**Strength in numbers**

“Omics” studies of *C. elegans* innate immunity

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For more than ten years the nematode *Caenorhabditis elegans* has proven to be a valuable model for studies of the host response to various bacterial and fungal pathogens. When exposed to a pathogenic organism, a clear response is elicited in the nematode, which is characterized by specific alterations on the transcriptional and translational levels. Early on, researchers took advantage of the possibility to conduct large-scale investigations of the *C. elegans* immune response. Multiple studies demonstrated that *C. elegans* does indeed mount a protective response against invading pathogens, thus rendering this small nematode a very useful and simple host model for the study of innate immunity and host-pathogen interactions. Here, we provide an overview of key aspects of innate immunity in *C. elegans* revealed by recent whole-genome transcriptomics and proteomics studies of the global response of *C. elegans* to various bacterial and fungal pathogens.

**C. elegans as a Model Host**

The nematode *Caenorhabditis elegans* was initially described as a model for bacterial infection in 1999¹,² and since then, it has proven to be an effective model host for several non-human and human pathogenic bacteria and fungi. In nature, *C. elegans* lives in rotting organic material and feeds on a variety of microorganisms and therefore, it continuously meets a diversity of bacterial and fungal pathogens³ from which the worm needs to defend itself, making the nematode a valuable model for studying the host response in a whole organism context. *C. elegans* lacks an adaptive immune system and it appears not to have specialized immune cells; however, infections trigger a clear response in the worm. *C. elegans* has become a valuable model host for the study of fundamental mechanisms in innate immunity and host-pathogen interactions, mainly due to its simplicity and ease of handling, and the wide range of experimental methods available for detailed studies in this organism. A hallmark of innate immunity is clearly present in the worm; a prominent defense response, including a battery of candidate immune effectors, is induced as *C. elegans* encounters various pathogens. Several immune signaling pathways have also been identified in the worm, and even though some host defense mechanisms in *C. elegans* have no homologs in the mammalian system, many pathways and effector molecules are conserved from worm to man.

In the laboratory, the nematode is routinely cultured on lawns of the non-pathogenic *Escherichia coli* strain OP50. Pathogenesis is easily evaluated in the worm by replacing the normal *E. coli* food source with the pathogen of interest and monitoring lifespan, or some other hallmark of the host response, like the expression of an immune effector gene. The normal median lifespan of *C. elegans* is 16–19 days on the standard *E. coli* food source, depending on the laboratory conditions. Different pathogens vary greatly in the time it takes for the worm to succumb to the bacterial infection; some pathogens kill within hours whereas the majority of pathogens used in laboratory experiments kill within 2 to 8 d.⁴

The mode of bacterial infection varies from *Yersinia pestis*, which forms a biofilm that will attach to and cover the nematode mouth as it moves through the bacterial lawn, to *Microbacterium nematophilum*, which adheres to the hindgut cuticle; however, the majority of bacteria form an intestinal infection in *C. elegans*.³ Fungi also vary in their mode of infection, as exemplified by *Drechmeria coniospora* that adheres to the cuticle and infects the nematode via its epidermis, and *Harposporium sp* and *Candida albicans* that infect *C. elegans* through its intestine.⁶⁻⁸ In recent studies the Gram-negative bacteria *Salmonella enterica* serovar Typhimurium and *Pseudomonas aeruginosa* were observed to escape from the intestinal lumen and invade the epithelial cells of the nematode.⁹,¹⁰ Furthermore, the microsporidium *Nematocida parisii* was shown to establish intracellular infections in the intestinal cells of *C. elegans*.¹¹ This pathogen, along with *D. coniospora*, is a natural pathogen of *C. elegans*, whereas the majority of pathogens used for *C. elegans* infection studies have not been observed infecting the worm outside of laboratory settings.

