

## Expression of ADAM-15 in rat myocardial infarction

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### Summary

A disintegrin and metalloprotease-15 (ADAM-15) is a potential novel regulator of inflammatory response and tissue remodelling, which is thought to have the ability to attenuate the cardiac function resulting from myocardial infarction (MI). Therefore, the aim of our study was to investigate the expression of ADAM-15 in rat MI. Wistar rats were subjected to MI by ligation of the left anterior descending coronary artery. Euthanasia was performed at 1, 3, 7 and 14 days following MI. The mRNA and protein expression levels of ADAM-15 were detected respectively by reverse transcription-polymerase chain reaction (RT-PCR) and Western blot. The localization of ADAM-15 protein was observed by immunohistochemistry. Compared with sham-MI, the expression of ADAM-15 in MI increased at day 1, reached to maximum at day 3, decreased at day 7 and day 14 gradually. In addition, we also found that the localization of ADAM-15 was mainly at cardiac myocytes in the border area of MI and some macrophages in the border and infarcted areas. This study revealed a significant difference of ADAM-15 expression in rat MI and indicated that ADAM-15 maybe one of the important factors involved in inflammatory response and cardiac remodelling of rat MI.

### Keywords

A disintegrin and metalloprotease-15, cardiac remodelling, inflammatory response, myocardial infarction

Acute myocardial infarction (MI) is one of the most common emergencies in clinical practice and is also a potential cause of death events (Herlitz *et al.* 2001); therefore, continuous efforts have been made to identify novel events, which may help to elucidate its mechanisms. Myocardial infarction is a complicated process, which can be affected by age, gender, diabetes, inflammatory response, cardiac remodelling and so on (Zornoff *et al.* 2000; Maekawa *et al.* 2004; Kruk *et al.* 2008; Van den Borne *et al.* 2009). An excessive inflam-

matory response following MI could affect the healing process and cardiac remodelling (Maekawa *et al.* 2004; Kruk *et al.* 2008; Van den Borne *et al.* 2008). Moreover, both inflammatory response and cardiac remodelling can cause deterioration of heart function (Fedak *et al.* 2005; Van den Borne *et al.* 2009). However, the molecular basis of the inflammatory response and cardiac remodelling in MI is still a matter of debate. Its understanding could have an important therapeutic impact in future.

A disintegrin and metalloproteases (ADAMs) are a large family of membrane-bound glycoproteins which consist of prodomain, metalloprotease domain, disintegrin domain, cysteine-rich domain, epidermal growth factor (EGF)-like domain, transmembrane domain, and cytoplasmic domain (Kratzschmar *et al.* 1996). ADAMs have been known to play important role in physiological and pathological processes such as proteolysis, adhesion, fertilization, fusion, migration, proliferation and cleavage-secretion of inflammatory factors (Black & White 1998; Schlondorff & Blobel 1999; Ding Rocks *et al.* 2008). Furthermore, some studies have confirmed that ADAMs could underlie inflammatory response and structural remodelling by regulating cell–cell and cell–matrix interactions (McCulloch *et al.* 2000; Arndt *et al.* 2002; Fedak *et al.* 2003, 2004, 2006; Worley *et al.* 2007; Charrier-Hisamuddin *et al.* 2008). Although previous studies have demonstrated that ADAMs such as ADAM-9, 10, 12, 15, 17 and 19 are expressed in myocardium (Arndt *et al.* 2002; Fedak *et al.* 2006), there is little data in evaluating these molecules in MI.

Human ADAM-15 is the only ADAM that has the RGD motif, an Arg–Gly–Asp tripeptide sequence, which can bind to integrin and participate in structural remodelling (Howard *et al.* 1999). Some studies have demonstrated that human ADAM-15 is mainly involved in the pathological process of inflammatory response and structural remodelling in some diseases such as atherosclerosis (Herren *et al.* 1997; Al-Fakhri *et al.* 2003), retinopathy of prematurity (Horiuchi *et al.* 2003), rheumatoid arthritis (Böhm *et al.* 2005) and inflammatory bowel disease (Mosnier *et al.* 2006). Furthermore, Arndt *et al.* and Fedak *et al.*, respectively, have confirmed that the increased ADAM-15 expression is one of the molecular mechanisms, which may contribute to the pathological process of atrial fibrillation (AF) and dilated cardiomyopathy (DCM) (Arndt *et al.* 2002; Fedak *et al.* 2006). However, the role of ADAM-15 in MI is not well understood.

