Caenorhabditis elegans as a Model System to Study Responses to Pathogens

*Caenorhabditis elegans* is a powerful experimental organism for a number of traits that facilitate genetic and genomic analysis, including the hermaphroditic lifestyle, short 2–3 week lifespan, and small genome, which offers an ideal compromise between complexity and tractability. Unlike bacteria, yeast, or other single-celled organisms, *C. elegans* has muscles, nerves, sexual organs, and guts, in spite of its one millimeter long body. It reacts to touch, can recognize odors, and exhibits different behaviors. In nature, *C. elegans* is found in the soil and decaying organic matter. To date, more than 40 microbes have been shown to be pathogenic to *C. elegans*, including bacteria, fungi, and viruses. The major routes of infection are through the intestine and the epidermis. Because the nematode lacks professional immune cells, intestinal and epidermal epithelial cells serve as the primary defense against pathogens, as they are in direct contact with different microbes. Despite lacking adaptive immunity, *C. elegans* can mount protective responses to pathogen infection by avoiding certain pathogens or by triggering evolutionarily conserved signaling pathways. Activation of these cellular signaling pathways can lead to production of immune effectors such as lectins, lysozymes, lipases, and antimicrobial peptides, which act directly to fight off the invading pathogens. The defensive response that results in activated signaling pathways and induced immune effectors is pathogen-specific, indicating that the nematode is able to distinguish different infecting microbes.

Overview of *C. elegans* Pathogens

*Caenorhabditis elegans* can be infected in its natural environment and in the laboratory setting by a large number of pathogens, including Gram negative bacteria, Gram positive bacteria, fungi, and viruses. These pathogens may vary in their mode of infection, site of replication and host responses they induce. Figure 1 illustrates site and mode of infection utilized by a number of the most highly studied pathogens in *C. elegans*.

The majority of bacteria and fungi remain extracellular. Gram negative pathogens, such as *Salmonella enterica* and *Pseudomonas aeruginosa*, colonize the digestive system of *C. elegans* causing lethal infections ([Aballay et al., 2000; Tan et al., 1999]). *Pseudomonas aeruginosa* can kill *C. elegans* using toxins in a matter of hours by a process termed ‘fast killing’ ([Mahajan-Miklos et al., 1999]). It can also kill nematodes in 2–4 days by an infectious-like process termed ‘slow-killing,’ which requires bacterial...
replication in the intestinal lumen of the host (Tan et al., 1999). Other Gram negative bacteria, such as Microbacterium nematophilum, and Yersinia pestis strains incapable of forming biofilms, also colonize the digestive tract, but cause rectal inflammation in the digestive tract (Hodgkin et al., 2000; Styer et al., 2005). Yersinia pestis strains capable of forming biofilm cover the mouth of C. elegans and prevent feeding, reminiscent of Y. pestis infection of plague carrier fleas (Darby et al., 2002). Gram positive bacteria such as Enterococcus faecalis and Staphylococcus aureus also colonize the intestine (Irazoqui et al., 2010; Garzin et al., 2001). An interesting aspect of S. aureus infection is that it causes extensive loss of intestinal microvilli of the host and rectal inflammation (Irazoqui et al., 2010).

Fungal pathogens can set up infection in the intestine of the nematode or the epidermis. The yeast form of the human opportunistic pathogen Cryptococcus neoformans accumulates in the nematode intestine and causes a lethal infection (Mylonakis et al., 2002). Drechmeria coniospora is a natural fungal pathogen of C. elegans that enters through the cuticle and penetrates all body tissues (Couillault et al., 2012; Jansson, 1994). Candida albicans, a fungus that causes nosocomial infections in humans, is pathogenic to C. elegans in both its hyphal and yeast forms. In turn, nematodes elicit distinct responses depending upon the site of infection (Pukkila-Worley et al., 2009; Breger et al., 2007).

