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HOST RESPONSE

Phagocytosis runs like clockwork

Susceptibility to microbial infection is strongly influenced by the efficacy of the host's immune response, which is known to fluctuate in animals depending on the time of day (termed circadian-regulated immunity). However, the mechanistic basis of this phenomenon is poorly understood. In a recent issue of *PLoS Pathogens*, Stone *et al.* describe how a component of the *Drosophila melanogaster* circadian machinery, the transcription regulator Timeless (TIM), mediates resistance to specific bacterial infections.

Previous studies have demonstrated that the circadian immune response of *D. melanogaster* is pathogen specific. In agreement with this, Stone *et al.* found that, compared with wild type, a *D. melanogaster* mutant lacking TIM was more sensitive to infection with *Streptococcus pneumoniae* and *Serratia marcescens* but not with *Burkholderia cepacia* or *Salmonella enterica* subsp. *enterica* serovar Typhimurium. Further investigations revealed that the resistance of wild-type flies to *S. pneumoniae* infection varied with the time of day and was positively correlated with TIM levels. In addition, wild-type flies depleted of TIM, as a result of constant light exposure, replicated the *tim*-null phenotype.

How does TIM regulate resistance to infection? The authors found that two of the three major immune defence pathways in *D. melanogaster* — the generation of reactive oxygen species through melanization, and antimicrobial-peptide synthesis — were not circadian-regulated responses. By contrast, the ability of *D. melanogaster* to phagocytose *Staphylococcus aureus* did follow a circadian rhythm, being low during the day and high at night, and this effect was TIM dependent. TIM appears to stimulate a bacterium-specific step of phagocytosis, such as substrate recognition or receptor binding, as the presence of TIM did not upregulate phagocytosis of *Escherichia coli*. Finally, the authors were able to demonstrate that the reduced resistance of the *D. melanogaster tim*-null mutant to *S. pneumoniae* infection was caused by loss of phagocytic activity.

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Taken together, these data indicate that phagocytosis in *D. melanogaster* is circadian regulated and are certain to spur further research in this poorly explored facet of infection biology.

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ORIGINAL RESEARCH PAPER Stone, E. F. *et al.* The circadian clock protein Timeless regulates phagocytosis of bacteria in *Drosophila*. *PLoS Pathog.* **8**, e1002445 (2012)