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Review

Myocardial repair/remodelling following infarction: roles of local factors

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Heart failure is a global health problem, appearing most commonly in patients with previous myocardial infarction (MI). Cardiac remodelling, particularly fibrosis, seen in both the infarcted and non-infarcted myocardium is recognized to be a major determinant of the development of impaired ventricular function, leading to a poor prognosis. Elucidating cellular and molecular mechanisms responsible for the accumulation of extracellular matrix is essential for designing cardioprotective and reparative strategies that could regress fibrosis after infarction. Multiple factors contribute to left ventricular remodelling at different stages post-MI. This review will discuss the role of oxidative stress and locally produced angiotensin II in the pathogenesis of myocardial repair/remodelling after MI.

1. Introduction

Following myocardial infarction (MI), cardiac structural remodelling is associated with an inflammatory reaction, followed by scar formation at the site of infarction as well as changes in the non-infarcted myocardium, including interstitial fibrosis and vascular remodelling. Fibrous tissue that forms at the site of cardiomyocyte loss preserves structural integrity and is integral to the heart's recovery, whereas structural remodelling of viable myocardium impairs tissue behaviour. Substances involved in cardiac repair/remodelling are of considerable interest and an important clinical issue, given that the repairing response can be subjected to pharmacological intervention. Multiple factors may, in fact, contribute to left ventricular remodelling at different stages post-MI. There is growing recognition and experimental evidence that oxidative stress mediated by reactive oxygen species (ROS) and locally produced angiotensin II (AngII) play a role in the pathogenesis of myocardial repair/remodelling after MI. Taking into account that there is a plethora of factors that contribute to remodelling and repair in the heart after MI, this review will address these cellular and molecular events related to cardiac repair/remodelling following MI, in particular discussing roles of locally produced ROS and AngII in promoting cardiac remodelling.

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2. Cardiac repair/remodelling following infarction

2.1 Infarct site

A highly regulated process of cardiac repair/remodelling follows the necrotic loss of cardiomyocytes after MI. It begins with the activation of latent matrix metalloproteinases (MMPs), which degrade the existing extracellular matrix and coronary vasculature.[1] This proteolytic activity declines by the end of week 1 post-MI and is coincident with the increased expression of MMP inhibitors, termed tissue inhibitors of MMPs or TIMPs.[2] Circulating inflammatory cells that include neutrophils and monocytes/macrophages arrive at the infarct site soon after MI. They respectively contribute to the proteolytic digestion and phagocytosis of the infarcted tissue. These inflammatory cells home to the site of MI drawn by adhesion molecules and chemoattractant cytokines (or chemokines) expressed by the endothelial cells of the coronary vasculature that borders on the infarct site. Their migration into the infarct site is facilitated by MMP proteolytic activity. This inflammatory response peaks at weeks 1 and 2 post-MI and then tapers off as inflammatory cells disappear from the infarct site within 3–4 weeks following MI, a consequence of their programmed cell death.

The fibrogenic component, which substitutes for lost parachymal cells, follows the initial phase of collagen degradation. It begins with the activation of transforming growth factor (TGF)-β1, the key mediator of fibrogenesis.

Increased synthesis of fibrillar type III and type I collagens is preceded by an increased expression of their mRNA transcripts.[3] Collagen fibres are morphologically evident at week 1 post-MI, while an organized assembly of these fibres in the form of scar tissue becomes evident at week 2.[4] This assembly continues to accumulate over 8 weeks.

2.2 Remote site

In addition to the infarcted myocardium, interstitial fibrosis is developed in the non-infarcted myocardium. Fibrous tissue formation, evidenced by hydroxyproline assay and histochemistry, is observed at week 3 at remote sites in hearts with extensive MI.[3] Perivascular fibrosis of intramyocardial coronary arteries is also seen at these sites. Thus, following large MI, extensive cardiac remodelling is developed not only in the infarcted myocardium, but also in remote sites.

