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

Yonggang Ma1* and Merry L. Lindsey1,2

1San Antonio Cardiovascular Proteomics Center and Jackson Center for Heart Research and Medicine Services, G.V. (Sonny) Montgomery Veterans Affairs Medical Center, USA
2Research and Medicine Services, G.V. (Sonny) Montgomery Veterans Affairs Medical Center, USA

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 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 stress [14].

Generally, MMPs levels increase post-MI and the deletion of multiple MMP genes attenuates cardiac remodeling, dilatation, 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 ventricle, 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-

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

We acknowledge support from NIH/NHLBI HHSN 26820100036C (N01-HV-00244) for the San Antonio Cardiovascular Proteomics Center, R01 HL075360, and PPG HL051971, and from the Biomedical Laboratory Research and Development Service of the Veterans Affairs Office of Research and Development Award 5I01BX000505 to MLL.

REFERENCES


