Circadian control of epigenetic modifications modulates metabolism

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Abstract

A new study in *Science* reveals how circadian epigenetic modification of DNA drives diurnal gene expression in mouse liver and is required for the maintenance of lipid homeostasis.

Numerous physiological processes (including sleep/wake cycles, body temperature, blood pressure, hormone secretion, metabolic pathways, etc display diurnal variations. These circadian rhythms are programmed centrally by light, allowing alignment to seasonal variations of night/day cycles, and peripherally by food availability. Disruption of these circadian rhythms (due to frequent jetlag, sleep restriction or rotating shift work) predisposes to metabolic disorders and cardiovascular diseases 1 . Genome-wide studies indicate that the expression of 10–15% of genes cycles in many organs involved in metabolic control, such as the liver, and cardiovascular function, such as the vascular wall and the heart. Although many of the transcription factors of the clock machinery also exert metabolic regulatory activities, the molecular mechanisms driving the rhythmic expression pattern of metabolic genes have been unclear until now.

Feng et al. now identify circadian variations in chromatin modifications as one contributing mechanism 2 . In a series of elegant experiments they show that histone deacetylase 3 (HDAC3) binding to DNA occurs in a circadian manner, with more than 14,000 specific binding sites present during the inactive light phase, whereas only 120 sites are occupied during the dark phase active feeding period in mouse liver. This rhythmic DNA binding pattern was retained in constant darkness, but reversed upon feeding restriction to daytime, indicating that this binding rhythm is under the control of the clock machinery and can be entrained by food availability in the liver. HDAC3 is a histone lysine deacetylase, which modifies chromatin compaction, hence rendering DNA less accessible for transcription. In line, Feng et al. observed an opposite circadian pattern of H3K9 acetylation and recruitment of RNA polymerase II to gene transcription start sites, revealing a parallel rhythmicity between HDAC3 recruitment and repression of gene transcription. Since histone modifying enzymes do not bind directly to DNA, the authors went on to show that HDAC3 recruitment to DNA oscillates in phase with the circadian expression of the nuclear receptor and transcriptional repressor Rev-erbα, and that HDAC3-binding regions overlap with binding sites for Rev-erbα and the nuclear co-repressor NCoR. Consistent with this model, the same group previously reported abnormal histone acetylation and circadian profiles of gene repression in mice expressing a mutant NCoR protein unable to interact with HDAC3 3 . Together these data indicate that rhythmic recruitment of a HDAC3/Rev-erbα/NCoR repressive complex to specific sites in the DNA elicits a strong diurnal pattern of gene expression.

What is the biological implication of these observations? In addition to being part of the molecular clock machinery 4 , Rev-erbα is a metabolic regulator controlling lipid 5 , glucose 6 and bile acid metabolism 7 , as well as adipogenesis [8 ;9] . In line, the authors found that HDAC3/Rev-erbα/NCoR recruitment triggers an anti-phasic hepatic expression pattern of genes involved in lipogenesis, suggesting that this transcription complex exerts circadian control of lipogenesis.

Surprisingly, liver triglycerides accumulated not only in hepatic HDAC3-null but also in Rev-erbα–null mice. This contrasts with a publication by Le Martelot et al.10 , who observed markedly reduced hepatic triglycerides in livers of Rev-erbα-deficient mice. These authors reported that Rev-erbα regulates temporal SREBP1c nuclear translocation through circadian regulation of INSIG2, a lipid level sensing protein, resulting in a phase-shift of SREBP1c target genes involved in *de novo* lipogenesis in Rev-erbα-deficient mice. Apart from differences in the background and construction of the mouse models, it is not clear why these two studies led to these conflicting results.

Chow-fed whole-body Rev-erbα-deficient mice displayed a fairly modest liver lipid accumulation compared to mice depleted in hepatic HDAC3 2 . Contrastingly, *de novo* lipogenesis was induced to higher levels in Rev-erbα–deficient mice. Plausible, but yet to be proven explanations are compensation of Rev-erbα action by Rev-erbβ, compensation by Rev-erbα-deficiency in other tissues, and possibly, a counterbalancing increase in fatty acid oxidation. Rev-erbα also regulates hepatic glucose metabolism by repressing gluconeogenic gene expression 6 , and chow-fed NCoR mutant mice display increased hepatic glucose output 3 . However, high fat-fed NCoR mutant mice are more insulin-sensitive, due to an increased energy expenditure, decreased fat mass and increased lipid burning associated with altered circadian expression patterns of genes involved in β-oxidation which were increased during the inactive light phase. In line, the >13,000 sites bound by both Rev-erbα and HDAC3 are likely not restricted to lipogenesis only and most of the processes in which these genes are engaged remain to be elucidated. Overall, it is likely that rhythmic recruitment of repressive transcriptional complexes contributes to the control of lipid metabolism. However, the versatility of the observed phenotypes suggests that the circadian clock acts as a modulator, rather than primary regulator of hepatic metabolism.

Alternatively, it cannot be excluded that other factors control the activity of clock transcription factors and/or that part of their actions are independent of their role as clock regulator. This raises another challenging question, not addressed in the study by Feng et al.: what is the respective contribution of nutritional vs circadian regulatory signals in the control of lipogenesis? Major regulators of *de novo* lipogenesis are the nutritional state, with insulin and glucose playing a crucial role in the regulation of lipogenesis through the SREBP1c and ChREBP regulatory pathways. Intriguingly, Le Martelot et al. reported that dysregulation of SREBP1c target genes resulted in significantly reduced liver triglycerides only during the light phase, but not at night during the feeding phase. In addition, nutritional regulation (by fasting and high-carbohydrate refeeding) of lipogenic genes was retained in Rev-erbα-deficient mice, indicating that both circadian and nutritional signals regulate hepatic lipid metabolism through both interconnected and independent mechanisms 10 .

This elegant study by Feng et al demonstrates that epigenomic circadian gene regulation orchestrates metabolic function, providing a mechanism linking the misalignment of circadian gene regulation to metabolic disorders. In humans, circadian disruption associated with chronic sleep disorders or rotating shift work increases the risk for the metabolic syndrome. In addition, cardiovascular function also displays circadian variations. For instance, blood pressure and heart rate have a rhythmic profile, and acute cardiovascular events such as myocardial infarction occur predominantly in the early morning hours. A recent study indicated that shift-workers display accelerated atherosclerosis 11 . Interestingly, mice with disrupted clock components display impaired vascular remodeling and aberrant ischemia/reperfusion responses, suggesting a direct role of the clock genes in vascular function [12 ;13] . Rev-erbα modulates the fibrinolysis cascade through regulation of PAI-1 expression 14 , and the inflammatory response 15 . Deletion of PPARγ, which regulates expression of the clock component Bmal1, in endothelial or smooth muscle cells, as well as deletion of Bmal1, results in blunted daily blood pressure variations 16 . All these finding reinforce the idea that circadian anticipation is critical for normal energy homeostasis and cardiovascular function.

Major gaps in our understanding of circadian control of metabolism still remain. First, how does the nutritional state and circadian clock connect to control metabolism? Second, since it is unlikely that Rev-erbα is the sole mediator of all HDAC3 actions, which are the other HDAC3 partners in the epigenomic control of metabolism? Third, what is the impact of the clock (and clock disorders) on human (patho)physiology, and, in particular, on cardiovascular diseases? Future studies should also address the question whether pharmacological modulation of nuclear receptor activity may provide a means to improve circadian disorder-related metabolic and cardiovascular dysfunctions.

References:

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Figure

Circadian HDAC3/NCoR recruitment to DNA regulates hepatic lipid homeostasis.