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Current Opinion in Biotechnology

Caenorhabditis elegans as a model system for human diseases

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The nematode *Caenorhabditis elegans* offers unique advantages that enable a comprehensive delineation of the cellular and molecular mechanisms underlying devastating human pathologies such as stroke, ischemia and age-associated neurodegenerative disorders. Genetic models of human diseases that closely simulate several disease-related phenotypes have been established in the worm. These models allow the implementation of multidisciplinary approaches, in addition to large-scale genetic and pharmacological screenings, designed to elucidate the molecular mechanisms mediating pathogenesis and to identify targets and drugs for emergent therapeutic interventions. Such strategies have already provided valuable insights, highly relevant to human health and quality of life. This article considers the potential of *C. elegans* as a versatile platform for systematic dissection of the molecular basis of human disease, focusing on neurodegenerative disorders.

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Current Opinion in Biotechnology 2020, **63**:118–125

This review comes from a themed issue on **Systems biology**

Edited by **Marco Ercole Vanoni** and **Pasquale Palumbo**

https://doi.org/10.1016/j.copbio.2019.12.011

Introduction: an overview of *Caenorhabditis elegans* as a versatile model organism

Caenorhabditis elegans is a non-parasitic, free-living nematode found worldwide feeding on various bacterial species. Besides, the worm can be also easily cultivated in large numbers on agar plates or in liquid medium supplemented with *Escherichia coli*. This simple multicellular organism exists primarily as a hermaphrodite, although males arise occasionally at a frequency of ≤0.2%. Mature adults are 1 mm long and consist of 959 and 1031 somatic cells, the hermaphrodites and the males respectively. The anatomical arrangement of all somatic cells together with their entire cell lineage is known. The nervous system of *C. elegans* is fully charted with the position and the connectivity of each of 302 neurons precisely described [1,2]. The nematode has a short life cycle of ~3.5 days at 20°C from egg through four larval stages to egg-laying adult and lives up to 2–3 weeks under favourable conditions. A wild-type worm can generate about 300 progeny by self-fertilization and over 1000 progeny when fertilized by a male. With its transparent body at all stages of its life cycle, which enables the use of fluorescent markers, and its small size, *C. elegans* lends itself to non-invasive optical monitoring and manipulation methodologies. Such approaches have helped to investigate the molecular mechanisms underlying normal function and dysfunction at all levels from cellular organelles to the whole organism during development and ageing. The completely sequenced *C. elegans* genome, which is only 97 Mb in size, has an estimated 60–80% of genes with homologues in humans [3,4]. These unique advantages together with the development of powerful molecular biology and genetic methodologies such as transgenesis, mutagenesis, gene targeting, among others, have enabled the dissection of classical signalling pathways that underlie development, neurobiology, cell death and ageing [5–8]. Besides, *C. elegans* research has advanced our understanding of the causal mechanisms behind a range of common human pathologies such as ischemia, stroke, and protein misfolding and aggregation diseases, including age-related neurodegenerative disorders. Noteworthy, the range of resources that are available to the worm community has contributed significantly to the rapid adoption of *C. elegans* as a model system for biomedical research. One such worm-specific resource is the WormBase (www.wormbase.org), the central data repository for *C. elegans* and other related nematode species. WormBase contains a wealth of information about gene structures, mutant and RNAi phenotypes, gene expression patterns based on microarray and RNA-seq data, gene-interaction and protein-interaction networks, among other experimental data sets [9]. An article just published describes the most recent improvements to the WormBase services with respect to: 1) literature curation; 2) new interfaces that allow users to query and visualize sequence and phenotype ontologies and 3) the architecture of the WormBase website [10•]. In conclusion, the powerful platform that *C. elegans* offers for a thorough dissection of the molecular and cellular basis of human disease, together with a wide range of resources and tools make the worm a valuable disease model (Table 1).

Modelling a human disease in the worm requires genetic engineering to alter the animal's genome. This can be

Table 1

Selected *C. elegans* human disease models

Disease	Disease-associated protein	Synopsis of pathological features in *C. elegans*	References
Neurodegenerative/Neuromuscular disorders			
AD	Human Amyloid β (Aβ) peptide	Muscle-associated $A\beta_{1-42}$ oligomers cause paralysis	[15]
		Neuronal Aβ expression leads to chemotaxis defects	[26•]
	APP/APL-1	Inactivation or overexpression of *apl-1* causes severe developmental defects	[52]
AD-relevant tau			
	PHP-tau	Increased tau aggregation, locomotion defects and neuronal dysfunction	[19,53]
PD	Human α-synuclein	Misfolded α-synuclein aggregates, dopaminergic neuron loss	[37]
	PARK9/ATP13A2/CATP-6, DJ-1/DJR-1.1/DJR-1.2, PINK1/ PINK-1	RNAi-mediated knockdown enhances α-synuclein misfolding /increases mitochondrial accumulation and compromises stress resistance	[35,42]
	LRRK2/LRK-1	Enhanced loss of dopaminergic neurons	[42]
	polyQ expansion	Muscle (polyQm) or neuronal (polyQn) expression induces toxicity	[44,48]
PQ			
HD	Expression of human Htt in body wall muscle or sensory (ASH) neurons	Motility defects or ASH neurodegeneration	[4,54]
ALS	SOD1	Pan-neuronal expression causes severe locomotion defects	
		Mutations cause mild toxicity in body wall muscles influenced by the genetic background	[54]
	ALS8/VPR-1	Inactivation leads to dysregulation of Eph receptor signalling *in vivo*	
SMA	SMN/SMN-1	Late larval arrest, lifespan shortening, defects in motility, decreased pharyngeal pumping	[55]
DMD	Dystrofin/DYS-1	Mutants display muscle degeneration	[4,54]
Laminopathies	LMNA/LMN-1, emerin/EMR-1	Mutations cause severe muscle lesions leading to crawling and swimming motility defects	[55]
OPMD	PABPN1	Mutants exhibit muscle cell degeneration and abnormal motility	[56]
Stroke-Excitotoxicity			
	Specific ion channels (DEG-1, MEC-4, DEG-3, GSA-1 in nematode)	Neurodegeneration	[54]
	Specific proteases (calpains CLP-1, TRA-3 and aspartyl proteases ASP-3, ASP-4 in nematode)		
Metabolic disorders			
Obesity, insulin resistance, type II diabetes)	OGT-1, OGA-1	Null mutants exhibit alterations in carbohydrate and lipid metabolism	[57,58]
Genetic kidney diseases			
Cystic kidney diseases and ciliopathies			
ADPKD	PDK-1 (LOV-1), PDK2 (PDK-2)	Gene knockdown causes male mating defects	[4]
Bardet-Biedl syndrome	BBS1(BBS-1), BBS-2(BBS-2), BBS7 (OSM-12) BBS8(BBS-8), BBS9 (BBS-9), MKS1 (MKS-1)	Mutants exhibit structural and functional cilia defects	[59]
Cancer	c-Met	Locomotion defects, low fecundity and abnormal larval development	
	LET-60/Ras	Multivulval phenotype	[60]
	CEP-1/p53	Mutations cause apoptotic defects linked to tumorigenesis and resistance to chemotherapeutic drugs	
Innate Immunity			
Host-pathogen interaction	P38 MAP/PMK-1	Loss of function mutations cause hypersensitivity to infections	[61]

AD, Alzheimer's disease; ADPKD, autosomal dominant polycystic kidney disease; ALS, amyotrophic lateral sclerosis; c-Met, receptor tyrosine-protein kinase Met; DMD, Duchenne muscular dystrophy; HD, Huntington's disease; Htt, Huntingtin; LMNA, lamin-A/C; LRRK2, leucine-rich repeat kinase 2; OGA-1, an orthologue of O-GlcNAcase; OGT-1, an orthologue of O-linked N-acetylglucosamine (GlcNAc) transferase; OPMD, oculopharyngeal muscular dystrophy PD, Parkinson's disease; PDK, polycystin; PQ, polyglutamine disorders; P38 MAP/PMK-1, mitogen-activated protein kinase 1; SMA, spinal muscular atrophy; SMN, survival motor neuron protein; SOD1, Cu/Zn superoxide dismutase.

achieved either by disrupting the expression of the *C. elegans* homologue of the human disease gene to induce a mutant phenotype or by overexpressing the human gene implicated in disease ubiquitously or in specific tissues so as to reproduce disease-related phenotypes in the worm [4]. The nematode model can then be used in forward and reverse genetic screens aiming to identify modifiers of the disease phenotype. The identified genes can be subsequently cloned and thoroughly characterized with the ultimate goal of investigating their functional conservation in more complex vertebrate disease models.

Here, we focus on *C. elegans* models that have contributed substantially to our understanding of devastating neurodegenerative disorders, highlighting recent advances that shed light on the cellular and molecular mechanisms underlying pathogenesis.

Modelling neurodegenerative diseases in *C. elegans*

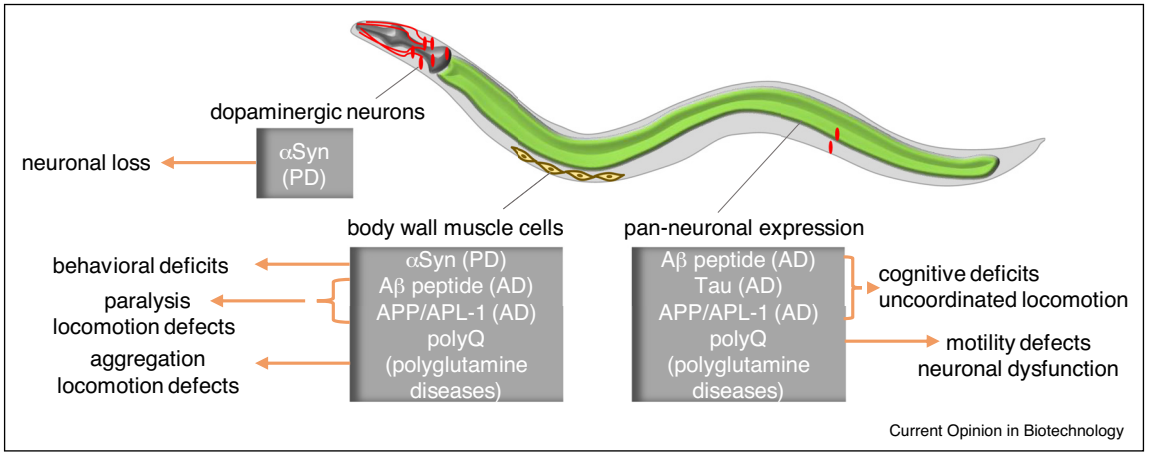
Ageing in diverse organisms is associated with a collapse of protein homeostasis (hereafter, proteostasis) [11]. Moreover, loss of proteostasis is a hallmark of distinct neurodegenerative diseases. Indeed, it is becoming progressively clear that age-related misfolding and aggregation of neurotoxic peptides is responsible for several neurological disorders such as Parkinson's disease, Alzheimer's disease and Huntington's disease, among others [12]. Recent studies capitalize on the genetic malleability of *C. elegans* to investigate the mechanisms underlying proteotoxic diseases. Below, we selected a few key discoveries in the field of neurodegenerative diseases that have emerged during the last years using *C. elegans* as a model system (Figure 1).

Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, with predicted prevalence of 66 million people by 2030. The mechanisms underlying the pathogenesis of AD remain largely unknown and its pattern of inheritance most likely depends on a combination of genetic and environmental factors. The disease pathologically is characterized by the presence of plaques of amyloid β peptides and intraneuronal tangles of hyperphosphorylated forms of microtubule-associated protein tau [13]. Mutations in the presenilin 1 *(PS1)*, presenilin 2 *(PS2)* and amyloid β-protein precursor *(APP)* genes, which are linked to familiar AD, increase the extracellular concentration of the most toxic form of the amyloid β peptide ($A\beta_{1–42}$) [14]. It is worth noting that genome wide association studies of large cohorts of patients with AD over the past decade have culminated in the identification of novel risk genetic loci for AD [13].

Several transgenic *C. elegans* models of AD have been established by expressing either human amyloid β (Aβ) or tau in specific cell types such as body wall muscle cells and neurons. Interestingly, expression of the $A\beta_{1–42}$ peptide in body wall muscle cells causes accumulation of toxic Aβ oligomers and paralysis that is exacerbated during ageing [15–17]. Another transgenic nematode strain that expresses $A\beta_{1–42}$ driven by the *eat-4* gene promoter exhibits progressive loss of glutamatergic neurons during ageing. This strain has been used to validate the functional link between Aβ toxicity and endocytic trafficking previously revealed by a genetic screen in yeast. To this end, animals expressing the p_{eat-4} $A\beta_{1–42}$ transgene were crossed with animals that express *C. elegans* homologues of the yeast genes involved in clathrin-mediated endocytosis, namely *unc-11*, *unc-26* and

Figure 1



Modelling human diseases in *C. elegans* by expressing human genes implicated in disease in specific cell types. Selected nematode models of Parkinson's disease (PD), Alzheimer's disease (AD) and polyglutamine diseases are depicted. Aβ: amyloid beta; APP: amyloid-precursor protein; αSyn: α-synuclein; polyQ: polyglutamine repeats.

Y44E3A.4, under the control of *eat-4* promoter. All three genes mitigated glutamatergic neuron loss by promoting Aβ detoxification and restoration of endocytic homeostasis [18].

Animals expressing the highly amyloidogenic tau species specifically in neurons display increased tau aggregation accompanied by neuronal dysfunction and motility defects that are manifested as uncoordinated (Unc) locomotion [19,20]. Reverse and forward genetic screens for suppressors of the tau-induced Unc phenotype have identified *sut-1* and *sut-2*, respectively, as determinants of tau-mediated neurotoxicity. Accordingly, *sut-2* overexpression exacerbates tau–associated pathology. By contrast, *sut-2* knockdown protects against tau-induced neuronal dysfunction [21,22]. A novel *C. elegans* AD model with constitutively pan-neuronal $A\beta_{1-42}$ expression has provided new insight into the metabolic basis of AD pathogenesis. Indeed, this AD model displays markedly reduced ATP levels and dysfunctions in electron transport chain (ETC) complexes that precede global metabolic failure. In addition, Aβ-expressing animals experience neuromuscular defects and middle-age onset behavioural phenotypes [23]. A recent comprehensive review summarizes the various Aβ and tau *C. elegans* models of AD that have been used to identify genetic and pharmacological modifiers of the disease [24].

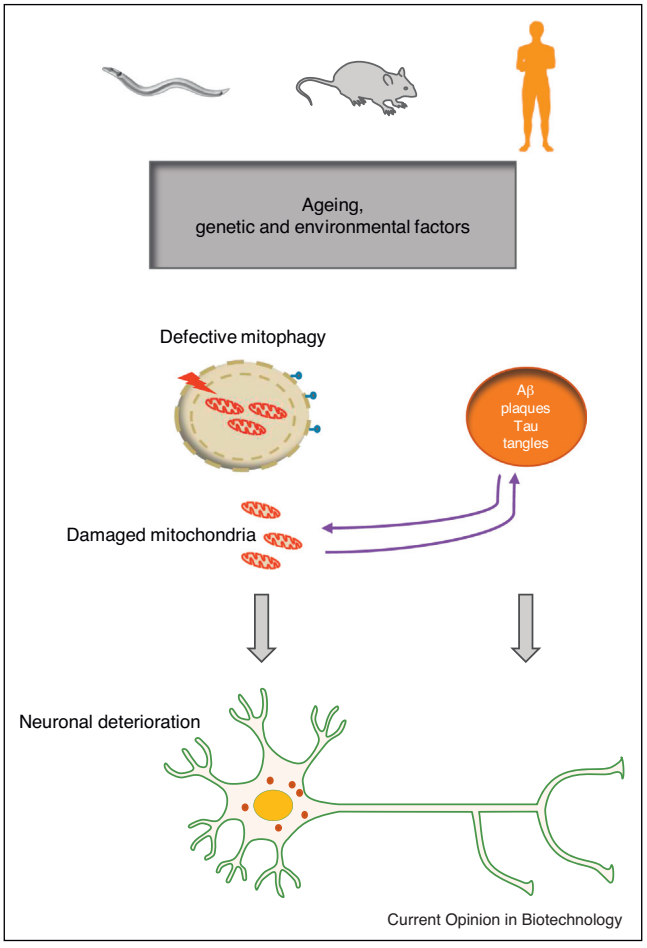
Recently, a collaborative study established the contribution of defective mitophagy to AD onset and progression in a manner that is conserved from *C. elegans* and mice to humans. Focusing on *C. elegans*, it has been shown that mitophagy induction through supplementation of NAD^+, urolithin A, and actinonin is able to reverse cognitive deficits in both Aβ and tau nematode models of AD. This amelioration of memory performance depends on the PINK-1 (PTEN-induced kinase-1), PDR-1 (Parkinson's disease-related-1/ Parkin) or DCT-1 (DAF-16/FOXO-controlled germline-tumour affecting) pathways (Figure 2) [25••].

