Biochemical and Biophysical Research Communications 388 (2009) 606–611

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Angiotensin II receptor blockade improves matrix metalloproteinases/tissue inhibitor of matrix metalloproteinase-1 balance and restores fibronectin expression in rat infarcted myocardium

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ARTICLE INFO

Article history:
Received 5 August 2009
Available online 18 August 2009

Keywords:
Matrix metalloproteinases
Tissue inhibitors of matrix metalloproteinases
Myocardial infarction
Myocardial remodeling
Fibronectin
Angiotensin II receptor blockade
Valsartan

ABSTRACT

Matrix metalloproteinases (MMPs) and the tissue inhibitors of MMPs (TIMPs) have been recognized to play a pivotal role in matrix remodeling following myocardial infarction (MI). The aims of the present study were to examine the expression profile of MMPs/TIMP-1 after MI and to determine whether angiotensin II receptor (ATR) blockade improves MMPs/TIMP-1 balance. Compared with sham-operated rats, *in vivo* MI-induced a significant elevation of MMP-2, MMP-3 and MMP-9 levels and a marked reduction of TIMP-1 and fibronectin (FN) expressions in infarcted left ventricular free wall (LVFW) and hypertrophic interventricular septum (IS) but not in non-infarcted right ventricle (RV). In addition, regional MI increased MMP-2, MMP-3 and MMP-9, while decreased TIMP-1 and FN in infarcted LVFW and hypertrophic IS compared with the non-infarcted RV. Compared with vehicle-treated MI rats, oral valsartan, but not PD123319, limited infarct size, normalized MMPs/TIMP-1 balance and restored FN level. The present findings might further our understanding of the regulatory mechanisms of valsartan in myocardial remodeling after MI.
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Introduction

Post-myocardial infarction remodeling plays an important role in the progression to heart failure in patients with nonfatal acute myocardial infarction (MI) and is associated with worsened survival [1]. Recently, the myocardial remodeling is viewed as both a gross structural event involving the size and shape of the left ventricle and a cellular process involving the cardiomyocytes and the extracellular matrix (ECM) [2]. The ECM of the heart, once seemed as an inert scaffold for myocytes, is now known to play a pivotal role in myocardial remodeling [3,4]. The enzyme system primarily responsible for ECM turnover is the matrix metalloproteinases (MMPs), which could be blocked by the tissue inhibitors of MMPs (TIMPs) [5,6]. An increase in MMP activity or imbalance between MMPs and TIMPs has been suggested to accelerate myocardial remodeling after MI [5,7]. This provides a new conceptual framework for future research on therapeutic interventions against myocardial remodeling aiming at MMPs/TIMPs balance [8–10].

It has been well-documented that angiotensin II (Ang II) type 1 (AT1) receptor blocker (ARB) can attenuate myocardial remodeling and preserve cardiac function in infarcted heart [11]. However, the underlying mechanism remands elusive. The stimulatory role of Ang II in the activity of MMPs has been recognized recently [12]. Therefore, it is likely that the beneficial effect of ARB on myocardial remodeling is attributed to its inhibitory property on Ang II-induced MMPs activation.

Fibronectin (FN) is a major component of ECM [13]. Break down of FN by MMPs will facilitate myocardial remodeling [14]. The present study was designed to determine whether MI is associated with an imbalance between myocardial MMPs (MMP-2, MMP-3 and MMP-9) and TIMP-1 and a change in FN level, and whether Ang II receptor blockade could normalize the MMPs/TIMP-1 balance and restore the expression level of FN in rat infarcted myocardium.

Materials and methods

Animal care

Male Wistar rats, 6–8 weeks of age were obtained from local animal center. Rats were housed under a 12 h/12 h day/night cycle, with ad libitum food and water. Experimental procedures were approved by the Local Animal Care and Use Committee.

Myocardial infarction protocol

All surgical procedures were performed using aseptic techniques. Rats were anesthetized with a mixture of ketamine and xylazine injected i.p. (50 and 10 mg/kg, respectively). Left ventricular free wall (LVFW) MI was induced by ligation of the left coronary artery as

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0006-291X/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2009.08.073

described previously [15]. Rats were allocated to sham operation in a random manner. These rats underwent the same surgical procedure as the infarct rats but the suture was not tied. Only rats that survived 24 h post-operatively were used in the following experiments.

Experiment 1

MMPs/TIMP-1 and FN profiles following MI in the rat. Sham-operated and MI rats that survived 24 h post-operatively were randomized into groups and killed on days 1, 3 or 7. In all hearts, the LVFW, interventricular septum (IS) and right ventricle (RV) were dissected and frozen at −80 °C for Western blotting and immunofluorescence.

Experiment 2

Effects of AT receptor blockade on MMPs/TIMP-1 and FN. MI rats were randomized to oral valsartan (selective AT1 receptor antagonist, 1 mg/kg/day), PD123319 (selective AT2 receptor antagonist, 30 mg/kg/day) or saline for 7 days. Sham-operated rats were received only vehicle. All rats were killed on day 7. A thin transverse slice of LVFW was removed from the midline and fixed in 10% buffered formalin and paraffin embedded. Sections were stained with Masson's trichrome for assessment of infarct size. The remaining LVFW, IS and RV were dissected and frozen at −80 °C for Western blotting and immuno fluorescence.

