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INNATE 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 fruitfly *Drosophila melanogaster* that functions to dampen the immune response to commensal bacteria.

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 depend on the presence of commensal bacteria; flies that were raised in germfree conditions made significantly less *pims* mRNA than flies raised under conventional conditions. Moreover, the expression of *pims* increased further when conventionally raised *D. melanogaster* was infected either with *Escherichia coli*, through a septic injury, or after oral infection with the Gram-negative bacteria *Erwinia carotovora* subsp. *carotovora 15*. Both the basal level of PIMS expression and the increased expression following bacterial infection were found to depend on the nuclear factor-κB orthologue Relish, which is an integral member of the IMD-dependent signalling pathway.

In PIMS-deficient flies, transcription of the gene that encodes the AMP diptericin (*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, the production of AMPs was increased in the *pims*-mutant flies compared with wild-type flies.

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

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