3. Cells involved in cardiac remodelling by fibrous tissue

3.1 Infarct site

Cells responsible for fibrous tissue formation at the site of MI consist principally of phenotypically transformed fibroblast-like cells having distinctive morphological features and phenotypic characteristics. Their expression of α-smooth muscle actin (SMA) microfilaments, which give them contractility, earns them the name myofibroblast (myoFb).[5,6] MyoFbs are found at the infarct site soon after the arrival of inflammatory cells. Cells that account for the appearance of myoFbs are uncertain. They may include: interstitial fibroblasts; adventitial fibroblasts; pericytes; a population of circulating fibroblasts known as fibrocytes; circulating monocytes; or circulating bone marrow-derived progenitor cells that transdifferentiate at the infarct site. Specific factors that facilitate this differentiation process have been identified. It is presumed that TGF-β_1, elaborated by macrophages, governs the appearance of the myoFb phenotype.[7] Evidence supporting this hypothesis can be seen in cases of ischaemia–reperfusion, wherein TGF-β1 plays a central role in the oxygen-dependent differentiation of cardiac fibroblasts to myoFbs triggered by perceived hyperoxia.[8] After its appearance, MyoFbs rapidly proliferate and accumulate in the infarcted myocardium and are responsible for the formation of the scar via their expression of type I and III fibrillar collagens at both mRNA and protein levels.[3,9] Gabbiani *et al*.[10] demonstrated the contractile behaviour of myoFbs in scar tissue and is confirmed by other findings.[11] MyoFbs and their α-SMA microfilaments are joined to one another through gap junctions. This creates a contractile scar tissue assembly.

MyoFbs have a diverse portfolio of metabolic activities. Studies have shown that these cells express renin, angiotensin-converting enzyme (ACE), and angiotensin receptors at the infarct site.[12,13] MyoFbs obtained from the 4-week-old infarct scar and that are studied in culture under serum-deprived conditions that eliminate circulating renin, ACE, and AngI are found to express angiotensinogen, cathepsin D, ACE, and AngII receptors.[14] Given the presence of α-SMA in myoFbs, which is also present in vascular smooth muscle cells, it is not surprising that AngII, endothelin-1, and vasopressin promote scar tissue contraction.[14,15]

3.2 Remote site

Interstitial fibroblasts are responsible for normal collagen turnover. In the infarcted heart, interstitial/perivascular fibrosis is developed at remote sites in the later stage of MI.[3,16] Cells contributing to fibrosis in the non-infarcted myocardium are primarily interstitial fibroblasts. MyoFbs, however, do not appear at remote sites.

4. Role of oxidative stress in cardiac repair/remodelling following myocardial infarction

4.1 Formation and metabolism of reactive oxygen species

Superoxide (O_2^-), hydroxyl (OH^-), and peroxynitrite ($ONOO^-$) are simple molecules characterized by the presence of unpaired electrons. ROS can be produced intracellularly through electron leakage from the mitochondria during oxidative phosphorylation and through the activation of several cellular enzymes, including NADPH oxidase, xanthine oxidase, and nitric oxide synthase.[17–19] O_2^- can rapidly react with nitric oxide (NO) to form $ONOO^-$ or convert to H_2O_2 to form OH^-.[17]

ROS in low concentrations serve as signalling molecules.[20] However, these agents elicit harmful effects when produced in excess.[17] Toxicity associated with the excessive production of these compounds is prevented by antioxidant defence systems that maintain a healthy cellular environment. Living cells have both enzymatic and non-enzymatic defence mechanisms to balance the multitude of oxidative challenges presented to them. The enzymatic subgroup includes superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSHPx).[21,22] Dismutation of O_2^- by SOD results in the generation of H_2O_2, which catalase further metabolizes into water and oxygen. The non-enzymatic group includes a variety of biological molecules, such as vitamins E and C.[23] In the normal myocardium, as in other tissues, antioxidants protect cells by maintaining O_2^- and H_2O_2 at low levels.

4.2 Oxidative stress in the infarcted heart

Oxidative stress occurs when ROS production is enhanced and/or antioxidant reserve is suppressed. Following acute MI, oxidative stress is developed in both infarcted and non-infarcted myocardium. NADPH oxidase is a major source of O_2^- in the heart.[24] After MI, NADPH oxidase expression ($gp22^{phox}$ and $gp91^{phox}$ subunits) is significantly increased in the infarcted myocardium,[25,26] with neutrophils and macrophages as the primary cells expressing the enzyme (*Figure 1*). Furthermore, macrophage-derived inducible nitric oxide synthase, a major source of NO in the repairing tissue, is significantly increased in the infarcted myocardium,[27] leading to enhanced NO production. As a result, ROS production is elevated in the infarcted myocardium and contributes to the development of oxidative stress in the infarcted heart.

