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Drosophila immunity: two paths to NF-κB

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Recent studies of *Drosophila* immune responses have defined the immune deficiency (IMD) signaling pathway that mediates defense against Gram-negative bacterial infection. Like the Toll pathway, the IMD pathway regulates antimicrobial peptide gene expression via a Rel/nuclear factor (NF)-κB-like transcription factor. However, the two pathways do not appear to share any intermediate components. Maintaining distinct immune response pathways might be one mechanism by which flies mount adapted immune responses.

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Insects possess efficient mechanisms for detecting and neutralizing microbial infection. The application of *Drosophila* genetics to deciphering these mechanisms has generated insights into insect immunity and uncovered similarities with mammalian innate immune responses (for comprehensive reviews on *Drosophila* immunity see Refs 1–4). A powerful feature of studying immunity in flies is the ability to identify genetic mutations that render flies susceptible to microbial infection. For instance, analysis of immune-compromised flies has demonstrated that the Toll signaling pathway, previously characterized as a regulator of dorsal–ventral polarity in developing embryos, also regulates antifungal defense[5,6]. Toll-deficient flies are susceptible to fungal infection, and this susceptibility is correlated with the reduced induction of genes encoding peptides with antifungal activity in the fat body, an analog of the mammalian liver. Antimicrobial peptides synthesized in the fat body are secreted in the hemolymph to high concentrations; one role of the Toll pathway in the *Drosophila* immune response is to activate the synthesis of these peptides after fungal infection[6] (Fig. 1).

The identification of Toll as a mediator of fly immunity facilitated the identification of Toll-like receptors (TLRs) in mammals (reviewed in Refs 1,7,8). TLRs regulate mammalian innate immune responses via the TLR/interleukin 1 receptor (IL-1R) signaling pathway, which is similar to the Toll pathway[1,3,8]. The recruitment of similar receptors and pathways in both insects and mammals in the fight against infection suggests an evolutionary link between the regulation of antimicrobial peptide gene expression in flies and the regulation of mammalian innate immune responses, and illustrates the potential of using *Drosophila* as a model for studying animal immunity (Fig. 2).

In addition to the antifungal peptides, Toll also regulates, in part, the expression of some antibacterial peptides; however, Toll-deficient flies are not susceptible to bacterial infection, indicating that flies rely on other mechanisms for combating bacteria[6] (Fig. 1). The first clue as to the presence of a second pathway mediating fly immunity was the identification of the *immune deficiency* (*imd*) mutation: *imd* mutant flies are highly susceptible to Gram-negative bacterial infection but remain resistant to fungal and Gram-positive bacterial infection[9]. The *imd* mutation alters the expression of a subset of peptides with antibacterial activity (Fig. 1). Flies that carry mutations in both *Toll* and *imd* do not express any antimicrobial peptides and are susceptible to fungal, Gram-negative and Gram-positive bacterial infection, demonstrating that Toll and IMD are major regulators of antimicrobial gene expression[6] (Fig. 1).

'Rel/NF-κB-like transcription factors are major regulators of antimicrobial gene expression in flies.'

Many components of the Toll pathway that participate in antifungal responses were identified as mutations that effect dorsal–ventral patterning (reviewed in Ref. 5). By contrast, factors that function with IMD to regulate antibacterial responses remained largely unknown. However, seven recent studies have greatly enhanced our understanding of *Drosophila* immune responses by characterizing new components of antibacterial defense, as reviewed below[10–16].

