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Models for VEGF-B induced physiological and pathological cardiac hypertrophy
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Background/Introduction

Cardiovascular diseases are the leading causes of mortality; they have become the single most important cause of non-communicable diseases and heart failure forms a growing burden to society. We have previously reported that mice expressing a cardiomyocyte-specific aMHC-VEGF-B show an impressive expansion of the coronary vasculature and develop cardiac hypertrophy without significant compromise of heart function, mimicking physiological "athlete-like" cardiac hypertrophy (1). This was interesting as it led to speculations on the possible therapeutic potential of VEGF-B.

Purpose

In our current work, we have asked how the VEGF-B induced cardiovascular effects differ, when VEGF-B is expressed specifically in the endothelium instead of the cardiomyocytes. We created a novel mouse model, where the VEGF-B gene (genB) was inserted under the control of the adipocyte protein 2 (aP2/Fabp4) regulatory sequences (2). We found that the endogenous Fabp4 gene and the aP2-VEGF-B transgene were both highly expressed in adipose tissue and in endothelial cells of coronary vessels (2). Interestingly, the aP2-VEGF-B transgenic mice developed in pathological cardiac hypertrophy (Figure 1).

Methods

We carried out an extensive echocardiographic, histological, cellular and molecular analysis of the aP2-VEGF-B hearts. RNA sequencing from the aP2-VEGF-B and aMHC-VEGF-B hearts on embryonic day 18.5, and neonatal, and seven-day postnatal timepoints, as well as from adult hearts were carried out.

Results

Besides the massively increased heart weight, the aP2-genB transgenic mice showed an impaired cardiac function in echocardiography. They also had significantly bigger cardiomyocytes and increased vessel density, when compared to wildtype mice. They had increased expression of pathological cardiac markers, consistent with the cardiac maladaptation. The transgenic embryos did not show any obvious phenotype, but about one third of them died after birth. Results from the further comparison of the aP2-VEGF-B and aMHC-VEGF-B phenotypes will be shown in the poster.
Conclusions

Cardiac hypertrophy induced by VEGF-B is likely mediated by an "angiocrine" signal from the endothelium to the cardiomyocytes. In the aMHC-VEGF-B model, VEGF-B overexpression in cardiomyocytes leads to physiological hypertrophy, whereas aP2-VEGF-B transgene expression in endothelial cells leads to pathological hypertrophy. Knowledge of the activated pathways and signal transduction mechanisms in these two models could offer new druggable targets to treat heart failure.

Figure 1: Cardiac hypertrophy in aP2-VEGF-B and aMHC-VEGF-B transgenic mice. (A-B) Heart weight normalised to body weight (mg/g) and macroscopic images of the hearts. Mean ± SEM, ***p=0.001, **p=0.01 & *p=0.05. Scale bar= 300 µm.