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Angiotensin-(1-7) receptor Mas is an essential modulator of extracellular matrix protein expression in the heart

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ABSTRACT

In this study we investigated the effects of genetic deletion of the Angiotensin-(1-7) receptor Mas or the Angiotensin II receptor AT_2 on the expression of specific extracellular matrix (ECM) proteins in atria, right ventricles and atrioventricular (AV) valves of neonatal and adult mice. Quantification of collagen types I, III and VI and fibronectin was performed using immunofluorescence-labeling and confocal microscopy. Picrosirius red staining was used for the histological assessment of the overall collagen distribution pattern. ECM proteins, metalloproteinases (MMP), ERK1/2 and p38 levels were quantified by western blot analysis. Gelatin zymography was used to evaluate the activity of MMP-2 and MMP-9. We observed that the relative levels of collagen types I and III and fibronectin are significantly higher in both the right ventricle and AV valves of neonatal $Mas^{-/-}$ mouse hearts (e.g., collagen type I: 85.28 ± 6.66 vs 43.50 ± 4.41 arbitrary units in the right ventricles of $Mas^{+/+}$ mice). Conversely, the level of collagen type VI was lower in the right ventricle and AV valves of $Mas^{-/-}$ mice. Adult $Mas^{-/-}$ mouse hearts presented similar patterns as observed in neonates. No significant differences in ECM protein level were detected in atria. Likewise, no changes in ECM levels were observed in AT_2 knockout mouse hearts. Although deletion of Mas induced a significant reduction in the level of the active form of MMP-2 in neonate hearts and a reduction of both MMP-2 and MMP-9 in adult $Mas^{-/-}$ mice, no significant differences were observed in MMP enzymatic activities when compared to controls. The levels of the active, phosphorylated forms of ERK1/2 and p38 were higher in hearts of both neonatal and adult $Mas^{-/-}$ mice. These observations suggest that Mas is involved in the selective expression of specific ECM proteins within both the ventricular myocardium and AV valves. The changes in the ECM profile may alter the connective tissue framework and contribute to the decreased cardiac performance observed in $Mas^{-/-}$ mice.

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1. Introduction

The extracellular matrix (ECM) has been described as a supportive scaffold which is important in both formation and maintenance of tissues. In the heart, ECM forms an elaborate, stress-tolerant network, interconnecting myocytes to each other and myocytes to capillaries within the ventricular wall [1]. Interactions between cells and the surrounding ECM play critical roles in a number of cellular processes, including migration, proliferation, differentiation and survival. The interstitial network within the myocardium is composed predominantly of fibrillar collagen types I and III [2]. Cardiac fibrillar collagen provides structural scaffolding for cardiomyocytes and coronary vessels and imparts cardiac tissue with physical properties that include stiffness and resistance to deformation [2,3]. It is now clear that the ECM is a dynamic structure whose organization and composition are known to modulate various cellular processes. Events that alter the molecular composition of the ECM, or the structural organization of ECM components, can induce profound changes in cellular functions [4]. Excessive deposition of collagen is thought to contribute to abnormal stiffness and function of the ventricular myocardium [5]. In many cases these changes are associated with activation of humoral systems such as the renin–angiotensin system (RAS) [6].

Components of the circulating and local RAS are closely involved in the development of myocardial fibrosis in hypertensive heart

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disease and chronic heart failure. The classical effector of this system, the octapeptide Angiotensin (Ang) II, exerts its effects through specific Ang II receptor isoforms, AT_1 and AT_2. Ang II binds AT_1 receptor and stimulates synthesis and deposition of collagen in a dose-dependent manner and suppresses the activity of matrix metalloproteinase (MMP) 1, an enzyme which plays an important role in interstitial collagen degradation [7]. On the other hand, accumulating lines of evidence support the broad view that Ang II can bind to the AT_2 receptor and induce growth suppression [8]. Conversely, Ang-(1-7), a biologically active member of the RAS and an endogenous ligand for the G protein-coupled Mas receptor [9], has been suggested to act as an antiproliferative [10–14] and anti-fibrotic peptide [13,14]. Ang-(1-7) inhibits growth of cardiomyocytes through Mas-mediated events, which include ERK1/2 activities [13]. In addition, Ang-(1-7) and its analog AVE 0991 have been shown to attenuate the development of heart failure after myocardial infarction, a finding that suggests a role for this peptide in cardiac remodeling [15,16]. In keeping with these data, AVE 0991 also prevented isoproterenol-induced cardiac remodeling [17]. These effects are apparently independent of changes in blood pressure since Grobe and colleagues [18,19] have demonstrated that the anti-fibrotic and anti-hypertrophic actions of Ang-(1-7) are still observed in Ang II-infused [19] or in DOCA-salt hypertensive rats [18]. Overexpression of the main Ang-(1-7)-forming enzyme, angiotensin-converting enzyme 2 (ACE2), in a rat model of myocardial infarction protected the infarcted myocardium against pathological remodeling and cardiac systolic dysfunction [20]. The anti-fibrotic and anti-