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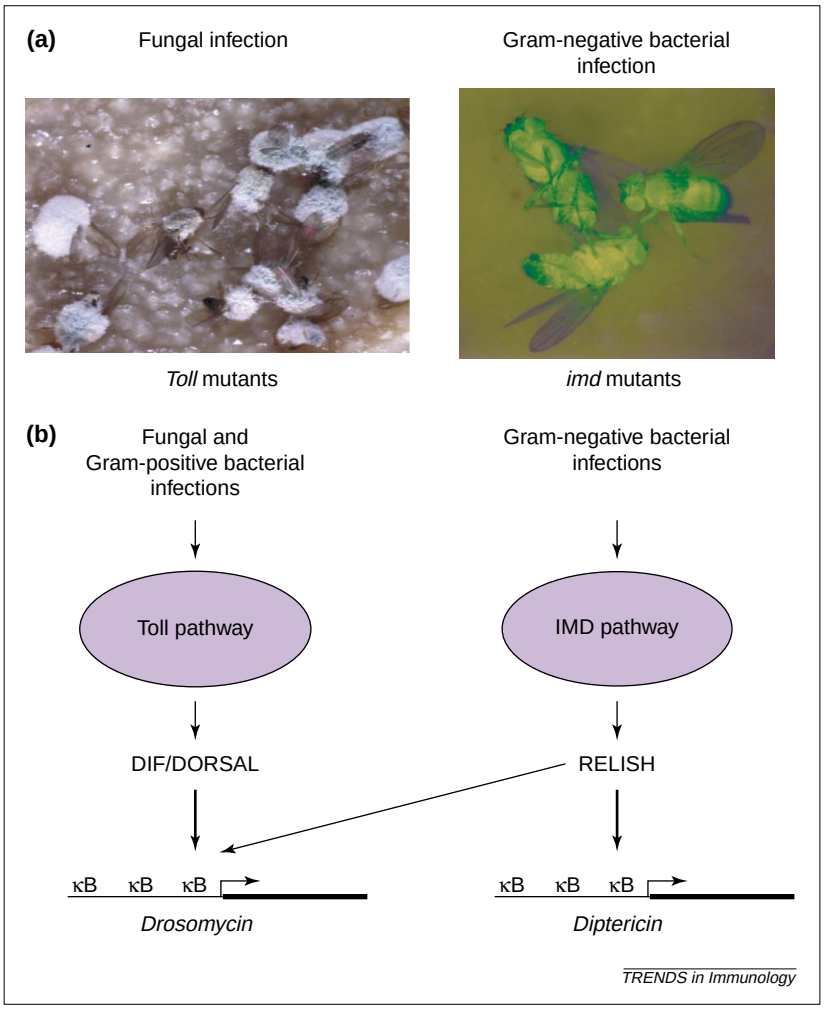

Fig. 1. Multiple immune response pathways enable flies to mount adaptive immune responses. The *Drosophila* immune system discriminates between pathogens and responds by inducing the expression of pathogen-specific antimicrobial peptide-encoding genes via distinct signaling cascades. (a) Two classes of genetic mutation demonstrate separate mechanisms for combating fungal and Gram-negative bacterial infection. *Toll* mutants inoculated with spores of *Aspergillus fumigatus* are killed by fungal infection, yet resist Gram-negative bacterial infection[6]. *imd* mutants inoculated with green fluorescent protein (GFP)-expressing cells of the Gram-negative bacterial species, *Erwinia carotovora carotovora*, are rapidly killed by bacterial infection, and bacterial proliferation inside these flies is demonstrated by high levels of GFP expression. By contrast, *imd* mutants resist fungal infections[6]. (b) The induction of each antimicrobial gene is thought to be regulated by a balance of inputs from the Toll and IMD pathways that are manifested by specific combinations of the Rel proteins Dorsal-like immune factor (DIF), Dorsal and Relish[26]. The DIF, Dorsal and Relish dimers interact with antimicrobial gene promoter sequences, and the different patterns of antimicrobial peptide genes induced by various types of infections are believed to reflect the sensitivity of these two pathways to different microbes. The *Drosomycin* gene, for example, is predominantly regulated by the Toll pathway and is more strongly induced by fungal and Gram-positive bacterial infection. *Diptericin*, however, is almost completely regulated by the IMD pathway and is largely induced by Gram-negative bacterial infection[13,15,19,27].

