Role of DNA-Binding Proteins Interacting With α-Myosin Heavy Chain Gene Repressor Element in Cardiac Hypertrophy

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Background: Losses of myocardial α-myosin heavy chain (α-MHC) content is associated with reduced contractile function during heart failure. We have previously identified a highly conserved putative trans-repressor element (P-RER) participating in the reduced expression of this gene. This study describes isolation and characterization of P-RER interacting proteins.

Methods: Expression screening was performed on 14-day mouse embryonic heart cDNA library using P-RER element as probe. Gel shift assay analyzed the DNA-protein interaction. Protein levels were measured by western analysis. Effect of cloned cDNA on endogenous levels of α-MHC transcripts utilized primary cultures of cardiac myocytes derived from neonatal rat hearts and adenoviruses expressing full-length cloned proteins.

Results: After screening two million plaques, three proteins, Ptx, Pur-a and Pur-b were isolated. Gel shift assay defined the sequence specific binding of these proteins to P-RER element. Ptx and Pur-p do not bind to the sense-strand α-MHC element. In vivo synthesized Ptx protein inhibited binding of Pur-a and Pur-b proteins to P-RER element, suggesting competition between these and Pur-p proteins in this binding. By western analysis, Pur-a and Pur-p, but not α-MHC, were expressed in rabbit hearts (n=5) subjected to pressure overload, as well as in human failing hearts (n=7). Adenoviral vectors expressing full-length Pur-a or Pur-b proteins were injected into primary cultures of rat cardiac myocytes to study the effects of these proteins on endogenous expression of α-MHC gene. Over-expression of Pur-a had marked negative regulatory effect (86%) on the expression of endogenous α-MHC transcripts, however, Pur-b had mild positive regulatory effect (20%). When both Pur-a and Pur-b were expressed in combination, a synergistic negative regulatory effect on α-MHC gene expression was observed.

Conclusion: The single strand DNA-binding proteins, Pur-a and Pur-b, contribute to the reduced expression of α-MHC transcripts seen in heart failure.

1136-05 Treatment With Eplerenone, an Aldosterone Antagonist Improved Ventricular Remodeling and Function Post Myocardial Infarction

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Background: Post myocardial infarction (MI), aldosterone can directly cause myocyte hypertrophy, fibroblast proliferation and inflammatory response, leading to maladaptive remodeling. Hypothesis: Aldosterone antagonists, such as Eplerenone, can favorably influence markers of remodeling. Methods: In a project to study the effects of aldosterone on isolated rabbit hearts (n=5) subjected to pressure overload, as well as in human failing hearts (n=7) with Eplerenone administered in the diet (100 mg/kg/day) at day 35 post MI, animals were evaluated for in vivo LV area at end-diastole (LVAED) and LV Fractional Shortening (%FS) using echocardiography. In vitro ventricular function was assessed by Langendorff to determine LV systolic pressured (SysP, mmHg). Results: Eplerenone significantly ameliorated LV remodeling post-MI by improving contractile function and decreasing LV area. Taken together these results indicate that aldosterone may be an important contributor to post MI remodeling.

Conclusion: Improved Ventricular Remodeling and Function Post Myocardial Infarction by Eplerenone.