The Role of TGFβ Signaling in a Fibrotic cMyBP-C HCM/HF Model

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PURPOSE: Hypertrophic cardiomyopathy (HCM) is considered one of the most common genetic heart disorders with a prevalence of about 1 in 500 people, with 35% of those affected being attributed to mutations within the gene encoding cardiac myosin-binding protein C (cMyBP-C). Cardiac stress, as well as cMyBP-C mutations, can trigger production of a 40kDa truncated fragment derived from the amino terminus of cMyBP-C. Genetic expression of this 40kDa fragment in mouse cardiomyocytes (*Mybp3*^{40kDa}) leads to HCM, fibrosis and heart failure, mimicking human disease progression. The transforming growth factor-β (TGFβ) signaling pathway has been implicated in a variety of fibrotic processes. The goal of this study is to define the role of TGFβ signaling **in distinct cell populations, the cardiomyocyte and fibroblast**, in the cMyBP-C HCM/HF model.
Methods and results: Masson's Trichrome staining, PCR arrays, immunohistochemistry and western blots were performed to characterize the fibrotic progression in *Mybp3*^{40kDa} transgenic mice. Cardiac fibrosis was initially detected 4 weeks after transgene expression. Extensive interstitial fibrosis and severe atrial fibrosis were detected at 16 weeks. Both canonical and non-canonical TGFβ pathways were active during fibrotic progression. To specifically block TGFβ signaling in *Mybp3*^{40kDa} transgenic mice, compound mutant mice were generated, in which the *tgfbr1*or *tgfbr2* alleles were ablated, either in cardiomyocytes or in activated fibroblasts (myofibroblasts) by αMHC-Cre or Periostin-MerCreMer-Cre respectively. Blockage of TGFβ signaling in either cardiomyocytes or myofibroblasts alleviated cardiac fibrosis. Furthermore, treatment with the non-canonical TGFβ signaling inhibitor MMI-0100 also alleviated cardiac fibrosis and increased the life span of the *Mybp3*^{40kDa} transgenic mice.
Conclusions: TGFβ signaling is activated in the *Mybp3*^{40kD} HCM/HF model. Genetic or pharmaceutical inhibition of TGFβ signaling inhibited fibrosis and increased the life span in this model.

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