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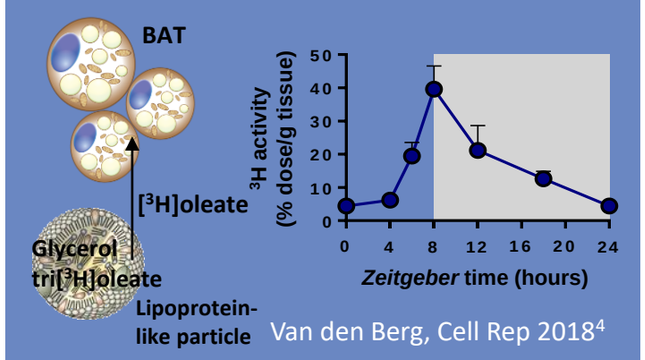
Angiopoietin-like 4 dictates the day-night rhythm of metabolic brown adipose tissue activity

Background

Brown adipose tissue (BAT) burns fatty acids (FAs) derived from triglycerides (TGs) in lipoproteins in order to produce heat[1], and the presence of metabolically active BAT in humans is associated with cardiometabolic health.[2,3]

Interestingly, BAT shows a strong day-night rhythm in TG-derived FA-uptake, peaking around wakening (see figure below).[4]



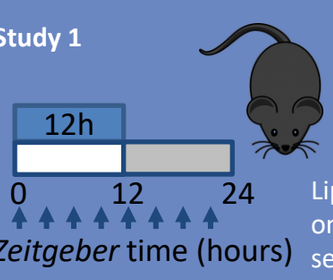
Van den Berg, Cell Rep 2018[4]

Aim

Here we aimed to gain insight in the diurnal regulation of metabolic BAT activity, as this may provide novel insights in how to target this tissue and attenuate (cardio)metabolic disorders.