A small number of natural pathogens can cause intracellular infections in C. elegans. Examples include Nematocida parisii, which is a microsporidian parasite related to fungi, and a natural pathogen of C. elegans (Troemel et al., 2008; Felix and Duveau, 2012). Orsay virus and other viruses of the nodoviridae family cause intracellular invasion in the intestine of C. elegans and related species (Felix et al., 2011; Franz et al., 2014).

Pathogen Recognition by C. elegans

The mechanisms by which C. elegans identifies pathogens remain elusive. In plants and higher animals, pathogen recognition is mainly mediated by a set of PRRs that detect conserved pathogen-derived molecules, known as pathogen-associated molecular patterns (PAMPs) or MAMPs. The best characterized PRRs are a family of conserved transmembrane Toll-like receptors (TLRs) that recognize various microbial products, such as bacterial cell-wall components and flagellin, and trigger multiple defense response pathways. The genome of C. elegans does not encode the majority of known PRRs and lacks genes of some key components of the TLR pathways such as NF-kB homologs and the TLR adaptor MyD88. Nematode orthologs of a single Toll-like receptor (TOL-1), TNF receptor associated factor-1 (TRAP-1), Pelle and IL-1R-associated kinases (PIK-1) and inhibitor of NF-kB (IKB-1) do not seem to play key roles in immunity. However, it is worth noting that TOL-1 has been implicated in immune signaling against S. enterica (Tenor and Aballay, 2008) and that TIR-1, a scaffold protein containing Toll/IL-1R (TIR)–protein–protein interaction domain, is involved in antimicrobial defense against a variety of C. elegans pathogens (Liberati et al., 2004; Couillault et al., 2004). Caenorhabditis elegans is also capable of activating immune pathways when exposed to heat-killed S. aureus and C. albicans, suggesting that the nematode can detect pathogenic microbes via MAMP recognition (Irazoqui et al., 2010; Pukkila-Worley and Ausubel, 2012).

While MAMP/PRR interactions capable of eliciting immune responses in C. elegans remain elusive, emerging evidence supports the notion that the nematode can recognize pathogen attack through the detection of disturbances of cellular homeostasis. Caenorhabditis elegans appears to have evolved cellular surveillance systems to monitor its core cellular activities and interpret disruption of these activities as evidence of pathogen attack. The innate immunity elicited by this kind of indirect recognition is similar to effector-triggered immunity (ETI) that was originally demonstrated in plants (Jones and Dangl, 2006) and later found conserved across invertebrate and vertebrate animals (Boyer et al., 2011; Kleino and Silverman, 2012). An example of ETI in C. elegans is its response to a virulence factor of P. aeruginosa, Exotoxin A (ToxA). Upon infection with P. aeruginosa, ToxA enters the intestinal epithelial cells, likely via endocytosis, and inhibits protein translation by modifying elongation factor 2 via ADP-ribosylation, which triggers the host to up-regulate immune defense genes (Dunbar et al., 2012; McEwan et al., 2012). Besides protein translation, disruption of many other cellular functions such as mitochondrial respiration, ubiquitin-proteasome system activity, or actin cytoskeleton and microtubule dynamics, results in activation of detoxification and immune responses in C. elegans (Melo and Ruvkun, 2012; Bakowski et al., 2014). Pore-forming toxins (PFTs), the single largest class of proteincous bacterial virulence factors that perforate host cell membranes, can also trigger ETI in the nematode, although the precise molecular mechanisms remain unknown (Engelmann and Pujol, 2010). It has been suggested that the host cells can sense disruption of cell membrane, potassium efflux or calcium influx and respond with antimicrobial signaling and membrane repair pathways (Los et al., 2013; Los et al., 2011). ETI offers C. elegans an effective and versatile strategy to detect and distinguish pathogens from surrounding microbes. On the one hand, this allows the nematode to combat a wide variety of microbes without evolving the full repertoire of PRRs; on the other hand, it remains to be addressed how the nematode can distinguish infecting microbes if different pathogens disrupt the same cellular processes, as immune responses are not only pathogen-shared but also pathogen-specific (Wong et al., 2007; Shivers et al., 2008; Alper et al., 2007; Irazoqui et al., 2010; Schulenburg et al., 2008).

