NF-κB)

TLR signalling converges on the activation of the transcription factor NF-κB, a key signalling component for early inflammatory activation. As for TLRs, the role of NF-κB in healing can only indirectly be deduced from heart failure as well as ischaemia/reperfusion models. NF-κB-dependent signalling mechanisms in ischaemia/reperfusion injury are

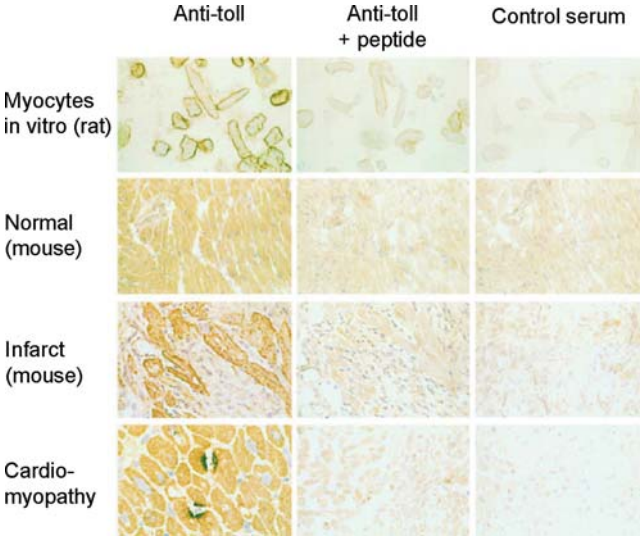

Figure 1 TLR4 in rat, murine, and human myocardium. Primary isolates of adult rat ventricular myocytes 24 h after isolation, stained with a polyclonal antibody targeted to a TLR4-specific epitope adjacent to the cytoplasmic TIR domain of hTLR4 (upper panel). Normal murine cardiac muscle (magnification 200×; second panel) exhibited diffuse, homogeneous myocyte staining. However, cardiac myocytes adjacent to an area of ischaemic injury induced by coronary artery ligation exhibited intense sarcolemmal TLR4 staining. Finally, cardiomyocytes from humans with dilated cardiomyopathy (lower panel) displayed intensely stained focal expression of TLR4 (figure reprinted with permission of Frantz *et al.*[10]).

well defined by now.[15] After ischaemia/reperfusion injury, NF-κB activation is biphasic, with peaks after 15 min and 3 h, i.e. early in the healing process.[16,17] As for TLR, ischaemia/reperfusion injury is reduced by the inhibition of NF-κB using molecular [inhibition of p65 by double-stranded oligonucleotides[18] and use of an IκB triple mutant (S32A, S36A, and Y42A) completely abrogating NF-κB activation[19]], as well as pharmacological methods (IKK inhibition[20]). We recently demonstrated that mice with targeted deletion of the NF-κB subunit p50 are protected against ischaemia/reperfusion injury.[21] KO and WT animals underwent 30 min of coronary artery ligation and 24 h of reperfusion *in vivo*. Ischaemia–reperfusion damage was significantly attenuated in the p50 KO, compared with WT mice. Although adhesion molecules such as intercellular adhesion molecule-1 (ICAM) were upregulated in left ventricles of p50 KO animals, fewer neutrophils infiltrated the infarct area, suggesting leukocytes as a potential mediator of protection observed in p50 KO. This was confirmed in adoptive transfer experiments: transplantation of KO bone marrow in KO animals sustained the protective effect on ischaemia–reperfusion injury, whereas transplantation of WT bone marrow in KO animals abolished it. Thus, impaired NF-κB activation in p50 KO leukocytes attenuated cardiac damage.

After permanent coronary artery ligation, activation of NF-κB peaks after 3 days (*Figure* 2).[22,23] Mice with targeted deletion of the NF-κB subunit p50 are protected from left ventricular dilatation after MI and have preserved left ventricular function. Collagen content and matrix metalloproteinase (MMP)-9 expression are significantly lower in KO mice after MI and may account for improved left ventricular remodelling.[24]

Thus, NF-κB is important for activation of inflammation and healing after MI. The effects on healing seem to be cell type-specific.

