Editorial

A new altruist on the block: effects of adrenomedullin after myocardial infarction

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The first few weeks after myocardial infarction (MI) are critical to the evolution of compensated to decompensated heart failure; it is generally agreed that the rapidity of cardiac dysfunction in these hearts depends on the magnitude of the initial insult [1]. From a clinical standpoint, it stands to reason that any process that may interrupt or abrogate secondary ventricular remodeling with attendant loss of normal chamber geometry may also attenuate the rate of functional decline of the remnant heart. The hallmark of maladaptive change in the post-MI heart is increased myocyte size; this change is associated with decreased intrinsic cardiac performance [2]. Alternatively, the premise that post-MI heart failure stems from not only abnormalities in cardiac myocytes but may also be linked to unusual behaviour of non-myocytes, i.e., myofibroblasts, seems to be borne out by data from recent studies [3,4]. Recent attention has focused on the acute pattern of changes that transpire in the healing infarct scar and remnant myocardium, loosely connected by the general hypothesis that events in early post-MI healing may serve to set the pace for the onset of cardiac decompensation. In this context, basic cardiovascular research specializing in a subset of novel factors that may have anti-growth and anti-proliferative properties for cardiac cells is burgeoning. In this scenario, multiple factors with opposing functions (operating via autocrine or paracrine modes) may participate in the acute phase of wound healing and continue to exert their effects in the chronic post-MI heart. As (i) the prognosis for patients who manage to survive the acute phase of a large MI and who yet go on to develop maladaptive hypertrophy remains dismal, and (ii) the list of new agents for treatment of this disease has not grown appreciably in the last 10 years, an understanding of naturally occurring factors that tend to oppose cardiac remodeling per se is well worth further investigation. An improved understanding of endogenous adaptive changes of the myocardium may provide a basis for exploitation in delaying the onset of maladaptive hypertrophy.

1. Early events in wound healing after myocardial infarction

Wound healing and scar formation following myocardial infarction is marked by inflammation and clearance of necrotic myocytes followed by proliferation of interstitial fibroblasts where they synthesize new extracellular matrix proteins and mediate contraction of the infarct scar [5,6]. Multiple cell types in the surviving tissues and in the infarct zone undergo phenotypic changes and participate in subsequent cardiac remodeling. Myocytes grow larger and express a characteristic subset of protein isoforms specific to the fetal gene programming, while fibroblasts tend to proliferate and undergo a phenotypic change to become actin-expressing contractile myofibroblasts. These changes are initiated by, and tend to offset, increased net mechanical stress of the ventricular wall. Various cell mediators and cytokines are well known to play integral roles in this phenomenon, including angiotensin II, endothelin-1, and transforming growth factor β. Nonetheless, the number of putative players that may participate in the acute and net heart function in vivo is increasing. For example, recent discoveries of the ACE homologue, ACE2, and cardiotrophin-1 (CT-1; a member of the IL-6 family of cytokines) and that of their effects on cardiac-specific cell types has generated new interest in the contribution of angiotensin1–9, angiotensin1–7, as well as CT-1 in the

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pathogenesis of cardiac remodeling [7,8]. The putative loss of balance of multiple positive and negative effects of these cytokine/growth factors in post-MI heart is of particular interest. The majority of well-characterized mediators of phenotypic end-points are trophic and associated with maladaptive remodeling in the post-MI heart. For example, angiotensin II is an important stimulator of cell proliferation and extracellular matrix protein synthesis while TGF-β is a potent mediator of extracellular matrix protein synthesis and cardiac fibroblast phenotype. In primary cardiac fibroblasts, angiotensin II may mediate the rapid phosphorylation and nuclear translocation of R-Smad proteins, which are classically phosphorylated by the kinase motif on the TβRI receptor [9]. CT-1 has been shown to be elevated in the serum of patients with various cardiac diseases including unstable angina pectoris [10], myocardial infarction [11], and heart failure [12]. CT-1 induces cardiomyocyte hypertrophy [8] and cardiac fibroblast proliferation [13]. Angiotensin II is known to increase CT-1 expression in fibroblasts [14]. Thus it could be argued that this subset of trophic factors function in a coordinated manner via a significant modicum of post-receptor cross-talk. If the fate of cardiac myocytes is considered, this group of trophic factors tend to share the same end-point; i.e., eventual maladaptive cardiac hypertrophy typified by cardiac myocyte growth and expansion of the cardiac interstitium. While much of the thinking behind current therapeutic approaches to treat post-MI heart failure deals with abrogation of specific trophic pathways, implementation of naturally occurring factors that a priori delay the onset or otherwise ameliorate cardiac remodeling are now being pursued. What of novel factors that may exert inhibitory effects on growth or proliferation with regard to cardiac myocytes and myofibroblast proliferation? Is their role important to the onset and severity of cardiac remodeling, and thus to the pathogenesis of post-MI heart failure? Finally, is the presence of anti-trophic factors significant in the post-MI heart insofar as they may mediate so-called adaptive changes and thus provide a balancing influence to the effects of trophic factors?