**-Omics Studies of Innate Immunity**

The *C. elegans* genome was the first completed animal genome and its completion opened up the way for large-scale investigations in this versatile biological model organism. Early on in the field of host-pathogen interactions, researchers took advantage of
the possibility to gain genome-wide information of the innate immunity response in the worm, and several approaches have been used in the search for *C. elegans* immune defense genes or proteins. Microarrays were employed on worms infected by *Serratia marcescens*, *D. coniospora*, *M. nematophilum*, *P. aeruginosa*, *Staphylococcus aureus*, *Y. pestis*, *C. albicans*, *Bacillus thuringiensis* and a comparative study with *S. marcescens, Enterococcus faecalis, Erwinia carotovora* and *Photorhabdus luminescens*. In addition to these transcriptional analyses of pathogen response, microarray was also performed to study the response to the pore-forming toxin Cry5B from *B. thuringiensis*. Recently, tiling-arrays and RNA sequencing were used to study and compare the responses to *S. marcescens, E. faecalis, P. luminescens, D. coniospora* and *Harposporium*. Studies focusing on the protein level during infection have also been performed, where the response to *Aeromonas hydrophila* and *S. aureus*, respectively, was investigated using differential gel electrophoresis, and infection with the pathogenic *E. coli* LF82 was analyzed using metabolic labeling and quantitative mass spectrometry. A list of all -omics experiments targeting the *C. elegans* host response during infection can be seen in Table 1. These large-scale studies are in their nature very different since the pathogen, time points and methods vary between experiments. However, taken together, this large number of -omics studies hold a great deal of information on how *C. elegans* defends itself from a large variety of pathogens. When combining data from all -omics experiments, 30% have only been found in one single experiment, suggesting that each pathogenic organism induces a specific immune response together with a more shared response. This review will focus on this shared portion of the *C. elegans* immune response.

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**Table 1.** Genome-wide studies on the host response in *C. elegans*

| Pathogen | Method (proteomics/transcriptomics) | Time of sampling | References |
|----------|-------------------------------------|-----------------|------------|
| *B. thuringiensis* | T | 8 h | Boehnisch et al. |
| *S. aureus* | P | 1, 4, 8, 24 h | Bogaerts et al. |
| *A. hydrophila* | P | 1, 3, 5 d | Bogaerts et al. |
| *Y. pestis* | T | 24 h | Bolz et al. |
| *S. marcescens, E. faecalis, P. luminescens, D. coniospora* and *Harposporium* | T | 24 h (D. coniospora 12 h) | Engelmann et al. |
| *B. thuringiensis* toxin Cry3B | T | 3 h | Huffman et al. |
| *S. aureus* | T | 8 h | Irazoqui et al. |
| *M. nematophilum* | T | 6 h | O’Rourke et al. |
| *D. coniospora* | T | 24 h | Pujol et al. |
| *C. albicans* | T | 4 h | Pukkila-Worley et al. |
| *P. aeruginosa* | T | 4, 12, 24 h | Shapira et al. |
| *E. coli* LF82 | P | 24, 72 h | Simonsen et al. |
| *P. aeruginosa* | T | 4, 8 h | Troemel et al. |
| *S. marcescens, P. luminescens, E. faecalis* and *E. carotovora* | T | 24 h | Wong et al. |

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**C. elegans Core Set of Immune Effectors**

In an attempt to define a core set of *C. elegans* immune regulators, we focused on genes/proteins, which were regulated (positively or negatively) in response to infection in eight or more experiments (out of the total 24 different large-scale infection experiments). This resulted in a set of 315 genes/proteins, of which 245 are mostly upregulated and 49 are mostly downregulated, whereas 21 genes/proteins are equally regulated (up or down) in at least eight experiments (Table S1). This core set is enriched in several protein families, domains and functional classes as can be seen in Figure 1. The most common protein families identified in the core set are C-type lectins, DUF274 proteins, lysozymes, collagens and UDP-glucosyltransferases. The core data set is also enriched in CUB-domains and Metridin-like ShK toxin domains as well as a large number of genes/proteins with reported peptidase activity. These protein families will be described in detail below.

