REV-ERBα Regulates SUMO3 Rhythm in Liver

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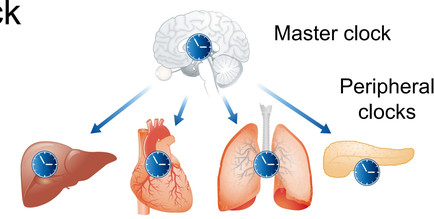
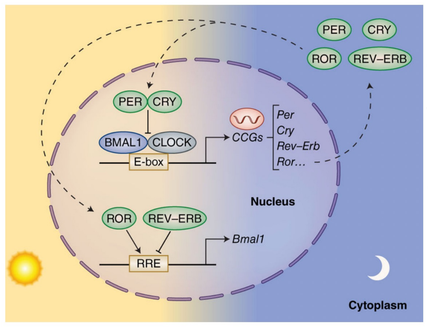
Introduction

The circadian clock allows us to anticipate the environmental changes that happen every 24hrs.



Dierickx PJ, Van L aake LW, Geijsen N. *EMBO Reports*. 2018.

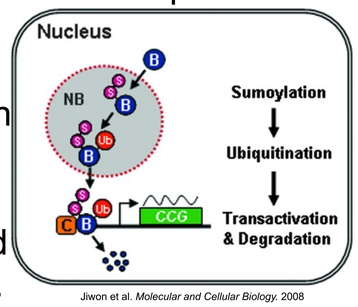
Circadian misalignment leads to increased risk of metabolic disease.



Masri S, Sassone-Corsi P. *Nature Medicine* 2018.

The circadian clock is a transcriptional/ translational feedback loop that is tightly regulated. The nuclear receptors REV-ERBα and β are part of this loop by repressing *Bmal1*. Another important regulatory process happens at the post-translational level.

One such post-translational modification (PTM) is SUMOylation. BMAL1 protein degradation is controlled by SUMO3 modification.



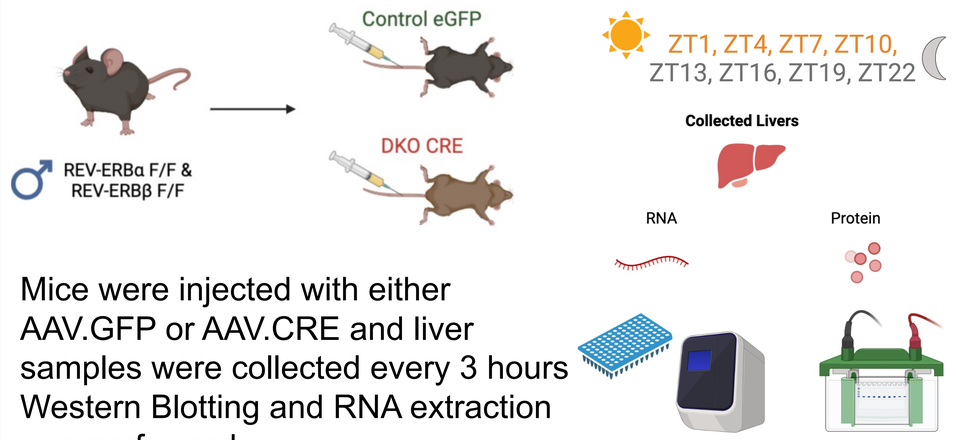
Jiwon et al. *Molecular and Cellular Biology*. 2008

Rationale

REV-ERBα has important functions in the liver that are incompletely understood.