Impaired antioxidant capacity also plays a role in oxidative stress in the infarcted heart. Singal and colleague[26] have shown evidence of the progressive decrease of SOD, catalase, and GSHPx activity as well as vitamin E levels in the infarcted rat heart, first in the infarcted myocardium followed by the non-infarcted myocardium.[28] Our study

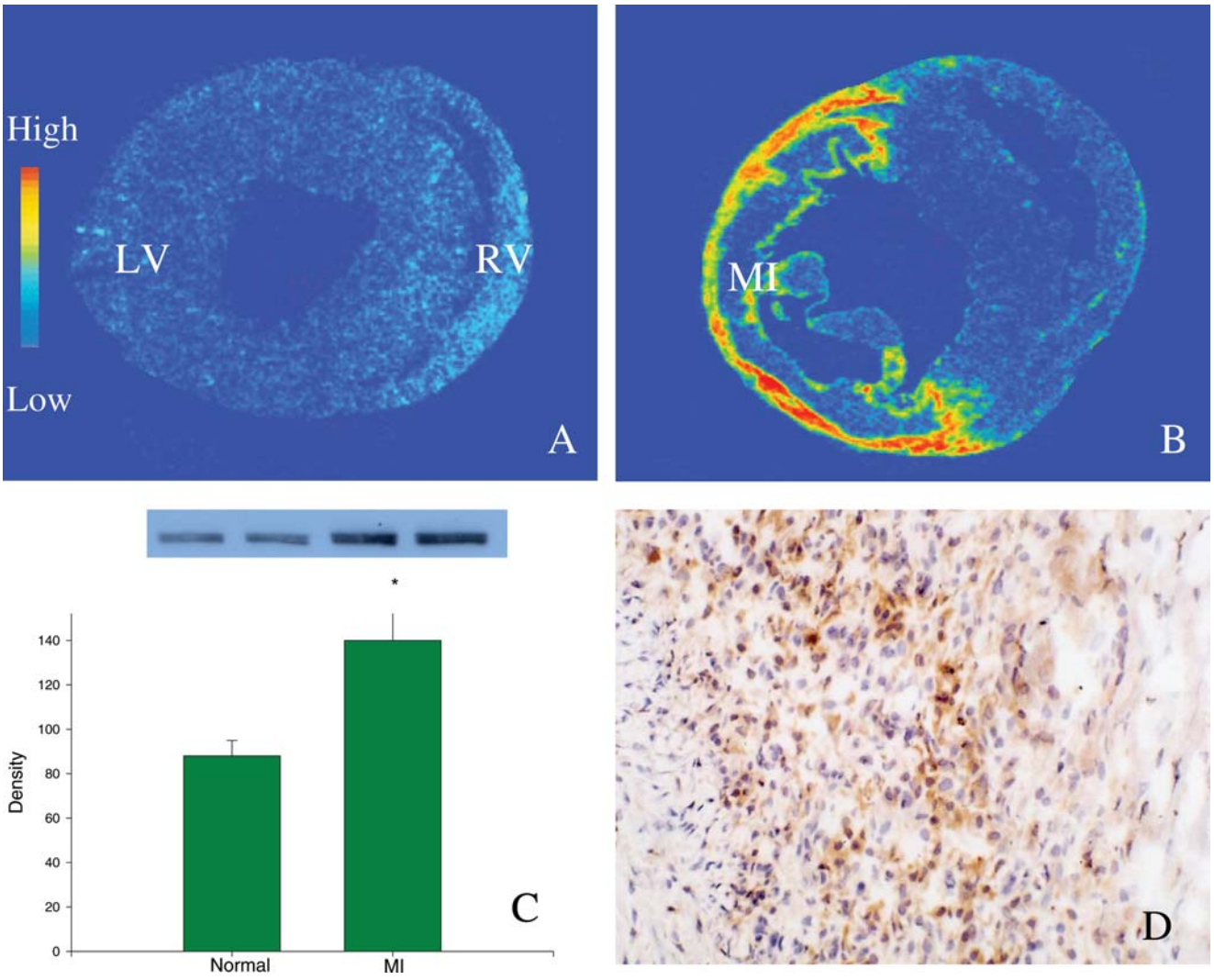

Figure 1 NADPH oxidase (gp91^{phox}) expression in the infarcted rat heart. Detected by *in situ* hybridization, low levels of gp91^{phox} mRNA are present in both left and right ventricles (LV, RV) of the normal heart (*A*). At 1 week post-myocardial infarction, cardiac gp91^{phox} mRNA levels are largely increased, particularly at the site of myocardial infarction (*B*). Detected by western blot, gp91^{phox} protein levels are significantly increased in the infarcted myocardium compared with the normal myocardium (*C*). Immunohistochemistry reveals that cells expressing gp91^{phox} in the infarcted myocardium are primarily inflammatory cells (*D*).

has shown reduced SOD gene and protein expression in the infarcted myocardium (*Figure 2*). Cardiac glutathione levels are also decreased in patients with acute MI.[29] Moreover, the expression of malondialdehyde (MDA) and 3-nitrotyrosine, markers of oxidative stress, are significantly increased in the infarcted myocardium, indicating the elevated occurrence of cardiac oxidative stress following MI (*Figure 2*).[26]