Factors that mediate responses to Gram-negative bacteria

Rel/NF-κB control of antibacterial immunity

Rel/NF-κB-like transcription factors are major regulators of antimicrobial gene expression in flies. Two Rel proteins, Dorsal and Dorsal-like immune factor (DIF), are controlled by the Toll pathway: Dorsal and DIF function redundantly in the regulation of antifungal peptide genes such as *Drosomycin* during the larval stage, although, in adults, DIF is the primary mediator of the antifungal response and *dif* mutants are susceptible to fungal infection[17–19]. The third *Drosophila* Rel protein is Relish, and *relish* mutants, like *imd* mutants, do not express peptides with antibacterial activity and are more susceptible to Gram-negative bacterial infection than to fungal infection[20].

Relish is similar to the mammalian p105 and p100 Rel proteins, which comprise N-terminal Rel-homology domains and C-terminal inhibitory (I) κB-like domains separated by a nuclear localization signal[21]. p105 and p100 are processed to release their N-terminal domains, which then homodimerize or heterodimerize with other Rel proteins to generate NF-κB transcriptional regulators; their C-terminal domains are completely degraded. Two pathways appear to regulate p105 processing: a signal-independent pathway wherein p105 processing is linked to p105 translation[22], and a signal-dependent pathway wherein stimuli such as cytokines and bacterial lipopolysaccharide (LPS) induce processing[23]. In both pathways, cleavage is proteasome dependent. However, in spite of the structural similarities between Relish and p105, Stöven *et al.*[14] reported distinct differences in Relish processing: Relish cleavage occurs by an endoproteolytic mechanism that appears to be entirely signal dependent and is not blocked by proteasome inhibitors. Furthermore, the C-terminal domain remains detectable in the cellular cytoplasm while the Rel-homology domain is translocated to the nucleus[14]. The function of the Relish C-terminal domain after cleavage is not apparent, although it is conceivable that this domain acts as an IκB-like factor to modulate Rel protein activity.

'The mechanisms that link Gram-negative bacterial recognition and the IMD pathway still pose intriguing questions.'

An IKK complex in flies

How is Relish targeted for cleavage after infection? In mammals, signals activate a complex of IκB kinases (IKKs) that, in turn, phosphorylate p105 and IκB and target them for proteasome-mediated degradation[24]. Several recent studies provide evidence for an IKK complex in flies. In two genetic studies, Rutchmann *et al.*[15] and Lu *et al.*[16] showed, respectively, that mutations in the *kenny* and *immune response deficient 5* (*ird5*) genes generate phenotypes similar to the *imd* and *relish* mutations. *kenny* encodes DmIKKγ, a fly homolog of mammalian IKKγ/NF-κB essential modulator (NEMO) that is a structural component of the IKK complex[15], and *ird5* encodes DmIKKβ, a homolog of the mammalian kinase IKK-β (Ref. 16). In parallel studies, Kim *et al.*[10] and

