Review

Healing after myocardial infarction

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Abstract

Wounding and healing are archaic principles, prerequisite for survival of any biologic material. However, strategies to cope with wounding may be quite different among organisms, species, or among various organs of one species. Today, myocardial infarction and the consequent loss of fully functional myocardium is the major aetiology for heart failure. Despite aggressive primary therapy, prognosis remains serious in patients with large infarction and severe left ventricular dysfunction. Thus, it would be highly desirable to influence healing of the cardiac wound to maintain structure and function of the heart. Herein, we review different, important factors of cardiac healing including reperfusion, mechanical stress, gender, and neurohormonal factors as well as specific factors essential for healing which may be genetic or acquired, emphasizing similarities and discrepancies between different organs and species.

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extraordinary regenerative capacity being able to regenerate large sections of its heart in response to tissue damage or removal dependent on cellular dedifferentiation [9,10]. The ideal therapy obviously would direct the cardiac healing process to complete regeneration. The use of various types of cells for myocardial regeneration is one approach. Perhaps in future we can learn from zebra fish and the newt but on our way to such a hopeful fiction, we need to test other concepts to improve cardiac wound healing.

Time course of morphologic and histological changes of infarcted myocardial tissue has recently been reviewed in some detail [11,12]. After cardiomyocyte death and perhaps with some time overlap, an inflammatory reaction starts within the first day after MI. Inflammatory cells invade the infarct and, somewhat later, myofibroblasts appear in the wound. Alterations of connective tissue are present as early as 40 min after an experimental coronary occlusion and degradation of collagen is significant at 24 h in the rat. The normal collagen structure virtually disappears during the first week after the infarct (Fig. 2). The extent of collagen damage correlates with the degree of infarct expansion [13]. Increased activities of collagenases and other neutral proteinases have been made responsible for the rapid degradation of extracellular matrix collagen in MI. Inflammatory cells release proteases and contribute to removal of necrotic tissue; myofibroblasts to the reconstruction of a new collagen network. The actions of the myofibroblasts are admirably systematic and are essential for the organization of scar formation under the difficult condition of the rhythmic contraction of the heart. After several weeks, a solid scar has been formed with a stable collagen structure, overall little cellularity, but some myofibroblasts remain in

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Fig. 1. Regeneration of ventricular myocardium in the resected zebrafish heart. Hematoxylin and eosin stain of the intact zebrafish heart before (A) and after about 20% ventricular resection (B). b.a., bulbous arteriosus. (C) An intact ventricular apex at higher magnification, indicating the approximate amputation plane (dashed line). All images in this and subsequent figures display longitudinal ventricular sections of the amputation plane. (D) 1 dpa. The large clot is filled with nucleated erythrocytes (arrowheads). (E) 9 dpa. The heart section is stained for the presence of myosin heavy chain to identify cardiac muscle (brown) and with aniline blue to identify fibrin (blue). The apex is sealed with a large amount of mature fibrin. (F) 14 dpa. The fibrin has diminished, and the heart muscle has reconstituted. (G) 30 dpa. A new cardiac wall has been created, and only a small amount of internal fibrin remains (arrowhead). (H) 60 dpa. This ventricle shows no sign of injury [8].

Fig. 2. Collagen after myocardial infarction in the mouse. Representative examples of picrosirius red stained hearts under polarized light 3 days, 1 week, and 6 weeks after experimental myocardial infarction.
the scar tissue [14]. Thus, healing is a complex process of invasion, transformation and apoptosis of various cell types which is highly regulated and may well be subject to disturbances and interventions.

Some factors have been identified which may contribute to infarct healing. Reperfusion may limit infarct size by stopping the loss of viable myocardium but also by an additional beneficial effect on healing [15]. Mechanical stress may result in infarct expansion [16]. Age, sex, neurohumoral factors and drugs have also been suggested to contribute to healing and infarct expansion. More recently specific factors essential for healing and scar formation have been analyzed by their specific antagonists or transgenic mouse models. So far little is known about a genetic or acquired general healing deficiency which may contribute to infarct expansion. The purpose of this article is (1) to review factors which influence infarct healing, (2) to test the hypothesis that conditions of general healing deficiency may exist, (3) to discuss complex genetic diseases as models for the concept of a genetic healing deficiency.