In remote sites, multiple sources contribute to oxidative stress. Increased mitochondrial production of ROS has been suggested in the non-infarcted myocardium.[30] Increased ROS levels in remote sites also reflect the increased activity of intracellular oxidase complexes, such as NADPH oxidase, xanthine oxidase, and nitric oxide synthase.[31] In addition, reduced SOD levels were observed in the failing heart with infarction.[32] These observations indicate that the imbalance between ROS production and antioxidant defence capacity leads to oxidative stress in non-infarcted myocardium.

Experimental studies have demonstrated that oxidative stress can induce most, if not all, of the changes that are thought to contribute to myocardial remodelling, including pro-inflammatory response, cardiomyocyte apoptosis, fibrogenesis, cell proliferation, and hypertrophy. Herein, the potential relevance of oxidative stress on inflammatory/fibrogenic responses will be discussed.

4.3 Reactive oxygen species and cardiac inflammatory response following myocardial infarction

MI is associated with an inflammatory response, ultimately leading to healing and scar formation. Inflammatory response in the infarcted myocardium is related to the coordinated activation of a series of cytokine and adhesion molecule genes. A critical element in the regulation of these genes involves nuclear factor-kappa B (NF-κB), a redox-sensitive transcription factor. NF-κB maintains an inactive form bound to its inhibitory subunit I kappa B under normal conditions. When tissue is injured, NF-κB is activated by various local substances including ROS.[33] Upon activation, NF-κB stimulates inflammatory and immune responses and cellular growth by increasing the