G protein-coupled receptors (GPCRs) may play a direct or indirect role in pathogen recognition in C. elegans. The nematode uses neuronal GPCR-mediated signaling to sense bacterial compounds and to respond by avoiding pathogens and activate immune pathways (Sun et al., 2011; Styer et al., 2008; Pradel et al., 2007; Reddy et al., 2009). Furthermore, a GPCR that functions in the epidermis activates innate immunity by recognizing an endogenous ligand. This ligand potentially acts as a danger molecule to alert the organism of fungal infections (Zugasti et al., 2014).

Immune Effectors

Upon infection, a number of immune effectors are produced in C. elegans and confer the nematode protective immunity
against microbial pathogens (Table 1). These effectors either directly inhibit the growth of invading pathogens or counteract their effects on host cells.

**Antibacterial Factors (ABFs)**

ABF-1 to ABF-6 in *C. elegans* are small cationic peptides similar to human defensins. ABF-2 has antimicrobial activity against Gram negative bacteria, Gram positive bacteria, and yeast (Kato et al., 2002). ABF-1 and ABF-2 are expressed in the pharynx of *C. elegans*, which is one of the first organs that gets in direct contact with pathogens, and their expression requires TOL-1, and cell death receptor CED-1.

**Caenacins**

These are putative antimicrobial peptides, structurally related to neuropeptide-like proteins. Some of these genes are upregulated in the epidermis following infection with the fungal pathogen *D. coniospora*. Up-regulation of caenacins in the epidermis requires neurally produced TGFβ homolog DBL-1 (Zugasti and Ewbank, 2009). In addition, overexpression of caenacins enhances *C. elegans* immunity against *D. coniospora*.

**Caenopores**

Caenopores are a family of proteins containing a saposin domain in *C. elegans*, similar to protozoan amoebapores, Table 1: Common immune effectors in *Caenorhabditis elegans*

<table>
<thead>
<tr>
<th>Immune effector</th>
<th>Description</th>
<th>Gene family</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Antibacterial factor (ABF)</td>
<td>Small cationic peptides similar to human defensins</td>
<td>abf-1 to abf-6</td>
<td>Kato et al. (2002)</td>
</tr>
<tr>
<td>Caenacin</td>
<td>Putative antimicrobial peptides, structurally related to neuropeptide-like proteins antimicrobial activity</td>
<td>cnc-1 to cnc-11</td>
<td>Zugasti and Ewbank (2009)</td>
</tr>
<tr>
<td>Caenopore</td>
<td>A family of proteins containing saposin-domain, similar to protozoan amoebapores, mammalian NK-lysin, and granulysin</td>
<td>28 spp genes encoding 33 different caenopores</td>
<td>Roeder et al. (2010); Banyai and Patthy (1998); Hoeckendorf and Leippe (2012); Hoeckendorf et al. (2012)</td>
</tr>
<tr>
<td>C-type lectin</td>
<td>Proteins that contain one or more C-type lectin-like domains (CTLD) and recognize complex carbohydrates on cells and tissues</td>
<td>278 genes encoding CTLD proteins</td>
<td>Drickamer and Dodd (1999); Takeuchi et al. (2008); Schulenburg et al. (2008); Simonsen et al. (2012)</td>
</tr>
<tr>
<td>CUB domain protein</td>
<td>The CUB domain is a structural motif of approximately 110 residues. They resemble immunoglobulin and occur in large gene clusters</td>
<td>More than 50 genes encoding CUB domain proteins</td>
<td>Bork and Beckmann (1993); Bolz et al. (2010)</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozymes are glycosyl hydrolase enzymes present in microbes, insects, plants, and animals</td>
<td>10 protist type lysozyme encoding genes (lys-1 to lys-10) and 5 invertebrate type lysozyme encoding genes (ilys-1 to ilys-5)</td>
<td>Schulenburg and Boehnisch (2008); Mallo et al. (2002); Jensen et al. (2010); Marsh et al. (2011)</td>
</tr>
<tr>
<td>Neuropeptide-like protein (NLP)</td>
<td>The NLPs are a diverse group of neuropeptides that have little similarity among them</td>
<td>42 genes encoding NLPs</td>
<td>Nathoo et al. (2001)</td>
</tr>
</tbody>
</table>
mammalian NK-lysin and granulysin. *Caenorhabditis elegans* has a group of 28 spp genes that encode 33 different caenopores (Roeder et al., 2010). Antibacterial, membrane-permeabilizing, and pore-forming activities have been demonstrated for SPP-1, SPP-3, SPP-5, and SPP-12 (Banyai and Pathy, 1998; Roeder et al., 2010; Hoeckendorf et al., 2012; Hoeckendorf and Leippe, 2012). SPP-1 protects *C. elegans* against *S. enterica* and *P. aeruginosa*. Down-regulation of SPP-1 by *P. aeruginosa* is under the control of the FOXO transcription factor DAF-16.

