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CIRCADIAN RHYTHMS

I'm not fat, I just need more sleep

> "there is a daily cycle of lipogenesis that is controlled by the circadian clock."

Quality of sleep affects many aspects of life; one well-reported observation is that shift-workers have a greater tendency towards metabolic syndrome and obesity. Now, Feng *et al.* reveal how the circadian clock controls normal hepatic lipid homeostasis by regulating the epigenome. They show that the circadian regulator REV-ERBα recruits the repressive chromatin modifier histone deacetylase 3 (HDAC3) to control the expression of lipid metabolism genes.

The authors used chromatin immunoprecipitation followed by sequencing (ChIP–seq) to investigate the diurnal variation in HDAC3-binding in adult mouse liver and found marked changes in binding between light and dark periods. In the light (when mice are inactive) HDAC3 bound at over 14,000 sites, whereas in the dark (when mice are active and feeding) there were only 120 binding sites. RNA polymerase II binding levels were reduced at the regions where HDAC3 bound in the light, suggesting transcriptional repression. Furthermore, depletion of HDAC3 led to upregulation of lipid metabolism genes and a nearly tenfold increase in the levels of total liver triglyceride. These results suggest that HDAC3 represses lipid metabolism genes in the light.

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Despite the striking changes in binding patterns, the global levels of HDAC3 remained constant, suggesting control at the recruitment level. Feng *et al.* show that the co-repressor and circadian regulator REV-ERBα colocalizes with HDAC3 at ~90% of the HDAC3 binding sites present in the light, suggesting that REV-ERBα controls the circadian recruitment of HDAC3. In addition, they found a reduction in HDAC3 recruitment in REV-ERBα knockout mice.

Thus, there is a daily cycle of lipogenesis that is controlled by the circadian clock. When REV-ERBα levels are low and mice are active lipid synthesis genes are expressed. When REV-ERBα expression levels rise, HDAC3 is recruited to the genome, preventing lipid synthesis in inactive periods. Disruption of circadian rhythms will change HDAC3 recruitment and contribute to fatty liver. These results reveal a perhaps surprisingly specific role for the general regulator HDAC3, and show how the control of recruitment of epigenetic modifiers can be crucial to metabolic processes.

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ORIGINAL RESEARCH PAPER Feng, D. *et al.* A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. *Science* **331**, 1315–1319 (2011)

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