Adipose tissue specific adipose triglyceride lipase as a major determinant for the development of pressure overload-induced heart failure

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Introduction: Myocardial metabolism undergoes a change in response to pathological hypertrophy, characterized by increased reliance on glucose oxidation, decreased free fatty acid oxidation, and a loss of metabolic flexibility. Cardiac metabolism is determined by whole-body metabolism and influenced by other organs such as adipose tissue. However, the molecular interaction between adipose tissue and the development of pathological hypertrophy is not well understood. Hence, we aimed to investigate the effect of Adipose Triglyceride Lipase (ATGL) in adipose tissue on the development of myocardial hypertrophy and heart failure in a pressure overload-induced cardiac hypertrophy model in mice.

Methods: Male adipose tissue specific ATGL knock out (atATGL-KO) and wild type littermate mice (WT) underwent sham surgery (sham) or transverse aortic constriction (TAC) at the age of eight weeks. After 11 weeks, animals were sacrificed and organs were harvested. Echocardiographic measurements were performed one week before and 11 weeks after surgery. End-diastolic interventricular septum (IVS-d), left ventricular internal diameter (LVID-d), posterior wall (LVPW-d) and heart rate (HR) were measured. Left ventricular mass (LVM), left ventricular mass/tibia length (LVM/TL) and ejection fraction (EF) were calculated accordingly.

Results: TAC led to a significant increase of LVM compared to sham in both genotypes. However, LVM/TL in WT was significantly higher compared to atATGL-KO mice (LVM/TL [mg/mm] WT-TAC: 18.0 ± 2.2; atATGL-KO-TAC: 13.1 ± 2.3; p < 0.01). When compared to mean LVM in sham after 11 weeks, LVM in WT-TAC increased by 110.9 ± 30.5 mg, whereas atATGL-KO-TAC increased by only 38.4 ± 28.3 mg (p < 0.005). The higher increase of LVM/TL and LVM in WT was associated with a larger LVID-d (LVID-d [mm] WT-TAC: 4.9 ± 0.4; atATGL-KO-TAC: 4.2 ± 0.3; p < 0.001). IVS-d and LVPW-d in WT and atATGL-KO significantly increased to a similar degree in TAC compared to sham respectively. Eleven weeks after TAC, reduction of EF was significantly more pronounced in WT compared to atATGL-KO (EF [%] WT: 28.81 ± 6.9 atATGL-KO: 42.39 ± 4.5; p < 0.01).

Conclusion: The present study demonstrates that ATGL in adipose tissue is a crucial determinant for the development of pressure overload-induced cardiac hypertrophy/failure. The lack of ATGL in adipose tissue, the associated reduction of fatty acid release in the circulation, and subsequent switches in cardiac energy substrates are potential underlying mechanisms of these processes.