In the current issue of *Cardiovascular Research*, Nakamura et al. investigate the general premise that long-term administration of human adrenomedullin (AM) to rats with large myocardial infarction is attended by the cardioprotective effects including attenuation of left ventricular remodeling, as well as normalizing effects on cardiac hemodynamics and endogenous hormonal flux in experimental hearts [15]. Their general hypothesis examined is that AM acts locally or systemically to halt the progression of left ventricular remodeling in post-MI rat heart. The data presented provides a significant extension of the literature and provides a catalogue of beneficial effects of chronic infusion of AM in post-MI heart failure. The progressive changes that normally occur in cardiac phenotype and function are significantly altered.

2. Adrenomedullin: an endogenous anti-remodeling factor?

Elevated cardiac biomechanical stress is a likely 'master-switch' that contributes to the release of an array of biochemical signals and secondary ventricular remodeling [16]. Data presented in this issue indicate that in rats infused with recombinant human AM for 4 weeks were characterized by significantly reduced heart left ventricular end-diastolic pressure, LV weight/body weight ratio, myocyte cross-sectional area, and collagen volume fraction (as determined by Sirius Red staining of LV segments) when compared to the saline-infused MI groups. AM has attracted the attention of clinicians and basic scientists as its baseline plasma levels are significantly elevated in patients with overt heart failure versus levels in healthy patients [17,18]. Recent work addressing the regional and systemic effects of exogenous AM provided data indicating significant reductions in mean arterial pressure and peripheral resistance but increased heart rate and cardiac index [19]. Further, AM is known to be up-regulated both in plasma of exercised patients [20] and in brain tissues following repeated bouts of hypoxia and reoxygenation; in the latter, AM may be an important contributor to hypoxic preconditioning in mammalian tissue [21]. How does AM manage to exert these effects? A recent study of experimental malignant hypertension provides evidence that chronic adrenomedullin infusion is renoprotective and may also inhibit the circulating and intrarenal renin–angiotensin system [22]. Others have reported that AM may inhibit ischemia–reperfusion injury via its NO-releasing activity [23]. Further, adrenomedullin’s effects may be potentiated by modification of adrenomedullin receptors in heart failure insofar as in failing, pressure-overloaded hearts, adrenomedullin receptor activity-modifying protein 3 (RAMP3) is upregulated versus expression in controls [24]. Adrenomedullin’s role in counteracting cardiovascular damage associated with angiotensin II and salt loading was recently addressed [25]. In studies using heterozygous AM knock-out mice (+/−) that express ~50% of plasma and organ AM of wild-type animals (+/+ ) significantly greater myocardial damage was noted versus AM (+/+ ) animals in the presence of high levels of exogenous angiotensin II and salt [25]. Damage to hearts in this study was gauged via coronary artery perivascular fibrosis and intimal hyperplasia. Burnett and co-workers [26] have provided a further connection of AM activation and angiotensin II in experimental pacing-induced failure wherein they have observed attenuated AM release in the presence of chronic ACE inhibition. Work carried out by Tsuruda et al. [27], as well as Tomoda et al. [28], indicate that AM is synthesized and released from cardiac myocytes and fibroblasts. The relatively early prediction by Horio et al. [29] that AM may function to suppress cardiac fibrosis in cardiac remodeling is borne out by the
results of Nakamura et al. in this issue. This work is exciting as it provides a direct assessment of the efficacy of the AM signal in delaying the onset of cardiac decompensation in post-MI heart. Finally, the findings are of clinical interest and provide the basis for a novel cardioprotective treatment modality in myocardial infarction.

References


