Lace1 deficiency accelerates browning of inguinal white adipose tissue in mice

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Abstract

Adipose tissue browning is essential for maintaining energy homeostasis against obesity. It is well known that Lactation elevated 1 (LACE1) is mitochondrial integral membrane protein that functions to mediate mitochondrial protein homeostasis. Here, we found that Lace1 was increased during beige adipogenesis and brown adipogenesis. Lace1 is also enrich in CL-316243 (CL) and cold induced beige fat compared to white fat. Remarkably, Lace1 knockout (KO) mice had improved adipose tissue browning ability concomitant with increased energy expenditure. Deletion of Lace1 accelerates lactate influx and lactate induced browning in subcutaneous fat compared to control littermates. We reported that the reason of enhanced browning capacity in Lace1 KO is increased lactate efflux by phosphorylation of PDH in heart. Taken together, our study revealed the role of Lace1 in mediating browning capacity of subcutaneous fat through phosphorylation of PDH in heart.

Results

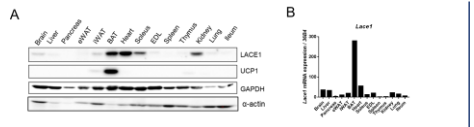


Figure 1. Lace1 expression in whole tissue (A) Lace1 protein expression in whole tissue. (B) Lace1 mRNA expression in whole tissue.

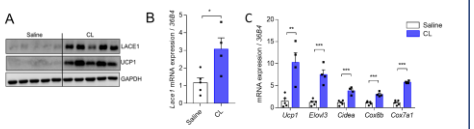


Figure 2. Increased Lace1 expression in CL-316,243 induced beige fat (A) Lace1, UCP1 protein expression in CL-316,243 induced beige fat. (B) Lace1 mRNA expression in CL-316,243 induced beige fat. (C) Thermogenesis related gene expression in CL-316,243 induced beige fat

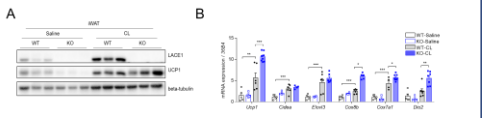


Figure 3. Increased browning related gene expression in CL-316,243 induced beige fat of Lace1 KO compared to control littermates (A) UCP1 protein expression in CL-316,243 induced beige fat of Lace1 KO. (B) Browning marker related gene expression in CL-316,243 induced beige fat in Lace1 KO.

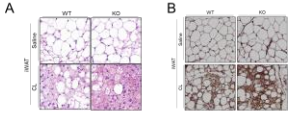


Figure 4. Enriched beige fat of CL-316,243 induced beige fat of Lace1 KO (A) H&E staining of iWAT in Lace1 KO. (B) UCP1 IHC staining of iWAT in Lace1 KO.

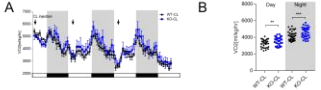


Figure 5. Improved energy homeostasis in Lace1 KO (A) VO2 in Lcae1 KO during CL-316,243 challenge. VO2 in (B) Day and night of Lace1 KO during CL-316,243 challenge

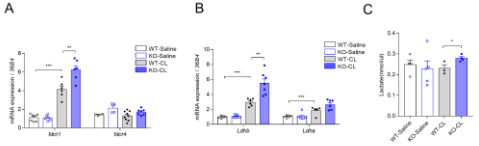


Figure 6. Increased Lactate induced browning in CL-316,243 induced beige fat of Lace1 KO (A) Lactate influx related gene(Mct1) expression and Lactate efflux related gene(Mct4) expression in CL-316,243 induced beige fat of Lace1 KO. (B) Enzyme that converts lactate to pyruvate related gene(Ldhb) / Enzyme that converts pyruvate to lactate related gene(Ldha) ratio in CL-316,243 induced beige fat of Lace1 KO. (C) Lactate assay in serum of Lace1 KO

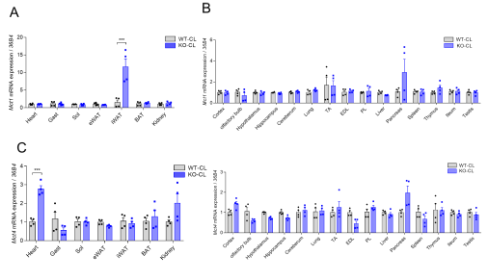


Figure 7. Enhanced Lactate influx capacity in CL-316,243 induced beige fat and Lactate efflux capacity in Heart of Lace1 KO (A-B) Lactate influx related gene(Mct1) expression in whole tissue of Lace1 KO. (C-D) Lactate efflux related gene(Mct4) expression in whole tissue of Lace1 KO

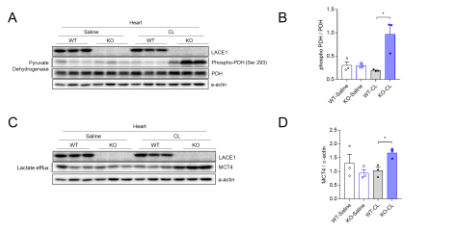
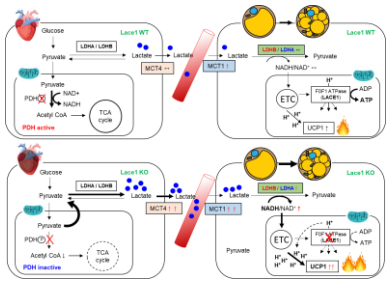


Figure 8. Increased phosphorylation of PDH and Lactate efflux in Heart of Lace1 KO (A-B) Phosphorylation of PDH of heart in Lace1 KO (C-D) Lactate efflux related Mct4 protein level in heart of Lace1 KO

Conclusions



- In summary, Lace1 is enriched in beige fat and brown fat upon CL-316,243 challenge.
- Browning capacity of iWAT is increased in Lace1 KO compared to control littermates
- The reason of enhanced lactate induced browning capacity in Lace1 KO is increased lactate efflux by phosphorylation of PDH in heart.