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GUT MICROBIOTA

Intestinal microbiota oscillations regulate host circadian physiology

> …the gut microbiome is key to the maintenance of systemic metabolome rhythms…

The intestinal microbiota in mice undergo rhythmic fluctuations in biogeography and metabolome patterns, according to a new study published in *Cell*. These oscillations result in system-wide effects on host circadian transcriptional, epigenetic and metabolite cycles that affect physiology and disease susceptibility.

The gut microbiota have previously been shown to feature diurnal rhythms in composition and function, but how these daily oscillations then affect host physiology was unknown. "We therefore focused on the characteristics of the microbiome that are most relevant for the physiology of the host, namely its metabolic function and its biogeographical localization in vicinity to the host's intestinal epithelial cells," explains corresponding author Eran Elinav.

First, using scanning electron microscopy and quantitative PCR, the colonic mucosa of mice was shown to be exposed to daily fluctuations in numbers and species of commensal bacteria. "We used microbiota imaging to understand the biogeographical aspects of diurnal host–microbiome interactions," says Elinav, which revealed rhythmic fluctuations in the thickness of the intestinal mucus layer and the magnitude of separation between the host epithelium and commensal bacteria.

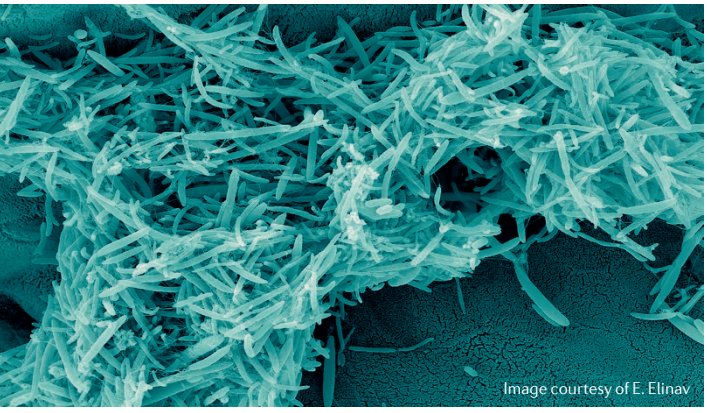

Image courtesy of E. Elinav

Investigating the effects of daily microbiome fluctuations on the intestinal epithelium, host circadian transcriptional responses were assessed every 6 h over two light–dark cycles using comparative RNA sequencing (RNA-seq) of colonic tissue from control and antibiotic-treated mice. "We found that the microbiome is involved in selecting the repertoire of genes in a tissue whose transcription undergoes circadian oscillations," reports Elinav. "Upon disruption of homeostatic microbiota rhythms, a large part of normally oscillating genes lost their rhythmicity, while another large set of genes gained oscillatory behaviour." Similar experiments were performed using chromatin immunoprecipitation followed by next-generation sequencing (ChIP-seq) to elucidate the regulatory mechanisms of the transcriptomic oscillations. These data revealed epigenomic cycling behaviour in agreement with the gene expression data, indicating that microbial colonization affects transcriptomic oscillations via effects on promoter and enhancer activity.

In examining the effects of the microbiome on host circadian rhythms beyond the gastrointestinal tract, RNA-seq analysis was also performed on liver tissue samples of antibiotic-treated and control mice at multiple intervals. As in the colon, disruption of the microbiota reprogrammed diurnal liver transcriptome oscillations. To account for this effect, the researchers profiled the temporal levels of serum metabolites in control, germ-free mice and antibiotic-treated mice. These data showed that rhythmic oscillations of serum metabolites detected in the control mice were abolished in the absence of the microbiota, suggesting that the gut microbiome is key to the maintenance of systemic metabolome rhythms that might then influence the hepatic transcriptome.

Finally, in demonstrating the functional implications of these findings, the investigators examined the effect of abrogated circadian rhythms on hepatic drug detoxification, which is known to be affected by the time of day. In germ-free and antibiotic-treated mice, the diurnal severity of paracetomol-induced hepatotoxicity was lost, indicating that the microbiota-mediated maintenance of the circadian transcriptome is necessary to maintain normal activity in hepatic drug metabolism.

The researchers now plan to further investigate how the gut microbiome affects systemic metabolites. "As metabolites have a profound impact on many aspects of physiology, including the immune and metabolic system, it will be interesting in the future to explore the consequences of diurnal microbiota disruption on diseases associated with disruptions of the circadian clock," concludes Elinav.

Iain Dickson

ORIGINAL ARTICLE Thaiss, C. A. *et al.* Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell* **167**, 1495–1510.e12 (2016)