**C-type Lectins**

C-type lectins are a group of proteins that contain one or more C-type lectin-like domains (CTLD) and that recognize complex carbohydrates on cells and tissues (Drickamer and Dodd, 1999; Takeuchi et al., 2008). 278 genes encoding CTLD proteins are present in the *C. elegans* genome (Schulenburg et al., 2008). More than 60 CTLD proteins are induced during pathogen infection. Distinct expression profiles of CTLD genes during different infections indicate that these proteins might contribute to pathogen specificity of *C. elegans* immune responses. For instance, RNAi knockdown of clec-17, clec-60 and clec-86 caused enhanced susceptibility to *M. nematophilum* (O’Rourke et al., 2006). Also, knockdown of clec-65 or clec-70 resulted in enhanced susceptibility to *Escherichia coli* LF82 or *S. aureus*, respectively (Simonsen et al., 2011; Ira佐qui et al., 2010). Simultaneous overexpression of clec-60 and clec-61, or clec-70 and clec-71 led to increased resistance to *S. aureus* but decreased resistance to *P. aeruginosa* (Ira佐qui et al., 2010). C-type lectins often bind carbohydrates in a Ca²⁺-dependent manner. However, a recent study revealed that CLEC-39 and CLEC-49 directly recognize live *Serratia marcescens* in a Ca²⁺-independent manner, suggesting a nonclassical recognition of *S. marcescens* by both CTLD proteins (Mirtsch et al., 2014).

**CUB Domain Proteins**

More than 50 genes in the *C. elegans* genome encode proteins containing a CUB (C1r/C1s, Ilecg, and Bmp1) domain, which is a structural motif of about 100 residues (Bork and Beckmann, 1993). RNAI inhibition of three of the CUB genes (F08G5.6, F20G2.5, dct-17) enhances *C. elegans* susceptibility to *P. aeruginosa* and RNAI inhibition of two other CUB genes (C17H12.8 and C32H11.12) enhances *C. elegans* susceptibility to *Y. pestis* infection. Interestingly, CUB genes that are usually upregulated in response to bacterial infections, are down-regulated in response to fungi such as *C. albicans* and *D. coniospora* (Simonsen et al., 2012).

**Lysozymes**

Lysozymes are glycosyl hydrolase enzymes that degrade bacterial cell walls and that are present in both plants and animals. The *C. elegans* genome has 10 protist type lysozyme encoding genes (lys-1 to lys-10) and 5 invertebrate type lysozyme encoding genes (ilys-1 to ilys-5) (Schulenburg and Boehnisch, 2008). Many lysozyme genes are expressed in the intestine and upregulated in response to microbial infections. RNAI inhibition of ilys-1 causes enhanced susceptibility to *S. aureus*, while overexpression of ilys-4 and ilys-5 increases resistance to *S. aureus* (Mallo et al., 2002; Jensen et al., 2010). Overexpression of ilys-4 enhances resistance to *S. marcescens* (Mallo et al., 2002). ilys-7 mutants are also more susceptible to *C. neoformans* infection but resistant to *S. typhimurium* infection (Marsh et al., 2011).