Western blot analysis

Protein lysates were obtained by homogenizing myocardial tissues with lysis buffer containing 1% Triton X-100, 150 mM NaCl, 1 mM EDTA, 2.5 mM sodium pyrophosphate, 1 mM

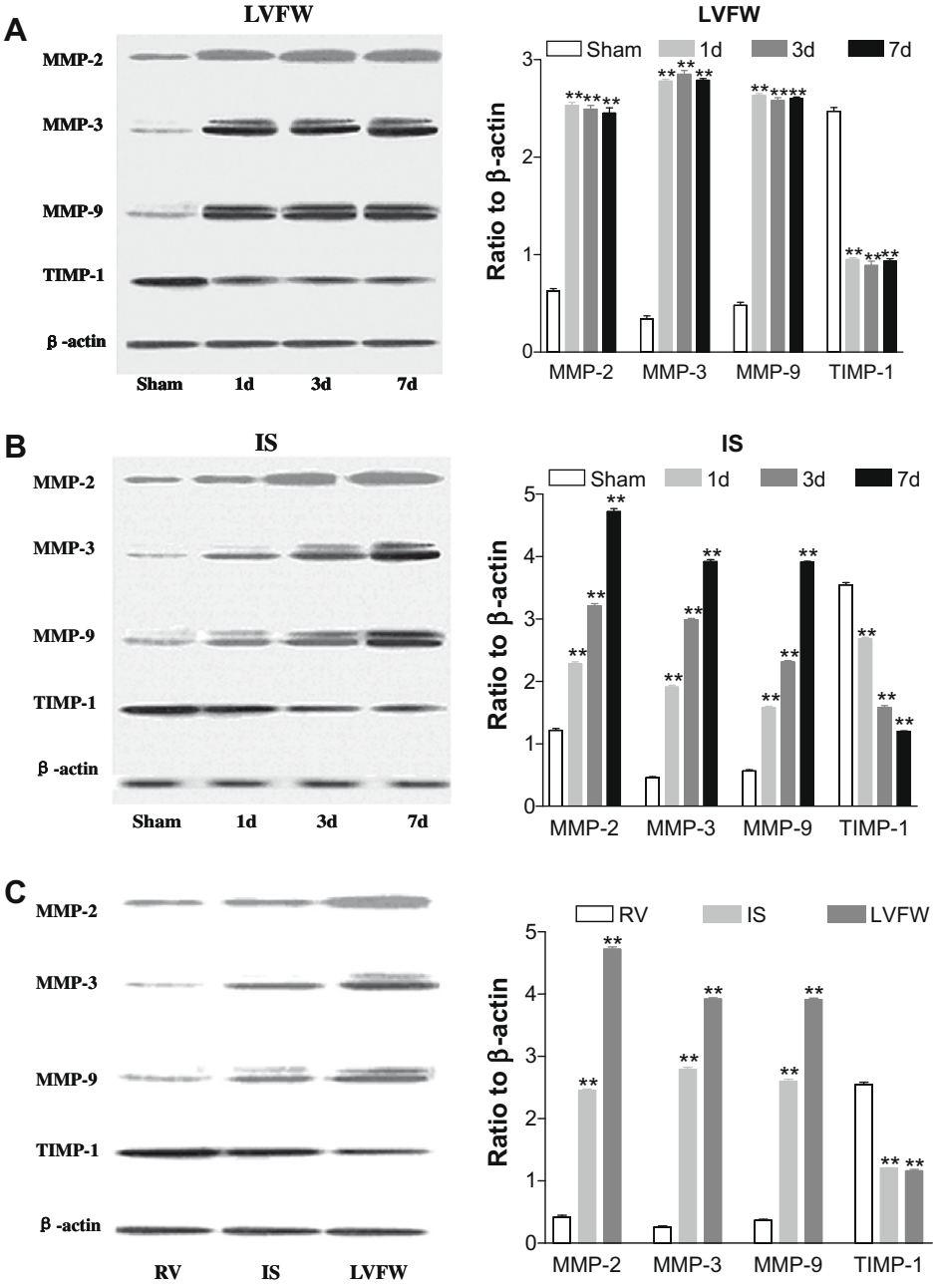

Fig. 1. MMPs/TIMP-1 protein levels in hearts from sham and MI rats. Total protein lysates were harvested from LVFW (A), IS (B) and RV (C) in sham rats and on days 1, 3 and 7 post-MI. MMP-2, MMP-3, MMP-9 and TIMP-1 were determined by Western blotting using specific antibodies. Equal protein loading was confirmed using β-actin antibody. Target proteins/β-actin is shown in the bar graph. $^{**}p < 0.01$ vs. sham ($n = 10$).

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