Review article

Intracardiac renin–angiotensin system and myocardial repair/remodeling following infarction

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ABSTRACT

The circulating renin-angiotensin system (RAS) is a classic endocrine system that regulates cardiovascular homeostasis during physiologic and pathologic states. Accumulated evidence has shown the presence of components of RAS in various tissues, which are upregulated in certain pathological conditions. Locally produced angiotensin (Ang)II may play an important role in tissue repair/remodeling in autocrine and/or paracrine manners. Following acute myocardial infarction (MI), cardiac repair occurs in the infarcted myocardium and structural remodeling is developed in noninfarcted myocardium, which are accompanied by activated cardiac RAS. In this review, the current understanding of independent activation of cardiac RAS and its regulation in the pathogenesis of myocardial repair/remodeling after MI is discussed.

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1. Introduction

The critical role of the circulating RAS in the regulation of arterial pressure and sodium homeostasis has been recognized for many years. AngII is the most powerful biologically active product of the RAS. AngII directly constricts vascular smooth muscle cells, enhances myocardial contractility, stimulates aldosterone production, stimulates release of catecholamines from the adrenal medulla and sympathetic nerve endings, increases sympathetic nervous system activity, and stimulates thirst and salt appetite. AngII also regulates sodium transport by epithelial cells in the intestine and kidney.

RAS is a coordinated hormonal cascade. Renin acts on the circulating precursor angiotensinogen to form AngI. AngI has no biological activity and is converted to AngII by endothelial angiotensin-converting enzyme (ACE). The actions of AngII are mediated by specific membrane-bound AngII type-1 (AT1) and type-2 (AT2) receptors with the majority of cardiovascular actions of AngII are mediated by the AT1 receptors. AT2 receptors induce a counter-regulatory vasodilatation that is largely mediated by bradykinin and nitric oxide. AngII has a very short half-life and is quickly degraded to active AngIII and Ang(1–7) and inactive fragments. AngIII has actions similar to those of AngII. Ang(1–7), via Mas receptors, exerts the hypotensive action through the release of bradykinin, prostaglandins, and endothelial nitric oxide [1]. Thus, Ang(1–7) acts as an endogenous inhibitor of AngII. ACE2 is the newest member of the RAS [1]. ACE2 is primarily expressed in endothelial cells in the heart and kidney. It

hydrolyzes AngII to Ang(1–7) and its enzymatic activity is not affected by ACE inhibitors.

There has also been a growing appreciation of the organ-specific roles exerted by AngII acting as an autocrine/paracrine factor. Local AngII production is activated in various pathological states, such as atherosclerosis [2], various injured tissues [3], hypertensive and diabetic kidney [4,5], MI [6,7], etc. AngII has been demonstrated to stimulate inflammation, cell growth, apoptosis, fibrogenesis, and differentiation, regulates the gene expression of bioactive substances, and activates multiple intracellular signaling pathways, all of which might contribute to tissue repair/remodeling [8,9].

Following MI, structural changes appear in both the infarcted and noninfarcted myocardium. Cardiac repair occurs in the infarcted myocardium, which is associated with an inflammatory reaction, angiogenesis and scar formation. Structural remodeling in the non-infarcted myocardium includes hypertrophy and interstitial fibrosis [10–12]. Fibrous tissue that forms at the site of cardiomyocyte loss preserves structural integrity and is integral to the heart's recovery, whereas structural remodeling of viable myocardium impairs tissue behavior. Substances involved in cardiac repair/remodeling are of considerable interest and an important clinical issue. Multiple factors may, in fact, contribute to left ventricular remodeling at different stages postMI. There is growing recognition and experimental evidence that cardiac RAS is activated following MI and locally produced AngII plays a central role in the pathogenesis of myocardial repair/remodeling after MI. This review will in particular address the regulation of locally produced AngII in promoting cardiac repair/remodeling following MI.

