EDITORIAL

Expanding the nematode model system: The molecular basis of inflammation and infection recovery in C. elegans

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Inflammation is an acute response to invading pathogens that temporarily reduces fitness, but allows the host to survive infection. Dysregulated inflammation is a chronic state that is now recognized as the central pathological process in a number of diverse diseases. In the past two decades, the initiation of inflammation has been extensively studied. The molecular basis of initiation of each of the four hallmarks of inflammation—heat, redness, swelling, and pain, has been revealed. Recently a number of anti-inflammatory drugs have come onto the market to treat or alleviate chronic inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, vitiligo, and lupus. However, studies have also shown that chronic inflammatory diseases result more from dysregulated resolution than dysregulated initiation. Pro-resolution drugs may prove superior to or synergistic with anti-inflammatory drugs, by short-circuiting the inflammatory process. However, the resolution of inflammation remains poorly understood.

Resolution pathways are heterogeneous, and may be tissue- and pathogen-specific. The progression from the inflammatory to the resolved state is no longer thought to occur when the pro-inflammatory cascade simply fizzles out due to a lack of stimuli. Instead, it is a complex interplay between many concurring pathways. First, once the source of the pathogen- or danger-associated molecular patterns (PAMPs and DAMPS) are eliminated, anti-inflammatory cytokines and regulatory T-cells inhibit pro-inflammatory immune responses. The remaining cytokines, chemokines, and reactive oxygen species are catabolized, stopping further immune cell recruitment. The remaining leukocytes and lymphocytes either reenter circulation or are cleared by alternatively activated (M2) macrophages by efferocytosis. M2 macrophages are activated by specific efferocytic receptors, engulf dying leukocytes, and produce additional anti-inflammatory cytokines. Underpinning each of these steps are highly conserved cell-to-cell receptor-ligand interactions, humoral-mediated signaling and intracellular kinase cascades. Recent studies have relied on in vitro assays to elucidate the genetic pathways of inflammation resolution. However, to fully understand the interplay between all the resolution and repair mechanisms, a whole-animal model system would be the best approach.

In this issue of Virulence, Head et al., used the whole-organism Caenorhabditis elegans-pathogen model to study the host recovery response from acute Pseudomonas aeruginosa infection. They utilized whole genome expression profiling to characterize the resolution process from the moment of pathogen exposure to early and late phases of recovery. The authors found 1,323 genes, or more than 6% of the genome, whose expression increased or decreased more than 2-fold during the four phases of recovery. The authors categorized the altered genes into four major groups with different responses during exposure and recovery. Furthermore, they compared the worm recovery responses to P. aeruginosa and Salmonella enterica to elucidate shared and pathogen-specific pathways. Clustering the shared and unique genes into gene ontology (GO) groups, the authors were able to see shared pathways, like the down-regulation of the antimicrobial C-type lectins and aging genes, and the up-regulation of the UGT/Transferase gene cluster. Taking advantage of the genetically tractable C. elegans system, they found that recovery was dependent on the GATA transcription factor elt-2 and the p38-mitogen-activated protein kinase (MAPK) pmk-1. Both of these pathways are highly conserved, and are
promising targets for future studies in mammalian inflammation resolution.

*C. elegans* provides an extremely useful model system in many areas of study, in part due to its size, relative simplicity, ease of use, exquisite genetics, and an available genomic sequence. Indeed, many important signaling pathways are highly conserved between *C. elegans* and humans. *C. elegans* has more than 7,500 genes with human homologs, representing approximately 65% of human disease-associated genes, including Alzheimer’s disease, type II diabetes, and depression. *C. elegans* has been used extensively to understand basic biological questions, including RNA interference, autophagy, aging, immunity, developmental biology, neurobiology, and many more. In fact, because all 959 cells of an adult *C. elegans* have been mapped and studied, a gene newly identified in human disease can be studied more productively in a much simpler and well-understood model organism.

*C. elegans* has four major immune-signaling pathways, all of which are conserved between *C. elegans* and humans. The *C. elegans* p38- and ERK-MAPK pathways are highly homologous to their human homologues and are critical for human immune and inflammatory signaling. The remaining *C. elegans* immune-signaling pathways, dbl-1, and the daf-2/daf-16 pathways are also highly conserved. Because the infection initiation pathways between *C. elegans* and humans are so well conserved, the molecular details on pathogen-specific *C. elegans* resolution pathways should shed light on their corresponding human pathways. The article of Head et al. makes an initial foray using the *C. elegans* model to discern the molecular dynamics of inflammation resolution and their findings will be helpful in discovering new targets for treating chronic inflammatory diseases.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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