1. Factors known to influence healing

Regional wall stress has predicted ventricular remodeling after anteroseptal MI in man [17]. Physical exercise or prolonged inotropic stimulation with digoxin started early after a MI has promoted infarct dilatation and thinning [16,18]. In contrast, mechanical unloading by vasodilators prevented infarct expansion and thinning in dog and man especially if combined with reperfusion [19].

Animal experiments have suggested that late reperfusion of MI after completion of the extension of cardiomyocyte death may prevent further infarct expansion and thinning [15]. Together with observations of benefit of late thrombolytic therapy or mechanical recanalization of occluded coronary arteries [20], and an open coronary artery in retrospective observations, these studies generated the hypothesis of an advantage of an open versus a chronically occluded coronary artery [21]. A patent infarct related coronary artery was related to less apoptosis in the associated myocardium [22]. Reperfusion may activate [23] or inhibit [24] matrix metalloproteinases, and thrombolytic therapy on its own may stimulate collagen break down [25]. Infiltrating neutrophils into reperfused myocardium are an early source of locally active MMP-9 after reperfusion [26]. Furthermore, apoptosis may contribute to reperfusion injury [27]. Clinical data are conflicting and today, clinical evidence is missing for a beneficial effect of reopening an occluded coronary vessel in the absence of symptoms.

1.1. Age

Half of the patients admitted to a hospital for acute MI and 80% of the patients who die are 65 years and older [28]. The exponential, age related increase in the mortality rate did not appear to be explained by larger infarcts [29].

Aging is associated with reduced deposition of specific extracellular matrix components, an up regulation of angiogenesis, an altered inflammatory response in wounds [30], reduction of vascular NO availability [31], an increased wound elastase and matrix degeneration [32]. Thus, numerous potential determinants of infarct healing are associated with age but their actual role has not been studied in detail and factors like gender, previous MI and MI localization [33] may have contributed to the age dependent effects.

1.2. Estrogen

Estrogen replacement resulted in an increased infarct size or infarct expansion and was unable to prevent left ventricular remodeling in ovariectomized rats [34]. However, high dose substitution of estrogen to supernormal levels produced thicker infarct scars and prevented remodeling in rats (Beer et al., personal communication). Younger, but not older women who survive hospitalization for MI have a higher long-term mortality rate than men [35] and initiation of hormone replacement therapy after MI is associated with more cardiac events during follow-up [36].

In cutaneous wounds, estrogen decreases elastase secondary to reduced neutrophil numbers, and decreases fibronectin degradation [37]. In vitro studies have shown that reproductive hormones influence cellular proliferation and cytokine production [38]. The rate of cutaneous wound healing is impaired in ovariectomized female rodents and post menopausal women but the quality of scarring is improved. The age related changes in women were reversed by systemic hormone replacement therapy. Topical estrogen accelerated cutaneous wound healing is associated with an increase in TGFβ1 levels in ovariectomized rats [39] and aged male and female humans [37]. Estrogen activates endothelial nitric oxide (NO) synthase [40], stimulates neuronal NO synthase protein expression in human neutrophils and mediates NO release [41]. Thus, there are numerous possible pathways by which estrogen might influence the inflammatory response and the following processes of wound healing. However, experimental and clinical studies are controversial and need further research.

1.3. Neurohumoral systems

1.3.1. The renin–angiotensin–aldosterone system

Angiotensin-converting enzyme inhibition delayed maturation of the infarct scar indicated by reduced collagen alignment and package (Fig. 3) [42]. Targeted deletion of angiotensin II type 2 receptor reduced collagen volume fraction and scar thickness in experimental infarcts and caused cardiac rupture [43]. Furthermore, Angiotensin II is a chemoattractant to inflammatory cells [44] and induces leukocyte-endothelial cell interactions via AT 1 and AT 2 receptor-mediated p-selectin upregulation [45]. Angiotensin
converting enzyme inhibitors and even more angiotensin II type 1 receptor antagonists reduce the inflammatory infiltrates into the infarct zone and prevent accumulation of type I myocardial collagen in the noninfarcted septum secondary to activation of TGF-beta 1. Redistribution of macrophages and activated myofibroblasts from the infarct zone are likely to play a paracrine role in mediating this inflammatory reaction in surviving myocardium [46].

