

Editorial

Matrix Metalloproteinase-28: A Novel Regulator of Post-Myocardial Infarction Cardiac Remodeling

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Following myocardial infarction (MI), cardiomyocyte death in the area downstream of the arterial occlusion initiates an acute inflammatory response. Neutrophils are the first responder leukocytes recruited into the ischemic area [1]. In addition to directly regulating acute inflammation, neutrophils pave the signaling way for subsequent macrophage infiltration by releasing a wide range of cytokines, chemokines, and granule components [2,3]. Troidl and colleagues have shown that macrophages are differentially activated during different phases of MI remodeling [4]. During the acute inflammatory phase, classical M1 macrophages predominate and facilitate inflammation and extracellular matrix (ECM) degradation. Afterwards, macrophages shift to an alternative anti-inflammatory M2 subtype, which activates fibroblasts, and promotes ECM synthesis and scar formation [4]. The timely shift and dynamic balance between M1 and M2 macrophages promote the resolution of inflammation and stable scar formation. During the wound healing phase, activated fibroblasts (myofibroblasts) secrete ECM proteins to form and stabilize the scar [5,6]. Appropriate myofibroblast function favors cardiac repair and well-managed scar formation. Insufficient myofibroblast density results in ventricular dilatation, wall thinning, and cardiac rupture, while excess myofibroblast accumulation contributes to myocardial stiffness (fibrosis) and dysfunction [7]. The underlying mechanisms regarding the sequential presence, activation, and interaction of neutrophils, macrophages, and myofibroblasts in the MI setting remain to be fully elucidated.

Matrix metalloproteinase-28, first cloned from cDNA libraries of human testis, keratinocytes, and lung in 2001, is the newest identified member of the MMP family [8,9]. MMP-28 possesses all typical MMP domains [10]. Due to the presence of a functional furin activation sequence located in the C-terminal end of the pro-domain, MMP-28 can be intracellularly activated by cleavage of its pro-domain with a furin-like proprotein convertase [11]. This feature is uncommon for soluble MMPs, which are normally

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released into extracellular space as a pro-form. As a proteinase, MMP-28 has been shown to degrade casein, Nogo-A (a myelin component), and neural cell adhesion molecule-1 [12]. Unlike other MMPs, MMP-28 can be expressed by parenchymal cells (e.g. cardiomyocytes) and inflammatory cells (neutrophils and macrophages) [13]. MMP-28 is highly expressed in many normal adult tissues and organs, including the heart. However, MMP-28 null mice show no abnormal cardiac phenotypes during development and adult mice have no overt cardiac phenotype in the absence of a stress [14].

Generally, MMPs levels increase post-MI and the deletion of multiple MMP genes attenuates cardiac remodeling, dilation, and/or dysfunction [15-17]. In contrast, we have recently demonstrated that MMP-28 expression decreases post-MI and MMP-28 deletion exacerbates cardiac dysfunction and rupture after myocardial infarction by regulating inflammatory and fibrotic responses [13]. This challenges our preconceived concept that all MMPs are detrimental and should be inhibited after MI. Therefore, care should be taken when using broad-spectrum MMP inhibitors in clinical trials.

Despite having no effect on macrophage infiltration, MMP-28 deletion reduces the expression of M2 macrophage markers in the infarct area at day 7 post-MI, indicating impaired M2 macrophage polarization [13]. Because we measured the M1 and M2 markers in the left ventricles, not in isolated macrophages, we could not exclude the contribution of other cells (e.g. lymphocytes and endothelial cells). Experiments that isolate macrophages from post-MI hearts over a temporal period and evaluate their phenotypes and functions will confirm the findings above. In vitro, MMP-28 null peritoneal macrophages display reduced response to pro-M2 stimulus (IL-4), suggesting direct involvement of MMP-28 in M2 macrophage activation. Using gene array, we also identified that a specific profile of inflammatory mediators are distinctly modulated by MMP-28 deletion [13]. However, which of these mediators is directly regulated by MMP-

28as substrates and which of these is an indirect consequence of MMP-28 deficiency need to be determined [18]. In view of the significance of neutrophils in MI remodeling, studies that investigate the effect of MMP-28 on early inflammation (days 1, 3, and 5 post-MI) and neutrophils are warranted [1].

Post-MI, transforming growth factor (TGF)- β 1 level increases to induce myofibroblast transdifferentiation and promote ECM secretion [19,20]. TGF- β 1 infusion has been shown to attenuate MI-induced cardiac rupture, indicating a pivotal role in cardiac repair [21]. The fact that MMP-28 promotes TGF- β 1-induced epithelial to mesenchymal transition in lung carcinoma cells associates MMP-28 with TGF- β 1 signaling pathway [22]. Our findings show that MMP-28 null mice have lower TGF- β 1 gene levels at day 7 post-MI, which could explain the reduced ECM content and increased rupture when MMP-28 is absent [13]. Consistently, myofibroblast numbers are also lower in MMP-28 null mice. In vitro experiments showed that MMP-28 deletion impaired fibronectin 1 expression in fibroblasts after TGF- β 1 stimulation, indicating an altered myofibroblast phenotype in the absence of MMP-28 [13]. Based on the data above, it would be interesting to determine if one could rescue the rupture phenotype in MMP-28 null mice by TGF- β 1 infusion.

In summary, MMP-28 regulates macrophage and fibroblast phenotypes, and may alter neutrophil functions, in the MI setting. MMP-28 overexpression or activation, rather than inhibition, may protect from MI-triggered adverse remodeling. On several levels, a better understanding of MMP-28 roles may provide novel intervention targets for MI patients.

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