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Endothelial dysfunction in a mouse model of human neutral lipid storage disease

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Background

Systemic knockout of adipose triglyceride lipase (ATGL), the rate-limiting enzyme of triglyceride catabolism, results in a murine phenotype characterized by progressive accumulation of lipids in the heart finally leading to lethal cardiac dysfunction. Since cardiac and vascular dysfunction are closely related we investigated endothelium-dependent and -independent vessel function of ATGL knockout (ATGL(-/-)) mice. Using mice with cardiomyocyte-restricted overexpression of ATGL (cardiac-rescued phenotype;

ATGL(-/-)/MHC-A35) we were able to differentiate between heart-related and -unrelated effects.

Results

Aortic relaxation studies and Langendorff perfusion experiments of isolated hearts demonstrated that ATGL (-/-) mice suffer from pronounced micro- and macrovascular endothelial dysfunction. Experiments with DEA/NO revealed the functional integrity of the smooth muscle cell layer. Since loss in vascular reactivity was restored by ~50 % in cardiac-rescued mice, this phenomenon seems partly a consequence of impaired cardiac contractility. Biochemical analysis revealed that aortic eNOS protein was down-regulated by more than 60% in aortas of ATGL (-/-) mice. As consequence, phosphorylation of VASP at Ser 239 was almost abolished. Both parameters were

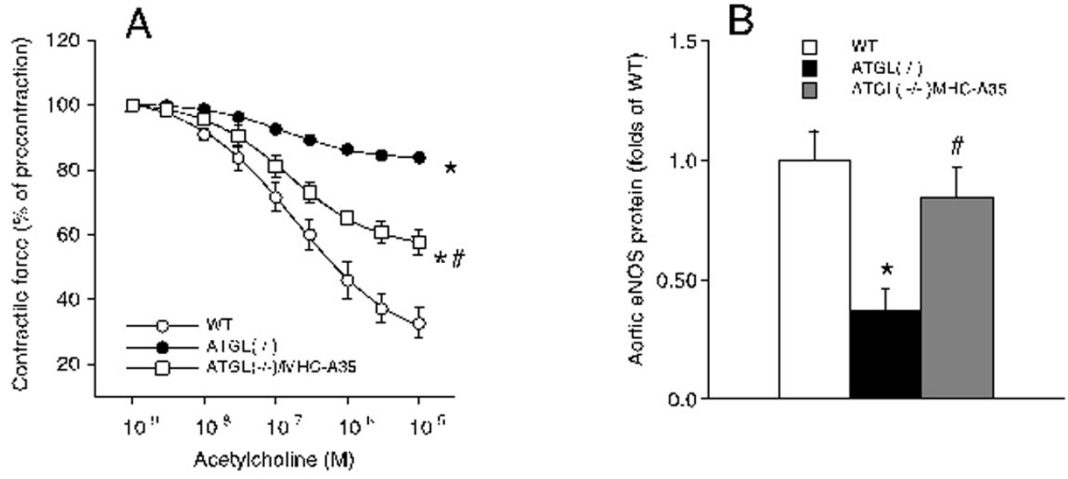

Figure 1 (A) Aortic relaxation to acetylcholine is blunted in ATGL deficiency and partly recovered in vessels of mice with a cardiac rescued phenotype. **(B)** Aortic eNOS expression in downregulated in ATGL deficiency an reversed upon cardiac rescue.

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totally reversed in vessels of cardiac rescued mice. Aortic expression of eNOS mRNA was not affect in ATGL deficiency excluding a transcriptional mechanism underlying the observed effect. Total levels of ubiquitinated proteins (a measure of vascular proteasomal activity) were down-regulated in ATGL-deficient aortas (~26% compared to WT controls) and fully recovered upon cardiomyocyte-restricted overexpression of ATGL.

Conclusion

Endothelial dysfunction in murine ATGL deficiency partly arises from impaired cardiac contractility and originates from down-regulation of aortic eNOS presumably due to activation of the vascular proteasome. Potential heart-independent mechanisms contributing to the observed defect are currently investigated.

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