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Host detection of pathogen-induced translational inhibition: a new pathogen-specific branch of the innate immune system?

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Both intracellular and extracellular pathogens ultimately disrupt processes inside the host cell to cause disease. While extracellular pathogens remain outside of the cell, they use a myriad of methods to deliver toxins into host cells, either directly with their own secretion systems or indirectly by exploiting host endocytosis. The AB toxins are a class of secreted bacterial proteins that have been studied extensively for the mechanisms by which they disrupt host processes, as well as their route of entry into host cells [1]. For example, exotoxin A (ToxA), an AB toxin produced by the bacterial pathogen *Pseudomonas aeruginosa*, was shown to enter host cells by receptor-mediated endocytosis in 1980 [2]. Once inside of cells, ToxA inactivates the host elongation factor EF2 to block host mRNA translation. ToxA is one of several bacterial toxins, including Diphtheria toxin and Shiga toxin, which act to block translational elongation. The host response to these toxins has been poorly explored until recently, when it was shown that the translation-blocking effects of these toxins can switch on a form of host defense termed 'surveillance immunity' [3–5] that is part of a framework for host responses called 'patterns of pathogenesis' [6,7]. This pathogen-specific immunity is part of an emerging branch of the host defense that is critical for survival of nonprofessional immune cells, and may be important for professional immune cells as well.

How do 'surveillance immunity' and 'patterns of pathogenesis' fit in with more well-characterized forms of immunity? Immune signaling pathways found in the professional immune cells can broadly be divided into adaptive immune pathways and innate immune pathways. Innate immune signaling has been called the front line of defense against invaders and an 'ancient' immune system. One of the best studied examples of innate immune signaling is mediated by Toll-like receptors, which were shown to be critical for defense in a range of animals from flies to humans by signaling through the transcription factor NF-κB [8]. Toll-like signaling pathways are triggered in professional immune cells by microbial components such as lipopolysaccharides (LPS) to provide defense of body cavities where any microbe is considered a threat. However, such pathways are not wired to provide the discrimination that is needed by epithelial cells, which are nonprofessional immune cells

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that are regularly exposed to a variety of microbes. Hosts do not want to kill off commensal microbes if they are providing key nutrients or keeping out pathogenic bacteria. Furthermore, they do not want to expend unnecessary energy fighting off harmless microbes that are not causing disease. Thus, a pathogen-specific discrimination system in epithelial cells makes evolutionary sense [6,9].

The nematode *Caenorhabditis elegans* is a major model organism for genetic studies and provides an opportunity to learn about pathogen-specific immunity of epithelial cells [10]. *C. elegans* can be infected by several kinds of pathogens in the intestine, which is composed of 20 epithelial cell types that share structural similarity with mammalian intestinal epithelial cells. *C. elegans* does not appear to use the well-characterized forms of innate immune signaling described above (TLR/NF-κB), but clearly thrives in the wild, leading to the question of how it fights off infections. Because *C. elegans* lacks obvious professional immune cells and relies predominantly on epithelial cells for defense, host/pathogen studies in this system address the question of how animals discriminate pathogens from other microbes. Pathogen infection of *C. elegans* induces robust transcriptional responses, including upregulation of genes that provide defense against infection. However, the pathogen cues that trigger activation of these defense pathways are poorly understood. These cues must include molecules that are distinct from the classical pathogen- associated molecular patterns (PAMPs) detected by TLR/NF-κB, because *C. elegans* intestinal epithelial cells encounter many kinds of microbes, and PAMPs are common to pathogens and nonpathogens alike. PAMPs have more recently been referred to as microbial-associated molecular patterns (MAMPs), which more accurately describes their source. For example, LPS is a PAMP/MAMP found both in the cell walls of *Escherichia coli*, which can be nonpathogenic to *C. elegans*, as well as in the cell walls of *P. aeruginosa*, which can be very pathogenic to *C. elegans*. In fact, *C. elegans* feeds on *E. coli* in the laboratory, and thus its intestinal cells are bathed in the so-called PAMPs/MAMPs that provide the cues for infection of professional immune cells patrolling the body cavity. The human intestine is also regularly exposed to LPS because a large number of bacteria colonize this site, and thus the human intestine also needs alternative cues to sense pathogens. The experimentally accessible nematode *C. elegans* provides a tractable system for determining which cues intestinal epithelial cells use for pathogen detection.

