Regulation of matrix metalloproteinases is at the heart of myocardial remodeling

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Regulation of matrix metalloproteinases is at the heart of myocardial remodeling contributing to the pathogenesis of cardiovascular disease, with the development of ventricular dilation being a fundamental component of this structural remodeling (16). A recognized prerequisite in order for dilation to occur is the degradation of the myocardial extracellular matrix (ECM) (2–4, 7, 9, 11, 15). The presence of an abundant latent collagenase system closely associated with the interstitial collagen matrix in the heart was first recognized by Montfort and Pérez-Tamayo in 1975 (10), and since that time over 20 known endogenous matrix metalloproteinases (MMPs) have been identified, each having specificity for one or more ECM components (15). Although numerous studies have established that MMP activation mediates myocardial remodeling in cardiac pathologies, the endogenous control systems that regulate the induction of MMP expression and activation are still relatively poorly understood.

Notwithstanding, remarkable progress has been made with respect to elucidating MMP biology and how it relates to myocardial matrix remodeling. In this vein, Zavadzkas et al. (19) reports that persistent myocardial extracellular MMP inducer (EMMPRIN) expression caused adverse myocardial remodeling consisting of left ventricular (LV) dilation, hypertrophy, and fibrosis associated with increased levels of membrane type-1 (MT1)-MMP and active MMP-2 in aging mice. Thus this study is the first to establish mechanistic evidence that increased EMMPRIN levels can cause LV remodeling, resulting in heart failure. Accordingly, this study should inspire focused efforts seeking to elucidate the signal transduction pathways responsible for the induction of EMMPRIN in cardiovascular disease, as well as the mechanisms by which EMMPRIN induces MMP expression.

Functional Role of EMMPRIN in the Heart

EMMPRIN (also known as Basigen, collagenase stimulatory factor, and CD147) is a novel 58-kDa transmembrane glycoprotein of the Ig superfamily (1). EMMPRIN has been most extensively investigated with respect to tumor invasion and metastasis, having been implicated in those studies as a factor contributing to the induction of MMP expression (1, 6, 17). However, significantly increased myocardial EMMPRIN expression has also previously been reported in patients with end-stage cardiomyopathy (8, 14). Some studies have identified cardiac myocytes as the cellular source of this increase in EMMPRIN (13, 14). In the vasculature, EMMPRIN was co-localized with macrophage infiltrates in atherosclerotic intima and vascular smooth muscle cells from human carotid endarterectomy specimens (18). This study found that stimulation with the proinflammatory cytokines interleukin-1β and tumor necrosis factor-α increased the expression of both EMMPRIN and MMPs in bone marrow-derived human monocyte cultures (18). Thus the cytokine-mediated regulation of EMMPRIN expression may prove to be the underlying mechanism responsible for the induction of MMPs and ECM remodeling in the heart (5, 8). Further evidence that EMMPRIN is induced in myocardial inflammatory cells is derived from the association of EMMPRIN upregulation with the increased expression of MT1-MMP on monocytes isolated from patients following an acute myocardial infarction (12). Therefore, in the context of pathological myocardial remodeling, EMMPRIN upregulation in multiple cell types appears to be critical to the transcriptional regulation of MMPs.

Selective Induction of Specific MMPs by EMMPRIN

Based upon the findings reported by Zavadzkas et al. (19), together with these past observations, an important aspect of EMMPRIN biology that requires further clarification is the supposition that EMMPRIN induces a limited portfolio of specific MMPs within the myocardium. If this should prove to be true, it would allow the implementation of targeted drug interventions aimed at either the specific MMPs mediating adverse myocardial remodeling or the upstream signaling pathways responsible for their induction. This would represent an important advance beyond the currently available broad spectrum MMP inhibitory compounds that have thus far been studied. Hence several important issues deserving of future research emphasis remain with respect to the regulation of MMPs in myocardial remodeling. These include the targeted modulation of the induction of MMP expression by EMMPRIN and other comparable pathways, delineation of the individual role of specific MMP isoforms in mediating myocardial remodeling, and identification of endogenous mechanisms regulating the activation of MMPs.

In summary, Zavadzkas et al. (19) found that the selective induction of specific MMPs concomitant with the chronic myocardial overexpression of EMMPRIN was sufficient to produce adverse LV remodeling and heart failure. Accordingly, identifying the signal transduction pathways mediating EMMPRIN expression in cardiovascular disease, as well as novel approaches by which to target EMMPRIN-induced MMP expression, constitute important avenues of further research.

REFERENCES


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