# Healing by the Clock

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Circadian rhythms keep time for all living things, from regulating when plants open their flowers to foiling people when they try to beat jet lag. Day-night cycles are controlled through ancient biological mechanisms, evolutionarily speaking, so in essence, a human has the same internal clock as a fly does.

These circadian clocks govern daily rhythms through genes that synchronize molecular pathways that promote or repress protein production, influencing a multitude of body functions. Even before waking, for example, our clock-driven metabolism turns on enzymes and transporters that prepare our bodies to eat and digest food.

One of the circadian clock's transcription factors, proteins that regulate gene activity, is called *period*. Stem cell biologist Phillip Karpowicz [1], HMS research fellow in genetics, did not expect to find *period* in the gut of a fly. Working in the lab of Norbert Perrimon [2], the James Stillman Professor of Developmental Biology in the Harvard Medical School Department of Genetics, Karpowicz studies flies to see how the intestine regenerates cells when they are injured.

Screening for transcription factors active in damage repair revealed that the gene *period* was needed. Further experiments showed that this component of the circadian clock is critical to intestinal regeneration, meaning that in flies, gut healing fluctuates according to the time of day. Karpowicz, Perrimon and their colleagues published their results April 11 in *Cell Reports* [3].

"We thought this was really weird. I would not have thought that regeneration would tend to work better at one part of the day versus another part of the day," Karpowicz said. "But now we've shown that there's a rhythm in stem cells that's really important for the regeneration process."

"This is a beautiful example of why we do genetic screens in the first place. By taking an unbiased approach, the fly tells us what is important to study," Perrimon said.

Intestines are hotbeds of regeneration because they are constantly vulnerable to damage. Harmful bacteria or harsh chemicals that animals ingest can injure cells lining their intestines, which are essential for absorbing nutrients or blocking infectious agents from crossing through thin intestinal walls.

To understand how a circadian clock might operate in intestinal stem cells, the scientists bred mutant flies to lack the *period* gene. The flies were normal except for their arrhythmic bursts of activity throughout the 24-hour day. Their intestines also appeared normal, until they ingested a chemical that caused inflammation.

Compared to other flies, the mutants mounted a weaker response to repair their damaged cells. Their stem cells divided poorly and in a more haphazard manner, impairing the healing process.

In further experiments, the scientists tested whether *period* was active in cells called enterocytes that surround the intestinal stem cells and absorb nutrients. Disrupting *period* in enterocytes also weakened the cells' response to damage. The scientists showed that this rhythm originates in the intestine, rather than in the brain, which typically controls circadian rhythms.

The scientists widened their lens to look at all the genes that were turned on or off during the day. Performing genome-wide expression studies, they discovered 430 genes—about 3 percent of the fly genome—that are rhythmically expressed in fly intestines.

"We think these cells may be more acutely sensitive to damage at a certain time of day," Karpowicz said.

The next step will be to confirm these fly findings in mice. The scientists have already contemplated the potential applications to human health, including the timing of chemotherapy so a patient might best tolerate the treatment's side effects.

"This could be quite relevant in terms of when you should time the absorption of those drugs to work in sync with the intestinal regeneration process," Karpowicz said.

This work was supported by the Human Frontier Science Program, the Harvard Stem Cell Institute and NIH grants GM66777 and GM79182.

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