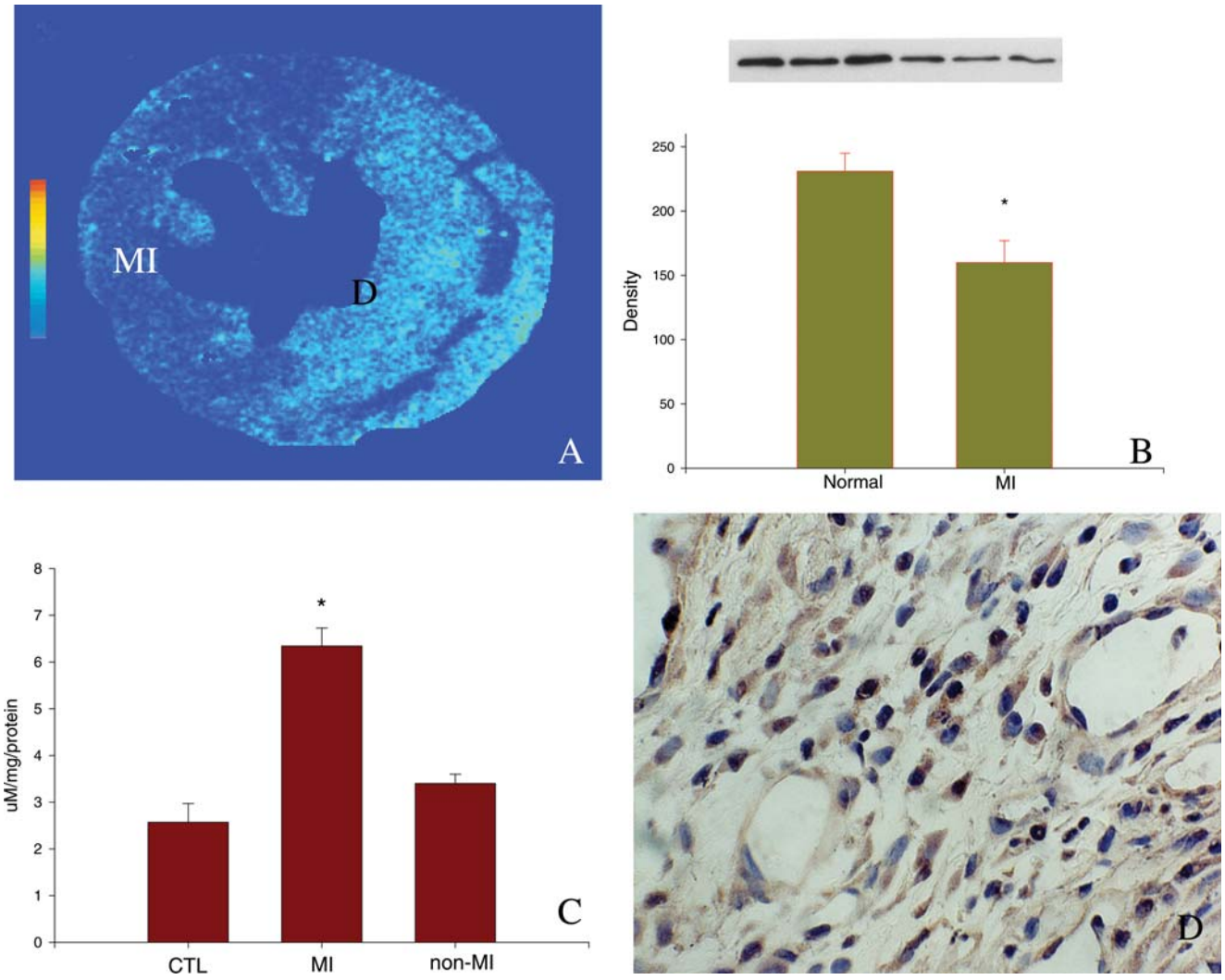

Figure 2 Expression of superoxide dismutase, malondialdehyde, and 3-nitrotyrosine in the infarcted rat heart. At 1 week post-myocardial infarction, superoxide dismutase mRNA (*A*) and protein (*B*) levels are significantly reduced in the infarcted myocardium. Compared with normal heart, malondialdehyde levels are significantly increased in the infarcted myocardium (*C*). 3-Nitrotyrosine is highly expressed by inflammatory cells at the infarct site (*D*).

expression of specific cellular genes. NF-κB activation has been demonstrated in various models of myocardial ischaemia.[34,35] Activated NF-κB triggers gene expression of interstitial and vascular adhesion molecules, as well as monocyte chemoattractant protein-1, leading to leucocyte infiltration into the infarcted myocardium.

NF-κB also triggers gene expression of pro-inflammatory cytokines, such as tissue necrosis factor (TNF)-α and interleukins, initiating an inflammatory response.[36] In rodent models of MI, TNF-α expression is significantly up-regulated in the infarcted myocardium as well as in the non-infarcted myocardium.[37] It plays a key role in stimulating inflammatory protein synthesis as well as macrophage phagocytosis, cell growth, differentiation, and apoptosis.[38]

In the infarcted myocardium, elevated NADPH oxidase is spatially coincident with activated NF-κB and enhanced TNF-α expression in inflammatory cells.[34] In addition to the NF-κB pathway, recent studies suggest that H_2O_2 can directly induce cardiac TNF-α production via the p38 MAPK pathway and, in turn, mediate myocardial inflammation.[39] Furthermore, free radical scavenger treatment has been demonstrated to diminish inflammatory response and cardiac remodelling.[40] The antioxidant, probucol, has been shown to attenuate cardiac inflammation and improve ventricular function.[41] These findings indicate that ROS serve as a pro-inflammatory mediator in cardiac healing process following infarction and its role in cardiac inflammation involves several pathways.

4.4 Reactive oxygen species and progressive myocyte death following myocardial infarction

Following MI, leucocytes are recruited into the infarcted region and initiate cardiac repair. Phagocyte-derived oxidative stress occurs at the site of infarction. This is particularly evident at the border zone, the area adjacent to the non-infarcted myocardium. ROS can directly attack DNA, proteins, and cell membranes and therefore have the potential to injure myocytes and vascular cells in the neighbouring non-infarcted myocardium, causing additional cardiac damage and extending infarct size. Oxidative stress also activates multiple cellular pathways, leading to cardiac damage. In the murine myocardium following the initial insult caused by ischaemia–reperfusion, progressive

myocyte death is noted in the border zone. Thus, myocardial remodelling following ischaemia/reperfusion includes secondary myocyte death followed by the loss of cardiac function over time.[42]

4.5 Reactive oxygen species and cardiac fibrogenic response following myocardial infarction

A growing bulk of evidence supports a causative role of oxidative stress in fibrogenesis in various tissues including liver, lung, arteries, nervous system, and heart.[43,44] ROS is shown to up-regulate the expression of TGF-β and type I collagen in various tissues.[45,46] Following MI, enhanced expressions of TGF-β and NADPH oxidase are spatially coincident at the site of the infarcted myocardium (*Figures 1* and *3*). Treatment with the antioxidant taurine reduces oxidative stress, suppresses TGF-β gene expression, and attenuates hepatic fibrosis.[47] Furthermore, *in vitro* studies have indicated that ROS promotes fibroblast proliferation and type I collagen gene

