ADIPONECTIN PROMOTES CARDIAC REMODELING IN INFLAMMATORY HEART DISEASE BY INDUCTION OF MATRIX METALLOPROTEINASE-9 ACTIVITY

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Background: Adiponectin (APN) is an immunomodulatory adipocytokine that has been shown to attenuate left ventricular hypertrophy and to diminish fibrosis after myocardial infarction. Coxsackievirus B3 (CVB3) causes severe myocarditis, which might progress to dilated cardiomyopathy. Here, we investigated whether APN modulates cardiac remodeling in CVB3 myocarditis by affecting matrix metalloproteinase (MMP) activity.

Methods: Myocarditis was induced by CVB3 infection of APN-KO and WT mice. MMP activity was measured by zymography. Gene expression was quantified by qRT-PCR. Protein expression and protein kinase activation was analyzed by immunohistochemistry and immunoblot, respectively.

Results: In cultured cardiac myocytes and fibroblasts APN induced MMP-9 expression and secretion through binding of APN receptors 1 and 2 and activation of AMPK and MEK1. Moreover, APN further enhanced the increase in MMP-9 activity triggered by pro-inflammatory stimulants TNFα, LPS and R-848 in vitro. Accordingly, cardiac fibroblasts from APN-KO mice displayed reduced expression and secretion of MMP-9 before and after stimulation with TNFα, LPS and R-848 ex vivo. In line with these observations, cardiac remodeling was attenuated in APN-KO mice following induction of CVB3 myocarditis. In the acute phase at day 3 postinfection (p.i.) cardiac gene expression of MMP-9 was significantly reduced in APN-KO mice. Consequently, in the subacute phase at day 7 p.i. proteolytic activities of MMP-9 were diminished and in hearts of APN-KO mice. Interestingly, splenic MMP-9 gene expression was also decreased in APN-KO mice on day 3 and 7 p.i. correlating with diminished immune cell infiltration within the myocardium of APN-KO mice. Accordingly, cardiac hemodynamics of APN-KO mice on day 7 p.i. were characterized by significant diastolic dysfunction as assessed by left ventricular relaxation (dP/dtmin) and left ventricular relaxation time (Tau).

Conclusion: Our observations indicate that APN promotes cardiac remodeling in inflammatory heart disease by induction of MMP-9 expression in resident cardiac and infiltrated immune cells resulting in increased turnover of extracellular matrix components.