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MICROBIOME

Rhythm and bacteria

> the gut microbiome contributes to the maintenance of systemic metabolome rhythms

Circadian systems are widespread in many organisms; in fact, recent studies have shown that the gut microbiota undergoes rhythmic oscillations in composition and function. However, how circadian rhythms are linked between the microbiota and the host is mostly unknown. In a recent study, Thaiss *et al* uncovered that the circadian changes in the biogeography and metabolic activity of the gut microbiota in mice influence host physiology in the intestine and the liver.

To elucidate circadian changes in the gut microbiota, the authors studied mice that were exposed to cycles of 12 hours of darkness followed by 12 hours of light. Substantial changes in the biogeography of colonic bacteria were observed; in particular, the number of bacteria in the epithelial mucus layer decreased during the period of light and was the highest during darkness. Some species, such as the typically mucus-dwelling bacterium *Mucispirillum schaedleri*, showed big changes in epithelial adherence. Furthermore, metagenomic sequencing showed that pathways that are involved in chemotaxis, flagellar motility and mucus degradation also underwent diurnal oscillations. These changes in bacterial biogeography were influenced by feeding patterns and epithelial barrier function, but not by the molecular clock of the host.

To evaluate the influence of microbiota oscillations on the host, the authors assessed host transcriptome and epigenome rhythmicity. Antibiotic-treated and germ-free mice had substantially altered oscillating transcriptome and epigenome profiles in the host intestine. Unexpectedly, following microbial depletion, genes and pathways that are involved in metabolic homeostasis gained rhythmicity, which led the authors to hypothesize that the host acquires new oscillatory functions to compensate for the absence of an intestinal microbiota. This was confirmed by colonizing germ-free mice with segmented filamentous bacteria from mice and rats, of which the former exhibited enhanced adherence to the murine intestinal epithelium. Only the bacteria that exhibited rhythmic epithelial tissue adherence were able to influence the programming of transcriptional host oscillations.

Furthermore, transcriptional rhythmicity not only differed locally in the intestines, but also hepatocytes showed different circadian transcriptome changes in antibiotic-treated and germ-free mice compared with non-treated controls. The authors hypothesized that this could be owing to changes in the rhythmic pattern of metabolite production by the gut microbiota. Indeed, numerous classes of metabolite, including amino acids and polyamines, oscillated diurnally in the gut and in the serum, and these oscillations were abolished following treatment with antibiotics or in germ-free mice. Remarkably, in mice that were fed a polyamine-deficient diet, polyamines and amino acids no longer showed oscillatory abundance and the hepatic circadian transcriptome was reprogrammed to compensate. This implies that the gut microbiome contributes to the maintenance of systemic metabolome rhythms.

In summary, this study provides important insights into the role of the gut microbiome in circadian physiology and in the regulation of transcriptional activity in peripheral organs, which may provide new strategies to treat human diseases that are associated with circadian clock dysfunction.

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