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Heart Failure and Cardiomyopathies

FOXO3A MODULATES CARDIAC REMODELING VIA INHIBITION OF MYOFIBROBLAST DIFFERENTIATION IN ACUTE MYOCARDIAL INFARCTION

Poster Contributions
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Background: FOXO3a is a transcription factor and key regulator of cell differentiation, cycle and size and might be involved in regulation of cardiac remodeling following acute myocardial infarction. Myocardial adverse remodeling and scar formation are largely regulated by TGFβ/SMAD3 signaling leading to transdifferentiation of fibroblasts into myofibroblasts possibly inhibited by FOXO3a.

Methods: Myofibroblast transdifferentiation markers were assessed following acute infarction in FOXO3-/- and WT mice (FVB) via permanent ligation of LAD. FOXO3a-/- and WT cardiac fibroblasts were investigated in transdifferentiation assays ex vivo. FOXO3a gene transfer was performed with gain of function adenoviral vectors. To test for a direct interaction between FOXO3a and SMAD3 western blotting and immunoprecipitation (IP) were used.

Results: Reduced rates of ventricle perforation led to significantly higher survival rates in FOXO3a-/- mice compared to WT. At 3 and 14 days post infarction myocardial expression of alpha smooth muscle actin (ASMA) and Collagen1A1 (Col1A1) was significantly enhanced in FOXO3a-/- mice associated with larger areas of fibrosis. In vitro cardiac fibroblasts isolated from FOXO3a-/- mice showed significantly enhanced expression of Col1A1 and ASMA 24 hours following stretch or TGF-β stimulation compared to WT cells. Moreover significantly higher protein expression of Col1A1 was shown in supernatants of FOXO3a -/- fibroblasts while FOXO3a gene-transfer dose-dependently downregulated Col1A1. FOXO3a gene transfer also led to significantly attenuated immunfluorescence staining for ASMA in cardiac fibroblasts. Interestingly IP showed direct interaction between FOXO3a and SMAD3a that was enhanced following activation of the transcription factor leading to diminished SMAD3 downstream gene expression.

Conclusion: We were able to show that FOXO3a regulates fibrosis and scar formation following myocardial infarction by direct inhibition of TGF- β regulated matrix remodeling via interaction with SMAD3. Thus the FOXO3a-SMAD3 axis might be of therapeutic interest to abate adverse myocardial remodeling.