1.3.2. Endothelin

Sakai et al. [47] and Fracarollo et al. [48] found that endothelin-A and endothelin-A and -B receptor antagonists substantially improved survival and left ventricular function and reduced remodeling and cardiac filling pressures. The dual endothelin-A and -B receptor antagonist tezosentan administered during the first day after MI increased long term survival and hemodynamic conditions [49]. In contrast, left ventricular dilatation was even aggravated by the use of endothelin-A receptor antagonists early after MI [50] by scar expansion and reduction of scar collagen [51]. This was most likely due to an activation of myocardial tissue metalloproteinases (Fig. 4). In contrast, others report a reduction of metalloproteinase activity by the endothelin-A receptor antagonist sitaxsentan [52]. Thus, the action of endothelin and its antagonists on myocardial healing remain controversial. They exemplify the potential of endogenous systems and their antagonist of ambiguous effects on healing and remodeling of the heart.

1.3.3. Nitric oxide
eNOS KO mice develop greater left ventricular enddiastolic dimensions and lower fractional shortening 28 days post MI [53]. This suggests a protective role of eNOS. In contrast, iNOS KO mice had improved contractile function and higher survival rates after MI without a difference in infarct size. Yet, as expected, less apoptosis was noted in iNOS KO mice when compared to matching wildtypes [54]. Effects of NO on cardiac matrix components were not investigated. However, nitric oxide has profound effects on cutaneous wound healing: In fact, eNOS [55] as well as iNOS KO [56] mice have delayed excisional wound healing. Therefore, direct effects of NO on cardiac wound healing seem to be very likely, but remain to be defined.

1.4. Cytokines

A variety of cytokines have been implicated in cardiac remodeling as well as in healing. We will exemplify their role by interleukin (IL)-1β and tumor necrosis factor (TNF) in this review.

Blood levels and/or intramyocardial expression levels of IL-1β are increased in patients with acute MI [57]. However, only little functional data exist about IL-1β function in the pathophysiology of heart failure: Indeed, early administration of inflammatory cytokines decreases myocardial injury [58]. In contrast, long term activation of cytokines seems to be detrimental: Mice lacking the active forms of IL-1β and IL-18 exhibited both improved peri-infarct survival and a decreased rate of ventricular dilatation. Interestingly, IL-1β and IL-18 are known to induce different MMPs and indeed MMP-3 and collagen content were decreased in animals lacking IL-1β and IL-18 [59]. Thus, long-term effects of cytokines on cardiac remodeling seem to be dependent on their influence on the cardiovascular matrix and healing.

The expression of another cytokine, TNF mRNA and protein can have multiple effects yet extracellular matrix remodeling seems to be of major importance [60]. Moreover, mice with overexpression of TNF develop LV dilatation and changes in collagen content prevented by an MMP inhibitor [61], further highlighting a potential importance of excessive
activation of proinflammatory cytokines on matrix remodeling and wound healing in the heart.

1.4.1. TGF (transforming growth factor β1)

TGF plays an important role in collagen production. Conclusively, animals with targeted deletion of TGF have reduced age dependent collagen deposition [62]. Overexpression of TGF in the heart leads to cardiac hypertrophy and interstitial fibrosis [63]. Somehow surprisingly, after myocardial injury, increased active TGF-β1 delayed wound healing [64].