In this study, we investigated the expression of ADAM-15 in rat MI and elucidated its possible mechanisms in the pathological process of MI. It will provide a novel insight into the mechanisms, which influence the inflammatory response and cardiac remodelling following MI.

## Materials and methods

### Animals

We used female Wistar rats, weighing 200–250 g, from Laboratory Animal Facility of Harbin Medical University. The animals were kept in cages, and fed on standard com-

mercial feed and water *ad libitum*, with controlled light in 12 h cycles, temperature (approximately 24 °C) and humidity. The experimental protocols were approved by the Animal Experiment Ethics Committee of Harbin Medical University.

### Myocardial infarction

Myocardial infarction was produced as per the method previously described (Ben-Dor *et al.* 2007; Wang *et al.* 2007). The rats were anaesthetized with a single intraperitoneal injection of 10% chloral hydrate in a dose of 3 ml/kg. Intubation was performed and the rats were ventilated with room air using a rodent mechanical ventilator (Harvard Apparatus, 55–7058). The chest was opened by left thoracotomy through the fourth intercostal space to expose the heart. The pericardium was opened and the proximal left anterior descending coronary artery was ligated with a silk 6-0 suture near its origin between the pulmonary outflow tract and the edge of the left atrium, which ensured permanent coronary occlusion. Regional MI was confirmed by observing a rapid change from reddish to a whitish-dark color on the anterior surface of the left ventricle (LV). The sham-operated animals underwent the same procedure, but without the ligation of the coronary artery.

### Reverse transcription-polymerase chain reaction (RT-PCR)

Rats were anaesthetized with 10% chloral hydrate at 1, 3, 7, and 14 days following surgically induced MI. The heart was stopped at diastole by injection of 10% KCl and removed. The LV free wall was dissected (Maekawa *et al.* 2004; Tang *et al.* 2006), washed with cold phosphate-buffered saline (PBS), quickly frozen in liquid nitrogen, and stored at –80 °C until use. Total RNA was isolated according to the direction of Trizol (Invitrogen Corp., Carlsbad, CA, USA), and dissolved in Rnase-free water (1‰ diethylpyrrocarbonate). The reverse transcription proceeded as per the direction (Promega Corp., Madison, WI, USA). The primer sequences of ADAM-15 for PCR were: 5′-ATGGACCACTCGACAAGCA-3′ and 5′-GCAGAACTCAGGCAAATCG-3′. The PCR reaction was inactivated for 5 min at 94 °C, 30 s of denaturation at 94 °C, 30 s of annealing at 50 °C, and 1 min of extension at 72 °C for 30 cycles, followed by an incubation at 72 °C for 5 min. PCR products were analysed by running on a 2.0% agarose gel and using the TANON GIS2010 Analysis (TANON GIS 2010 Analysis, Shanghai, China) software.

### Western blot

Total proteins were extracted as described previously (Fedak *et al.* 2003). Total tissue homogenates were harvested by lysing in RIPA: 1 × PBS, 1% NP40, 0.1% SDS, 5 mM EDTA, 0.5% sodium deoxycholate, 1 mM sodium orthovanadate and 1/100 phenylmethanesulfonyl fluoride (PMSF). 50 µg of the total protein, which was assayed by Bradford Protein Assay kit (Beyotime Corp., Haimen, JS, China), was fractionated by 8% SDS-PAGE and electrotransferred onto a polyvinylidene difluoride membrane (PVDF, Millipore Corp., Billerica, MA, USA). The membranes were blocked with 5% non-fat dry milk in 20 mM Tris-HCl (pH 8.8), 500 mM NaCl, and 0.05% Tween 20 (TBST, TBS containing 0.05% Tween 20) for 1 h at room temperature, then incubated with the rabbit polyclonal antibody for ADAM-15 (1:400, Santa Cruz Biotech, Santa Cruz, CA, USA) overnight at 4 °C. After being washed with TBST, the membranes were incubated with a goat anti-rabbit IgG (1:1000, Solarbio, Beijing, China) for 1 h at room temperature. Detection was done by reaction with freshly prepared diaminobenzidine (DAB) (Santa Cruz Biotech) substrate solution. Blots were scanned and analysed using the TANON GIS2010 Analysis software.