**Neuropeptide-Like Proteins**

Neuropeptides are bioactive peptides that play a role in synaptic signaling. *Caenorhabditis elegans* has 32 genes encoding neuropeptide-like proteins (NLPS) (Nathoo et al., 2001). Some of the NLPS encoding genes are upregulated during microbial infection. NLP-31 has antimicrobial activity in vitro and NLP-29 is expressed in the intestine and hypodermis (Couillault et al., 2004). Up-regulation of nlp-29 cluster (6 genes) in the hypodermis during *D. coniospora* infection requires signaling molecules such as TIR-1, PMK-1/p38 MAPK and DCAR-1/GPCR.

**Immune Signaling Pathways**

Detection of pathogen attack leads to activation of cellular signaling pathways that induce expression of defensive genes to limit microbial growth, destroy invading microbes, detoxify xenobiotics, and repair damage. These pathways include innate immune and stress response pathways activated in various tissues during infection with bacterial or fungal pathogens (Figures 2 and 3). Recent studies demonstrated the complexity and specificity of these responses: different signaling pathways regulate expression of distinct but overlapping sets of effector genes, individual pathogens induce genes controlled by multiple pathways, and the set of genes regulated by each pathway is also pathogen-specific.

**The p38 MAPK Pathway and Related Pathways**

The conserved p38 MAPK pathway plays a major role in the antimicrobial response of *C. elegans*. Forward and reverse genetic studies have demonstrated that the p38 MAPK pathway is required for immunity against a variety of pathogens and xenobiotics, including Gram negative and positive bacteria, fungi, PFTs, and many types of stress such as oxidative stress and heavy metal stress (Ermolaeva and Schumacher, 2014; Pukkila-Worley and Ausubel, 2012). This pathway includes the TIR domain protein TIR-1, neuronal symmetry family member 1 (nsy-1), SAPK/ERK kinase 1 (sek-1) and p38 MAPK family member 1 (*pmk-1*) (Kim et al., 2002, 2004). Signal is transduced in the form of protein phosphorylation, where NSY-1 phosphorylates SEK-1, which in turn phosphorylates PMK-1. TIR-1 and two protein kinases PKCδ and PKD act upstream of NSY-1 (Liberati et al., 2004; Ziegler et al., 2009; Ren et al., 2009). It has also been demonstrated that *C. elegans* ATF-7, a transcription factor orthologous to mammalian ATF2, functions downstream of PMK-1 as a repressor of PMK-1-regulated genes, and undergoes a switch to an activator upon phosphorylation by PMK-1 (Shivers et al., 2010).
Activation of the p38 MAPK pathway induces expression of a set of secreted immune response genes. Several microarray studies showed that genes upregulated by PMK-1 include those encoding proteins containing CUB-like domains, C-type lectins, antibacterial peptides, lysozymes, NLPs, and caenacins. Besides p38, two other MAPKs, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), are also involved in the nematode’s defense to infections. Upon infection with *M. nematophilum*, the ERK pathway is activated and mediates a protective response by inducing production of C-type lectins, lysozymes, proteases, and other defense-related proteins (Nicholas and Hodgkin, 2004; O’Rourke et al., 2006).

The JNK pathway is a key regulator of the transcriptional and functional responses to bacterial PFTIs (Kao et al., 2011).