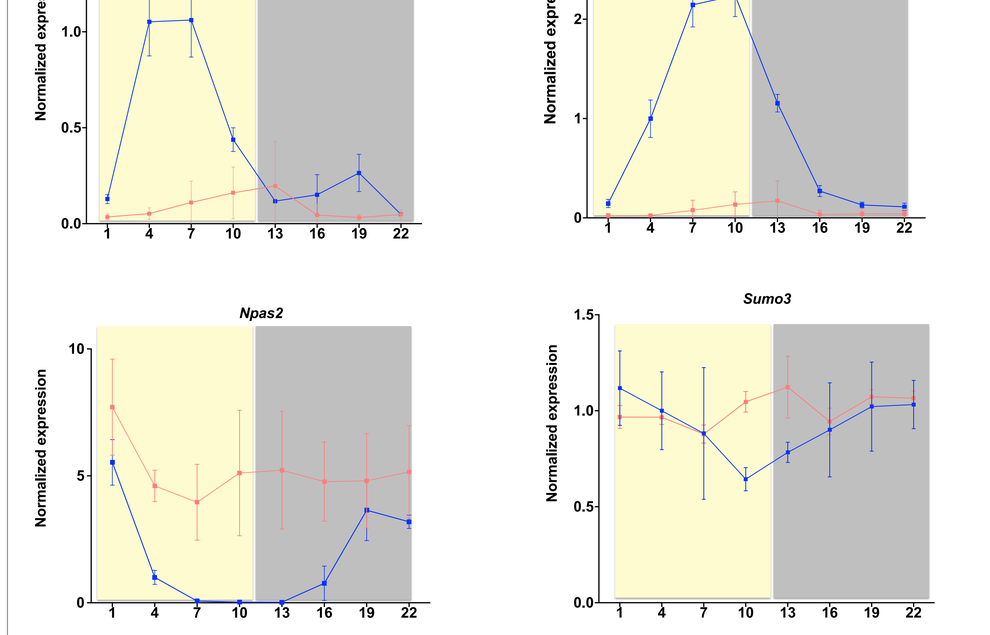
REV-ERBα may transcriptionally regulate machinery required for post-transcriptional modification of proteins in the liver.

Methods



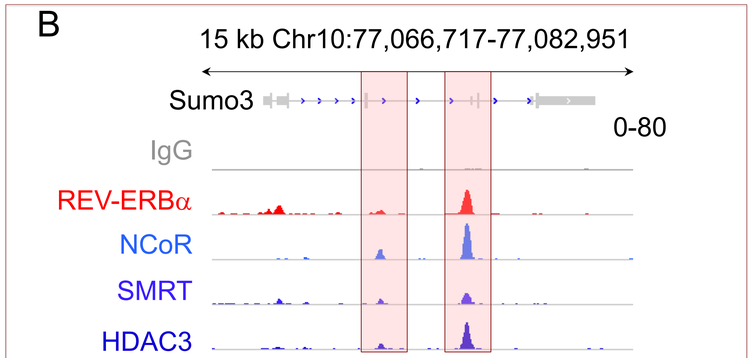
Mice were injected with either AAV.GFP or AAV.CRE and liver samples were collected every 3 hours Western Blotting and RNA extraction was performed.

Results



A. Graphs displaying basal (blue) mRNA expression and expression following REV-ERB dKO (red). REV-ERBα and β expression is ablated in the dKO, Npas2, a target of REV-ERBs, expression is derepressed. SUMO3 followed the pattern of canonical REV-ERB targets, and this is validated in the dKO measurements with SUMO3 mRNA being dysregulated.

Results



B ChIP-seq track showing REV-ERB and its co-repressive partners at the SUMO3 gene body.

Conclusions

- REV-ERBα transcriptionally represses SUMO3 mRNA.
- REV-ERBα binds at the *SUMO3* gene body, suggesting direct transcriptional control.

Future Directions

- Determine if SUMO3 regulation by REV-ERBα has an affect on the modification and function of Bmal1
- Determine if SUMOylation of other liver proteins is circadian, and to what extent the SUMOylation is controlled by REV-ERBs.

Acknowledgments

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Citations

[1] Panda. Circadian physiology of metabolism. Science. **2016**
[2] Lazar, et al. Rev-erbα and Rev-erbβ coordinately protect the circadian clock and normal metabolic function. Genes & Development. **2012**