The absences of Growth Differentiation Factor 15 aggravates adverse cardiac remodeling upon pressure-overload

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Background: Growth differentiation factor 15 (GDF15) is a protein belonging to the TGF-β family. Under normal conditions, GDF15 is not highly expressed, but sharply increased upon injury. GDF15 influences many processes, such as inflammation, apoptosis and fibrosis. In heart failure (HF) patients, GDF15 plasma levels are increased and high GDF15 levels are associated with increased mortality. Yet, the exact role of GDF15 in adverse cardiac remodeling leading to HF is not known.

Purpose: We therefore studied GDF15 knock-out (-/-) mice and wild type (WT) in a pressure-overloaded HF model using transverse aortic constriction (TAC) with a 27 gauge needle.

Results: After 6 weeks of TAC, GDF15/-/- mice have increased end diastolic volume (EDV) and end systolic volume (ESV) (EDV: 93 µl versus 64 µl, p<0.001, ESV: 72 µl versus 38 µl, p<0.001). The accelerated worsening in GDF15/-/- mice were already visible 7 days after TAC in both ESV as in global longitudinal strain (-11.8±2.8 % vs. -15.5 ±2.7 %). Immunohistochemistry showed that cardiomyocyte hypertrophy (identified by WGA), fibrosis (picrosirius red), influx of leukocytes (CD3, MAC3, Ly6G), apoptosis (TUNEL) and proliferation (Ki67) were not different between WT and GDF15/-/- mice. RNA sequencing was performed on heart tissue 1 week post-TAC, which revealed that contractility pathways are affected in GDF15/-/-. In vitro individual cardiomyocyte contractility assays showed that stimulation with GDF15 increased contraction speed (Time to peak: control versus 100 ng/ml: 0.095±0.013 s vs 0.084±0.008 s) and a faster relaxation time (Time to 70% baseline: control versus 100 ng/ml: 0.16±0.03 s vs 0.14±0.02 s).

In conclusion, lack of GDF15 aggravates adverse remodeling upon pressure-overload. Our data suggests that GDF15 directly affects cardiomyocyte contractility. Further studies will focus on whether GDF15 functions through receptor signaling or by interfering with transcriptional regulation.