**The DAF-2/DAF-16 Pathway**

The DAF-2/DAF-16 pathway is well known for its regulation on the lifespan of *C. elegans*, and also plays important roles in the immune response to infection by several bacteria. Activation of the DAF-2 receptor by an agonist ligand, such as the insulin-like peptide DAF-28, activates a phosphorylation cascade that results in the phosphorylation of the FOXO family.
transcription factor DAF-16. Phosphorylated DAF-16 is retained in the cytoplasm. In daf-2 mutants or in the presence of an antagonist ligand such as INS-1, un-phosphorylated DAF-16 translocates into the nucleus, where it regulates expression of a wide variety of genes (Lin et al., 2001). It has been suggested that the PMK-1 and DAF-16 pathways act in parallel to promote immunity. While PMK-1 controls both basal and infection-induced expression of pathogen response genes, DAF-16 regulates a constitutively expressed response or a general stress response to microbes (Troemel et al., 2006; Shivers et al., 2008). This is in agreement with the role of DAF-16 in regulating the expression of many genes involved in resistance to various forms of stress, including heat, oxidative stress, hypoxia, osmotic stress, heavy metal toxicity, ultraviolet radiation, proteotoxicity, and microbial infection (Murphy and Hu, 2013). A number of antimicrobial effectors are regulated by DAF-16, including lysozymes LYS-7 and LYS-8, the saposins SPP-1, SPP-9 and SPP-12, DUF-23, and C-type lectins (Shivers et al., 2008; Murphy and Hu, 2013). Most of these effectors appear to be secreted proteins that function to disrupt microbial cell membranes.

**The DBL-1 Pathway**

The DBL-1 pathway in *C. elegans* is homologous to the mammalian TGFβ cascade, and was first described as involved in resistance to infection by *P. aeruginosa* and *S. marcescens* (Tan, 2001; Mochii et al., 1999; Mallo et al., 2002). The TGFβ family ligand DBL-1 binds membrane-anchored heterodimeric DAF-4/SMa-6 receptor, leading to the phosphorylation and activation of the cytoplasmic signal transducer SMaD complex (SMa-2, -3 and -4); the transducer then translocates into the nucleus, where it activates gene expression. *dbl-1* mutants exhibit increased susceptibility to infection with *S. marcescens*, and the DBL-1 pathway up-regulates the expression of many defense genes, including lectins and lysozymes (Mallo et al., 2002). Upon infection with fungus *D. coniospora*, *dbl-1* gene is also required for induction of cnc-2 expression (Zugasti and Ewbank, 2009).

**The Unfolded Protein Response Pathway**

In the endoplasmic reticulum (ER), proteostasis surveillance is mediated by the unfolded protein response (UPR). ER is an important intracellular organelle in which newly synthesized transmembrane and secretory proteins are folded, assembled and matured. ER homeostasis is critical for ensuring proper folding and release of modified proteins to the Golgi. In response to pathogen infection, increased demands on the protein folding machinery causes stress in the ER, which activates a series of UPR pathways to restore ER homeostasis. Activation of UPR in *C. elegans* is required for defense against a variety of pathogons including *B. thuringiensis*, *S. enterica* and *P. aeruginosa* (Bischof et al., 2008; Haskins et al., 2008; Richardson et al., 2010). UPR was found to be regulated by the p38, JNK and MAPK pathways in response to PFI3 (Bischof et al., 2008; Kao et al., 2011). Interestingly, activation of UPR is also required by p38 MAP kinase PMK-1 mediated defense against *P. aeruginosa* (Richardson et al., 2010). Upon infection with *S. typhimurium*, the apoptotic receptor CED-1 activates the expression of *pqn/aun* genes in the noncanonical UPR pathway to promote immune response (Haskins et al., 2008). In light of recent studies indicating that there is a strong developmental regulation of certain *aun/*pqn genes (George-Raizen et al., 2014), further investigation will be required to fully address whether such genes are part of the UPR and whether their role in resistance to pathogen infection is related to cuticle and pharynx integrity rather than UPR. A recent study by Glover-Cutter et al. demonstrated that SKN-1, the *C. elegans* homolog of Nrf1/2/3 that functions in oxidative stress resistance and longevity, transcriptionally regulates core UPR transcription factors and downstream effectors in the ER-stress response, and the UPR plays a role in activation of the antioxidant/detoxification response (Glover-Cutter et al., 2013).