### Histology

Rats were anaesthetized with 10% chloral hydrate at 1, 3, 7, and 14 days following MI. The heart functioning was stopped at diastole by injection of 10% KC1. Hearts from all animals were excised and soaked with 10% formalin for at least 24 h. Measurements were performed on midventricular sections about 5–6 mm from the apex, on the assumption that the left midventricular slice showed a close linear relation with the sum of the area measurements from all heart sections (Zornoff *et al.* 2000). The sections were embedded in paraffin, sectioned into 5 µm and stained with haematoxylin and eosin (H&E), or for immunohistochemical study.

### Immunohistochemistry

Sections were deparaffinized and rehydrated in a graded alcohol series, and antigen retrieval was performed in 10 mM citrate buffer pH 6.0 at 100 °C for 15 min. Incubation with rabbit polyclonal antibody for ADAM-15 (1:100, Santa Cruz Biotech) was performed in a moist chamber at 37 °C for 1 h. Polyvalent anti-rabbit IgG (Santa Cruz Biotech) was incubated at room temperature for 30 min. Followed by another 30 min of incubation with horseradish peroxidase (Santa Cruz Biotech) at room temperature.

Immunostaining was visualized by DAB solution. Washings between steps were performed using PBS (Arndt *et al.* 2002; Campos *et al.* 2008). The sham-MI group was euthanized 14 days after surgery. We have confirmed that sham operations have no time effect on any parameter measured.

### Histological evaluation

Stained sections were photographed with a JVC digital camera (TK-C 1381, Nikon, Sendai, Japan) mounted on an Olympus microscope (BH-2, Olympus, Tokyo, Japan). Multiple digital images were taken and staining was analysed using MOTIC IMAGE software (MOTIC IMAGES 2000, Xiamen, FJ, China). The number of ADAM-15-positive cells was counted by the total positive stained area of the myocardium to the total area in five standard randomly selected different fields.

### Statistical analysis

All statistical analyses were performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Statistical differences between means were determined by analysis of variance (ANOVA) followed by least significant difference (LSD) tests. Values are expressed as mean ± SEM, with  $P < 0.05$  considered to be significant.

## Results

### ADAM-15 mRNA expression

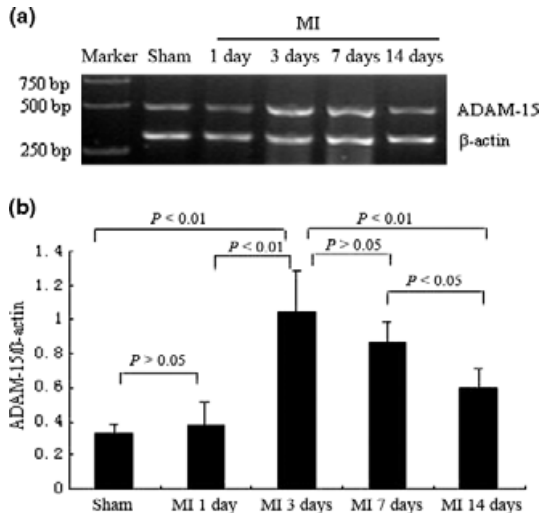
ADAM-15 was observed at mRNA levels. In this study, we showed that ADAM-15 mRNA expression was not at the same level in rat MI at 1, 3, 7 and 14 days. As shown in Figure 1, compared with sham-MI ( $0.322 \pm 0.061$ ), the mRNA expression of ADAM-15 increased at day 1 ( $0.377 \pm 0.139$ ;  $P > 0.05$  vs. sham-MI), reached statistical significance at day 3 ( $1.048 \pm 0.235$ ;  $P < 0.01$  vs. sham-MI,  $P < 0.01$  vs. day 1), decreased at day 7 ( $0.863 \pm 0.126$ ;  $P \leq 0.01$  vs. sham-MI,  $P \leq 0.01$  vs. day 1,  $P > 0.05$  vs. day 3) and reduced gradually at day 14 ( $0.6 \pm 0.108$ ;  $P \leq 0.05$  vs. sham-MI,  $P \leq 0.05$  vs. day 1,  $P < 0.01$  vs. day 3,  $P < 0.05$  vs. day 7). The time-course of ADAM-15 mRNA expression was expressed as the ratio of ADAM-15 to  $\beta$ -actin.

