Help from within: cardioprotective properties of hepatocyte growth factor

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See article by Ueda et al. [20] (pages 41–50) in this issue.

Relative volume overload in the aftermath of the acute death of large numbers of cardiac myocytes after myocardial infarction (MI) is causal to progressive cardiac dysfunction. Initially, the myocardium responds to the loss of sarcomeric contractile units with the induction of compensatory cardiac growth. In clinical terms, this response is marked by normalization of wall stress and preservation of pump function within normal limits. The severity of eventual secondary cardiac hypertrophy is variable depending on the initial size of infarction [1,2]. In the event of a large MI, the affected ventricular chamber may undergo dilatation at a point well after the initial insult [3]. At this stage of hypertrophy, increased myocyte size is associated with decreased intrinsic cardiac performance [4]. In other words, the heart reaches a decompensated hypertrophic state. Furthermore, it is clear that the pathogenic progression to heart failure in post-MI patients involves both cardiac myocytes and nonmyocytes (i.e. myofibroblasts), and that these cell groups respond independently to volume overload [5]. Despite the current extensive armamentum of pharmacological interventions available to the clinician to combat this syndrome, the prognosis for patients who manage to survive the acute phase of a large MI remains grim. An improved understanding of endogenous adaptive changes of the myocardium may provide a basis for exploitation in delaying the onset of maladaptive hypertrophy.

1. Mechanisms of heart failure after myocardial infarction

The complexity of post-MI heart failure is marked by the multitude of triggers that contribute to its pathogenesis. The loss of myocytes heralds abnormally elevated biomechanical stress; at the same time, or in some cases perhaps subsequent to this, activation of multiple trophic factors occurs including angiotensin II, transforming growth factor β1 (TGF-β1) and cardiostrophin-1 (CT-1) which may target receptors on multiple cardiac cell types [6,7]. Incidence of heart failure is marked by the reprogramming of gene expression in affected cardiac cells i.e. the hypertrophic (or fetal) gene program in cardiac myocytes and modulation of fibroblast phenotype (i.e. the appearance of cardiac myofibroblasts) and metabolism [6,8,9]. The latter alterations may persist even in the absence of continued chronic biomechanical stress, for example when afterload reduction therapy is initiated [5]. The cumulative effects of these changes are cardiac myocyte dysfunction and overt cardiac fibrosis in areas adjacent to and remote from the site of infarction, and current pharmacological strategies directed at their reversal have proven to be partially effective when considering the broad spectrum of subcellular abnormalities that mark pathological hypertrophy and failure [5,6]. Recent evidence points to the possible contributory role of myocyte apoptosis manifested as either sporadic or massive acute myocyte cell drop-out in chronic cardiac disease and infarction, respectively, in the development of heart failure [10]. For example, during chronic aortic pressure overload, the occurrence of sporadic cardiac myocyte apoptosis has been suggested to effect the transition between compensated and decompensated cardiac hypertrophy [11]. In contrast, there is little subtlety in the nature of the acute ultrastructural havoc typical of myocyte necrosis in acute MI, and the arguments for the putative benefits of cardiac myocyte preservation in this setting require little emphasis. The development of (i) abortive therapeutic strategies either to minimize the extent of infarction via rapid reperfusion or (ii) management therapies to maintain adequate post-MI cardiac function in patients with healed infarcts are characterized by a modicum of success and continue to evolve. Investigation of endogenous cardioprotective factors that may augment the adaptive compen-
satory response at or near the time of infarction is an exciting and novel avenue for therapy, partially because of the lack of complete efficacy of current interventions in halting the progression and severity of the disease. The concept of infarct size reduction vis a vis reduction of myocyte loss through necrosis and/or apoptosis at the time of infarction bears investigation. While the suppression of proinflammatory cytokines is an emerging concept for the treatment of heart failure [12–14], the use of cardioprotective cytokines to modulate the progression of acute ischemic cardiac damage [15–17] and for alleviation of heart failure represents a novel mode of therapy [18,19].

In the current issue of *Cardiovascular Research*, Ueda et al. investigate the general premise that myocyte death due to oxidative stress in acute MI may be attenuated by the cardioprotective effects of hepatocyte growth factor (HGF) [20]. Their general hypothesis was that increased expression and activation of HGF itself as well as c-Met/HGF receptors in cardiac myocytes might confer cardioprotection to cardiac myocytes at risk. The in vitro system (rat — chronic infarction) and in vivo models (to assess the effects of HGF in acute oxidant stress) used in these studies are suitable for the examination of cardiac myocyte function as well as the functional and morphological characteristics of post-MI hearts. In particular, the rat post-MI model of heart failure is useful for the examination of responsiveness of gene expression in the border zone tissue, remnant myocardium and infarct scar [21–27]. The data presented is provocative and provides a significant step in determining the cardioprotective efficacy of HGF in post-MI heart failure.

2. HGF: a novel cardioprotective trophic factor that activates ERK1/2

It is well entrenched in the literature that the function of the scarred ventricle depends on evolving changes in trophic cytokine or factor signaling, triggered in autocrine or paracrine modalities or secondary to elevated cardiac biomechanical stress. The data presented in this issue indicate that the c-Met/HGF receptor and HGF mRNAs are elevated in post-MI rat heart when compared to noninfarcted control hearts, and that HGF itself is able to delay the death of cultured cardiac myocytes exposed to H$_2$O$_2$. HGF expression is upregulated in rat heart following myocardial ischemia and reperfusion [28] and has been identified as a marker of acute MI in humans [29]. HGF has also attracted attention for its angiogenic properties [30]. Evidence for this mode of protection have been previously explored however a detailed understanding of HGF protection in post-MI hearts is not yet well understood nor have the acute effects of this cytokine been well studied in myocytes suffering acute oxidative stress; the current work addresses these questions.

Similar to the downstream effects of IGF-1, HGF directly activates ERK1/2. This pattern of activation seems to be unique to HGF insofar as Akt is not also a primary target for phosphorylation in the presence of HGF. The current data also show that the c-Met receptor is localized to cardiac myocytes and vascular endothelial cells both on myocardial infarct border zone and in heart remote to the infarct. The current finding provides support for the supposition that myocytes are a primary target of endogenous HGF. Nevertheless, other recent work has focused on the anti-fibrotic role of HGF and the involvement of cardiac fibroblasts [31]. Whether the effects of cardiac HGF are more apparent in myocytes over cardiac fibroblasts may depend on the type and stage of heart failure; this question awaits further investigation. The findings of Ueda et al. are of considerable clinical interest and provide the basis for a novel cardioprotective (and a putative adaptive) mechanism in myocardial infarction. The strong positive correlation of HGF’s antioxidant effects and its upregulation in tissues bordering the infarcted heart and remote to the infarct site are exciting developments with considerable promise for development.

References

[7] Aoyama T, Takimoto Y, Pennica D et al. Augmented expression of trophic cytokine or factor signaling, triggered in autocrine (rat — chronic infarction) and in vivo models (to assess the effects of HGF in acute oxidant stress) used in these studies are suitable for the examination of cardiac myocyte function as well as the functional and morphological characteristics of post-MI hearts. In particular, the rat post-MI model of heart failure is useful for the examination of responsiveness of gene expression in the border zone tissue, remnant myocardium and infarct scar [21–27]. The data presented is provocative and provides a significant step in determining the cardioprotective efficacy of HGF in post-MI heart failure.

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