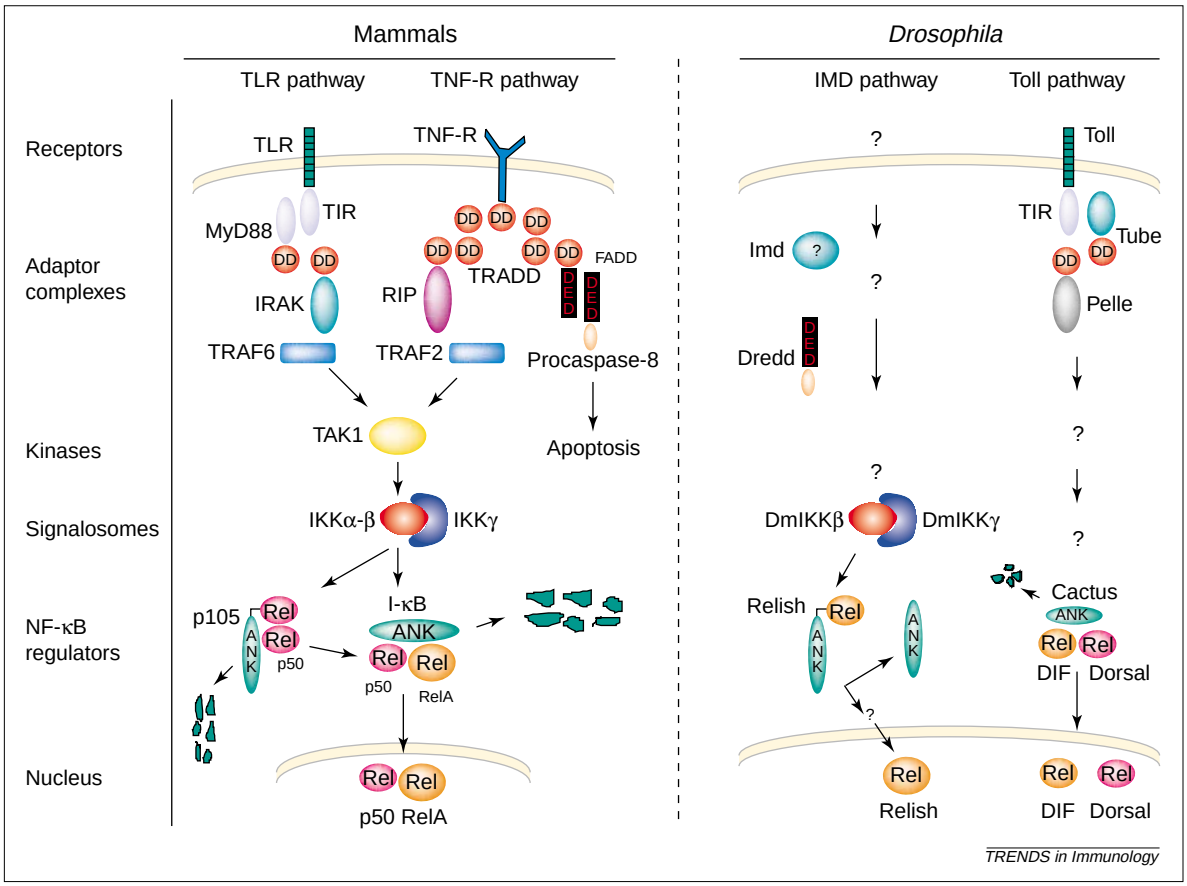

Fig. 2. Similar pathways regulate Rel/nuclear factor (NF)-κB in mammals and *Drosophila*. Steps in the pathways that are mediated by factors that have not been characterized are indicated with question marks. Genes encoding additional homologs of components of the mammalian TLR/IL-1R and TNFR pathways exist in flies: these include homologs of RIP, MyD88, FADD, TRAF2 and TRAF6, which are components of receptor-associated complexes in mammals, and a homolog of TAK1, which regulates the mammalian IKK complex[4]. Some of these putative *Drosophila* genes may function in the Toll and IMD pathways. Abbreviations: ANK, ankyrin domain; DD, death domain; DED, death effector domain; FADD, Fas-associated death-domain-containing protein; IKK, IκB kinase; IL-1R, interleukin 1 receptor; IRAK, IL-1R-associated kinase; Rel, REL homology domain; RIP, receptor-interacting protein; TAK1, transforming growth factor β (TGF-β)-activated kinase; TIR, Toll/IL-1R domain; TLR, Toll-like receptor; TNFR, tumor necrosis factor receptor; TRADD, TNFR-associated death-domain-containing protein; TRAF, TNFR-associated factor.

Silverman *et al.*[11] showed that DmIKKβ is activated by LPS and mediates antibacterial peptide expression. Silverman *et al.* also demonstrated that (1) DmIKKβ interacts with DmIKKγ in yeast two-hybrid assays; (2) DmIKKβ can phosphorylate Relish *in vitro*; and (3) DmIKKβ and DmIKKγ activity is required for Relish cleavage in cultured cells[11]. These genetic and biochemical data demonstrate that an IKK complex regulates Relish cleavage and activation.