Several genes/proteins are found to be exclusively upregulated in the 24 -omics studies and curiously, very little is known about the immune regulators exclusively upregulated in half or more studies: The F53A9.1, F53A9.2 and C50F7.5 genes encode completely uncharacterized proteins, and oac-31 encodes a O-Acyltransferase homolog. Also among the most often upregulated genes are *cdr-4*, a cadmium responsive gene; and *clc-1*, a claudin homolog, which is an important component of tight junctions and believed to maintain the impermeability of the epithelial layer. *clc-1* was shown to be required for resistance toward *S. aureus* in the nematode.

Interestingly, no genes/proteins are found to be exclusively downregulated; however, several genes are found to be much more often downregulated than upregulated as a response to a
pathogen. Among these are *vit-1* and *vit-3*, two vittelogenins, the major egg yolk proteins in *C. elegans*, as well as the two *C. elegans* metallothioneins *mtl-1* and *mtl-2*. Metallothioneins are small, cysteine-rich metal-ion binding proteins, which serve roles in cadmium toxicity protection, zinc homeostasis, and even a role in immunosuppression has been found,25,26 Their role, if any, in the *C. elegans* immune response remains unknown. The downregulated core set also includes *cen-2*, which encodes an antimicrobial peptide of the caenacin family known to promote survival of *C. elegans* after fungal infection,27 and *thn-2* encoding an antimicrobial protein of the thaumatin family conferring resistance to infection by pathogens such as *P. aeruginosa*28 and *M. nematophilum*.14 At first glance, downregulation of host defense effectors in response to infection may appear rather surprising. However, in some cases this may reflect a mechanism by which pathogens overcome the immune defenses of *C. elegans*, as demonstrated for *P. aeruginosa*.28 The presence of several immune defense effectors among the core set of genes mostly downregulated upon infection suggests that suppression of host immunity is a general strategy employed by pathogens to resist *C. elegans* host defenses.

**C-Type Lectins**

In *C. elegans*, C-type lectins have been reported in the response to almost every single pathogen tested, and the total number of different C-type lectins induced is over 60.7,10,14-16,19,22,23,28,29 Thirteen C-type lectins and an additional two lectins are found in the core set of *C. elegans* immune regulators. C-type lectins belong to a large superfamily (> 200 proteins) containing C-type lectin-like domains (CTLDs). A classical C-type lectin binds carbohydrate structures in a Ca2+-dependent manner, but many CTLDs bind carbohydrates independently of Ca2+ and some bind lipids or other ligands.30 The domain architecture of the vertebrate CTLDs differ from the invertebrates; the only common architecture found is a single CTLD, which is also the most common architecture in *C. elegans*.31 The differential pattern exhibited by C-type lectins to different pathogens was proposed as a potential mechanism for the innate immune specificity observed in *C. elegans*,32 but clearly, a part of the C-type lectins are induced in response to several different pathogens. Interestingly, of the C-type lectins found in the core set, the two fungi *C. albicans* and *D. coniospora* seem to mostly downregulate the expression of these proteins, whereas the majority of the other pathogens seem to upregulate them. Only one C-type lectin (clec-61) is more often downregulated than upregulated. A subset of *C. elegans* C-type lectins have been tested directly with respect to their effect on survival of the host, and clec-17, clec-60 and clec-86 were reported to cause enhanced susceptibility to *M. nematophilum* when knocked down by RNAi.14 Also, knockdown of clec-70 resulted in enhanced susceptibility to *S. aureus*,10 and simultaneous overexpression of clec-60 and clec-61, or clec-70 and clec-71 resulted in enhanced resistance to *S. aureus* but, interestingly, decreased resistance to *P. aeruginosa*.10 RNAi knockdown of clec-65 also caused enhanced susceptibility to the *E. coli* LF82.23 In mammals, the C-type lectins mouse RegIIIy and human HIP/PAP were shown to be induced by intestinal bacteria and to bind pepdidioglycan, and they possess direct antimicrobial activity against Gram-positive bacteria.33 However, so far, no functional studies can confirm whether any of the *C. elegans* C-type lectins share this function with their mammalian counterparts.