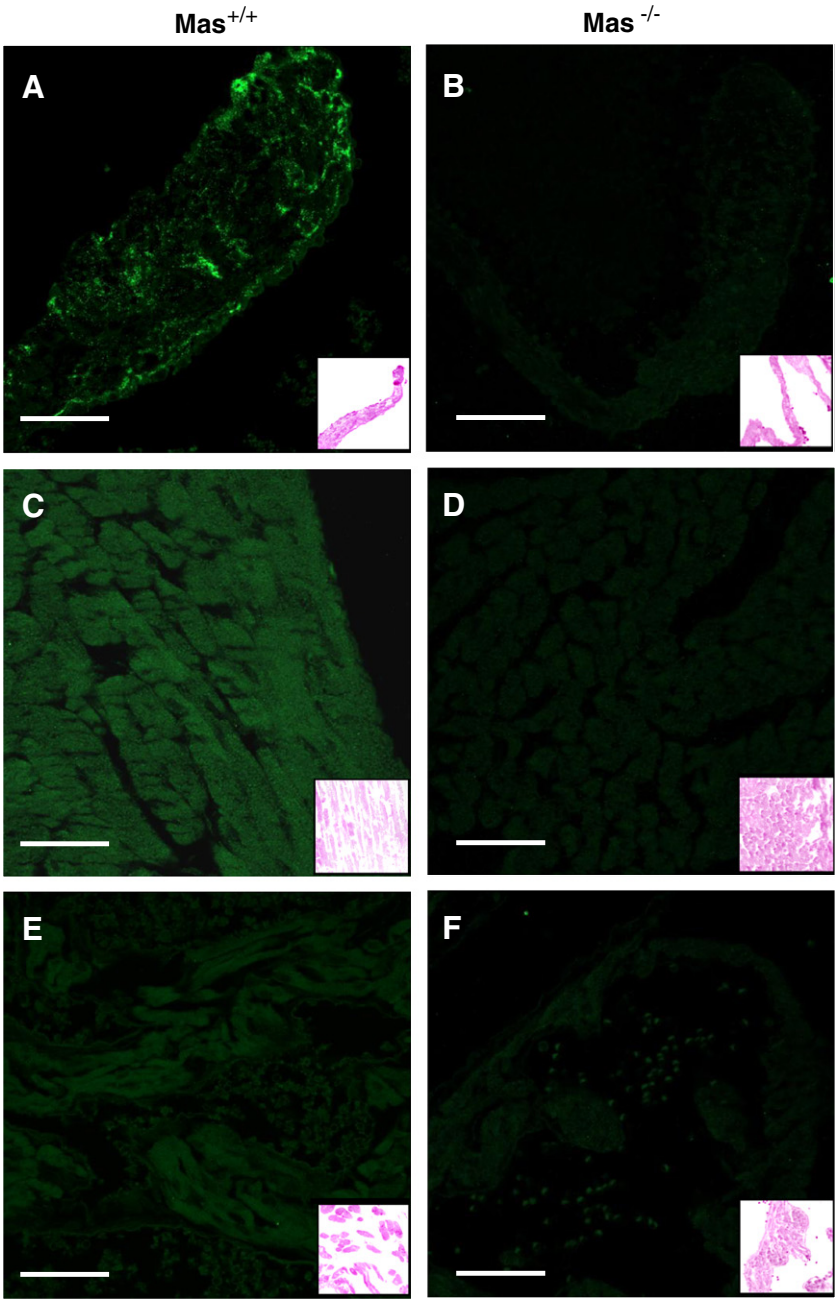

Fig. 1. Immunofluorescent localization of Mas in hearts. Mas is present in tricuspid valve (A), right ventricle (C) and atria (E) of adult $Mas^{+/+}$ mouse hearts but absent in the tricuspid valve (B), right ventricle (D) and atria (F) of adult $Mas^{-/-}$ mouse hearts. No immunostaining was detected in any of the samples when the primary antibody was omitted from the incubation procedure (not shown). Insets are low magnification views of the tissue areas analyzed. Representative figures of three different animals. Bar = 50 μm.

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