Methods

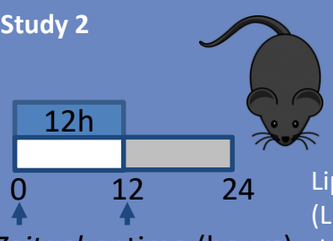
Study 1



C57Bl/6J wild type, male, 8 weeks of age, chow diet

Lipidomics, transcriptomics, and PPARγ ChIP-seq analysis in BAT

Study 2



Angiopoietin-like 4 (*Angptl4*) knockout and transgenic *vs.* C57Bl/6J wild type

Lipoprotein lipase (LPL) activity, TG-derived FA-uptake by BAT

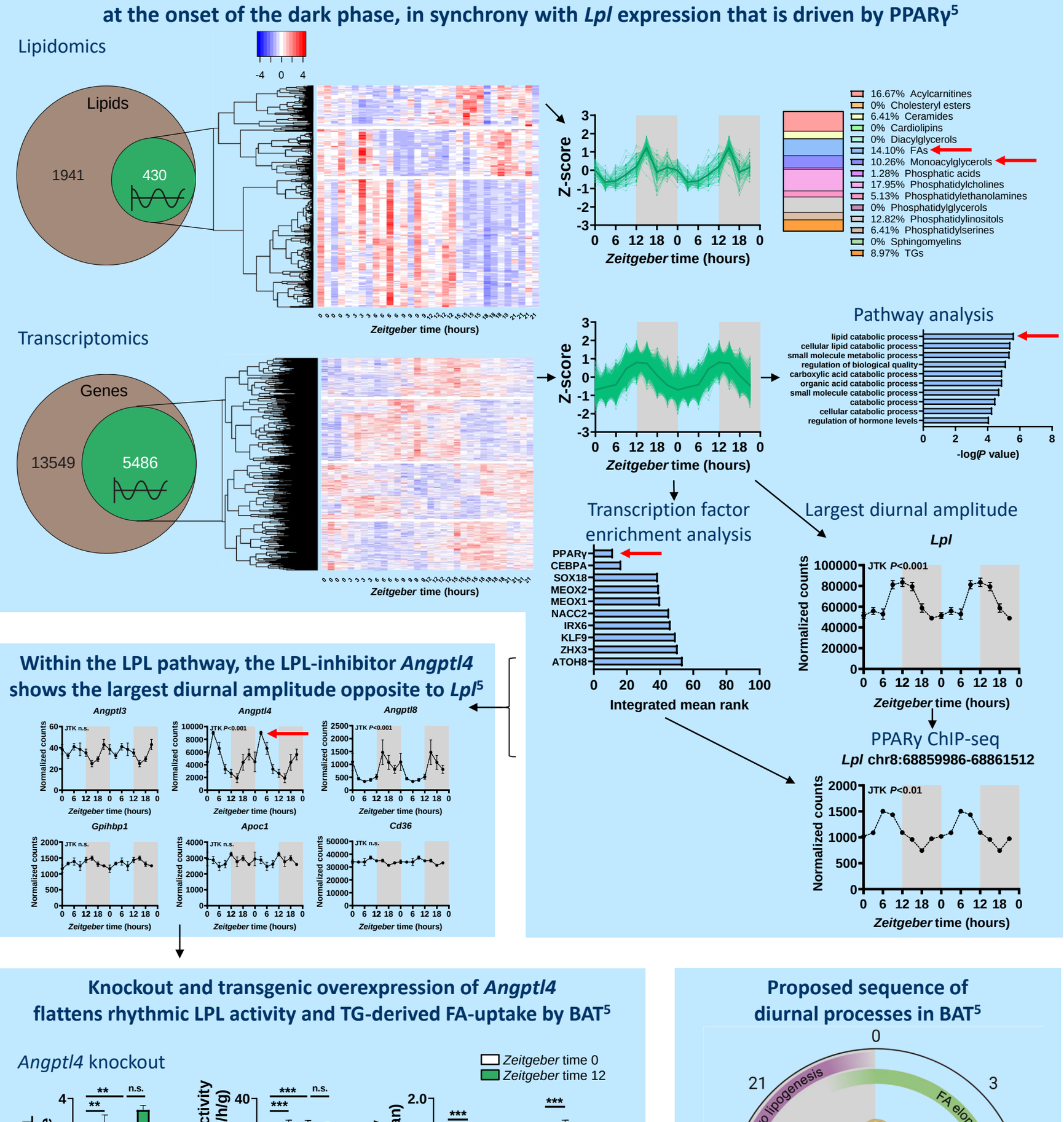
Conclusions

- BAT lipolytic activity is highly rhythmic, with a peak at the onset of the dark phase, driven by LPL
- LPL is rhythmically regulated by PPARγ on transcriptional level, and by ANGPTL4 on protein level

Implications

- Timing of measurements should be considered when studying BAT
- Timing of administration of currently developed ANGPTL4 inhibitors should be considered when aiming at maximizing metabolic BAT activity throughout the day to improve metabolic health

Unbiased diurnal lipidomics and transcriptomics analysis in BAT reveal pronounced lipolytic activity at the onset of the dark phase, in synchrony with *Lpl* expression that is driven by PPARγ[5]

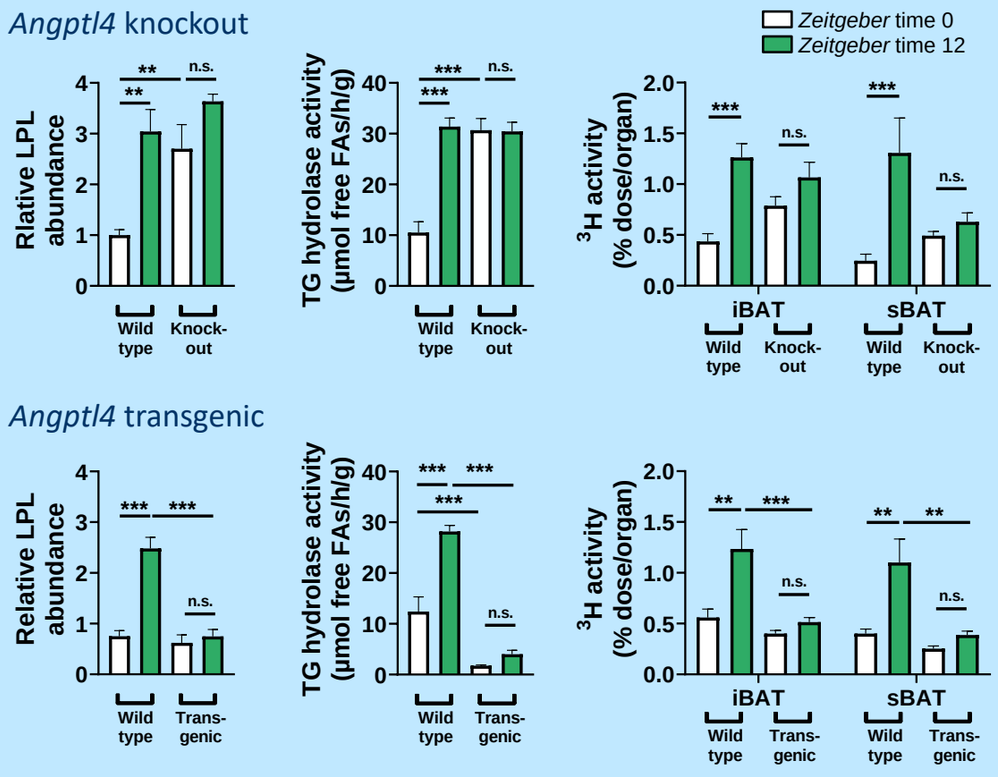


Within the LPL pathway, the LPL-inhibitor *Angptl4* shows the largest diurnal amplitude opposite to *Lpl*[5]

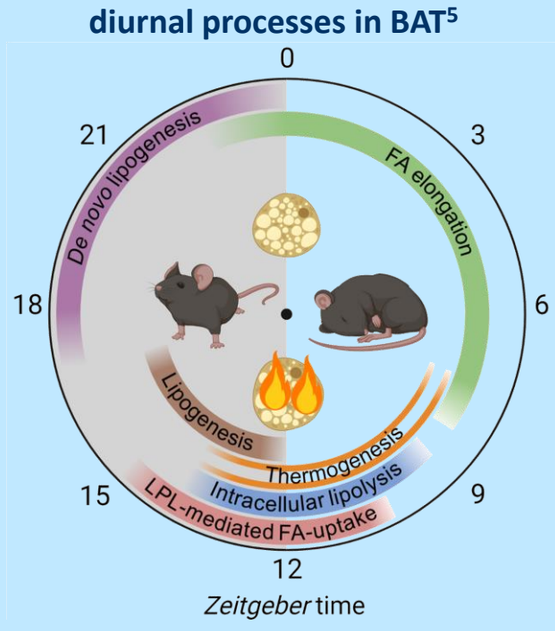
PPARγ ChIP-seq

Lpl chr8:68859986-68861512

Knockout and transgenic overexpression of *Angptl4* flattens rhythmic LPL activity and TG-derived FA-uptake by BAT[5]



Proposed sequence of diurnal processes in BAT[5]



References

[1]Khedoe, J Lipid Res 2015; [2]Becher, Nat Med 2021; [3]Herz, Diabetes 2021; [4]Van den Berg, Cell Rep 2018; [5]Van Eenige, Mol Metab 2022.

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