2. Cardiac repair/remodeling following infarction

2.1. Infarcted myocardium

A highly regulated process of cardiac repair follows the necrotic loss of cardiomyocytes after MI. It begins with the activation of matrix metalloproteinases (MMPs), which degrade the existing extracellular matrix and coronary vasculature in the infarcted myocardium [13,14]. This proteolytic activity declines by the end of week 1 postMI [13,14]. Circulating leukocytes infiltrate into the infarct site soon after MI, while monocyte-derived macrophages are the major population of inflammatory cells in the infarcted myocardium (Fig. 1). The leukocytes home to the site of MI drawn by adhesion molecules and chemokines expressed by the endothelial cells of the coronary vasculature that borders on the infarct site [15,16]. Their migration into the infarct site is facilitated by MMP proteolytic activity.
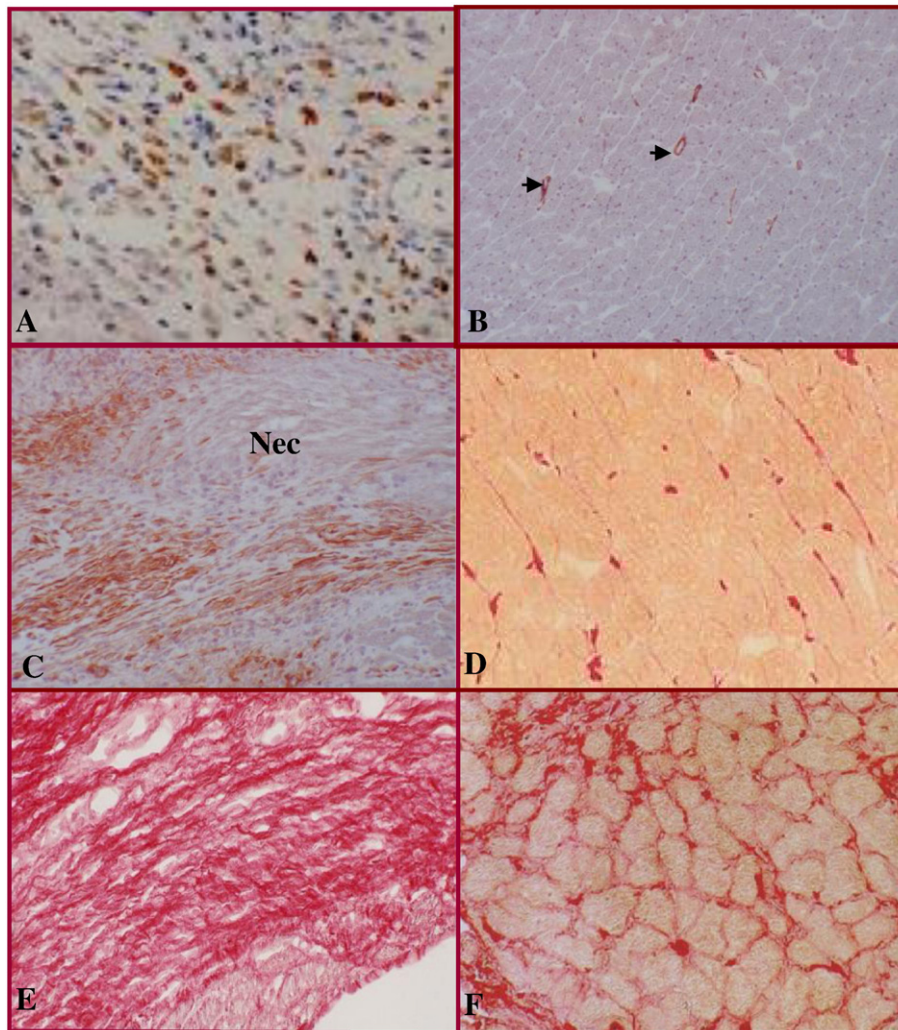
Fig. 1. Cardiac fibrosis and cells responsible for cardiac repair postMI: Following MI, abundant ED-1^{+} macrophages appear in the infarcted myocardium at week 1 (panel A, brown), while the population of neutrophils and lymphocytes is low (not shown). Interstitial α-SMA[+] myoFb are not present in the normal myocardium (panel B, arrows: blood vessels). Following MI, myoFb (brown) are accumulated in the infarcted myocardium at week 1 and located primarily around necrotic tissue (Nec) (panel C). Normal myocardium contains a small amount of collagen (red, picrosirius red staining) in the interstitial space (panel D). Following MI, scar is formed in the infarcted myocardium (panel E) and interstitial fibrosis (panel F) is developed in the noninfarcted myocardium at 4 weeks postMI.