**CUB Domains**

The core set is highly enriched in proteins containing CUB (or CUB-like) domains (C1r/C1s, Uegf and Bmpl1). More than 50 CUB-like proteins are encoded from the *C. elegans* genome. The CUB domain is a structural motif of approximately 110 residues found almost exclusively in extracellular and plasma membrane-associated proteins with a diverse range of functions. It has been suggested that *C. elegans* CUB-domain proteins function in innate immunity, due to the organization of their genes in large clusters and the similarity of CUB domains to immunoglobulins.34 Indeed, functional roles in pathogen resistance have been demonstrated for several of the 18 CUB-like genes belonging to the core set of upregulated genes. Inhibition of F08G5.6 enhanced the susceptibility of *C. elegans* toward both *P. aeruginosa*15,35 and *Y. pestis*.17 Knockdown of F20G2.5 and dcr-17 also led to an increased sensitivity to *P. aeruginosa*,15,35 whereas RNAi inhibition of C17H12.8 and C32H11.12 enhanced the susceptibility of *C. elegans* to *Y. pestis* infection.17 Curiously, the fungi *C. albicans* and *D. coniospora* appear to downregulate several CUB-like genes mostly upregulated by other pathogens (see Table S1).

**DUF274 Proteins**

The *C. elegans* genome encodes 22 proteins with the domain of unknown function 274 (DUF274); a gene family unique to Caenorhabditis. A remarkable ten DUF274 proteins are part of the core immune response, yet very little functional information is available for this protein family, in which all members consist solely of the DUF274 domain. Only one study has shown a role...
for a DUF274 protein; RNAi knockdown of Y41D4B.16 significantly reduced the lifespan on the pathogenic *E. coli* LF82, but the very strong presence of this protein family in the core set suggests an important function for the DUF274 proteins in the *C. elegans* immune response. Interestingly, the fungus *D. coniospora* seems to downregulate expression of the DUF274 proteins, whereas the rest of the pathogens almost exclusively upregulate these proteins.

**UDP-Glucuronosyltransferases and Metridin-Like ShK Toxin Domains**

The *C. elegans* core immune response is enriched in enzymes, which transfer a glycosyl group from an UTP-sugar to a small hydrophobic molecule, the UDP-glucuronosyltransferases (UGTs). This glucuronidation reaction is an important detoxification process in vertebrates, however, UDP-glucuronosyltransferases (together with cytochrome P450s and glutathione S-transferases, of which cyp-25A2, cyp-34A9, cyp-35C1, gst-20 and gtt-38 are also in the core response) have also been associated with olfactory processing. Little functional information is available for the UGTs in *C. elegans*, but their presence in the core response is intriguing, since *C. elegans* has been shown to exhibit olfactory learning against pathogenic bacteria, but if this involves the UGTs is yet to be determined. Moreover, functional annotation of the UGTs implies that this class of enzymes could be involved in transfer of a glycosyl group to lipids, suggesting that lipid modification is involved in the core host response against pathogens. Previously, it was suggested that *C. elegans* resists the toxic Cry5B produced by *B. thuringiensis* by making specific glycolipid-binding galectins, which compete out and hence prevent Cry5B binding in the intestine of *C. elegans*.

Metridin-like ShK toxin domains have a structural resemblance to ShK toxin produced by sea anemones, which is known to block potassium channels, however, the metridin-like ShK toxin domain lacks a lysine residue necessary for this function. The functional relevance of this protein domain in the *C. elegans* immune response is completely unknown.