### ADAM-15 protein expression

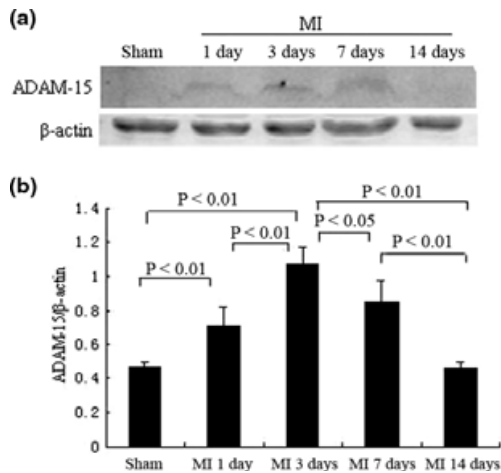
The protein expression of ADAM-15 was detected by Western blot. As shown in Figure 2, ADAM-15 protein

was expressed in a pattern, which was approximately correlated with the mRNA pattern. Compared with sham-MI ( $0.471 \pm 0.029$ ), the protein expression of ADAM-15 increased immediately at day 1 ( $0.71 \pm 0.108$ ;  $P < 0.01$  vs.

sham-MI), reached to maximum at day 3 ( $1.071 \pm 0.102$ ;  $P < 0.01$  vs. sham-MI,  $P < 0.01$  vs. day 1), fell thereafter at day 7 ( $0.852 \pm 0.127$ ;  $P \leq 0.01$  vs. sham-MI,  $P \geq 0.05$  vs. day 1,  $P < 0.05$  vs. day 3), and reduced by degrees at day 14 ( $0.46 \pm 0.041$ ;  $P \geq 0.05$  vs. sham-MI,  $P \leq 0.01$  vs. day 1,  $P < 0.01$  vs. day 3,  $P < 0.01$  vs. day 7). The time-course of ADAM-15 protein expression was expressed as the ratio of ADAM-15 to  $\beta$ -actin.



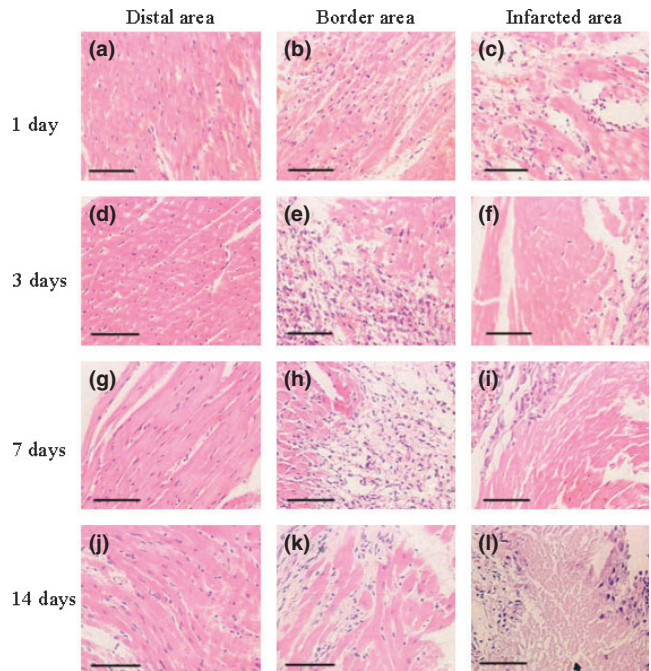
**Figure 1** The mRNA expression of A disintegrin and metalloprotease-15 (ADAM-15) in rat myocardial infarction (MI). (a) reverse transcription-polymerase chain reaction (RT-PCR) analysis of ADAM-15 mRNA expression; and (b) The relative abundance of ADAM-15 by RT-PCR analysis is shown in the graph as percentage (mean ± SEM) from different time-course groups ( $n = 7$ ).



