ADIPONECTIN INHIBITS TOLL-LIKE RECEPTOR 4 MEDIATED CARDIAC INFLAMMATION AND INJURY

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Sunday, March 25, 2012, 9:30 a.m.-10:30 a.m.

Session Title: Pericardial/Myocardial Disease I
Abstract Category: 12. Pericardial/Myocardial Disease
Presentation Number: 1125-56

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Background: Adiponectin (APN) is an immunomodulatory and cardioprotective adipocytokine that is also expressed in cardiac myocytes. Toll-like receptor 4 (TLR4) is essential for the progression of major inflammatory cardiac diseases including autoimmune myocarditis. Here, we investigated if APN inhibits cardiac inflammation and injury by interfering with TLR4 signaling.

Methods: APN overexpression in murine experimental autoimmune myocarditis (EAM) was achieved by adenoviral gene transfer. Gene expression was analyzed by qRT-PCR and ELISA. NFκB activation was measured by ELISA. Splenocyte migration, dendritic cell (DC) activation and T cell proliferation was quantified by FACS. Apoptosis was measured by TUNEL.

Results: APN overexpression in EAM downregulated cardiac expression levels of TLR4 and its major downstream immune response mediators TNFα, IL-6, IL-12, CCL2 and ICAM-1 resulting in reduced infiltration of CD3+, CD14+ and CD45+ immune cells and diminished cardiac apoptosis. In cardiac myocytes and fibroblasts APN inhibited the induction of a TLR4 mediated inflammatory phenotype by exogenous and endogenous TLR4 ligands as assessed by attenuated NFκB activation and reduced expression levels of NFκB target genes TNFα, IL-6, CCL2 and ICAM-1. Moreover, APN inhibited the TLR4 mediated increase in TNFα expression in DCs, CD19+ and CD14+ immune cells. Accordingly, splenocytes from APN-/− mice showed enhanced expression levels of TNFα, IL-6, IL-12, CCL2 and ICAM-1 after TLR4 ligation. In addition, TLR4 stimulated DCs from APN-/− mice displayed decreased ability to induce T cell proliferation. Finally, APN diminished splenocyte migration towards TLR4 activated cardiac myocytes and inhibited apoptosis of TLR4 stimulated cardiac myocytes after cocultivation with splenocytes. Mechanistically, APN interfered with TLR4 signaling in cardiac myocytes through a COX-2-, PKA- and ERK 1/2- dependent way.

Conclusions: Our observations indicate that APN interferes with TLR4 signaling in cardiac and immune cells thereby protecting against TLR4 mediated myocardial inflammation and injury in EAM. APN thus represents a promising new option for the therapy of inflammatory cardiac diseases.