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CARDIAC FUNCTION AND HEART FAILURE

INHIBITION OF CARDIAC FIBROSIS MEDIATED BY NON-MYOCYTE PROLIFERATION IN HYPERTROPHIC CARDIOMYOPATHY

ACC Poster Contributions
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Background: Hypertrophic cardiomyopathy (HCM) is a prevalent genetic cardiac disorder, characterized by hypertrophy, interstitial fibrosis and myocyte disarray. The mechanisms contributing to cardiac hypertrophy and fibrosis triggered by sarcomere gene mutations are incompletely elucidated. We studied two HCM mouse models that carry the Arg403Gln or Arg719Trp missense mutations of α-cardiac myosin heavy chain (αMHC mutant). Comprehensive analyses of RNA expression in prehypertrophic αMHC mutant mouse hearts revealed significant induction of transforming growth factor-β (tgfβ) 1, 2 and periostin (postn) transcripts ($p<0.01$ for each).

Hypothesis: Cardiac fibrosis and associated non-myocyte proliferation would be reduced by inhibiting TGFβ signaling and/or periostin.

Methods and Results: To study the functional consequences of periostin in cardiac fibrosis in HCM, we crossed mice carrying αMHC mutant with postn-null mice (postn-/-). Cardiac fibrosis associated with non-myocyte proliferation was significantly attenuated in αMHC mutant/postn-/- mice compared with αMHC mutant mice with normal periostin expression ($p=0.03$). To interrogate the impact of blocking TGFβ signaling we also treated prehypertrophic αMHC mutant mice with pan-specific TGFβ neutralizing antibody and observed significantly reduced cardiac hypertrophy ($p=0.009$) and fibrosis with non-myocyte proliferation ($p=4.5x10-8$) and decreased periostin protein expression ($p=0.02$). To assess whether pharmacologic inhibition was efficacious we treated prehypertrophic mice with the angiotensin II type 1 receptor and TGFβ antagonist losartan for 30 weeks (15 mg/kg/day oral) and observed marked diminution in the development of hypertrophy ($p=2.14x10-10$) and fibrosis associated with non-myocyte proliferation ($p=2.5x10-10$). However, losartan treatment given to mice with overt HCM was not able to reverse existing fibrosis or hypertrophy.

Conclusions: TGFβ inhibition in prehypertrophic HCM attenuates pathologic remodeling in response to sarcomere protein gene mutations. Early pharmacologic inhibition of TGFβ in human patients with HCM mutations may delay disease onset and/or retard disease development.