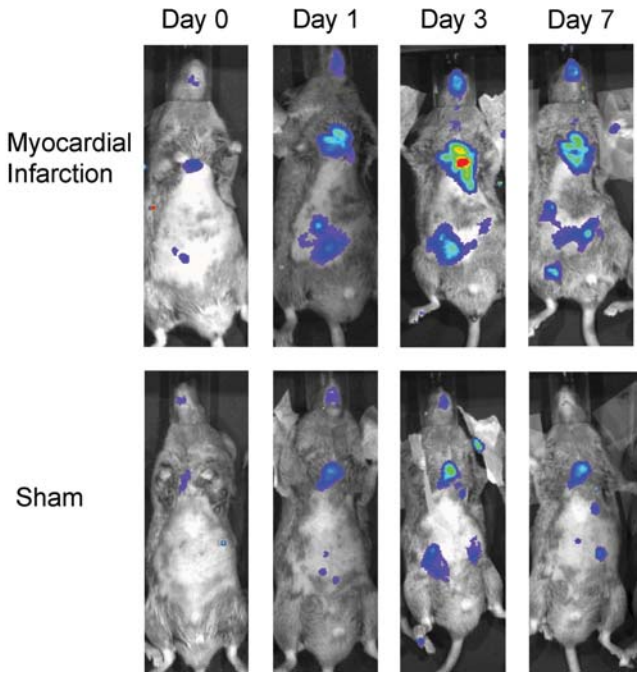

Figure 2 NF-κB activation in the heart after ischaemic injury. In transgenic mice that express a luciferase reporter whose transcription is dependent on NF-κB, light generated at the site of NF-κB activation within the transgenic mouse is sufficiently intense to be detected externally by a light-sensitive camera upon injection of luciferin. Myocardial infarction induced NF-κB-dependent *in vivo* luminescence in the heart of transgenic mice when compared with sham-operated mice. Maximal NF-κB activity was observed 3 days after myocardial infarction by serial molecular imaging (figure reprinted with permission of Tillmanns *et al.*[22]).

3.1.3 Complement

The complement system is central to the innate immune system. It can be activated via the classical, alternative, and lectin pathway. Complement has long been implicated in mediating tissue injury in ischaemic organs, with or without reperfusion.[25–28] Activation of complement is an early event in ischaemia/reperfusion injury and healing, although the mechanism(s) leading to complement activation has only recently been identified. Carroll and coworkers[28,29] have demonstrated that selective depletion of natural IgM is sufficient to abrogate most ischaemic–reperfusion injury in both murine hindlimb[28] or murine intestinal[29] reperfusion injury models. The self-target for this monoclonal natural IgM is non-muscle myosin heavy chain type II A and C.[30] These data could also be reproduced for the heart.[31] Mice baring an altered natural IgM repertoire ($Cr2^{-/-}$) were protected from ischaemia/reperfusion injury and had a reduction in inflammatory infiltrates. This effect could be blunted by IgM reconstitution, suggesting that neoepitopes recognized by natural IgM appear on the surface of endothelium damaged by reperfusion injury. In conclusion, complement is activated and an important mediator of neutrophil and monocyte recruitment early after injury.[32]

3.1.4 Oxidative stress

ROS are atoms or molecules with unpaired electrons in their outer orbit. It can directly react with lipids, proteins, and DNA causing cell injury and death. It can trigger cytokine and chemokine release partially mediated by NF-κB. Oxidative stress produces myocardial contractile dysfunction and structural damage and has been implicated in the development of heart failure and left ventricular remodelling following MI.[33–35] Indeed, cardiac tissue itself is a rich source of ROS, and NADPH oxidases, xanthine oxidases, and mitochondria are critical determinants of myocardial ROS generation.[36,37]

The normal heart possesses substantial ability to neutralize ROS; however, in the injured heart, the antioxidant defence is overwhelmed, resulting in the generation of oxygen-related free radicals. Markers of oxidative stress are elevated after MI.[38] Various antioxidant approaches reduce adverse cardiac remodelling,[39] for example, overexpression of glutathione peroxidase.[40] Despite the damaging effects of oxidation itself, ROS can directly influence signalling, for example, increased ROS production promotes the development of interstitial fibrosis and extracellular matrix turnover, in part through activation of matrix metalloproteinases. Thus, ROS are able to generate an inflammatory response of the healing phase by necrosis and redox signalling.

