Abstract: **P121**

**Gene expression profiling of hypertrophic and failing cardiomyocytes to identify new players in pathological remodeling**

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Background - Pathological cardiac remodeling in response to pressure overload is characterized by cardiomyocyte hypertrophy and fibroblast activation. Although those processes are initially beneficial, when prolonged can cause stiffness of the heart, loss of contractility and will ultimately lead to heart failure. So far, the mechanisms driving progression from compensatory hypertrophy to failure remain insufficiently understood. As a result, there is a lack of therapies to reverse maladaptive remodeling or prevent cardiac failure.

Purpose - By identifying novel factors driving cardiomyocyte hypertrophy and failure, we can offer new insights in these mechanisms and contribute to the development of new, improved therapies.

Methods - We induced pressure overload by transverse aortic banding (TAB) in mice to study the functional, histological and molecular consequences at different time points that allowed us to identify the hypertrophic and failing state. Additionally, to study genome-wide gene expression changes specifically in cardiomyocytes, we made use of a reporter mouse Myh6-Cre-tdTomato where we label all cardiomyocytes allowing for Fluorescence-activated Cell Sorting (FACS). We then performed RNA sequencing on sorted tdTomato positive cardiomyocytes from the hypertrophic and failing hearts. To validate the relevance of our discoveries in human, we established a stress model of human iPS-derived cardiomyocytes (hIPS-CMs) using norepinephrine treatment.

Results - One week after banding the hearts presented compensatory hypertrophy shown by a functional improvement. This was determined by an increase in fractional shortening (FS) and in cardiomyocyte size. At eight weeks after banding clear signs of cardiac failure could be detected, presented by a decline of 25% in fractional shortening and a significant induction of fibrosis. Transcriptomic profiling of cardiomyocytes identified different subset of genes and pathways to be differentially regulated and specific for hypertrophic and failing stage, as Col3a1 and Nppb, respectively. We also identified a group of genes that so far have not been associated to cardiomyocyte hypertrophy or failure. Stressed human IPS-derived cardiomyocytes showed an increase in cardiac failure markers, as Nppb and Abra. Currently, the biological significance of the newly identified genes is being tested by examining the functional impact of targeted gene inhibition in these cells.

Conclusions - Our findings indicate that cardiomyocyte specific transcriptomic analysis allows for the identification of hypertrophic and failing gene expression profiles and might help to unveil novel genes relevant for heart disease. This will increase our understanding of the molecular mechanisms underlying the shift from hypertrophic to failing cardiomyocytes, providing novel inroads for development of new therapeutics for heart failure.