Many *C. elegans* signaling pathways are required for survival upon intestinal infection, but only some of these pathways are activated by infection. For example, both the conserved DAF-2/DAF-16 insulin-like signaling pathway and the conserved PMK-1 p38 MAPK signaling pathway promote survival upon *P. aeruginosa* infection of the intestine [11,12]. However, the DAF-2/DAF-16 pathway is not required for infection-induced gene expression, while the PMK-1 pathway together with other pathways such as the ZIP-2 bZIP transcription factor pathway are required for such induction [13,14]. Pathways required for gene induction upon infection are likely to be directly involved in detecting infection, thus identifying the pathogen cues that activate these pathways will uncover the logic and framework underlying the *C. elegans* immune response.

Recently, an important pathogen cue sensed by *C. elegans* was discovered to be translational inhibition as caused by *P. aeruginosa* ToxA [3,4]. This translation-blocking toxin triggers expression of *C. elegans* genes regulated predominantly by the ZIP-2 bZIP transcription factor pathway. The ZIP-2 pathway, the PMK-1 pathway and the FSHR-1 pathways were all shown to provide defense against killing by ToxA. These pathways appear to act in parallel to control expression of a suite of defense genes including those that encode candidate antimicrobial peptides, transporters and detoxifying enzymes.

Inhibition of host translation appears to selectively activate ZIP-2 protein expression, an effect mediated by an upstream open reading frame (uORF) of ZIP-2 that represses ZIP-2 translation during uninfected conditions. This mode of activation bears similarities to uORF-regulated pathways in yeast and mammals that are triggered by amino acid starvation [15,16]. Thus, genomically encoded sensors such as uORFs may provide 'receptors' that sense the effects of translation-blocking toxins and upregulate defense pathways. Inhibition of host translation elongation is a common strategy deployed by bacterial pathogens, presumably to prevent synthesis of secreted antimicrobials that would kill off these microbes. Using translational inhibition as a trigger to upregulate host defense may thus be an example of the coevolutionary arms race undertaken by hosts and pathogens. Induction of host defense by translational inhibition does not appear to be restricted to *C. elegans*, as it has long been known that translation blockade in mammals can induce cytokine expression. More recently, secreted toxins from *Legionella pneumophila* were shown to block host translation and induce cytokine expression. This cytokine expression may be mediated in part by NF-κB, although other components of this response remain to be identified [7]. In addition, the response against viral infection involves host-directed inhibition of mRNA translation, because viruses are dependent on host translational machinery and thus act to exploit it to their own ends [17]. In antiviral defense, host cells inhibit translation initiation by phosphorylation of eukaryotic initiation factor eIF2-α, which results in a block of viral replication. A related stress response that involves blockade of translation initiation has recently been described in the *Drosophila* and mammalian response to bacterial infection [18,19]. While this eIF2-α phosphorylation and host-directed blockade of translation initiation may also occur upon exposure to elongation-blocking toxins such as ToxA, the effects of inhibiting initiation versus elongation appear to be distinct [3,20]. Many questions remain about how pathogen-directed inhibition of elongation may trigger responses distinct from those triggered by host-directed inhibition of initiation. Despite these unanswered mechanistic questions, the importance of translational inhibition in the immune response has now been shown in several systems, and may constitute a key 'pattern of pathogenesis' used by host cells to recognize pathogens.

One surprising aspect of *C. elegans* host defense has been the fact that it lacks NF-κB, despite this gene being a critical player in innate immunity of flies and mammals, and being present in the genomes of other metazoans [21]. The most parsimonious explanation for the phylogenetic distribution of NF-κB is that it was present in the last common ancestor of worms, flies and mammals, but was lost in *C. elegans*. Why would the nematode dispense with such a key pathway? The answer may lie in the body plan and lifestyle of *C. elegans*. This animal does not have a true body cavity and it feeds on microbes. Therefore, it may not need or want a system that upregulates a defense response to the mere presence of microbes. A single Toll-like receptor exists in *C. elegans*, and while there are questions about its role in *C. elegans* defense, it does not appear to upregulate defense pathways in most infection models. These observations indicate that *C. elegans* deploys pathogen-specific defense pathways such as those activated by translational blockade caused by ToxA, in lieu of the classical innate immune pathways used by professional immune cells in flies and mammals. As we learn more about the mechanisms used to recognize translational inhibition as a 'pattern of pathogenesis' in *C. elegans*, it will be particularly interesting to translate these findings into mammals.

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Biography

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