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

Qinghang Meng, Bidur Bhandary, Cincinnati Children's Hosp Medical Ctr, Cincinnati, OH; Md. Shenuarin Bhuiyan, Louisiana State Univ Health Sciences Ctr, Shreveport, LA; Hanna Osinska, Jeffrey Robbins, Cincinnati Children's Hosp Medical Ctr, Cincinnati, OH

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 (Mybp340kDa) 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 Mybp340kDa 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 Mybp340kDa 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 Mybp340kDa transgenic mice.

Conclusions: TGFβ signaling is activated in the Mybp340kDa HCM/HF model. Genetic or pharmaceutical inhibition of TGFβ signaling inhibited fibrosis and increased the life span in this model.

Disclosure Block: