CHAPTER 6

INNATE IMMUNITY IN *C. ELEGANS*

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Abstract: The nematode *Caenorhabditis elegans* is proving to be a powerful invertebrate model to study host-pathogen interactions. In common with other invertebrates, *C. elegans* relies solely on its innate immune system to defend itself against pathogens. Studies of the nematode response to infection with various fungal and bacterial pathogens have revealed that the innate immune system of *C. elegans* employs evolutionary conserved signalling pathways. They regulate the expression of various effectors molecules, some of which are also conserved. Here, we summarize the current knowledge of the pathways and effector molecules involved in the nematode immune response, with a particular focus on the antifungal immune response of the *C. elegans* epidermis.

INTRODUCTION

C. elegans is a free-living soil nematode that feeds on bacteria and is therefore constantly exposed to potential pathogens.[1] Like other invertebrates, *C. elegans* lacks an adaptive immune system. In contrast to many invertebrate species, however, *C. elegans* does not appear to have specialized immune cells. For example, while Drosophila has macrophage-like hemocytes, which engulf invading microbes, the only cells in the nematode body cavity, the 6 coelomocytes, do not seem to be capable of phagocytosis but function as scavenger cells with a high endocytic capacity.[2]

C. elegans possesses three major mechanisms of defences against microbial attacks:[1] Avoidance behaviour: It has been demonstrated that worms are able to distinguish between different bacteria. Whereas most bacteria attract *C. elegans*, some repel the nematode and cause an avoidance behaviour. Such an aversive response can be specifically directed against the pathogenic strains of a bacterial species (reviewed in ref. 3). Olfactory neurons, G protein coupled receptors and the only Toll-like receptor (TLR) in *C. elegans*, TOL-1,

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are involved in triggering the avoidance behaviour to pathogenic *Serratia marcescens*.[4,5] Worms can "remember" odours[6] and can even learn to avoid bacteria that are recognized as noxious.[7] This discrimination relies in part on pairs of asymmetric chemosensory neurons.[8] Their correct development requires a signalling cassette that includes an intracellular TIR-domain adapter protein (TIR-1) acting upstream of a p38 MAPK cascade.[9] This cassette, which will be described in more detail below, appears also to play a direct behavioural role as it has been found to be involved in the neuroendocrine regulation of serotonin-dependent aversion to *Pseudomonas aeruginosa*.[10,2] The second axis of protection against pathogen invasion is a strong cuticle, made of collagen and chitin and constituting the exoskeleton of the worm. It acts as a physical barrier that is relatively resistant to puncturing. As a complement, the pharyngeal grinder destroys pathogens that are taken up during feeding. It prevents live pathogens from reaching the intestine and establishing an infection. Indeed, mutants with defective grinder function are more susceptible to infection.[11,12,3] The third line of defence involves inducible mechanisms. These will be the main focus of this chapter. *C. elegans* possesses a complex inducible defence system involving multiple signalling cascades that regulate the production of antimicrobial peptides (AMP) and proteins in a pathogen- and tissue-specific way.

ROUTES OF INFECTION

Most of the known pathogens of *C. elegans* use two main routes of infection, through the pharynx or the epidermis (Fig. 1). Many Gram-positive and Gram-negative bacteria as well as yeast, infect worms upon oral up-take during feeding and establish an intestinal infection. They must survive the passage through the grinder to reach the intestine, proliferate and establish an infection. In some cases, it has been shown that the pathogen destroys the grinder,[13] in others it appears that the infectious particles, such as the spores of *Bacillus thuringensis* are resistant to the mechanical action of the grinder.[14] Almost all characterised intestinal pathogens of *C. elegans* remain extracellular, apart from *Salmonella typhimurium* and the microsporidium *Nematocida parisii*, that have been shown to establish intracellular infection in the intestinal cells.[15,16]

Some pathogenic bacteria and fungi can adhere to the cuticle and infect the *C. elegans* epidermis. For example, *Microbacterium nematophilum* adheres to the anal region of the nematode and induces hindgut swelling[17] and *Leucobacter chromiireducens* is capable of causing lethal uterine infections[18] (Fig. 1). Different fungi that are pathogenic for nematodes, including *Drechmeria coniospora* and species of *Haptocillium*, produce spores that adhere and then penetrate the cuticle and grow into the epidermis (Figs. 1 and 2).[19,20] Although some pathogens, such as certain strains of *P. aeruginosa*, produce fast-acting toxins,[21] against which *C. elegans* appears defenceless, in many cases, infection provokes an immune response.