**Lysozymes**

Lysozymes are antimicrobial proteins present in microbes, insects, plants and animals. They cause lysis of bacterial cells by breaking down peptidoglycan, the major component of the bacterial cell wall. *C. elegans* has ten genes encoding lysozymes (*lys-1 to lys-10*), which belong to the protist-type lysozymes, and an additional five invertebrate-type lysozymes (*ilys-1 to ilys-5*). The lysozymes have been studied with regards to many different infections in *C. elegans*. It is therefore to be expected that several lysozymes are part of the *C. elegans* core immune response. Five lysozymes are more often seen to be upregulated in response to pathogenic infection (*lys-1, -2, -4, -6 and ilys-2*); one (*lys-5*) is regulated equally up and down, whereas *ilys-3* is more often downregulated in response to infection. Overexpression of *lys-1* made *C. elegans* more resistant to a specific strain of *S. marcescens*, and knockdown of *lys-1* caused enhanced susceptibility to *S. aureus*. Simultaneous overexpression of the genomic neighbors *lys-4* and *lys-5* caused resistance to *S. aureus* while the loss of *lys-7* resulted in less resistance to *M. nematophilum* and the pathogenic *E. coli* LF82. Knockdown of *lys-7* also caused enhanced susceptibility toward *P. aeruginosa* and, interestingly, this pathogen suppresses the expression of *lys-7* as part of its pathogenicity strategy. In contrast, more resistance toward *S. Typhimurium* was observed in a *lys-7* mutant, which was also shown to be more susceptible to infection with the fungus *Cryptococcus neoformans*. Furthermore, knockdown of *ly-2, lys-5* and *lys-7* led to decreased resistance against *B. thuringiensis*, whereas overexpression of *lys-5* and *lys-7*, but not *lys-2*, resulted in an increase in resistance. The direct mode of action of any lysozyme has not been confirmed in *C. elegans*, but their large representation in the core set of immune effectors suggests an important function in the defense system of the worm.

**Collagens**

Collagens, which are the major part of the *C. elegans* exoskeleton called the cuticle, are also among the highly regulated genes/proteins in the host response. The majority (nine out of ten) are more often upregulated in response to an invading pathogen, and the trend seems to be that the two fungi Harposporium and *D. coniospora* strongly downregulate the expression of numerous collagens, whereas the bacterial pathogens are found to both up- and downregulate the collagens. The collagenous cuticle is an important line of defense for *C. elegans*, and with *D. coniospora* infecting via the cuticle, it comes as no surprise that this pathogen would potentially target the collagens. However, Harposporium, and the many bacterial pathogens observed to regulate collagens, all infect via the intestine, and the role of the collagens here is less obvious. The collagen genes in *C. elegans* have highly similar nucleotide sequences and thus cross-hybridization is likely to occur on the microarrays, so when examining this group of genes, this potential error needs to be taken into account.

**Signaling in the Immune Response**

Several signaling cascades involved in the response to pathogenic attack have been identified in *C. elegans* and importantly, the major pathways have all been shown to play important roles in mammalian innate immunity as well. Key components in the nematode host response include the p38 mitogen-activated protein kinase (MAPK), the transforming growth factor-β (TGFβ) and the insulin-like DAF-2–DAF-16 pathways, but also the bZIP transcription factor ZIP-2 is involved in responding to pathogens. Interestingly, the Toll-like receptor (TLR), which has a very central role in mammalian innate immunity, does not seem to be an important component of the immune response of the worm, since partial loss of function in the single TLR homolog in *C. elegans*, tol-1, does not affect the defense against the majority of pathogens tested, albeit an enhanced susceptibility to infection by *S. enterica* has been reported. Insights learned from *C. elegans* could therefore not only give novel information on the fundamental immune pathways conserved in humans and
nematodes; the nematode might also present an opportunity to identify TLR-independent mechanisms of innate immunity.

