Anti-TNF-α therapy ameliorates cardiac function in mice with reduced endogenous endothelin-1 and increased afterload

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Growing evidence indicates that endothelin-1 (ET-1) plays a role in the survival of several cell types. Cardiomyocyte-specific deletion of ET-1 causes decline of heart function in mice in response to increased afterload as well as in aging mice without any challenge. In aging mice, increased apoptosis with involvement of the tumor necrosis factor-alpha (TNF-α) pathway was observed. This led to the theory that ET-1 protects the heart by inhibiting TNF-α signaling related apoptosis.

The aim of this study was to find out whether ET-1 originated in endothelial cells has similar impact on heart function and cardiomyocyte survival, and if these factors can be influenced by the attenuation of the TNF-α pathway.

Transverse aortic banding (TAC) was performed in ten weeks old vascular endothelial cell-specific ET-1 knockout female mice (veETKO) and their wild type (WT) littermates. From the second week after surgery onwards, pentoxifylline (PTX) was added to drinking water (500µg/ml) in order to inhibit TNF-α production. After twelve weeks, echocardiography was performed and heart was harvested. Differences between the groups were compared by Mann-Whitney-U test.

Before surgery, there were no significant differences in body weight and systolic blood pressure between the both genotypes (WT: 20.0±2.4g, 113.5±7.7mmHg, n=23; veETKO: 20.8±2g, 110.5±9.5mmHg, n=38). Neither TAC nor PTX had an effect on blood pressure or weight gain in the course of the experiment. Twelve weeks after TAC surgery, veETKO mice showed impaired heart function compared to WT mice evaluated by fractional shortening and end systolic left ventricular diameter measurements (WT-TAC: 57±5%, 11.9±3.4mm, n=5; veETKO-TAC: 48±5%, 16.3±2.6mm, n=9; $p<0.05$). PTX treatment restored heart function in veETKO-TAC mice but impaired heart function in WT-TAC mice (veETKO-TAC-PTX: 55.5±7%, 11.9±3.7mm, n=6, $p<0.05$ vs. veETKO-TAC; WT-TAC-PTX: 51.9±7.4%, 13.8±4mm, n=8, $p<0.05$ vs. WT-TAC). Heart weight to tibia length ratio was 15-30% elevated in all TAC groups compared to sham operated groups and was not influenced by genotype or PTX treatment. Currently, we investigate heart morphology and the molecular mechanisms involved in TNF-α signaling related apoptosis.

This study shows that endothelial cell-derived ET-1 is required to maintain cardiac function under pressure overload conditions. Furthermore, the additional inhibition of TNF-α synthesis preserves heart function in veETKO mice but affects adversely WT mice. These results are in line with the disappointing results of endothelin receptor antagonists (ERAs) and anti-TNF-α therapy in heart failure. A better understanding of the interplay of these two systems could reveal new treatment strategies for heart failure patients, for instance, selecting patients with low levels of TNF-α for ERAs treatment or combining ERAs with anti-TNF-α therapy.