1.5. Leukocytes

The inflammatory reaction appears to be essential to initiate wound healing. However, adverse wound healing is accompanied in cutaneous wound models by increased invasion of inflammatory cells [6]. Leukocyte infiltration after a cardiac injury is a time dependent phenomenon regulated by a complex cascade of molecular events including the activation of selectins and integrins [65]. Leukocytes are mainly attracted by the complement factor C5a in the first hour, followed by TGF-β1 and monocyte chemoattractant protein (MCP)-1 in the next 2 h. Infiltration peaks between 2 and 4 days after MI [65]. Leukocyte infiltration is mostly restricted to the border zone of the area at risk and only few neutrophils are found in the center of the necrotic zone [66]. After invasion into the myocardial wound, leukocytes lead to more effective healing, regulate extracellular matrix metabolism through synthesis of MMPs and their inhibitors and are an important source of cytokines and growth factors.

1.6. Chemokines

Chemokines [67] are small polypeptides synthesized by many cells of the immune system as well as by a number of non-immune cells including, among others, endothelial cells
and keratinocytes. Chemokines can be induced by agents that induce tissue damage. 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, while CC chemokines, such as interleukin-8, mediate

Table 1
MMP subgroups and their function in healing and heart failure (DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy)

<table>
<thead>
<tr>
<th>Name</th>
<th>Number</th>
<th>Substrate/function</th>
<th>Regulation in CHF</th>
<th>Function in CHF (experimental data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial</td>
<td>MMP-1</td>
<td>Collagens I, II, III, VII, and basement membrane</td>
<td>Reduced [96]</td>
<td>Not causative for pathological LV remodeling [96]</td>
</tr>
<tr>
<td>Collagenase 3</td>
<td>MMP-13</td>
<td>Collagens I, II, and III</td>
<td>Increased [97]</td>
<td></td>
</tr>
<tr>
<td>Gelatinases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatinase A</td>
<td>MMP-2</td>
<td>Gelatins, collagens I, IV, V, VII, and basement</td>
<td>Increased in DCM, unchanged in ICM [96]</td>
<td>MMP-2 KO mice have significant better survival, decreased LV rupture and decreased LV dilatation after experimental MI [98]</td>
</tr>
<tr>
<td>Gelatinase B</td>
<td>MMP-9</td>
<td>Collagens IV, V, XIV, and basement membrane components</td>
<td>Increased [96]</td>
<td>MPP-9 KO have improved cardiac remodeling [70] and decreased left ventricular rupture [99] after experimental MI</td>
</tr>
<tr>
<td>Stromelysins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stromelysin 1</td>
<td>MMP-3</td>
<td>Fibronectin, laminin, collagens III, IV, IX, and MMP</td>
<td>Increased in DCM, unchanged in ICM [96]</td>
<td>LV rupture is unchanged after experimental MI in MMP-3 KO [99]</td>
</tr>
<tr>
<td>Membrane-type MMPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT1-MMP</td>
<td>MMP-14</td>
<td>Collagens I, II, III, fibronectin, laminin-1: activates proMMP-2 and proMMP-13</td>
<td>Increased [96]</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Heart failure drugs and their influence on healing (results of animal models unless stated otherwise)