The core set of immune effectors identified from the large-scale infection experiments in *C. elegans* does indeed suggest that the known signaling pathways are very important in the shared host response. Several immune effectors in the core immune response are known to be regulated by the MAPK pathway in *C. elegans*, including *lys-1*, *lys-2*, three DUF274 proteins and several CUB-like proteins. The conserved p38 MAPK pathway includes the two upstream kinases NSY-1, SEK-1 and the MAPK PMK-1, which cause enhanced susceptibility to *P. aeruginosa* when mutated. One of the transcription factors downstream of PMK-1 is ATF-7, and lack of this conserved transcription factor causes hyper-susceptibility to some pathogens. A similar p38 MAPK cascade also plays an important role in innate immunity in the mammalian system, where it is present downstream of the TLR, but as mentioned above, the single TLR in the nematode is not central in the innate immune response for *C. elegans*. In addition to *tol-1*, *C. elegans* *tir-1* contains a Toll/IL-1R homology (TIR) domain; the cytoplasmic signaling domain of the mammalian TLR. *tir-1* was shown to function upstream of NSY-1 in the p38 MAPK cascade, and mutations or knockdown in *tir-1* resulted in susceptibility to a variety of pathogens. The upstream components of the MAPK cascade differ depending on the tissue. In the intestine, the protein kinase Cδ (PKCδ) TPA-1 activates the protein kinase D DKF-2, which in turn activates the PMK-1 cassette. Lack of DKF-2 caused less resistance to *P. aeruginosa* and *E. faecalis*, and inactivation of TPA-1 also caused less resistance to *P. aeruginosa*. In the hypodermis, the PKCδ TPA-1 is also involved in this signaling, and a study identified two PLCs, EGL-8 and PLC-3, and the two proteins Gα GPA-12 and Gβ RACK-1, as additional upstream components.

The core immune response also comprises several known targets of the TGFβ-signaling pathway, including four C-type lectins and *irg-2*. In *C. elegans*, DBL-1 (a TGF-β homolog) binds to the DAF-4/SMAD-6 receptor and acts through the SMAD complex. *dbl-1* mutants are hypersensitive to infection with *S. marcescens*, and the *dbl-1* gene was also shown to be necessary for the expression of *cnc-2* after *D. coniospora* infection. In the epidermis, the smad proteins SMA-2 and SMA-4 were not necessary for the induction of *cnc-2*.

The FOXO transcription factor DAF-16 regulates several genes involved in stress-response, longevity and innate immunity in *C. elegans*, including eight genes named on the basis of their regulation by DAF-16: *dct-7*, *dct-7*, *dan-17* and *dan-18* and *dod-3*, *dod-3*, *dod-19* and *dod-19*. The DAF-2 insulin/IGF-1-like receptor inhibits DAF-16 by phosphorylation via a kinase cascade, including AGC-1, PDK-1, AKT-1, AKT-2 and SGK-1. In DAF-2 mutants, DAF-16 is constitutively active, and pathogen-resistance of *daf-2* mutants has been observed with numerous pathogens; this phenotype is DAF-16 dependent. The DAF-2-DAF-16 pathway also regulates lifespan, and the *daf-2* mutants are long lived in addition to being resistant to pathogens. These observations could be two alternative descriptions of the same phenomena; however, this is not the case, since regulation of lifespan and pathogen resistance can function independently, and different components of the insulin-like signaling pathway distinctly regulate lifespan and pathogen resistance. Along with DAF-2, AGE-1, AKT-1 and AKT-2 regulate both lifespan and resistance, whereas SGK-1 and PDK-1 regulate lifespan but have no effect on pathogen resistance.