PATHOGEN RECOGNITION

The first step of an inducible defence is the recognition of the pathogen. Conserved structures on pathogens that are not present in the host and thus recognized as foreign, so called microbe-associated molecular patterns (MAMPs), bind to pattern recognition

receptors (PRRs) in many organisms.[22] PRRs include peptidoglycan recognition proteins (PGRP), Gram negative binding proteins (GNBP), nucleotide-binding oligomerization domain (NOD) and NACHT domain proteins.[23] Genes encoding proteins of these families are absent from the *C. elegans* genome.

One prominent class of PRRs, in vertebrates the TLRs, can sense outer membrane components of the bacteria, RNA or DNA.[22] As mentioned above, the single worm TLR, TOL-1, is involved in behavioural avoidance of some pathogenic bacteria,[4,5] but does not seem to play a role in the resistance to several pathogens,[5] nor in the regulation of certain immune effectors.[24] One study showed that *tol-1* mutants are more susceptible to *S. typhimurium* infection,[25] but it is unclear whether this is due to an involvement of *tol-1* in a protective immune response or rather due to a defect in cell adherence in the pharynx of the *tol-1* mutant leading to a defect in a physical barrier thus favouring pathogen invasion.

TLRs, as well as a number of other PRR families, in both plants and animals, share a common domain, the leucine rich repeat (LRR) domain. In a recent study, the role in host defences of each of the 14 predicted transmembrane proteins with LRR domains encoded in the *C. elegans* genome, was assayed. Loss-of-function mutants in one gene, *fshr-1*, which encodes a glycopeptide hormone receptor homologue, were found to be more susceptible to infection by Gram positive and Gram negative bacteria. It has yet to be determined if FSHR-1, which is expressed in the intestine, acts as a pathogen receptor or rather functions as a positive modulator of the nematode immune response.[26]

C-type lectins are carbohydrate-binding proteins that can exhibit very narrow ligand specificity. In mammals, a number of C-type lectins have established roles in innate immunity. For example, Dectin-1 is highly expressed on macrophages and recognizes beta-glucan, a component of the fungal cell wall and thereby acts as a PRR.[23] *C. elegans* possesses 278 genes encoding C-type lectins, but it is currently unclear as to whether any of them function as PRRs or rather as effector molecules (see below).

While there is no clear Dectin-1 orthologue in *C. elegans*, there are a number of potential scavenger receptors (SR), another class of protein known to be involved in pathogen recognition in other species.[27] Indeed, there are six proteins homologous to CD36 and Croquemort, members of the SR-B family and one well-characterised SCARF orthologue CED-1. Because of its expression in the intestine throughout development, one of these, C03F11.3, was suggested a number of years ago to be potentially involved in the recognition of microbial molecules.[28] A study published last year supports such an idea, as CED-1/SCARF and C03F11.3/CD36 appear to function in host resistance to *Candida albicans* and *Cryptococcus neoformans* in *C. elegans*.[29] Whether in the nematode these proteins in fact recognize yeast cell wall beta-glucans and act as PRRs has not been formally demonstrated. Alternatively, given CED-1's known function in recognizing dying cells during programmed cell death, it might instead recognize damaged host material and then induce the unfolded protein response (UPR, see below) in an attempt to contain this damage. So we still do not know whether the worm responds through the detection of specific MAMPs or more generally to the cellular damage and stress caused by the pathogen (so-called danger theory[30]) or both. Nevertheless, the finding that *C. elegans* shows distinct immune responses to different pathogens that infect via the same route and have similar levels of virulence,[31,32] clearly supports a model of *C. elegans* specifically recognizing pathogens.

