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By Carrie Arnold

Malaria parasites synch with host

Plasmodium microbes that cause malaria coordinate with the internal clocks of their hosts to increase their chances of survival

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Plasmodium parasites responsible for deadly outbreaks of malaria synchronize their emergence and development with the circadian rhythms of their hosts to maximize their survival and spread.

The results, published online today (January 5) in *Proceedings of the Royal Society B*, give clues to why circadian clocks are maintained in so many parasite species, and may hold implications for when to administer malaria treatments to infected individuals.

Image: Sarah Reece and Sinclair Stammers

"This study is incredibly important," said Deborah Bell-Pedersen, a molecular biologist at Texas A&M University, who was not involved in the study. "It helps us appreciate the role of clocks in organisms, and how they provide an advantage to their growth and well-being."

For years scientists have recognized the special timing of malaria infections: millions of *Plasmodium* parasites emerge en masse from red blood cells to cause the fever, chills, and anemia that characterize malaria. This military precision is believed to be crucial to the microbes' survival, as the host immune response that follows efficiently mops up any straggling *Plasmodium* that emerge after the group. In other words, the parasites have adopted a "safety in numbers" technique.

The symptoms of malaria, caused by the physiological stress of the parasite influx combined with the host immune response, tend to return regularly, often at the same time of day. To Sarah Reece, a malaria researcher at the University of Edinburgh in the UK, this meant that the malaria parasites must be able to tell time. Indeed, previous studies have shown that *Plasmodium* could sense their host's melatonin levels, a reliable proxy for the body's clock.

To determine how the parasites use this information, Reece and her colleagues created a mismatch between the circadian clocks of the *Plasmodium* microbes and their mice hosts. The researchers kept one group of

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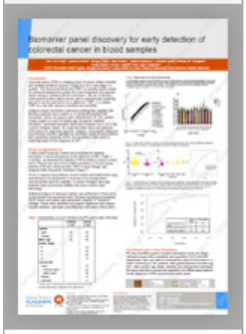
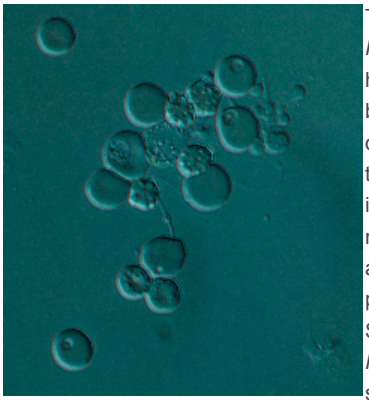


mice on their normal light schedule of 7am to 7pm, but kept a second group of mice on a reversed, 7pm to 7am schedule. After two weeks, the team infected the mice with *Plasmodium* in the "morning" -- 7am for the first group and 7pm for the latter -- and watched the resulting disease develop.

In both groups, the parasites emerged during normal evening hours, but in the group with a mismatch between the host and parasite internal clocks, only half as many *Plasmodium* appeared, suggesting the parasite were less likely to survive the host's massive immune response.



Malaria parasites (*Plasmodium chabaudi*) in the blood
Image: Sarah Reece and Sinclair Stammers

The circadian mismatch also halved *Plasmodium*'s ability to spread to other hosts. Before they emerge from the red blood cells, a few of the parasites differentiate into gametes that combine to form the next generation when an infected host is again bitten by a mosquito. The *Plasmodium* in the asynchronous mice, however, only produced half the number of gametes. So this circadian mismatch hits *Plasmodium* twice: it halves its ability to survive in its host, and it halves its chances of transmission.

"These results show that the [circadian] clock has had a role in the evolution of the parasite itself," Bell-Pedersen said. "This is the first time that this has been shown experimentally."

"Everything pretty much has a circadian clock, but we don't really know why," Reece said. These results help explain the evolutionary forces that have been maintaining these circadian clocks in these parasites for hundreds of millions of years.

While interesting, the finding won't necessarily translate into new malaria treatments, said Bell-Pedersen, but the results may have implications for the timing of existing malaria treatments. Therapies may work better, for example, if the medication is given at different times, or if the patients are placed on different light/dark schedules, she said.

Furthermore, the findings may apply to other types of infections, Reece said. If other parasites have this need to synchronize with their hosts, "then this might be something to use to treat all kinds of diseases," she said.

A.J. O'Donnell, et al., "Fitness costs of disrupting circadian rhythms in malaria parasites," *Proceedings of the Royal Society B*, doi:10.1098/rspb.2010.2457.

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