Paraoxanase-1 Modulates Cardiotonic Steroid Induced Cardiac Inflammation and Fibrosis in Dahl Salt Sensitive Model of Chronic Kidney Disease

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Objective: Cardiotonic steroids (CTS) are known ligands of the Na+/K+-ATPase (NKA) and chronic elevations in volume expanded conditions such as hypertension and chronic kidney disease (CKD). Paraoxonase-1 (PON1) is a lactonase enzyme that can hydrolyze CTS to inactive open-ring forms making them incapable of stimulating NKA and initiating pro-inflammatory signaling cascades. We hypothesized that PON-1 can attenuate the progression of cardiac inflammation in CKD via modulating the pathogenic pathways induced by CTS signaling using a well characterized Dahl salt-sensitive rat model of hypertensive renal disease and elevated CTS.

Methods: Dahl salt-sensitive wild type, PON1 knockout, and PON1 knockout rats that were treated with 3E9 anti-CTS monoclonal antibody were fed a high salt diet for five weeks to induce hypertensive renal disease and elevate CTS levels. Hematoxylin and Eosin (H&E) staining was performed on hearts to analyze immune cell infiltration. Real-time PCR analysis was performed for markers of inflammation (IL-6, IL1β, and CCL2), hypertrophy (Myh7, NPPA, and Slc8a), and fibrosis (Timp-1).

Results: RT-PCR analysis revealed significantly increased expression of cardiac inflammatory, hypertrophy, and fibrotic markers in SS-PON1 KO compared to SS-WT rats after high salt feeding. Treatment of SS-PON-1 KO rats with 3E9 mAb significantly decreased expression of Timp-1, IL-6, Ccl2, IL1β, NPPA, Myh7 and Slc8a. H&E analysis of hearts revealed significantly decreased immune cell infiltration in SS-PON-1KO rats treated with 3E9 mAb.

Conclusion: Our findings suggest that PON-1 via its counter-regulatory mechanism of the CTS signaling axis exhibits a cardioprotective role in chronic kidney disease.

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