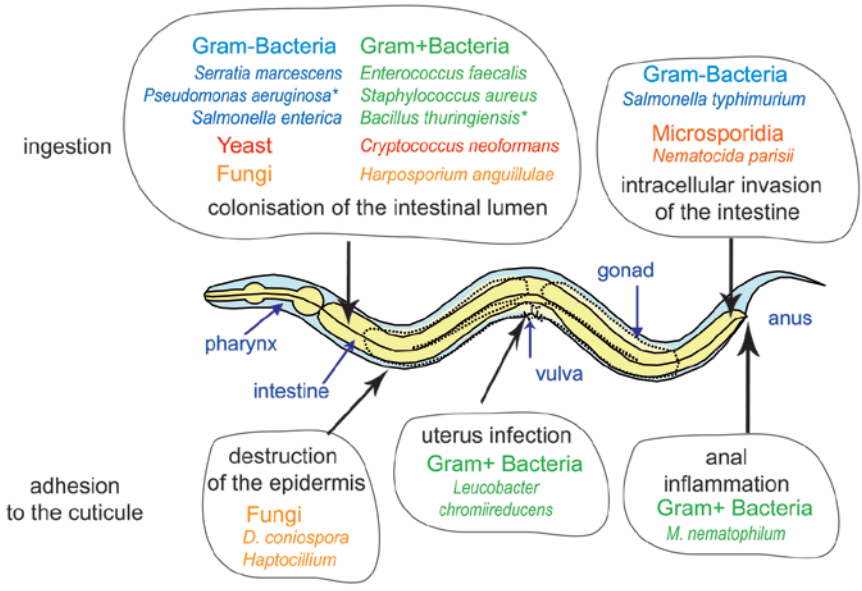

Figure 1. Pathogens of *C. elegans* and their route of infection. Most known pathogens of *C. elegans* are ingested and establish an infection in the intestinal lumen. Certain bacteria produce toxins (*) that can kill the nematode. The fungus *D. coniospora* and the bacteria *M. nematophilum* adhere to the cuticle and infect the nematode via the epidermis. Not all known pathogens of *C. elegans* are shown.

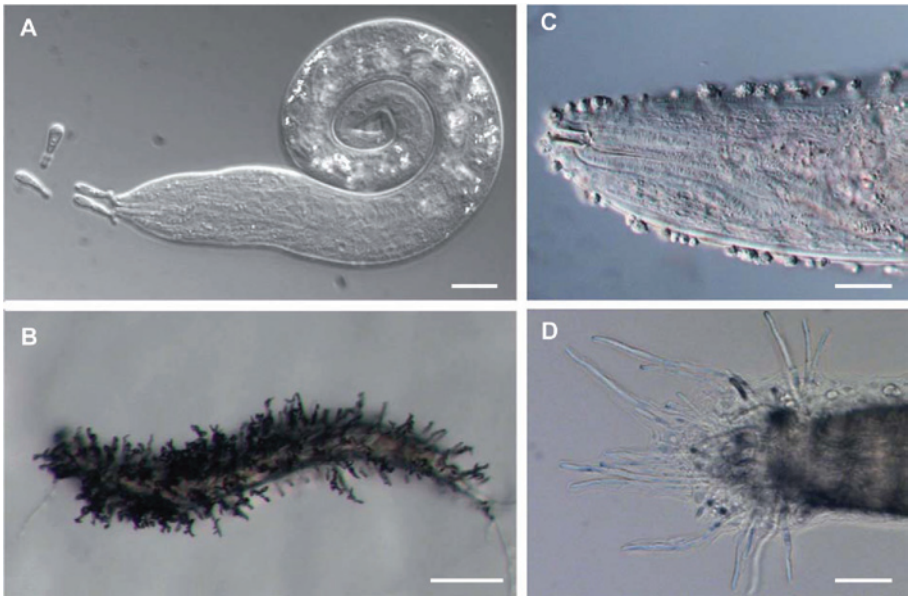

Figure 2. Fungal infection of *C. elegans*. (A and B) *D. coniospora*, (C and D) *Haptocillium*. (A and C) adhesion of the spores to the cuticle after few hours, (B and D) after 2 days fungal hyphae grow out of the worm. Scale bars are 10 μm (A), 100 μm (B) and 50 μm (C and D).

Table 1. Summary of the major signalling pathways in the *C. elegans* Immune System (updated from ref. 86)

Pathway	Tissue	Components	Homologues	References
p38 MAPK	Epidermis	GPA-12, RACK-1	G protein subunits	82
		EGL-8, PLC-3	Phospholipase C	82
		NIPI-3	Tribbles kinase	35
	Epidermis and intestine	TPA-1	Protein kinase C	82,87
		TIR-1	SARM	24,34,88
		NSY-1, SEK-1, PMK-1	MAP kinases	12,35
FSHR-1	Intestine	FSHR-1	G protein coupled receptor	26
ZIP-2	Intestine	ZIP-2	b-zip transcription factor	65
Insulin signalling	Nervous system	INS-7	Insulin-like peptide	76
	Intestine	DAF-2	Insulin receptor	42
		AGE-1	PI3 kinase	42
		AKT-1, AKT-2	Akt kinase	43
		DAF-16	FOXO transcription factor	42
TGF-β	Nervous system epidermis	DBL-1	TGF-β	54,55
		SMA-6	TGF-βreceptor	55
		SMA-3	SMAD protein	55
Wnt/Hox	Intestine/ Hindgut	BAR-1	β-catenin	61
		EGL-5	Hox transcription factor	61,64
ERK MAPK	Hindgut	LIN-45, MEK-2, MPK-1	ERK MAP kinase	39
		EGL-8	Phospholipase C	89
		SUR-2	Mediator component	39
UPR[1]	Intestine	XBP-1	X box protein	50,52
		HSP-4	Heat shock protein	
	Pharynx	CED-1, C03F11.3	Scavenger receptor	51
Autophagy	Intestine	BEC-1, LGG-1	ATG proteins	16

[1]The recent results of Richardson et al suggest that the primary function of the UPR is to protect against ER stress arising from the increase secretory response. Whether this is the case for Bt toxin[50] and for the noncanonical UPR[51] remains to be seen.

