Chronic β-adrenergic receptor (β-AR) overstimulation, a hallmark of heart failure, is associated with increased cardiac expression of matrix metalloproteinases (MMPs). MMP-1 has been shown to cleave and activate the protease-activated receptor 1 (PAR1) in noncardiac cells. In the present study, we hypothesized that β-AR stimulation would result in MMP-dependent PAR1 transactivation in cardiac cells. β-AR stimulation of neonatal rat ventricular myocytes (NRVMs) or cardiac fibroblasts with isoproterenol transduced with an alkaline phosphatase-tagged PAR1 elicited a significant increase in alkaline phosphatase-PAR1 cleavage. This isoproterenol-dependent cleavage was significantly reduced by the broad-spectrum MMP inhibitor GM6001. Importantly, specific MMP-13 inhibitors also decreased alkaline phosphatase-PAR1 cleavage in isoproterenol-stimulated NRVMs, as well as in NRVMs stimulated with conditioned medium from isoproterenol-stimulated cardiac fibroblasts. Moreover, we found that recombinant MMP-13 stimulation cleaved alkaline phosphatase-PAR1 in NRVMs at DPRS(42)?(43)FLLRN. This also led to the activation of the ERK1/2 pathway through G?q in NRVMs and via the G?q/ErbB receptor pathways in cardiac fibroblasts. MMP-13 elicited similar levels of ERK1/2 activation but lower levels of generation of inositol phosphates in comparison to
thrombin. Finally, we demonstrated that either PAR1 genetic ablation or pharmacological inhibition of MMP-13 prevented isoproterenol-dependent cardiac dysfunction in mice. In this study, we demonstrate that β-AR stimulation leads to MMP-13 transactivation of PAR1 in both cardiac fibroblasts and cardiomyocytes and that this likely contributes to pathological activation of Gq and ErbB receptor-dependent pathways in the heart. We propose that this mechanism may underlie the development of β-AR overstimulation-dependent cardiac dysfunction.