In the clinical arena, the results of antioxidant therapy are discouraging. In the HOPE and Heart Protection study, cardiovascular events were not improved by vitamin E treatment.[35] There are a number of reasons why vitamin E supplementation did not have the proposed effect: usage of the wrong antioxidant, necessity of other antioxidative cofactors, binding of vitamin E to the cell membrane while oxidative stress is intracellularly generated, and the

problem that a single supplement may not be able to compensate for other coexisting abnormalities. Thus, the final role of antioxidant medication remains to be determined.

3.1.5 Coagulation cascade

In the first stage of wound healing, activation of the coagulation cascade is necessary to prevent ongoing blood and fluid loss. Haemostasis is achieved by the formation of a platelet plug, which becomes a scaffold for infiltrating cells. Several coagulation factors are able to activate an innate immune response, for example, thrombin and factor Xa promote cytokine and chemokines synthesis.[41]

With respect to healing and inflammation after MI, blood coagulation factor XIII (FXIII) has been most thoroughly investigated. It is activated by thrombin in the final stage of the clotting cascade. $FXIII^{-/-}$ mice invariably die after MI due to left ventricular rupture accompanied by reduced migration of neutrophils into the ischaemic zone.[42] FXIII levels are decreased in patients with insufficient healing after MI.[43] Gene variants (L34) increasing FXIII activity are associated with improved survival after MI.[44] The most likely source of FXIII in healing infarcts are invading macrophages.[45]

3.2 Mediators of inflammation

Upon activation of the innate immune system by ischaemic injury, several inflammatory mediators are released and inflammatory cells are attracted to the site of injury. All these humoral and cellular factors have distinct function for the healing process.

3.3. Humoral immune response

3.3.1 Cytokines

A variety of cytokines are activated after MI and implicated in healing. We will exemplify their role by focusing on interleukin (IL)-1β and tumour necrosis factor (TNF) in this review.

Blood levels and/or myocardial expression levels of IL-1β are increased in patients with coronary artery disease,[46] acute MI,[47] dilated cardiomyopathy,[48,49] and in patients and animal models of congestive heart failure.[50] There are two peaks of IL-1β expression after MI in the rat: there is an initial rise in the healing phase, within 24 h, that appeared on immunohistochemical analysis to be located predominantly in the microvascular endothelium and a second peak at 7 days with predominant staining of infiltrating macrophages in the infarct zone.[51]

Despite these observations, there have been only a few reports about IL-1β function in ischaemic heart disease. Indeed, in some experimental models, early administration of inflammatory cytokines decreases myocardial injury. Brown *et al*.[52,53] observed protective effects of TNF and IL-1β in a model of ischaemia/reperfusion injury. Pretreatment with IL-1β in an ischemia/reperfusion model in the isolated rat heart increased the pressure developed in the left ventricle and decreased the area at risk.[54] In contrast, long-term activation of cytokines seems to be detrimental: mice lacking the active forms of IL-1β and IL-18 (i.e. a caspase-1 knockout model) exhibited both improved peri-infarct survival and decreased ventricular dilatation after experimental MI, possibly due in part to a decrease in MMP-3 activity and reduction of apoptosis.[55,56] With respect to the healing phase, in IL-1 receptor KO mice, myofibroblast infiltration and collagen deposition were decreased as was the development of adverse left ventricular remodelling after experimental MI.[57] Thus, IL-1 signalling is essential for the activation of inflammatory pathways in the healing infarct.

The role of another innate immunity cytokine, TNF, has been extensively investigated after cardiac injury. In fact, TNF can mimic several symptoms of heart failure: mice overexpressing TNF develop heart failure.[58,59] Systemic infusions of recombinant TNF that yielded blood concentrations of TNF seen in patients with advanced heart failure depressed left ventricular function and caused left ventricular dilatation.[60] Moreover, the expression of TNF mRNA and protein is elevated in patients and in animal models with advanced heart failure due to a number of different aetiologies.[50,61] Importantly, TNF has also a prognostic impact: TNF was elevated in a large portion of heart failure patients with preserved and reduced ejection fraction and was associated with a large decrease in survival.[62] However, the function of TNF is much more complex than initially anticipated: double knockout mice for the TNF receptor 1 and 2 had larger infarct sizes and increased apoptosis after MI, indicating that TNF has also protective functions for the myocardium.[63]