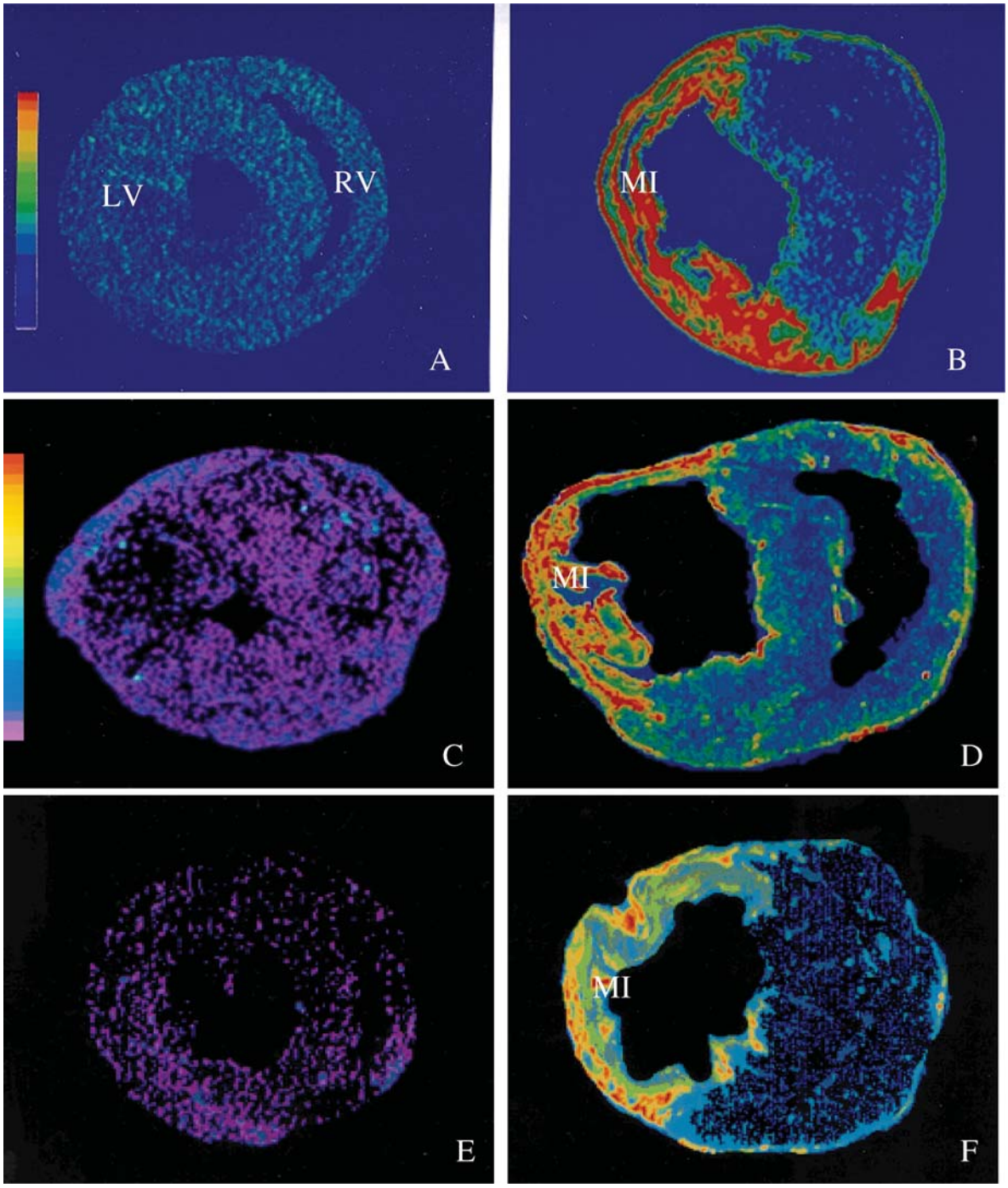

Figure 3 Transforming growth factor-β1, angiotensin-converting enzyme, and AT1 receptor expression in the infarcted heart. By *in situ* hybridization, normal myocardium contains low levels of Transforming growth factor-β1 (*A*). At week 1 post-myocardial infarction, Transforming growth factor-β1 gene expression is largely increased at the site of myocardial infarction (*B*). Detected by autoradiography, binding density of angiotensin-converting enzyme (*D*) and AT1 receptors (*F*) are largely increased in both the infarcted and non-infarcted myocardium compared with the normal heart (*C* and *E*, respectively).

expression in cardiac fibroblasts.[48] Chronic antioxidant treatment is shown to attenuate cardiac fibrosis.[49–51]

After acute MI, progressive global left ventricular dilation occurs over the following months.[52] MMPs favour this adverse remodelling. It was shown that inhibition of MMPs decreases the severity of remodelling in the infarcted heart.[53] *In vitro* studies have shown that ROS activates MMPs in cardiac fibroblasts.[54] Oxidative stress may, therefore, play a role in the pathogenesis of left ventricular dilation following infarction. However, *in vivo* studies on the regulatory role of ROS on MMPs and cardiac dilation are lacking and further studies are required on this concept.