**Figure 2** The protein expression of A disintegrin and metalloprotease-15 (ADAM-15) in rat myocardial infarction (MI). (a) Representative examples of ADAM-15 immunoblots are depicted; and (b) Bar graph showing relative abundance of ADAM-15 was by Western blot analysis in a time-course manner ( $n = 7$ ).

### Histology

The H&E picture of sham-MI was not shown because its character was similar to that of the distal area following MI at day 1 (Figure 3a). Furthermore, there were no obvious changes in the distal area at day 1, 3, 7 and 14 following MI (Figure 3a, d, g, j). There were few macrophages in the border area at day 1 (Figure 3b), and the infarcted area was largely occupied by coagulative necrosis and haemorrhage (Figure 3c). There were intramural haemorrhage with widespread macrophages, neutrophils and fibroblast infiltration in the border area (Figure 3e), and the coagulative necrosis was aggravated in the infarcted area at day 3 (Figure 3f). Compared with day 3, less inflammatory cells infiltration and more fibroblast could be seen in the border area at day 7 (Figure 3h),

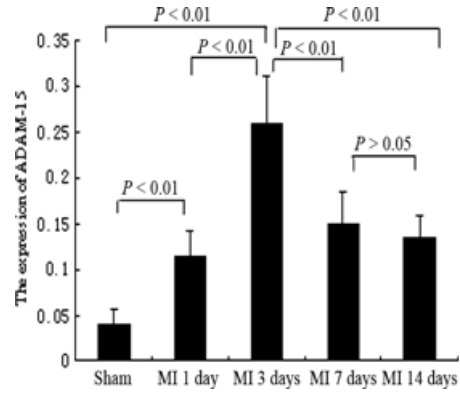


**Figure 3** Haematoxylin and eosin (H&E) staining of rat myocardial infarction (MI). Histological features in distal, border and infarcted areas at 1, 3, 7 and 14 days of rat MI. (Bar = 50  $\mu$ m).

while the myocardium was completely necrotic with fibroblasts in the infarcted area (Figure 3i). At day 14, it was characterized by fibrosis with interstitial collagen fibres, and a little infiltration of inflammatory cells in the border area (Figure 3k). There were multiple foci of myolysis and fibrosis in the infarcted area (Figure 3l).

**Immunohistochemistry**

As shown in Figure 4, ADAM-15 was mainly expressed at cardiac myocytes (arrow) in the border area (Figure 4b, e, h, k) and some macrophages (thick-arrow) both in the border area (Figure 4e) and infarcted area (Figure 4f, i). In distal (Figure 4a, d, g, j) and infarcted areas (Figure 4c, f, i, l), the stained sections were weakly to moderately labelled. In addition, the time-course of ADAM-15 expression by the immunohistochemical staining in the border area was noted to correspond with those of RT-PCR and Western blot. Compared with sham-MI ( $0.039 \pm 0.016$ ), ADAM-15 expression increased at day 1 ( $0.116 \pm 0.026$ ;  $P < 0.01$  vs. sham-MI), reached maximum at day 3 ( $0.26 \pm 0.052$ ;  $P < 0.01$  vs.



