INNAE IMMUNITY

PIMS knows friends and foes

How do metazoans balance immune responses to commensal and pathogenic bacteria? In a paper just published in *Cell Host & Microbe* Lhocine *et al.* report the identification of a protein in the fruit fly *Drosophila melanogaster* that functions to dampen the immune response to commensals.

Infection of *D. melanogaster* with Gram-negative bacteria activates the IMD (immune deficiency) signal transduction system, which results in the synthesis of antimicrobial peptides (AMPs). Curiously, although bacterially derived peptidoglycan activates the IMD system, peptidoglycan from the millions of commensal bacteria that colonize the gut of healthy *D. melanogaster* fails to elicit an immune response. *D. melanogaster* therefore seems to strike a balance between producing AMPs in response to pathogens while tolerating commensals. Lhocine and colleagues show that the protein PIMS (peptidoglycan recognition protein (PGRP)-LC-interacting inhibitor of IMD signalling), which is synthesized in response to peptidoglycan-dependent IMD signalling, functions as part of a negative feedback pathway that inhibits the production of AMPs in response to commensal bacteria.

Basal levels of PIMS transcription are dependent on the presence of commensal bacteria; flies that were raised in germ-free conditions made significantly less *pims* mRNA

than flies raised under conventional conditions. Moreover, expression of *pims* increased further when conventionally raised *D. melanogaster* was infected either by *Escherichia coli*, through a septic injury, or after oral infection with *Erwinia carotovora* subsp. *carotovora* 15. Both the basal level of PIMS expression and the increased expression following Gram-negative bacterial infection were found to be dependent on the nuclear factor- κ B orthologue Relish, which is an integral member of the IMD-dependent signalling pathway.

In *pims* mutants, transcription of the gene that encodes the AMP dipterecin (*dpt*) was increased and ectopically induced in tissues that, under non-challenged conditions, do not express *dpt*. Also, downregulation of *pims* mRNA by RNA interference resulted in widespread expression of *dpt* throughout immune responsive tissues in the fly body. Strikingly, during oral challenge with bacteria, production of AMPs was increased in the *pims* mutants compared with wild-type animals.

Based on these results, the authors propose a model in which PIMS, together with the two previously described proteins PGRP-LB and PGRP-SC1, ensures immune tolerance by providing a buffered threshold for activation of the immune response by peptidoglycan. In the presence of commensal bacteria, PIMS is produced at a low level and prevents signalling through the IMD

pathway, thus shutting off synthesis of AMPs. An increase in the bacterial (and peptidoglycan) load is sufficient to induce production of the AMPs.

Using co-immunoprecipitation studies, the authors demonstrated a physical interaction between PIMS and PGRP-LCx, one of the plasma-membrane receptors for peptidoglycan that initiates signalling by the IMD pathway. Co-expression of PIMS and PGRP-LCx *in vitro* led to a change in the subcellular localization of PGRP-LCx from the plasma membrane to perinuclear structures. However, the exact mechanism by which PIMS prevents the surface availability of PGRP-LCx remains unclear.

Christiaan van Ooij

ORIGINAL RESEARCH PAPER Lhocine, N. *et al.* PIMS modulates immune tolerance by negatively regulating *Drosophila* innate immune signaling. *Cell Host & Microbe* 4, 147–158 (2008)