The extensive body of literature in animal studies suggests that there is great potential benefit in therapies that can improve cardiac remodelling and function in humans. However, existing evidence for the role of oxidative stress in the pathogenesis of cardiac remodelling and ventricular dysfunction in humans is not compelling. Clinical trials of antioxidant therapy for heart failure are few in number and so far have failed to demonstrate convincing benefits. This might be due to several potential reasons.

First, ROS are derived from multi-sources in the failing heart. ROS can be produced intracellularly through electron leakage from mitochondria during oxidative phosphorylation and through the activation of several cellular enzymes, including NADPH oxidase, xanthine oxidase, and nitric oxide synthase. Treatment with a specific antioxidant, such as NADPH oxidase inhibitor, may therefore not suppress oxidative stress due to the redundant sources of ROS production.

Secondly, most currently recognized antioxidants that were used in animals including probucol, pyrrolidine dithiocarbamate, vitamin E or C, and *N*-acetyl cysteine are not either a strong antioxidant or a specific antioxidant with many other effects. Moreover, combination of antioxidants, dosing and timing of treatment, and duration of the process need to be further established in patients with heart failure.

5. Cardiac angiotensin II and myocardial repair/remodelling

In addition to oxidative stress, AngII is considered another local factor in mediating cardiac remodelling following MI. Circulating AngII has multiple well-known endocrine properties in the cardiovasculature. AngII, produced *de novo* within the heart independent of plasma angiotensinogen, plasma renin activity, and endothelial cell-bound ACE, also has various autocrine and paracrine properties on resident cells. These cells include cardiomyocytes, representing one-third of all cells found in the myocardium; and fibroblasts, endothelial and vascular smooth muscle cells, and macrophages, which represent the remaining two-thirds. Based on current evidence, AT_1 receptor-ligand binding accounts for the majority of these respective endocrine and auto-/paracrine actions of AngII on blood vessels and cardiac tissue.

5.1 Cardiac angiotensin II production

Renin expression (mRNA and protein) is undetectable in the normal myocardium. Low ACE levels are present throughout the myocardium of the right and left atria and ventricles of the adult rat heart, as is also the case for AngII receptors. Following experimental MI in rats, renin, ACE, and AT1 receptor expression is significantly increased at the infarcted myocardium, coincident with inflammatory response and the initial accumulation of fibrillar collagen.[12,13,55–57] Moreover, elevated AngII concentration is found at the infarct site.[58] Renin is expressed by macrophages and myoFbs at the infarct site.[13] ACE-positive cells at the infarct site involve endothelial cells of the neovasculature (constitutive ACE) and macrophages and myoFbs (recruitable ACE).[57,59] AT1 receptors are primarily expressed by macrophages, myoFbs, and vascular smooth muscle cells in the infarcted myocardium.[56] The expression of ACE and AT1 receptors in macrophages and myoFbs in the infarcted heart suggests that locally generated AngII plays a role in inflammatory and fibrogenic reactions in an autocrine manner.

Non-ischaemic models of cardiac repair have also been examined relative to ACE expression. They included: AngII infusion via an implanted mini-pump;[60] administration of isoproterenol, a synthetic catecholamine;[61] and chronic ($>$3 weeks) administration of aldosterone by a mini-pump in uninephrectomized rats on a high salt diet.[62] At each site of non-ischaemic cardiac repair, and irrespective of its aetiological basis, the temporal and spatial appearance of high levels of ACE expression is coincident with fibrous tissue formation that resembles reparative responses observed with ischaemic necrosis following MI. Thus, irrespective of the aetiological basis of cardiac injury, a recruitable source of ACE appears at sites of cardiac repair and contributes to local AngII production and consequently cardiac repair.