Caspase regulation of Rel activity

A somewhat unexpected regulator of fly immunity was identified in independent screens by Elrod-Erickson *et al.*[12] and Leulier *et al.*[13], who determined that the gene *dredd*, which encodes a protease of the caspase family, mediates resistance to bacterial infection. Leulier *et al.* further determined that mutations in *dredd* are phenotypically similar to *imd* and *relish* mutations[13]. Finally, Stöven *et al.*[14] showed that mutations in *dredd* appear to block Relish cleavage in larvae. The function of Dredd in mediating antibacterial resistance is not clear, but one possibility is that Dredd cleaves Relish directly after infection.

'…DmIKKβ, DmIKKγ and Dredd appear to be components of one pathway, the IMD pathway…'

A pathway emerges

Several similarities characterize the three novel components of the *Drosophila* immune response, DmIKKβ, DmIKKγ and Dredd: all three, like IMD and Relish, are required for both antibacterial peptide expression and resistance to Gram-negative bacterial infection, and all three regulate Relish activity. Consequently, DmIKKβ, DmIKKγ and Dredd appear to be components of one pathway, the IMD pathway, which mediates responses to Gram-negative bacterial infection via the Rel protein Relish (Fig. 1). As discussed, flies might utilize the caspase activity of Dredd to cleave Relish. However, the function of Dredd in this pathway also suggests parallels with the tumor necrosis factor receptor (TNFR) pathway in

mammals: the TNFR pathway utilizes procaspase 8 in a receptor-associated complex to regulate apoptosis[8] (Fig. 2). Although a homolog of TNFR is not readily apparent in the *Drosophila* genome, homologs of other components of the TNFR pathway exist, indicating that additional similarities between the IMD pathway and the TNFR pathway might arise[4] (Fig. 2).

Two distinct immune-response mediators

In mammals, signals mediated by the TLR/IL-1R and the TNFR pathways converge on a single IKK complex[8]; in flies, however, the two pathways that regulate Rel proteins do not appear to share intermediates (Fig. 2). The phenotypes generated by mutations in *DmIKKβ* and *DmIKKγ*, together with the biochemical analysis of DmIKKβ activity, demonstrate that the IKK complex identified in flies functions exclusively in the IMD pathway[11,15,16]. An IKK intermediate in the Toll pathway has not been identified, although there is a putative *Drosophila* homolog of the mammalian gene encoding the IKKε kinase that might fullfil this role[4,25]. The antimicrobial genes are thought to integrate signals from both pathways by responding to combinations of the different Rel proteins[26] (Fig. 1). Nevertheless, a single pathway can activate some of the genes. For example, *Drosomycin* induction via the Toll pathway is not impaired by mutations that block the IMD pathway, and *Diptericin* induction via the IMD pathway is not affected by mutations that block the Toll pathway[6]. These genetic studies demonstrate that the two pathways can function independently. However, full *Diptericin* activation in the absence of both DIF and Dorsal activity is surprising[17,18] as Relish does not appear to contain a transcriptional activation domain[21]. Relish might, however, possess an uncharacterized activation domain or interact with transcription factors other than DIF and Dorsal.

What lies upstream?

The activation of the Toll pathway by fungal infection and the activation of the IMD pathway by Gram-negative bacterial infection demonstrate that flies possess highly specific mechanisms for differentiating between microbes[13,15,19,27,28]. However, little is known about microbial recognition in flies[4,29,30]. In contrast to some of the mammalian TLRs, Toll does not appear to function as a direct sensor of microbial compounds: the Toll ligand, Spaetzle, is a small cytokine-like protein, which is activated via different proteolytic cascades during development and after infection[5,6,31]. Receptors that function in the IMD pathway have not been identified although, because TLR4 mediates Gram-negative bacterial recognition in mice[7], it is tempting to speculate that one of the eight Toll-like proteins present in the *Drosophila* genome might function in the IMD pathway. However, expression of these Toll homologs in tissue cell cultures does not provide a clear demonstration of their function in an antibacterial response[32]. A mutation in the *Drosophila Toll*-like gene, *18-wheeler*, does reduce the expression of some of the antibacterial peptide genes in larvae after bacterial infection[33]; *Diptericin*, however, remains almost fully inducible in the *18-wheeler* mutant. Thus, it must be emphasized that, despite what has been implied in several recent reviews[34,35], *18-wheeler* is not the primary receptor for the IMD pathway. The mechanisms that link Gram-negative bacterial recognition and the IMD pathway still pose intriguing questions.