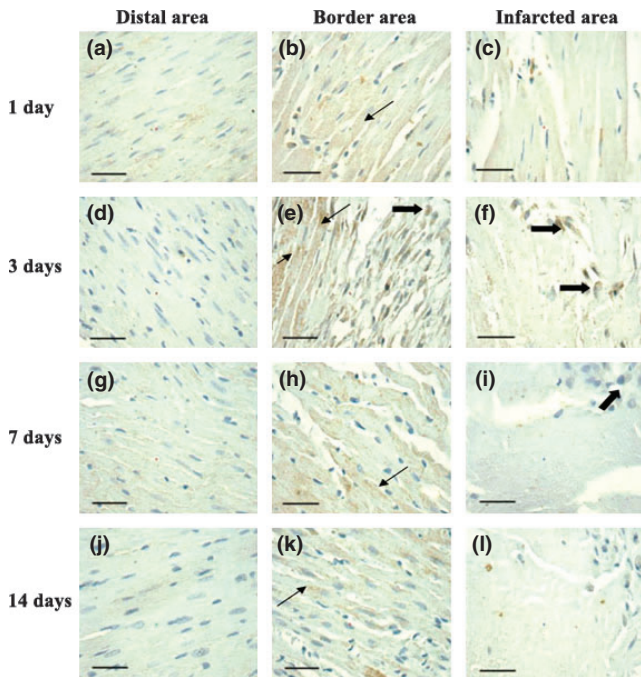
**Figure 5** Semi-quantitative analysis of A disintegrin and metalloprotease-15 (ADAM-15) positive staining in border areas of rat myocardial infarction (MI) was in the graph as relative percentage (mean  $\pm$  SEM). Similar results were obtained from three independent experiments.

sham-MI,  $P < 0.01$  vs. day 1), and declined at day 7 ( $0.15 \pm 0.035$ ;  $P \leq 0.01$  vs. sham-MI,  $P \geq 0.05$  vs. day 1,  $P < 0.01$  vs. day 3), then fell again at day 14 ( $0.136 \pm 0.023$ ;  $P \leq 0.01$  vs. sham-MI,  $P \geq 0.05$  vs. day 1,  $P < 0.01$  vs. day 3,  $P > 0.05$  vs. day 7) (Figure 5).

**Discussion**

Inflammatory response and cardiac remodelling influence the pathological process of MI. They are major factors, which affect the progression of MI (Maekawa *et al.* 2004; Kruk *et al.* 2008). For defining new therapeutic targets that control the progression, novel biomolecules and mechanisms must be discovered (Fedak *et al.* 2006). This study indicated, for the first time, that ADAM-15 was not conserved in rat MI. Our results showed that: (i) ADAM-15 increased at day 1, reached to maximum level at day 3, then gradually decreased at day 7 and day 14 following MI; (ii) The localization of ADAM-15 was mainly at cardiac myocytes in the border area and some macrophages in the border and infarcted areas. Therefore, we consider that the time-course of ADAM-15 expression was similar to those of some inflammatory cells and remodelling gene or protein expressions in MI, indicating that it may be essential for inflammatory response and cardiac remodelling in MI.

Following MI, the heart undergoes a dynamic healing process, characterized by infiltration of inflammatory cells, activation of matrix metalloproteases (MMPs), degradation of extracellular matrix (ECM), and deposition of collagen, which are associated with LV dysfunction (Yang *et al.* 2002; Jugdutt 2003; Wang *et al.* 2007). Factors which impair the process of MI may deteriorate heart function. Inflammatory



**Figure 4** The localization of A disintegrin and metalloprotease-15 (ADAM-15) in rat myocardial infarction (MI) detected by immunohistochemistry. The representative localization of ADAM-15 (brown stained) were observed under light microscopy. ADAM-15 was mainly expressed at cardiac myocytes (arrow) in the border area and some macrophages (thick-arrow) both in the border area and infarcted area. (Bar = 40  $\mu$ m).