Defense against *P. aeruginosa* is also mediated by the bZIP transcription factor ZIP-2. *P. aeruginosa* infection involves the action of exotoxin A, which causes translation inhibition; this blockade of host protein translation will in turn activate the ZIP-2 pathway and several immune genes are consequently transcribed. Curiously, ZIP-2 affects the expression of genes belonging to the core host response, including *irg-2* and Y58A7A.5, suggesting that ZIP-2 could be involved in defense responses to more pathogens in addition to *P. aeruginosa*. This is very interesting since ZIP-2 signaling has been speculated to be used by the *C. elegans* host to discriminate between non-pathogenic bacteria and pathogenic bacteria causing disruption in cellular homeostasis. ZIP-2 has no direct homolog in mammals; however the bZIP transcription factor class has been shown to be involved in mammalian innate immunity.

**Variance between Large-Scale Investigations**

A hierarchical clustering analysis of the core immune response reveals that responses of different pathogens show varying degrees of similarity among each other (Fig. 2). Especially the response toward *D. coniospora* seems to be mainly oppositely regulated; however, this fungus also infects *C. elegans* differently than the majority of the other pathogens by adhering to the cuticle of the worm and then infecting via the epidermis. To a lesser degree, the response reported toward *C. albicans* is also largely opposite to the bacterial pathogens tested, even though this fungus infects via the intestine, so it would seem that the worm responds differently toward fungi than to bacterial pathogens. Interestingly, the two fungi seem to mainly downregulate genes, whereas the majority of bacterial pathogens induce upregulation of a much larger number of genes than they downregulate. To date, the large-scale investigations of *C. elegans* immunity show large variance, even for studies of responses to the same pathogen; e.g., two different investigations of *S. marcescens* infection proved less than 2% overlap, and in the case of different studies on *P. aeruginosa* infection, the overlap was less than 20%. Data from microarray and proteomics investigations of *S. aureus* infection differs even more; only five proteins of the 108 proteins reported as differentially regulated in the proteomics study were also seen regulated on the transcriptional level. Despite these large differences, an increasingly more thorough picture of *C. elegans* immunity is emerging based on the accumulation of all these observations. By focusing on genes/proteins only expressed in eight or more -omics experiments, a common set of immune modulators was defined, including well known immune effectors, such as the C-type lectins, lysozymes and CUB-domain proteins, which have all been described as induced by the majority of pathogens investigated. Additionally, our core set of immune effectors also shows how collagens and UDP-glucuronosyltransferase are very common in the *C. elegans* host response.
The *C. elegans* immunity response shares features of other stress responses such as heat shock, osmotic, ER (endoplasmatic reticulum) and heavy metal stress, but since an infection causes large cellular and eventually organinal damage, it seems only natural that many stress responses overlap. Importantly, a large pool of large scale data is now available for the innate immune response of the worm. This opens up for the comparison with this data to other biological responses, as has been exemplified in several studies, including analyses of miRISC-associated mRNAs (mRNAs) in the intestine, and animals containing mutations in the DICER gene, respectively, demonstrating a significant overlap with pathogen-responsive mRNAs.

**Future Directions**

The techniques for performing -omics experiment are constantly improving and as such the precision and quality of data will as well. The majority of experiments have been performed using microarray, but with the recent addition of RNA-sequencing employed to deduce the host response, an unprecedented quantitative measure of transcript levels can be obtained. So far, the transcriptional responses to invading pathogens were investigated in far greater detail than the translational response. However, with the recent elegant approach enabling stable-isotope labeling with amino acids in cell culture (SILAC) in *C. elegans* by feeding worms a heavy lysine- and heavy arginine-labeled *E. coli* strain, resulting in very precise and deep investigation of the proteome, quantitative proteomics should in the future be used to gain further information on the infection response on the protein level. The complex host-pathogen relationship could also benefit from simultaneous large-scale investigation of the response of the host as well as the pathogen. To our knowledge, such experiments have not been performed in *C. elegans*. Future -omics investigation in *C. elegans* will help give more knowledge on the host response to various pathogens, but one major concept is already clear; *C. elegans* is clearly capable of mounting both pathogen-specific and pathogen-shared responses to an infection.

**Supplemental Material**

Supplemental material may be found here: www.landesbioscience.com/journals/virulence/article/21906

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