# REPLY TO FURLAN ET AL.:
# The role of SIRT1 in cell autonomous clock function

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As the mathematical model developed by Woller et al. (1) also considers the role of SIRT1 in circadian clock, we regret not citing this work. However, we feel the inferences drawn in Furlan et al.'s (2) letter conflate 2 distinct studies with disparate purposes and methods.

In Foteinou et al. (3), we address the role of SIRT1 in cell-autonomous clock function. We undertook this experimentation and modeling to resolve the conflicting reports by Asher et al. (4) and Nakahata et al. (5), elucidating core clock molecular targets of SIRT1 deacetylation. We validated our model predictions experimentally in a series of in vitro experiments testing genetic (epistatic) interactions in cell-autonomous clock models. The results of our experiments strongly support PER2 as the primary target of SIRT1, as reported by Asher et al. (4). Further, they also support the cell-autonomous action of SIRT1 on PGC1α, explaining experimental observations in *SIRT1* and *BMAL1* double-knockdown experiments.

In contrast, Woller et al. (1) focused on a mathematical model linking feeding and fasting cycles to clock function in the liver. While the models share common features (e.g., core clock factors and SIRT1), the impetus and goals of the models are different. Woller et al. were motivated to explain the impact of nutritional status on liver clock function, while we (3) were motivated to determine and experimentally validate the role of SIRT1 in cell-autonomous clock function. The liver is not cell autonomous, and no experiments were undertaken to validate the role of specific clock proteins (e.g., PER2) in the Woller et al. model. Instead, paralogous clock proteins were grouped as single entities (e.g., PER1, PER2, PER3 = PER). Therefore, while our model does not attempt and cannot address the role of feeding/fasting cycles on liver clock function, their model does not attempt and cannot address the role of specific clock factors in cell-autonomous clock function. The models are different.


1 A. Woller, H. Duez, B. Staels, M. Lefranc, A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function. *Cell Reports* **17**, 1087–1097 (2016).
2 A. Furlan *et al.*, Mathematical models converge on PGC1α as the key metabolic integrator of SIRT1 and AMPK regulation of the circadian clock. *Proc. Natl. Acad. Sci. U.S.A.*, 10.1073/pnas.1907751116 (2019).
3 P. T. Foteinou *et al.*, Computational and experimental insights into the circadian effects of SIRT1. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 11643–11648 (2018).
4 G. Asher *et al.*, SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* **134**, 317–328 (2008).
5 Y. Nakahata *et al.*, The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* **134**, 329–340 (2008).


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The authors declare no conflict of interest.



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