3.3.2 Chemokines

Chemokines[64] are small polypeptides synthesized by a number of cells of the immune system as well as by a number of non-immune cells including endothelial cells and keratinocytes. All chemokines are related in their amino acid sequences and function primarily as chemoattractants for phagocytic cells. Generally, CXC chemokines, such as RANTES, promote neutrophil migration, whereas CC chemokines, such as IL-8, mediate migration of monocytes and other cell types. A number of CXC chemokines, including IL-8 and others, appear to play a role in mediating angiogenesis. Induction of chemokines occurs in the post-infarction inflammatory response.[65] IL-8 is a critical regulator of neutrophil influx in inflammatory processes. The inhibition of IL-8 in a rabbit ischaemia/reperfusion model reduced necrosis without altering inflammatory cell invasion.[66] However, the role of other chemokines in cardiac wound healing has not been extensively investigated so far.

3.4 Cellular immune response

Neutrophils are important mediators of the inflammatory response. They release oxidants and proteases, secrete mediators for inflammatory cell recruitment, and phagocyte cell debris, and dead cells.

The recruitment of neutrophils to ischaemic tissue requires neutrophil–endothelial interactions that are regulated by a cascade of molecular steps. After activation, leukocytes roll along post-capillary venules, change shape, and extravasate in the tissue. The selectin family (E-, L-, P-selectin) of adhesion molecules mediates the initial capture of leukocytes. The importance of these proteins for healing is documented by the fact that E- and P-selectin knockout mice are protected from ischaemia/reperfusion injury and have reduced inflammatory cell infiltrates,[67] as are feline hearts treated with an antibody against L-selectin.[68]