5.2 Regulation of angiotensin II on cardiac repair/remodelling

A paradigm of tissue repair has been proposed in which ACE and local AngII are integral to the orderly and sequential nature of repair that eventuates in fibrosis.[63] ACE is involved in a two-part *de novo* generation of AngII within the granulation tissue that forms at the infarct site. The first component to local AngII generation is provided by activated macrophages. In an autocrine manner, macrophage-derived AngII stimulates NADPH oxidase expression that induces ROS production, triggering inflammatory response in various tissues.[26,64–66] MyoFbs next generate AngII whose autocrine induction of TGF-β_1 regulates collagen turnover at sites of fibrous tissue formation.[1] ACE expression is spatially and temporally concordant with the expression of TGF-β_1 mRNA, type I collagen mRNAs, and AT1 and TGF-β receptors at these sites. Studies have demonstrated that cardiac AngII stimulates TGF-β_1 expression, thus promoting cardiac fibrosis.[67]

ACE inhibitors and AT1 receptor blockers have been proven effective in modulating the process of remodelling and in reducing the occurrence of adverse events in heart failure. Chronic treatment of ACE inhibitor decreased cardiac fibrosis after MI in rats.[68–70] Captopril and enalapril begun at or close to the onset of MI have each reduced infarct size, infarct expansion, and thinning, and hydroxyproline concentration at the infarct site.[71–73] Losartan begun on day 1 after coronary artery ligation in a dose that reduced AT_1 receptor binding by 50% reduces infarct scar area.[74] Moreover, the expected rise in tissue Ang II

concentration found at the infarct site 3 weeks after coronary artery ligation in rats is markedly attenuated by either delapril or TCV-116, an AT_1Ra, introduced on post-operative day 1, so did left ventricular remodelling.[58] It has also been demonstrated that the combination of AT1 receptor blockade and ACE inhibitor is more effective than individual treatment on ventricular remodelling and survival after MI in rats.[69]

Fibrous tissue formation at sites remote to MI is also influenced by these pharmacological interventions. Perindopril, given 1 week after MI, attenuates the endocardial fibrosis that appears in the non-necrotic segment of the rat left ventricle.[75] Captopril, commenced at the time of coronary artery ligation, attenuates the expected fibrosis of the non-infarcted left and right ventricles of the rat[76] and proliferation of fibroblasts and endothelial cells that appears at remote sites 1 and 2 weeks following MI.[76] Losartan likewise prevents fibrosis at remote sites.[74,77,78]

These favourable tissue-protective effects of ACE inhibition or AT_1 receptor antagonism are not confined to the infarcted heart. These interventions prevent the appearance of fibrosis in diverse organs with experimentally induced or naturally occurring tissue injury, where the circulating renin–ngiotensin system is not activated. These include: pericardial fibrosis post-pericardiotomy;[4] tubulointerstitial fibrosis associated with unilateral urethral obstruction[79–81] or renal injury following irradiation;[82] cardiovascular and glomerulosclerosis that appear in stroke-prone spontaneously hypertensive rats;[83–86] or interstitial pulmonary fibrosis that follows irradiation.[87] Attenuation of fibrous tissue formation by these interventions in diverse organs with various forms of injury supports the importance of local AngII in promoting fibrosis.

Aldosterone production in the heart as well as aldosterone plasma levels are increased after MI and in congestive heart failure, correlating with the severity of disease. Aldosterone promotes sodium and water retention, sympathoadrenergic activation, endothelial dysfunction, and cardiovascular fibrosis and hypertrophy. Studies have demonstrated that aldosterone receptor blockade markedly reduces mortality among patients with heart failure. Reduction of excessive extracellular matrix turnover leading to decreased fibrosis appears to be the most important effect of mineralocorticoid receptor antagonism in heart failure. Other mechanisms such as regression of hypertrophy, improvement of endothelial function, reduction of superoxide formation, and enhanced renal sodium excretion may contribute. Recent data showed that in rats with left ventricular dysfunction after extensive MI, eplerenone on top of ACE inhibition more effectively improved cardiac remodelling and molecular alterations than ACE inhibition alone.[88,89]

6. Summary

Following MI, cardiac structural remodelling is associated with an inflammatory reaction, followed by scar formation at the site of infarction as well as interstitial fibrosis and vascular remodelling in the non-infarcted myocardium. Factors that regulate cardiac repair/remodelling include ROS and AngII produced in the infarcted heart. ROS mediate cardiac repair via activating NF-κB with its pro-inflammatory cascade, promoting fibrogenic cytokine production. Local AngII regulates cardiac remodelling by stimulating NADPH oxidase, which, in turn, enhances ROS production and promotes TGF-β synthesis in an autocrine manner. Blockade of ACE and/or AT1 receptors are effective in attenuating tissue fibrosis in animals and patients. Suppression of cardiac oxidative stress improves cardiac remodelling and ventricular dysfunction in animals with MI. However, the potential regulation of oxidative stress in the pathogenesis of cardiac remodelling and ventricular dysfunction requires further studies in patients with MI and heart failure.

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