Emerging findings indicate that neuronal or intestinal expression of the active form of the endoplasmic reticulum unfolded protein response (UPR^{ER}) transcription factor XBP-1, XBP-1s, protects against multiple proteotoxic species including $A\beta_{1-42}$ peptide. Specifically, it has been shown that the expression of *xbp-1s* in neurons or the intestine rescues the loss of chemotaxis in nematodes expressing $A\beta_{1-42}$ pan-neuronally (*snb-1pA*β_{1-42}). In this context, enhanced neuroprotection is mediated by the upregulation of lysosomal genes resulting in increased lysosomal function across tissues [26•].

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after AD, affecting roughly 2% of the population over 65 years of age [27••].

Figure 2



Mitophagy defects play a crucial role in neuronal deterioration and cognitive decline associated with amyloid-β (Aβ) and tau pathology in Alzheimer's disease (AD).

Currently, a combination of genetic and environmental factors is believed to be the cause of disease onset and progression in many cases [28,29]. Clinically, the disease is defined by motor symptoms including tremor, bradykinesia, rigidity and problems with balance and coordination. These symptoms are primarily due to the gradual loss of dopaminergic neurons in the substantia nigra pars compacta, leading to decreased release of the neurotransmitter dopamine that activates dopamine receptors. People with PD may also experience non-motor symptoms such as cognitive impairment, sleep disturbances, abnormal olfaction, anxiety and depression. Pathologically, PD is characterized by the formation of intraneuronal Lewy bodies and Lewy neurites composed mainly of α-synuclein [30]. This is a protein of 140 residues predominantly expressed in the human brain, where it localizes to presynaptic nerve terminals [31]. Notably, a growing body of evidence supports a crucial role for α-synuclein in regulating dopamine metabolism and neuro-transmission

[32]. Readers are referred to a comprehensive survey of the cellular and molecular mechanisms underlying PD pathogenesis, where recent advances in diagnostics screening and prevention are also discussed [27••].

C. elegans PD models that express human α-synuclein under the control of cell-type specific promoters have enabled researchers to monitor the formation of α –synuclein inclusions in living animals (Figure 1). Specifically, worms expressing human α-synuclein fused to yellow fluorescent protein in the body wall muscle have been shown to display an increased formation of inclusions with aggregated α-synuclein during ageing. This model has been used in a genome-wide RNAi screen for modifiers of inclusion formation. The screen revealed 80 genes, including ageing-associated genes, 49 of which have a human orthologue [33]. An extension of this work identified the tryptophan-converting enzyme tryptophan 2,3-dioxygenase (TDO-2) as a crucial regulator of protein homeostasis during ageing. In fact, knockdown of *tdo-2* increases tryptophan levels and suppresses α-synuclein-induced toxicity in *C. elegans*, suggesting that *tdo-2* regulates proteotoxicity through tryptophan. Moreover, TDO-2 depletion extends lifespan in these worms [34]. A similar *C. elegans* model of PD that expresses a fusion of human α-synuclein to GFP in body wall muscles has been used in a hypothesis-based RNAi screen for enhancers of age-associated accumulation of α-synuclein aggregates. In this case, nematode orthologues to established human familiar PD genes were preselected as a foundation to compose a candidate gene list. A set of initially identified α-synuclein modifiers was further tested in a nematode model of PD that expresses α-synuclein under the control of the dopamine transporter (*dat-1*) gene promoter. This analysis revealed five potentially neuroprotective genes, the most representative of which were involved in vesicular trafficking [35]. The same transgenic *C. elegans* strain was previously used to validate the neuroprotective potential of TOR-2 (the nematode orthologue of human torsin family 1 member B) and mammalian Rab1A, a GTPase involved in ER-to-Golgi transport [36,37]. Collectively, these studies support the notion that α-synuclein toxicity is largely associated with defective ER-to-Golgi vesicular transport.