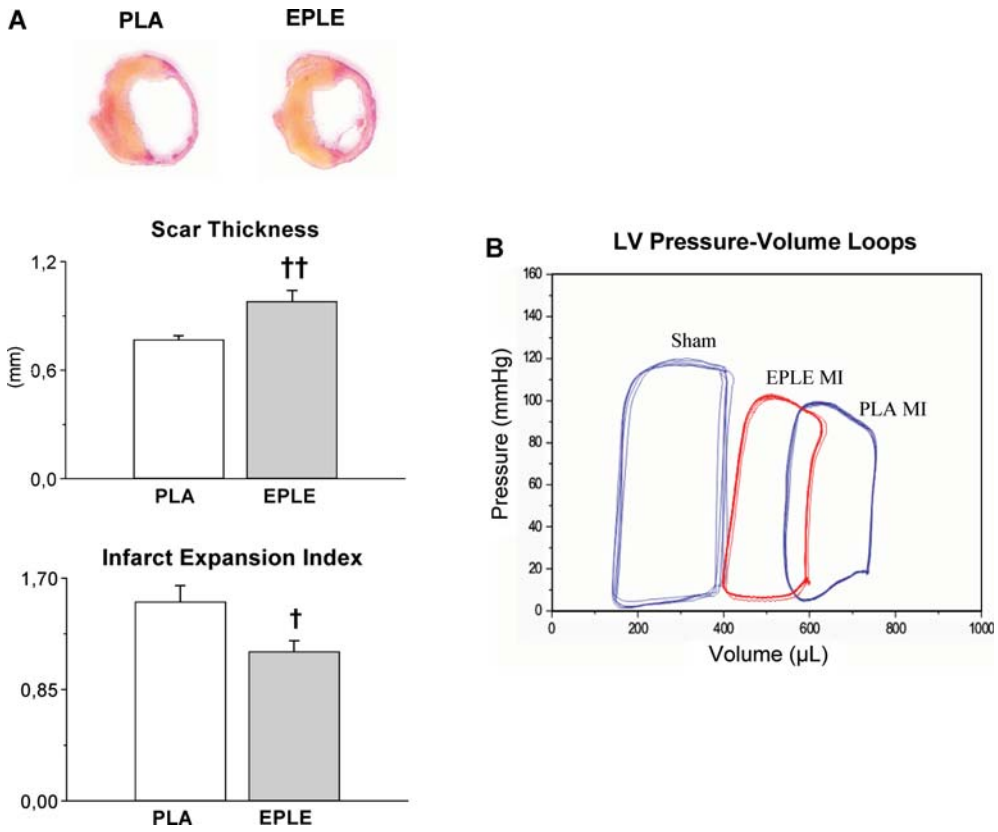

Figure 3 MR blockade after myocardial infarction reduced thinning and dilatation of the infarcted wall. (*A*) Typical sections from infarcted hearts, perfusion-fixed 7 days after myocardial infarction, scar thickness, and infarct expansion index in placebo (PLA) and eplerenone-treated rats (EPLE). Mean ± SEM ($n = 10$ to 14). †$P < 0.05$, ‡$P < 0.01$ vs. PLA. (*B*) Representative LV pressure–volume loops measured *in vivo* with conductance catheter in sham-operated rats (sham) and in placebo- (PLA) and eplerenone-treated (EPLE) rats 7 days after MI (figure reprinted with permission of Fraccarollo *et al.*[45]).

Selectin adhesion of leukocytes is not very tight. Firm adhesion and transmigration need the engagement of integrins. Integrins are a family of heterodimeric membrane glycoproteins. Consequently, integrin-related strategies have been used to mitigate ischaemia/reperfusion injury. Indeed, inhibition of integrin CD18 reduced infarct size.[67]

Crude depletion of neutrophils itself by leukocyte filters reduces infarct size in ischaemia–reperfusion models,[69] indicating a detrimental role of neutrophils for infarct healing. The detrimental effects seem to be mediated by ICAM-1-dependent neutrophil–cardiomyocyte adhesion, a primary ligand of CD18 integrin. ICAM-1 KO mice have less myocardial injury early after MI.[70] Neutrophils release various cytokines and growth factors important for healing. However, this effect is not essential for scar formation since depletion of neutrophils had no effect on granulation tissue formation in a cutaneous wound healing model.[71] It is especially problematic that neutrophil effects vary depending on the stage of activation. For example, it seems that neutrophils release toxic products almost exclusively when adherent to the vascular wall, but not when they have evaded in the tissue. Thus, although multiple experiments suggest a central role of neutrophils in myocardial healing, the function of neutrophils remains unclear.

3.4.1 Macrophages

Healing of MI requires monocytes/macrophages. The mononuclear phagocytes degrade released macromolecules and scavenge dead cardiomyocytes. Infarcted hearts modulate their chemokine expression profile over time, and they sequentially and actively recruit Ly-6C(hi) and -6C(lo) monocytes. Ly-6C(hi) monocytes dominate early and exhibit phagocytic, proteolytic, and inflammatory functions. Ly-6C(lo) monocytes dominate later. Consequently, Ly-6C(hi) monocytes digest damaged tissue, whereas Ly-6C(lo) monocytes promote healing via myofibroblast accumulation, angiogenesis, and deposition of collagen.[72] Depletion of macrophages in a murine cryoinjury model impaired wound healing since non-resorbed cell debris could not be discarded. This was accompanied by increased mortality. Macrophage accumulation in the healing heart is regulated by the renin–angiotensin–aldosterone system: selective mineralocorticoid receptor blockade immediately after MI improved healing (*Figure 3*), an effect that was blunted by macrophage depletion.[45] Thus, macrophages are of central importance for adequate healing after MI.

4. Post-inflammation phase

Following the initial inflammatory phase, optimal healing requires mechanisms that inhibit cytokine release, clear the inflammatory infiltrates, and initiate collagen production to institute a solid scar.

Granulocytic infiltrates are cleared by phagocytes after granulocyte apoptosis.[65] In contrast to necrosis that triggers an inflammatory response, apoptotic cells lead to the production of anti-inflammatory cytokines such as IL-10

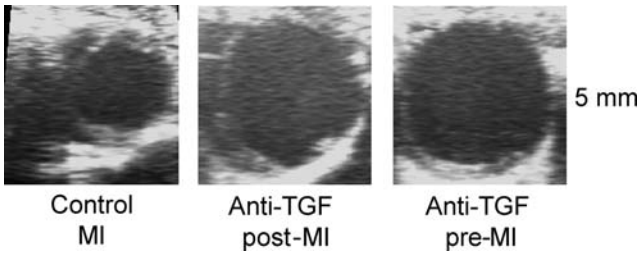

Figure 4 Detrimental left ventricular dilatation following myocardial infarction and inhibition of TGF. Illustrated are representative examples of two-dimensional echocardiography of mice treated with an anti-TGF-β antibody started either 1 week before (anti-TGF pre-MI) or 5 days after (anti-TGF post-MI) induction of myocardial infarction. Treatment with an anti-TGF-β antibody aggravated left ventricular dilatation (figure reprinted with permission of Frantz *et al*.[77]).

and transforming growth factor (TGF), initiating the transition phase from inflammation to fibrosis.

