

Immune response of *Drosophila* with

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How complex is the immune system of *Drosophila*?

Jean-Luc Imler: The immune system of insects, and *Drosophila* in particular, is obviously not as sophisticated as that of mammals, but is more complex than initially assumed. We have come to realize that fruit-flies discriminate between different types of microbes, and mount somewhat adapted responses. For example, infection with fungi strongly induces expression of Drosomycin and Metchnikowin, two antifungal peptides. And by contrast, infection with Gram-negative bacteria strongly induce expression of antibacterial peptides, such as Diptericin and Drosocin (1). We recently showed

that viral infection triggers still a different type of transcriptional response, although at this stage the identity of the effector antiviral molecules induced is not known (2).

Another emerging important aspect of the host-defence system in *Drosophila* is the cellular response. For example, the importance of the phagocytic receptor Eater on plasmatocytes, the most abundant blood cells, was recently established (3). A particularly interesting type of blood cell is the lamellocyte, which differentiates upon infection by large parasites, and participates in their clearance by encapsulation (4).

Why is it important to study host-defence in a model like *Drosophila*?

Jean-Luc Imler: A first reason pertains to the fact that molecular mechanisms controlling important aspects of the biology of multicellular organisms have often been conserved through evolution. Thus, by studying innate immunity in the fruitfly, it is possible using comparative genomics to uncover molecules or pathways regulating the mammalian immune system (e.g. Toll receptors) (1). A second reason is that the effec-

tor molecules operating in *Drosophila* to counter infections may be turned into therapeutics, or that the study of their mode of action may reveal novel ideas or targets to develop such therapeutics. The third reason is that other dipteran insects, in particular mosquitoes, are vectors for infectious microorganisms that can cause severe diseases upon transmission to mammalian hosts (e.g. malaria, dengue or West Nile fever) (5).

What can be learned from the study of antimicrobial peptides?

Jean-Luc Imler: Antimicrobial peptides (AMPs) are used by invertebrates, but also vertebrates, plants and even some fungi, to control microbial growth (6). Several of them act at the level of the cell-wall of bacteria. It is commonly admitted that this membrane-targeted mode of action may generate microbial resistance at a lower frequency than for conventional antibiotics acting on intracellular targets. *Drosophila* AMPs are secreted

into the hemolymph that bathes all organs. As a result, these molecules are usually less toxic than their mammalian counterparts, despite being as efficient in terms of microbicidal activity. Commercial development of AMPs as therapeutics has been essentially hindered by the technical challenge of producing them in a cost-effective way at the scale and purity required (6).

The study of the mode of action of AMPs can also

suggest novel targets for the development of original therapeutic strategies. For example, the characterization of the mode of action of the θ -defensin ret-

rocylin-2 (RC2) recently indicated that the displacement of proteins from the fusion zone was an essential step for the entry of enveloped viruses (7).

What type of signal pathways are involved?

Jean-Luc Imler: Using AMPs as markers, two pathways, regulating different members of the NF- κ B family of transcription factors, have been identified. The Toll pathway regulates expression of the antifungal peptide Drosomycin, whereas the Immune deficiency (Imd) pathway regulates expression of the antibacterial peptide Diptericin. The Toll pathway regulates the NF- κ B-like factor Dif, which is maintained in the cytosol of resting cells by the I κ B homologue Cactus. Other components of the pathway include the Toll receptor, the adaptor MyD88, and the IRAK4 homologue Pelle. The Imd pathway on the other hand involves the transcription factor Relish that is expressed as an inactive ankyrin-repeat containing precursor, like p105 in mammals. Proteolytic processing and activation of Relish involves the death-domain adaptor-like factor encoded by Imd, the adaptor dFADD, the caspase DREDD,

the kinase dTAK1, and the homologues of IKK β and NEMO/IKK γ . The most striking feature of the Toll and Imd pathways is that they involve molecules that have orthologues functioning respectively in the interleukin-1 (IL-1) and TNF pathways in mammals (1). Another evolutionary conserved signalling pathway, the JAK-STAT pathway, participates in the control of viral infections in flies (2). Thus, the three main pathways controlling inflammation in mammals (IL-1, TNF and IFN) may have been present as long as 800 million years ago, to control infections in the common ancestor of invertebrates and vertebrates.

Studies on blood cells differentiation also revealed interesting parallels with mammals. Indeed, involvement of the JAK/STAT and Notch pathways, and of the homologues of the transcription factors GATA and Early B cell factor (EBF) has been established (4,8).

How are microorganisms sensed by the immune system?

Jean-Luc Imler: Fungi and most Gram-positive bacteria activate the Toll pathway, whereas most Gram-negative bacteria activate the Imd pathway. Two families of receptors have been shown to participate in the sensing of infections, the peptidoglycan recognition proteins (PGRPs) and the β -glucan recognition proteins (β GRP), also known as Gram-negative binding proteins (GNBPs) (9).

Recognition of fungi and Gram-positive bacteria occurs in the hemolymph, and involves soluble receptors. In the case of Gram-positive bacteria, peptidoglycan (PGN), which contains a Lysine residue at the third position of the stem peptide (instead of a Diaminopimelic residue in the PGN from Gram-negative bacteria), is recognized by PGRP-SA, acting in concert with GNBPs and

in some cases PGRP-SD. Fungi on the other hand are sensed through GNBPs (9,10). These soluble receptors then activate proteases that cleave the cytokine Spaetzle, thus generating an active Toll ligand. Hence, Toll in *Drosophila* functions as a cytokine receptor, and does not directly sense microorganisms, like mammalian TLRs do. Gram-negative bacteria are detected by the transmembrane receptor PGRP-LC, which senses the Diaminopimelic acid-type PGN. PGRP-LC acts in concert with another member of the family, PGRP-LE. Thus, *Drosophila* makes use of two different families of innate immunity receptors, the PGRPs and the GNBPs/ β GRPs, to detect infectious agents. The receptors involved in sensing viral and parasitic infections have not been identified yet.

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