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IMMUNOGENETICS

A natural response

The regulation of some immune responses in insects and humans are remarkably closely conserved, and the signalling pathways in *Drosophila*, unraveled through elegant genetic studies, are providing an invaluable framework for understanding mammalian innate immunity — the rapid response to pathogen invasion. Vidal *et al.* now report a new and essential component of the innate immune response to Gram-negative bacteria in *Drosophila* — *dTAK1* — which, as a homologue of a mammalian MAPKKK kinase, has a conserved role in host defence.

In *Drosophila*, two innate immune response pathways induce distinct classes of antimicrobial peptides. Immunity to fungi depends on the Toll pathway, whereas the Imd pathway is required for resistance to Gram-negative bacteria. Although some components of the Imd pathway are known — for example, members of the I κ B kinase (IKK) complex, Dredd (a caspase) and Relish (Rel, an NF- κ B homologue) — others remain to be found. To fill these gaps, this group had previously screened mutagenized *Drosophila* for susceptibility to infection with Gram-negative bacteria, uncovering two genes — *Dredd*, and a second gene described here.

Four recessive mutations were identified that block the induction of the antimicrobial peptide *Diptericin* — a target of the Imd pathway — without impairing the functioning of the Toll pathway. The mutations map to a region that contains 25 genes,

one of which is *dTAK1*. As mammalian TAK1 is a potential regulator of NF κ B, *dTAK1* was an obvious candidate gene to study. Its role was confirmed in three ways. First, a wild-type *dTAK1* transgene rescued the mutants' lack of an antimicrobial response. Second, sequencing identified mutations within the catalytic domain of *dTAK1* in mutant flies. Third, expression of a dominant-negative form of *dTAK1* in wild-type *Drosophila* inhibited *Diptericin* induction in response to bacterial infection.

But where is *dTAK1* positioned relative to the other Imd-pathway components? This was resolved by overexpressing *Dredd* and *dTAK1* in *Imd*-, *IKK β* -, *IKK γ* -, and *Rel*-deficient backgrounds, and then assessing *Diptericin* expression. These experiments revealed epistatic relationships between the genes (see picture), placing *dTAK1* upstream of *IKK β* /*IKK γ* and *Dredd* downstream of the IKK complex.

According to this model, Imd pathway activation results in the cleavage of Relish, possibly by Dredd, and the subsequent nuclear translocation of the Rel activation domain. The authors predict that antimicrobial genes integrate signals from the Imd and Toll pathways by responding to specific combinations of the different Rel proteins that are end targets of these pathways. This combinatorial regulation of target genes might be key to how insects raise tailored immune responses to many different

pathogens from a limited number of recognition pathways.

Jennifer Bell, Associate Editor,
Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Vidal, S. *et al.* Mutations in the *Drosophila dTAK1* gene reveal a conserved function for MAPKKs in the control of rel/NF κ B-dependent innate immune responses. *Genes Dev.* **15**, 1900–1912 (2001)

FURTHER READING Kimbrell, D. A. *et al.* The evolution and genetics of innate immunity. *Nature Rev. Genet.* **2**, 256–267 (2001)

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