A pathway only for immunity?

In contrast to mutations affecting components of the Toll pathway, mutations affecting the IMD pathway

The next questions

The elucidation of the immune deficiency (IMD) pathway requires several future experiments, some of which are listed below.

Remaining components of the pathway

The viability of all known mutations in the IMD pathway suggests that it will be possible to identify additional components via simple screens for mutations that affect *Diptericin* gene expression or fly viability after Gram-negative bacterial infection. The molecular characterization of the *imd* gene will also provide increased definition to the pathway.

Ordering the pathway

The creation of gain-of-function alleles of genes in the IMD pathway, via over-expression constructs, will enable the analysis of epistatic interactions between the known components. Although biochemical evidence suggests that the DmIKK complex interacts directly with Relish, the positions of IMD and Dredd in the pathway remain undefined.

Interactions between Dredd and Relish

The observation that Relish processing is not proteasome dependent but does require Dredd activity suggests that Dredd might cleave Relish. Caspases have not been linked to p105 or p100 processing in mammals, and Dredd processing of Relish is an interesting possibility that could be addressed via assays of Dredd activity in tissue cell culture and via the measurement of direct interactions between Dredd and Relish *in vitro*.

Mechanisms of microbial recognition

The selective activation of the Toll and IMD pathways demonstrates that these signaling cascades are linked to distinct recognition factors. However, these factors have not yet been identified in screens for mutations affecting *Drosophila* immune responses, possibly due to genetic redundancy. One alternative strategy for isolating microbial receptors will be to identify genes that are induced by specific types of infection or that are homologous to genes linked to microbial recognition in other organisms.

do not display significant effects on development, viability or cellular immune responses such as hemocyte differentiation and proliferation[9,13,15,16,20]. In addition, IMD, but not Toll, regulates antimicrobial gene expression in epithelial tissues exposed to bacteria, reinforcing the idea that the IMD pathway functions primarily in antibacterial responses[36]. However, overexpression of *dredd* in cell lines induces apoptosis, suggesting that the IMD pathway might also function in the regulation of cell death[37]. In a possible parallel, mammalian TLR2, which mediates bacterial recognition and the activation of innate immune responses, was recently shown to regulate apoptosis via a pathway that includes MyD88, Fas-associated death-domain-containing protein (FADD) and caspase 8 (Ref. 38).

A mechanism for an adapted immune response?

The similarities between the regulation of mammalian innate immune responses and *Drosophila* antimicrobial gene expression suggest common evolutionary roots for the immune response pathways[1]. Nevertheless, flies maintain two distinct pathways for controlling Rel-protein-mediated immune responses whereas, in mammals, microbial recognition mediated by different TLRs activates cytokine production and inflammatory responses via a common TLR/IL-1R pathway[8,39]. This difference may exist because flies produce peptides with distinct antimicrobial activities in cells from one tissue – the fat body. The use of two distinct pathways in fat body cells to regulate these peptides may be an efficient mechanism for producing specific subsets of peptides against different pathogens. We speculate that mammals might also achieve adapted innate immune responses by expressing different recognition receptors on different types of effector cells and, thereby, generate pathogen-specific defense responses.

Acknowledgements
We thank Ennio de Gregorio for critical comments on the manuscript and Phoebe Tzou for providing figures. Work in our laboratory is supported by the Centre National de la Recherche Scientifique (CNRS), the Fondation pour la Recherche Médicale (FRM) and the Programme Microbiologie (PRMMIP98).

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