<table>
<thead>
<tr>
<th>Name</th>
<th>Remodeling after MI</th>
<th>Cytokines after MI</th>
<th>MMPs after MI</th>
<th>Fibrosis after MI</th>
<th>Leukocytes after MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>Protective, clinical data</td>
<td>Reduced cytokine expression [100]</td>
<td>Reduced MMP activation [48]</td>
<td>Reduced collagen formation [48]</td>
<td>Reduced leukocyte infiltration [46]</td>
</tr>
<tr>
<td>AT1 receptor antagonist</td>
<td>Protective, clinical data</td>
<td>Reduced cytokine expression in AT1 receptor KO mice [101]</td>
<td>Reduced MMP activation in AT1 receptor KO mice [101]</td>
<td>Reduced collagen formation [102,103]</td>
<td>Reduced leukocyte infiltration [101]. Reduced leukocyte infiltration [46]</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Protective, clinical data</td>
<td>Reduced cytokine expression [104]</td>
<td>Not determined</td>
<td>Reduced collagen formation [105]</td>
<td>Reduced infiltration of leukocytes after ischemia/reperfusion [106] and permanent coronary artery ligation [107]</td>
</tr>
<tr>
<td>Endothelin antagonists</td>
<td>Protective when started late after MI [48]. Not protective when started early after MI [51]</td>
<td>Not determined</td>
<td>Reduced MMP activation [48]</td>
<td>Reduced collagen formation [48]</td>
<td>Not determined</td>
</tr>
<tr>
<td>Mineralocorticoid receptor</td>
<td>Protective, clinical data</td>
<td>Not determined</td>
<td>Reduced MMP activation [108]</td>
<td>Reduced collagen formation [109]</td>
<td>Not determined</td>
</tr>
<tr>
<td>Statins</td>
<td>Protective, clinical data</td>
<td>Reduced cytokines in human CHF [110]</td>
<td>Some MMPs are inhibited after experimental MI [111]</td>
<td>Reduced collagen formation [112]</td>
<td>Reduced infiltration of leukocytes after ischemia/reperfusion [113]</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Inconclusive results</td>
<td>Different results ranging from depressed [116] to unchanged [115] cytokine expression</td>
<td>Unchanged [116]</td>
<td>Promotes cell differentiation in fibroblasts</td>
<td>Reduced infiltration of leukocytes after ischemia/reperfusion [117]</td>
</tr>
</tbody>
</table>
migration of monocytes and other cell types. Interestingly, a number of CXC chemokines, including IL-8 and others, appear to play a role in mediating angiogenesis. However, the role of chemokines in cardiac wound healing has not been investigated so far.

1.7. Matrix metalloproteinases

Extracellular matrix is controlled by a system of proteolytic enzymes, the matrix metalloproteinases (MMPs), and their inhibitors, the tissue inhibitors (TIMPs) of MMPs. Extracellular matrix degradation may be crucial for the healing process and MMP activity is increased in MI [68]. A “broad spectrum” MMP inhibitor attenuated early left ventricular enlargement after experimental MI in mice [69]. Actions of MMPs are interrelated, in the process of wound healing time dependent, and nomenclature is confusing (see Table 1). Targeted deletion of MMP 2 or 9 has decreased the incidence of rupture and attenuated left ventricular enlargement after MI in mice [70] suggesting importance of one specific MMP in the early healing process (see Table 1). The MMP system may be of particular importance since orally active inhibitors are available for a potential therapy and drugs may interfere with the MMP system.

1.8. Drugs

Drugs, currently known to influence cardiac remodeling may also have effects on myocardial healing. Results have been summarized in Table 2 including different drug effects on remodeling, cytokines, fibrosis, MMPs, and leukocyte infiltration after MI. So far, no drug has been developed on purpose to improve healing of the infarct wound. In fact, some drugs like ACE inhibitors and endothelin antagonists may interfere with healing of the infarct in experimental models [42,51]. The clinical relevance of these findings remains obscure. In general, drug effects on healing have not received adequate attention.

2. General healing factors

It is attractive to compare wounds of various organs to detect general principles of wound healing. External wound healing is one of the oldest challenges of medicine and relatively large experience on healing disturbances is available in cutaneous wounds. Animals lick their wounds and saliva contents may support wound healing, e.g. by growth factors and antibacterial properties [71,72]. However, discrepancies between skin wounds and myocardial infarcts are more obvious than similarities. The myocardial infarct develops during hours, remains ischemic if it is not reperfused, and faces the stress of rhythmic cardiac contraction. In addition, the paracrine and autocrine milieu is probably quite different between cutaneous and cardiac tissue. Nevertheless, a number of similar steps of healing may be observed in wounds and appear to be general characteristics of healing (Fig. 5). For instance, synthesis of collagen is dysregulated in fibroblasts derived from skin of subjects with varicose veins [73]. Fibroblasts isolated from venous ulcers have an impaired ability to synthesize collagen in vitro, especially under hypoxic conditions [74]. Thus beside confounding environmental factors, a genetic defect was assumed to transmit varicose vein pathology, a weakness of venous wall and, in general, a systemic biochemical defect of the extracellular matrix affecting the entire body structure [73]. Holbrook and Byers have defined skin as a window on heritable disorders of connective tissue [75].