TGF-β is a locally generated cytokine and of central importance for this transition phase:[73] TGF-β decreases leukocyte adhesion and stimulates fibroblast proliferation and extracellular matrix production.[74] TGF-β expression is increased in the ischaemic as well as hypertrophied heart.[75,76] TGF-β has an important function for healing after MI: We demonstrated recently that anti-TGF-β treatment in the first days after coronary artery ligation increases mortality and worsens left ventricular remodelling in mice with MI due to alterations in the extracellular matrix (*Figure 4*).[77]

A detailed review of the post-inflammation phase is beyond the scope of the present article due to space constraints.

5. How far is the translation of experimental inflammation/healing data from the present clinical arena?

The importance of inflammation for healing processes after MI has been recognized for several years, and pathophysiological concepts have been established by experimental data. Consequently, transfer of this knowledge into standard clinical practice has been tried: for example, inflammatory markers have been used to predict mortality. Indeed, some inflammatory proteins (e.g. TNF) are associated with outcome; however, they could not be established as standard clinical utility since other parameters turned out to be more powerful. The translation of the experimental knowledge into new therapeutic modalities turned out to be a difficult task. Several treatments have been tried after acute MI.

Complement inhibitors have been evaluated as an adjunctive therapy to fibrinolysis or percutaneous coronary intervention (PCI) in acute MI. A humanized monoclonal antibody against complement component C5, pexelizumab, was used that specifically binds to C5 with high affinity and prevents cleavage and generation of activated C5a and C5b-9. However, although pexelizumab had been previously shown to reduce infarct size and apoptosis in rats after ischaemia and reperfusion,[78] it had no effect on infarct size in patients treated with fibrinolysis (COMPLY trial[79]) or PCI (COMMA trial).[80]

In a multicentre, placebo-controlled trial, patients undergoing PCI for acute MI were treated with a blocking antibody for the CD11/CD18 integrin receptor. In 400 patients, infarct size and mortality were not improved by treatment.[81]

However, not all trials have been negative. For example, the data for the use of steroids after MI are not clear at the moment. Initial small and observational studies reported an increase in left ventricular rupture, i.e. impaired healing, and thus the concept was not thoroughly pursued. A recent meta-analysis ($n = 2646$) revealed decreased mortality in steroid-treated patients after MI, but summarized only data from small trials with no large, adequately powered study.[82]

Furthermore, established drugs in the treatment post-MI may play a role in inflammatory healing. For example, the early use of mineralocorticoid receptor antagonists reduces mortality after MI.[83]

The interpretation of clinical trials with regard to healing and inflammation is difficult due to confounding variables such as different infarct sizes, gender, age, and so on. For example, ageing is associated with decreased ability to control infection (so-called immunosenescence), alters the inflammatory response in wounds,[84] and changes inflammatory markers in heart failure.[85] Whereas infarct size is a major determinant of remodelling in patients younger than 65 years, in older patients, left ventricular remodelling can also occur even in the presence of small infarct sizes (PREAMI study[86]) potentially mediated by defects in healing.

Problematic for new anti-inflammatory approaches is that an intact immune system is necessary for many protective pathways and adequate healing in the beginning, whereas prolonged immune activation may also activate unfavourable signal cascades that drive disease progression. The major challenge of immunosuppressive drugs in the healing phase will be to limit detrimental innate immune influences while simultaneously maintaining and stimulating adequate and appropriate innate immune mechanisms. Nevertheless, there are several exciting targets such as the coagulation cascade, modulation of immune cell function, and the early use of RAS inhibitors to promote healing, improve the inflammatory response, and subsequently avoid adverse cardiac remodelling. Thus, further research is necessary to better understand the interaction of inflammation and cardiac healing. This will allow us to choose better targets at better time points for clinical intervention.

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