SIGNALLING PATHWAYS INVOLVED IN THE IMMUNE RESPONSE

Even if the manner in which the immune response in *C. elegans* is initiated has not been fully elucidated, several signalling cascades have been described that are activated specifically by certain pathogens (Table 1) and lead to the production of effector molecules which have the potential to destroy pathogens.

upstream of the PMK-1/p38 pathway (Fig. 3). The proximal elements of the pathways are, however, distinct. The former requires the conserved protein kinase Tribbles, NIPI-3, while the latter involves heterotrimeric G proteins acting upstream of a phospholipase C. All of the characterised components act in a cell-autonomous manner to control *nlp* gene expression in the epidermis.[35,82]

For the time being, the identity of the putative G-protein coupled receptor (GPCR) that activates the heterotrimeric G proteins is unknown, nor is it known how NIPI-3 is activated. There are, nonetheless, marked similarities between the molecular architecture underlying these pathways and the organisation of the signalling pathways that regulate the innate immune response both in Drosophila and in vertebrates. These led to the speculation that the innate immune response to *D. coniospora* arose from a GPCR-dependent mechanism

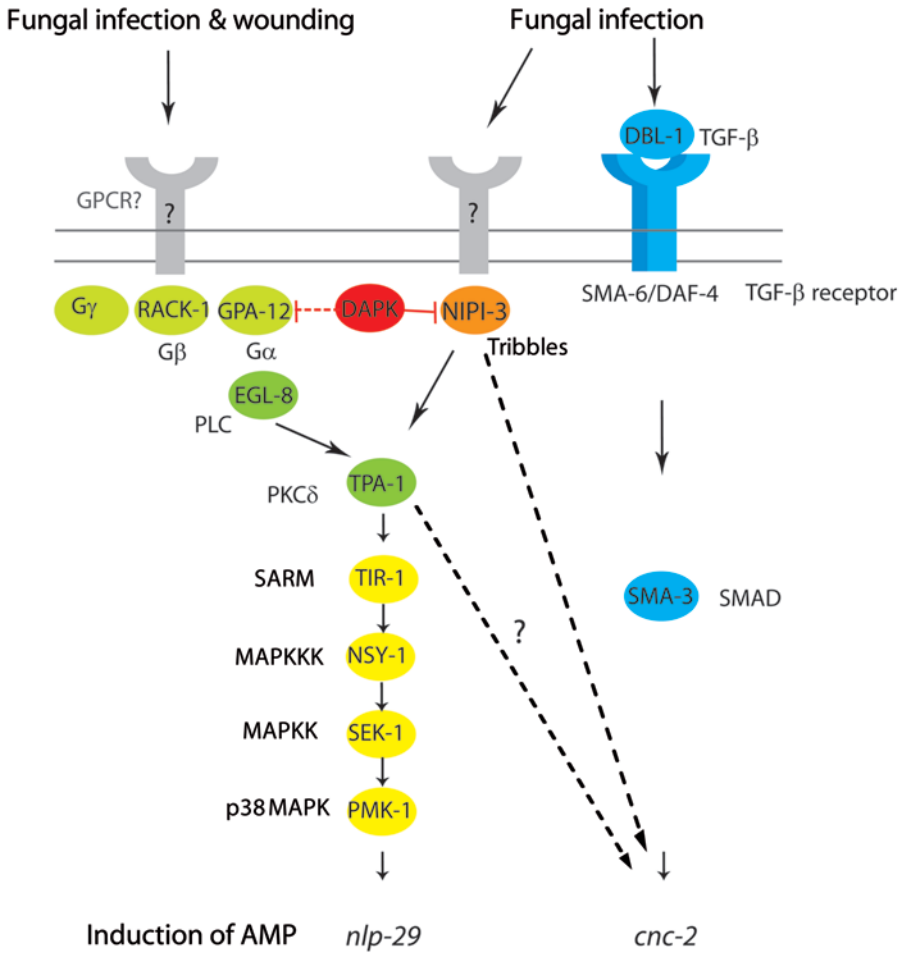

Figure 3. Schematic representation of the different signalling pathways and their components involved in the induction of antimicrobial peptides expression upon *D. coniospora* infection. Expression of the *nlp* genes is controlled by a PKC/SARM/p38 MAPK pathway and expression of *cnc* genes is controlled by a TGF-β pathway.

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