Several lines of evidence have somehow implicated the Ca^{2+}- and Mn^{2+}-transporting ATPase PMR-1 (plasma membrane-related Ca^{2+}-ATPase 1) in α-synuclein cytotoxicity. A recent study has revealed that heat preconditioning of nematodes expressing α-synuclein under the *dat-1* promoter at a mildly elevated temperature protects against dopaminergic neuron loss. Neuroprotection requires the heat shock transcription factor HSF-1 and the small heat shock protein HSP-16.1 that localizes to the Golgi, where it acts together with PMR-1 to maintain Ca^{2+} homeostasis, thereby alleviating neuronal demise. Noteworthy, this is an evolutionarily conserved hormetic mechanism that defends against various harmful insults, including heat-induced necrosis as evidenced in a *C. elegans* heat stroke paradigm [38].

In an attempt to shed new light on the pathogenic mechanisms of PD, a recent study has uncovered a crucial role for the mitochondrial endonuclease G (EndoG) in mediating α-synuclein cytotoxity. Consistently, depletion of the *C. elegans* EndoG homologue CPS-6 ameliorates dopaminergic neuron loss in animals that express *dat-1* driven α-synuclein. More importantly, this mechanism has been shown to be evolutionarily conserved [39]. Recently, the same PD model has been used for validating the results of a lipidomic analysis performed in yeast cells expressing α-synuclein. This analysis revealed that α-synuclein toxicity is causatively associated with alterations in lipid/fatty acid homeostasis, leading to excessive accumulation of oleic acid (OA) and diglycerides. Indeed, depletion of the FAT-6 and FAT-7 steroyl CoA desaturases, which convert stearic acid into the monounsaturated OA, rescued the α-synuclein -induced dopaminergic neuron loss in the nematode PD model. This cytoprotective mechanism is also evolutionarily conserved [40•].

One of the main challenges for PD research is to delineate the complex interactions between genes or between genes and the environment. In this regard, *C. elegans* hold promise for deciphering disease pathogenesis and thereof accelerating the development of effective intervention strategies [41•]. Indeed, transgenic and toxicant *C. elegans* models of PD are currently available, providing the essential tools required to explore the molecular mechanisms underlying the disease and to identify potential therapeutic targets [42].

Polyglutamine diseases

Polyglutamine expansion (polyQ) diseases comprise several neurodegenerative or neuromuscular disorders such as Huntington's disease (HD), several spinocerebellar ataxias and spino-bulbar muscular atrophy, among others. They are all associated with an expansion of GAC triplets in the coding region of seemingly unrelated genes encoding proteins with expanded glutamine stretches that are prone to aggregate. The length of polyQ expansions as well as the host sequences surrounding the repeats constitutes critical determinants of the severity and the age of the disease onset [43].

C. elegans models that simulate polyQ-associated aggregation and toxicity have been successfully used for delineating the cellular and molecular mechanisms underlying polyglutamine pathogenesis. More specifically, a transgenic strain that expresses expanded polyQ tracts fused to yellow fluorescent protein (YFP) under the control of the *unc-54* promoter has been generated to drive expression in body wall muscles. This model exhibits polyQ

