INNATE IMMUNITY

Worms: the new *Drosophila*?

Drosophila melanogaster has proven to be a useful model system for elucidating the pathways of innate immunity, but could worms become the new *Drosophila*? A new study shows that worms, although they lack the Toll and Imd pathways by which *Drosophila* respond to bacterial and fungal infections, can produce antimicrobial peptides in response to infection.

The authors used a microarray strategy to identify genes induced in worms after infection with the fungus *Drechmeria coniospora* and the Gram-negative bacterium *Serratia marcescens*. Only two genes (*nlp-29* and *cnc-2*), which encode peptide molecules, were strongly induced by both infections. An additional four genes were induced after infection with *D. coniospora*. A representative member of the peptide family, neuropeptide-like protein-31 (nlp-31), was synthesized and found to have antifungal activity *in vitro*.

To study the induction of these peptides *in vivo*, transgenic worms were generated expressing green fluorescent protein under control of the *nlp-29* and *nlp-31* promoters. Expression of nlp-31 in the hypodermis increased after *D. coniospora* infection. In addition to the hypodermal expression, localized expression was observed in the nlp-29-transgenic worms in the vulval region where the fungal spores adhered.

Worms have a single Toll-like receptor gene, *tol-1*. So, does tol-1 control expression of the antimicrobial peptides? *Tol-1* mutants were no more susceptible than wild-type worms to infection with *D. coniospora*, indicating that tol-1 does not control antifungal defence. But worms have an additional gene that encodes another Toll/interleukin-1 receptor (TIR)-domain-containing protein. The authors called this gene *tir-1*. Of the five possible isoforms, tir-1a is a homologue of the vertebrate TIR-domain-containing adaptor protein SARM (sterile α and armadillo motif protein), the function of which is unknown. When *tir-1* was inactivated by RNA interference, the worms were more susceptible to infection, and production of the antimicrobial peptides was reduced. Because tol-1 has no role in regulating peptide expression, it seems that tir-1 is not coupled to an upstream TIR-domain-containing receptor, and the authors suggest that this might also be the case for SARM.

To characterize tir-1 interactions, a yeast two-hybrid screen was carried out. Eight proteins, as well as tir-1, were identified in this screen. Two of these genes, corresponding to the small GTPase Rab1 and the f-subunit of ATP synthase, were required for expression of the antimicrobial peptides, although how these interactions control peptide expression has yet to be determined.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Couillault, C. *et al.* TLR-independent control of innate immunity in *Caenorhabditis elegans* by the TIR domain adaptor protein TIR-1, an ortholog of human SARM. *Nature Immunol.* **5**, 488–494 (2004)

FURTHER READING Kurz, C. L. & Ewbank, J. J. *Caenorhabditis elegans*: an emerging genetic model for the study of innate immunity. *Nature Rev. Genet.* **4**, 380–390 (2003)

WEB SITE

Jonathan Ewbank's lab: http://www.ciml.univ-mrs.fr/EWBANK_jonathan/JE-PRES-A01.htm

IN BRIEF

INNATE IMMUNITY

Effects of mosquito genes on *Plasmodium* development.

Osta, M. A., Christophides, G. K. & Kafatos, F. C. *Science* **303**, 2030–2032 (2004)

Previous analysis of the *Anopheles gambiae* genome, a mosquito vector for *Plasmodium*, identified 242 genes as potential mediators of innate immunity. In this study, the function of three of these genes was investigated by gene silencing. Functional deletion of two C-type lectins (CTLs), CTL4 and CTLMA2, resulted in the death of most *Plasmodium* ookinetes, indicating that these two CTLs protect parasites during development. By contrast, lack of leucine-rich-repeat immune gene (*LRIM*) function resulted in increased numbers of *Plasmodium* oocysts, providing evidence that LRIM antagonizes *Plasmodium* development. The identification of mosquito proteins that have positive and negative effects on *Plasmodium* provides new avenues of research in the quest to control malaria through the mosquito vector.

LYMPHOCYTE MIGRATION

Activated primary and memory CD8 T cells migrate to nonlymphoid tissues regardless of site of activation or tissue of origin.

Masopust, D. *et al. J. Immunol.* **172**, 4875–4882 (2004)

This study examines whether the site of antigen encounter determines the extralymphoid migratory properties of activated CD8$^+$ T cells. Antigen-specific CD8$^+$ T cells activated by localized intestinal viral infection were found not only in the intestine but also in other non-lymphoid tissues. This widespread distribution was observed for both the primary effector cells and virus-specific memory cells. Furthermore, memory CD8$^+$ T cells from non-lymphoid tissues, other than the intestinal mucosa, retained the ability to disseminate into multiple extralymphoid sites, albeit with some preference for their site of isolation. These findings have implications for immunotherapies that induce antigen-specific immunity or regulate disease by controlling T-cell migration.

ANTIGEN PRESENTATION

MHC class I molecules expressed with monoglucosylated N-linked glycans bind calreticulin independently of their assembly status.

Wearsch, P. A. *et al. J. Biol. Chem.* 31 March 2004 (doi:10.1074/jbc.M401721200)

This study used a novel glycosylation mutant strain of *Saccharomyces cerevisiae*, which could produce MHC class I molecules bearing the transient oligosaccharide intermediates recognized by calreticulin — monoglucosylated N-linked glycans — to investigate the precise role of this chaperone in generating peptide–MHC class I complexes. Calreticulin binding to these MHC class I molecules was dependent on the N-linked glycan, and specifically on the glucose residue. Calreticulin was found to bind correctly glycosylated MHC class I molecules irrespective of their conformation — free MHC class I heavy chains, empty MHC class I–β_2-microglobulin heterodimers and peptide-loaded MHC class I complexes — providing support for the hypothesis that, by binding monoglucosylated N-linked glycans, calreticulin cannot determine the conformation of the protein.