A number of factors meet the requirements of a potential “general healing factor”. Secretory leukocyte protease inhibitor (SLPI) is a constitutively expressed 12 kDa protein [76]. It was first recognized as a potent inhibitor.
of serine proteases such as neutrophil Elastase and cathepsin G [77,78]. Furthermore, SLPI controls the synthesis of intracellular enzymes, and suppresses production and activity of monocyte matrix metalloproteinase. SLPI KO mice exhibit wound healing defects, i.e. they have enlarged wounds with margins that fail to close. This deficiency is most likely due to unresolved inflammation, a failure of re-epithelialization, and an inability to generate matrix or to counter local proteolysis by serine proteases. This effect seems to be mediated by TGF-β as constitutively active TGF-β was increased in wounds of SLPI KO mice and neutralization of TGF-β in vivo reversed impaired healing. Moreover, our group could detect expression of SLPI in the heart and in heart failure. However, the function of SLPI in healing of the infarct wound remains to be defined.

**Osteopontin**, an extracellular matrix protein interacts with integrins and the CD44 receptor. It may contribute to cell adhesion, chemotaxis and signaling [79] and interacts with fibronectin and collagen [80]. Osteopontin deficiency leads to disorganization of the collagen matrix and smaller fibrils in skin wounds [81] suggesting a role in wound healing. Faint expression is detected in the normal mouse heart but abundant expression in infarcts during healing. Moreover, our group could detect expression of SLPI in the heart in chronic cardiac overload [82,83]. Osteopontin deficiency leads to increased expansion of the infarcted segment and remote myocardium and decreased collagen accumulation [82].

**Secreted protein acidic and rich in cystein (SPARC)** is an extracellular glycoprotein expressed in proliferating cells. It belongs to the matricellular proteins and is involved in cell-extracellular matrix interaction. SPARCs can regulate cell shape, cell adhesion, proliferation, migration and matrix turnover [84]. SPARC KO mice have retarded granulation and impaired fibroblast migration [85]. SPARCs are expressed in the heart; expression is increased with isoproterenol treatment [86]. However, the role of SPARCs in cardiac healing remains to be defined.

**Factors of the blood coagulation system**, for example Factor XIII may be involved in numerous cross-link reactions which form and stabilize the fibrin network. Factor XIII modulates intestinal epithelial wound healing in vitro [87], stabilizes bone defects in diabetic rats [88] and accelerates healing in diabetic food ulcer in man [89]. Inherited lack of factor XIII is rare but several clinical entities may result in deficiency of factor XIII. The role of factor XIII in infarct healing is unknown.

### 3. Complex genetic disorders relevant to healing

Only some examples can be given here. Chronic diabetic ulcer is a most obvious healing deficiency. Diabetic patients are at increased risk to develop heart failure after MI [90]. Results on diabetes effects on remodeling are controversial [91]. Diabetes enhances vascular MMP activity probably by an increased oxidative stress [92]. Hyperglycemia might be associated with impaired microvascular function after MI and thus impair healing [93].

Another model of deficient healing could be osteogenesis imperfecta which results from alterations of genes encoding type I collagen pro-α 1 and pro-α 2 chains. In the clinical situation, diagnosis is made on the basis of bone fragility, defective skeletal development, small stature, and blue sclera. Mice deficient of pro-α 2 I collagen have less and weaker collagen and develop a cardiomyopathy [94]. Aortic dissection, left ventricular rupture, and aortic or mitral valve incompetence have been observed in humans with osteogenesis imperfecta [95]. Most likely, this may be a genetic background which also contributes to deficient healing post MI. Other genetic disorders of connective tissue like the Ehlers-Danlos-Syndrome could serve as clinical models of impaired healing as well.

### 4. Conclusion

The reaction of the organism to tissue damage is well preserved throughout evolution. However, cardiac healing has specific characteristics. The time window for the rescue of viable myocardium after MIs is only several hours and often too small, the time window to influence healing of the scar would be sufficiently large to initiate an adequate therapy. Therefore, a better understanding of healing and support of healing mechanisms may help to develop new therapeutic options.

### References


