

## Lipid handling by endothelial cells of thermogenic adipose tissue

**Introduction** Brown adipose tissue (BAT) is able to combust fatty acids and other substrates to produce heat. Lipid uptake into BAT is not restricted to lipoprotein lipase (LPL)-mediated hydrolysis of triglyceride-rich lipoproteins (TRL), but also includes whole particle uptake by endothelial cells. The relevance for BAT function of endothelial TRL uptake and subsequent lysosomal processing is still unknown. We investigated the impact of impaired lipoprotein handling in endothelial-specific lysosomal acid lipase (LAL)-deficient mice with regard to BAT functionality and thermogenesis.

**Methods** Tamoxifen-inducible endothelial-specific LAL knockout (*Lipa*<sup>-/-</sup>*Cdh5*<sup>Tam-cre</sup>) mice were fed chow or Western-type diet and exposed to a cold environment. Magnetic-activated cell sorting (MACS) was used for cell type-specific analyses. Gene and protein expression in WAT and BAT, metabolic turnover studies and indirect calorimetry were employed to examine thermogenic adipose function. Cell culture experiments with primary cells were conducted to investigate the LAL-dependent signaling mechanisms involved in thermogenic differentiation.

**Results** MACS confirmed the specific LAL knockout in endothelial cells. Lipid uptake studies with radiotracers showed an accumulation of cholesterol and triolein in LAL-deficient endothelial cells indicating delayed lipid processing. In vivo, *Lipa*<sup>-/-</sup>*Cdh5*<sup>Tam-cre</sup> mice displayed only minor differences in BAT lipid uptake and beta3-adrenergic induced thermogenesis, what might be due to the compensatory induction of LPL and UCP1. Cold acclimation resulted in impaired thermogenic capacity accompanied by reduced browning of white adipose tissue (WAT), in WTD, but not chow-fed mice. While BAT appears unaltered, LAL activity is essential for differentiation of beige adipocytes in WAT depots. The impaired browning was reproduced in primary adipocytes during differentiation in cell culture.

**Conclusion** Our data show the relevance of endothelial lipoprotein handling in thermogenic adipose tissue function. Lysosomal lipoprotein processing is necessary for proper cold adaptation, since endothelial LAL-deficiency leads to impaired browning of WAT depots.

## References

Lysosomal lipoprotein processing in endothelial cells stimulates adipose tissue thermogenic adaptation. Fischer AW, Jaekstein MY, Gottschling K, Heine M, Sass F, Mangels N, Schlein C, Worthmann A, Bruns OT, Yuan Y, Zhu H, Chen O, Ittrich H, Nilsson SK, Stefanicka P, Ukropec J, Balaz M, Dong H, Sun W, Reimer R, Scheja L, Heeren J. *Cell Metab.* 2021 Mar 2;33(3):547-564.e7.