**Response Pathways to Intracellular Pathogen Infections**

Unlike in the case of bacterial intestinal infections, canonical defense pathways, such as p38 MAPK and insulin/insulin-like growth factor signaling pathways, do not appear to play roles in resistance to the intracellular pathogen *N. parisi* (Troemel et al., 2008). Ubiquitin-mediated pathways, the proteasome, and xenophagy components are involved in host response and defense against *N. parisi* infection (Bakowski et al., 2014). The ubiquitin-mediated response is also important for defense against the Orsay virus, another natural intracellular pathogen of *C. elegans* (Bakowski et al., 2014).

Both natural and nonnatural viral infection models have been established in *C. elegans*. Studies using laboratory introduced viruses such as Flock House virus (FHV), vesicular stomatitis virus (VSV), and vaccinia virus (VV) have identified a prominent role for the RNA interference (RNAi) machinery in viral restriction, a conserved defense mechanism that was first characterized in plants (Ermolaeva and Schumacher, 2014). These studies confirmed that the RNAi pathway is important for protection from viral infection. *Caenorhabditis elegans* mutants with defective RNAi had higher viral load, while mutants with hyperactive RNAi responses had lower viral load. More recently, three novel RNA viruses, Orsay, Santeuil, and Le Blanc viruses, were found to be able to naturally infect nematodes (Felix et al., 2011; Franz et al., 2012). All three viruses are distantly related to nodaviruses and cause morphological abnormalities in the nematode intestine (Franz et al., 2014). The RNAi pathway has also been implicated in the defense against these natural viruses. Nematode mutants lacking RNAi factors (RDE-1, RDE-4, RNaseD MUT-7, or dicer-related helicase DRH-1) had an elevated infection load.

**Conclusions and Perspectives**

*Caenorhabditis elegans* has been proven to be an excellent model system for studying host-pathogen interactions. Although it lacks typical MAMP/PRR-mediated pathogen recognition mechanisms, it can distinguish pathogens from innocuous microbes through surveillance-mediated recognition mechanisms that are capable of detecting disturbances in cellular homeostasis. This ancient mechanism has been
evolutionarily conserved across species. For example, inhibition of host protein synthesis by secreted *Legionella pneumophila* virulence factors activates an innate immune response in mouse macrophages (Fontana et al., 2011). *Escherichia coli*-encoded toxin CNF1 catalyzes deamidation of a host RhoGTPase and triggers NF-kB immune responses in both insects and mammalian cells (Boyer et al., 2011). Given that there are numerous microbial virulence factors and toxins in the environment aiming at crippling host functions, monitoring their own cellular activities offers the hosts a very effective and economic strategy to detect threats. The only caveat with this hypothesis is that it cannot explain how hosts distinguish between infecting pathogens and mount a pathogen-specific response if different pathogens disrupt the same cellular functions.

There is a complex signaling network in *C. elegans* that is activated in response to microbial infection and stress. This network includes several highly conserved signaling pathways, such as the MAPK pathways, the DAF-2/DAF-16 pathway, and the TGF-β/DBL-1 pathway. There are extensive interplays among immune signaling pathways, between immunity and stress response pathways, and between immunity and longevity pathways. For example, genetic analysis showed that the p38 MAPK pathway contributes to the enhanced longevity regulated by the DAF-2/DAF-16 pathway (Troemel et al., 2006). p38 MAPK signaling also mediates response to oxidative stress generated by the dual oxidase Ce-Duox1/BLI-3 during infection in *C. elegans* (Hoeven et al., 2011). The complexity and specificity of these pathways and their interactions make elucidating molecular details of innate immunity a challenging task, especially in humans. The simplicity of *C. elegans* anatomy and the wealth of genetic and genomic tools for *C. elegans* research make the nematode an outstanding system to dissect host responses to microbial infections at the cellular and molecular levels in a multicellular organism.

**See also:** Intracellular Infectiology: Cell Processes: Cellular Responses to Phagocytic Killing: Cellular Invasion by Bacterial Pathogens

### References