response is the necessary first step in wound healing, nevertheless exaggerated inflammatory cell infiltration may be detrimental (Gao *et al.* 2005). ADAMs are a unique class of MMPs (Spinale 2002). They are involved in inflammatory response and structural remodelling given their documented ability to activate cytokines and inflammatory factors (Fedak *et al.* 2003, 2004). Previous studies have indicated that ADAM-15 participated in some inflammatory disease or inflammatory response (Herren *et al.* 1997; Böhm *et al.* 1999, 2005; Al-Fakhri *et al.* 2003; Horiuchi *et al.* 2003; Mosnier *et al.* 2006). In this study, we observed that ADAM-15 increased at day 1, reached to maximum level at day 3, gradually decreased at day 7 and day 14 following MI (Figures 1, 2, 4, 5). The tendency was identical with that of the inflammatory response in MI, which has been confirmed in previous study (Yang *et al.* 2002). It has been shown that inflammatory cells such as macrophages are major source of early inflammatory response (Gao *et al.* 2005). In this study, we also found from the H&E staining that some macrophages infiltrated in early inflammatory response following MI. Moreover, the result of immunohistochemistry showed that ADAM-15 was expressed in some macrophages in the border and infarcted areas. Taken together, these findings implicated that ADAM-15 may be one of the genes involved in the inflammatory response of MI.

ADAMs can profoundly affect tissue architectures just like MMPs (Spinale 2002; Fedak *et al.* 2006), which may provide a novel mechanism of cardiac remodelling. ADAM-15 can cleave type IV collagen and gelatin, just like MMP-2 and MMP-9 (Arndt *et al.* 2002; Martin *et al.* 2002; Fedak *et al.* 2006). Previous studies showed that MMP-2 and MMP-9 were mainly expressed at cardiac myocytes in MI border area (Wang *et al.* 2007; Van den Borne *et al.* 2009). Our results showed that ADAM-15 was mainly expressed at cardiac myocytes in MI border area. Furthermore, we confirmed that the time-course of ADAM-15 expression following MI was similar to those of MMP-2 and MMP-9 expression, which has been studied before (Wang *et al.* 2007). Besides that, ADAM-15 can bind to integrin  $\alpha v \beta 3$  and  $\alpha 5 \beta 1$  in an RGD-dependent manner (Zhang *et al.* 1998; Nath *et al.* 1999; Elsherif *et al.* 2008), and to  $\alpha 9 \beta 1$  in an RGD-independent manner (Eto *et al.* 2000, 2002). Integrin  $\beta 1$  is an important integrin in the heart, which is involved in cardiac fibrosis, heart failure (Shai *et al.* 2002; Elsherif *et al.* 2008) and ischaemic cardiomyopathy (ICM) (Pfister *et al.* 2007). In heart, ADAM-15 maybe the shedding enzyme of integrin  $\beta 1$  (Arndt *et al.* 2002; Fedak *et al.* 2006). Therefore, we presumed that the function of ADAM-15 involving in cardiac remodelling may be like MMPs, or through integrin  $\beta 1$  and other integrins in RGD-dependent or independent

manner. However, the mechanisms need to be further studied.

Every domain of ADAM-15 has its own function: the catalytic activation is the metalloprotease domain; the disintegrin and cysteine-rich domain may mediate cell-cell or cell-matrix interactions, and the cytoplasmic domain may have a role in signalling or intracellular transportation (Schlondorff & Blobel 1999; Martin *et al.* 2002; Horiuchi *et al.* 2003; Elsherif *et al.* 2008). ADAM-15 has many functions such as: proliferation, adhesion and angiogenesis (McCulloch *et al.* 2000; Poghosyan *et al.* 2002) except inflammatory response and cardiac remodelling. Therefore, those functions of ADAM-15 may also have some important roles in the MI pathological process, which need to be further studied.

## Conclusion

This study revealed a significant difference of ADAM-15 expression in rat MI and indicated that ADAM-15 may be one of the important factors involved in inflammatory response and cardiac remodelling. Therefore, it is necessary to further elucidate the underlying mechanisms of ADAM-15 in rat MI; eventually, it would be more helpful in clinical practice of human MI in the future.

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