length-dependent aggregation and toxicity that exacerbate with age. The threshold for aggregation and polyQ-mediated motility defects is dynamic; an expansion of glutamine repeats beyond a critical length of Q35 to Q40 results in aggregate formation and cellular dysfunction [44]. A genome-wide RNAi screen using this polyQ-expansion model has revealed 186 genes involved in RNA metabolism, protein synthesis, protein folding and protein degradation that induce early onset polyglutamine aggregation when downregulated [45]. Another screen for suppressors of aggregation in Q35 worms, has identified genes categorized in diverse functional classes, namely cell structure, protein transport, cell growth and replication, energy and metabolism [46]. A recent study has shown that the negative regulator of cell cycle and apoptosis CCAR-1 worsens proteostasis impairment in this HD model by negatively regulating the heat shock response (HSR). Conversely, knockdown of *ccra-1* decreases polyglutamine aggregation and paralysis and inhibits the age-related decline of the HSR. Protection against polyQ toxicity depends on the activity of SIR-2.1, a bona fide protein deacetylase [47].

Moreover, *C. elegans* models that express polyQ repeats in specific neurons such as ASH sensory neurons and touch receptor neurons as well as throughout the nervous system have successfully recapitulated several pathological phenotypes of polyQ diseases and provided critical insights into the basis of neuron-specific pathogenesis [48,49]. Motor neurons of the ventral (VNC) and dorsal (DNC) nerve cord in Q40 expressing animals appear to be more vulnerable to polyQ aggregates than the ALM mechanosensory neurons, BDU interneurons, HSN motor neurons and the CAN neurons. These findings indicate that neuron-specific features such as neuronal function, connectivity and activity levels, among others, influence the aggregation of polyQ proteins at the pathogenic threshold [48].

Interestingly, emerging observations suggest that the age-related toxicity in protein misfolding disorders encompasses both cell-autonomous and non-cell autonomous effects [50]. Accumulating evidence indicates that the toxic protein aggregates in polyQ diseases can spread to neighbouring cells in a prion-like manner. Prion-like spreading has been successfully modelled in *C. elegans* through overexpression of glutamine/asparagine (Q/N)-rich prion domain NM of the cytosolic yeast prion protein Sup35. The NM domain forms aggregates with cell-autonomous and non-cell autonomous effects. Moreover, NM is targeted by the lysosomal-autophagy pathway and more importantly, the prion domain spreads between cells and tissues by vesicular transport [50].

As previously mentioned, expression of *xbp-1s* in either neurons or the intestine suppresses proteotoxicity by reducing the abundance of toxic protein species through lysosome activation across tissues, thus restoring proteostasis. This mechanism is responsible for the degradation of aggregated $polyQ_{40}$ and subsequent amelioration of neuronal function in a *C. elegans* HD model, wherein polyQ expansions are expressed pan-neuronally (*rgef-1pQ40::YFP*) [26•]. A follow- up study has shown that changes in lipid balance mediate protection against proteotoxicity downstream of lysosome activation in animals expressing *xbp-1s* specifically in neurons or the intestine. Furthermore, oleic acid supplementation is sufficient to promote clearance of at least neuronal polyQ40 aggregates and to reduce the levels of oxidized proteins, thereby protecting against proteotoxicity [51].

Concluding remarks

Although not perfectly recapitulating the complete pathophysiology of human diseases, *C. elegans* models have successfully contributed to the identification and thorough characterization of genes and molecular pathways involved in disease pathogenesis and to the identification of disease modifiers and candidate therapeutic targets. More significantly, these models have, in many cases, proved to be predictive for more complex organisms, therefore yielding critical insights with relevance to human health and quality of life.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Maria Markaki: Conceptualization, Writing - original draft. **Nektarios Tavernarakis:** Conceptualization, Writing - review & editing, Supervision, Resources, Funding acquisition, Project administration.

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Maria Markaki: Conceptualization, Writing - original draft. **Nektarios Tavernarakis**: Conceptualization, Writing - review & editing, Supervision, Resources, Funding acquisition, Project administration.

Acknowledgements

We gratefully acknowledge the contributions of numerous investigators that we could not include in this review, owing to space limitations. This work was supported by the European Research Council (ERC - GA695190 – MANNA) and the project "BIOIMAGING-GR" (MIS5002755), which is implemented under the Action "Reinforcement of the Research and Innovation Infrastructure", funded by the Operational Programme "Competitiveness, Entrepreneurship and Innovation" (NSRF 2014–2020).

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