INTERLEUKIN-18 IS A POTENT INDUCER OF EMMPRIN EXPRESSION BOTH IN VITRO AND IN VIVO, AND THEIR CROSSTALK INDUCES MMP9 EXPRESSION VIA PI3K-AKT-IKK-NF-κB SIGNALING.


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We have shown that interleukin (IL)-18 plays a role in myocardial injury and remodeling via induction of MMPs and other proinflammatory cytokines. Since the matricellular protein EMMPRIN is a potent inducer of MMPs, we investigated if IL-18 and EMMPRIN expression is cross-regulated, and whether IL-18-induced MMP9 expression is EMMPRIN-dependent. IL-18 potently induced EMMPRIN expression and secretion in adult mouse cardiomyocytes (ACM; inhibited by IL-18 neutralizing antibodies and IL-18BP-Fc). IL-18 stimulated both Sp1 and NF-κB activations in ACM. In neonatal mouse cardiomyocytes (NMCM), IL-18 stimulated EMMPRIN promoter activity was inhibited by mithramycin and over-expressed mutant Sp1, but not by dominant negative (dn) p65, dnIκB-α, or kdIKKβ. Mutation of the Sp1 binding sites blunted IL-18-stimulated EMMPRIN promoter activity. Transduction with Ad dominant negative constructs showed that IL-18-mediated Sp1 activation and EMMPRIN induction are MyD88/IRAK4/TRA66/JNK dependent. In contrast, similar approaches showed that EMMPRIN induced IL-18 via PI3K, Akt, IKK, and NF-κB. Importantly, both IL-18 and EMMPRIN induced MMP9 mRNA, protein, enzyme activities and promoter activation via NF-κB. EMMPRIN knockdown partially inhibited IL-18-induced MMP9 expression. IL-18 and EMMPRIN failed to affect cardiomyocyte viability, but IL-18 (not EMMPRIN) induced significant cardiomyocyte hypertrophy. Administration of IL-18, but not neutralized IL-18, daily for 7 days recapitulated IL-18 effects in vitro by inducing cardiomyocyte hypertrophy (increased cross-sectional area), enhanced EMMPRIN expression (localized to cardiomyocyte sarcolemma), and increased MMP9 expression and activity in LV extracts. Conclusions: Our studies define an IL-18-EMMPRIN-MMP9 pathway in myocardial remodeling. IL-18 and EMMPRIN regulate each other’s expression and induce MMP9 in an NF-κB-dependent manner. Since IL-18 induces MMP9 expression in part via EMMPRIN, and IL-18, but not EMMPRIN, induces cardiomyocyte hypertrophy, IL-18 is a potential therapeutic target in post-infarct and pressure-overload hypertrophy and remodeling.

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