

Caenorhabditis elegans as a Model for Conserved Physiological Processes in Humans and Other Mammals: A Literature Review.

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ABSTRACT

Caenorhabditis elegans (*C. elegans*) enables the mechanistic dissection of physiological processes conserved across animals. This review integrates evidence from major domains, including neural signaling and circuit function, aging and longevity, energy regulation and metabolism, development, programmed cell death, stress responses, and immune adaptation. It emphasizes conserved genetic and regulatory frameworks that interconnect these systems and support hypothesis-driven testing in vivo. The literature collectively establishes *C. elegans* as a complementary model to mammalian systems, connecting genes to physiology and expediting the identification of conserved mechanisms pertinent to health and disease.

Keywords: Caenorhabditis elegans, neurobiology, aging, metabolism, energy balance, stress responses, innate immunity

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INTRODUCTION

The tiny nematode *Caenorhabditis elegans* (*C. elegans*) has become an indispensable model in modern biology. Sydney Brenner chose this soil worm, originally isolated from decomposing plant material in temperate regions, as a research model in the 1960s due to its exceptional properties.(1,2) Only about 1 mm long, *C. elegans* has extraordinary features that enabled Brenner and subsequent researchers to conduct systematic behavioral and genetic experiments on a scale that was not possible in more complex animals. Over time, *C. elegans* has transitioned from an obscure organism to a widely recognized model, offering profound insights into developmental processes and aging, neurobiology, and metabolism, which ultimately enhance our understanding of mammalian and human physiology(2–4).

Several biological features underline the worm's success in scientific research. Its transparent body makes it possible to monitor cellular events in living animals without the need for invasive techniques(2). In addition, every adult hermaphrodite contains a fixed number of somatic cells (959 in total), and the nervous system is composed of just 302 neurons, whose synaptic connections have been largely mapped(5,6). The invariant pattern of cell division and differentiation in *C. elegans* allows researchers to meticulously track the lineage of each cell from its embryonic origin to the adult stage(7,8). The life cycle is rapid: at 20 °C, fertilised eggs hatch and develop into

reproductive adults in less than three days(9). Its post-embryonic development proceeds through four distinct larval stages (L1–L4). Under stressful conditions, larvae can enter a dauer stage, an alternative and non-ageing form, that enhances survival until favorable conditions return(10). Hermaphrodites lay around 300 self-produced offspring(11). Although males are rare in laboratory cultures, appearing at roughly one in a thousand animals, they enable outcrossing when needed. Moreover, worms can be frozen and revived, so mutant lines can be maintained over long periods without continuous culture. The adult worm typically lives for two to three weeks, allowing researchers to study aging and disease progression within a short timeframe(2).

The worm genome, the first of a multicellular organism to be sequenced, revealed a surprising degree of conservation with mammals. Roughly 38 % of *C. elegans* genes have clear human counterparts(12), and, depending on the criteria used, about half of human genes have worm orthologues. About 40 % of the genes implicated in human diseases are conserved in the worm(13,14).

Practical considerations have also contributed to the worm's popularity. *C. elegans* thrives on agar plates and can be grown in liquid culture, making it inexpensive and space-efficient. Hundreds of animals can be maintained on a single Petri dish. Its small size means that entire populations fit easily in microtiter plates for automated imaging or drug screening(15–18). Gene function can be precisely manipulated using a variety of genetic tools, such as

chemical mutagenesis, transgene expression, RNA interference using bacteria that produce double-stranded RNA, and, more recently, CRISPR/Cas9 genome editing(2).

C. elegans is a powerful model for conserved biological processes, but its limitations must be acknowledged. Key mammalian organs such as the liver, kidneys, heart, lungs, and circulatory system are absent, constraining direct study of processes like blood pressure regulation and systemic hormone transport (14,19). In addition, some experimental techniques are limited by the worm's small size, and the cuticle can reduce compound permeability. Nevertheless, the model remains highly valuable for dissecting fundamental cellular mechanisms that are frequently validated in more complex organisms (20,21). Accordingly, this literature review synthesizes findings across neurobiology, aging and longevity, metabolism and energy regulation, stress and immune responses, and development, highlighting shared conserved "physiological hubs" (e.g., insulin/IGF-1–FOXO, mTOR, AMPK, and stress-response programs) and emphasizing how these modules interact across systems rather than being reintroduced independently in each section. This integrative framing clarifies where worm studies provide robust mechanistic insight relevant to humans and other animals, and where biological differences limit direct translation.

Neurobiology and Nervous System Function

Although *C. elegans* is a small and anatomically simple organism, its nervous system is remarkably sophisticated.

Sydney Brenner chose the worm in part because its small number of neurons would make it feasible to map every synaptic connection, and this goal has been realised. Electron micrographs of serial sections allowed researchers to reconstruct the entire wiring diagram of the hermaphrodite nervous system; the adult hermaphrodite has exactly 302 neurons organised into 118 distinct classes (22–24). These neurons form roughly 5,000 chemical synapses and about 600 gap junctions(24,25). Male worms have a larger nervous system with 385 neurons, of which 91 are male-specific, while eight neurons are hermaphrodite-specific. Among the 294 shared neurons, approximately two-thirds show sex-specific wiring differences(26,27). This comprehensive anatomical knowledge allows researchers to link neuronal circuits to behaviors and to compare the structure of circuits across sexes and developmental stages.

The neurons of *C. elegans* are divided into two largely independent nervous systems: a large somatic nervous system and a small pharyngeal nervous system (23,28). The somatic system controls locomotion and other bodily

functions, featuring a circumpharyngeal nerve ring, ventral, dorsal, lateral, and sublateral nerve cords, head and tail ganglia, body-extending axons, and sensory dendrites that detect mechanical, chemical, and thermal stimuli (24,29,30). The small pharyngeal nervous system contains 20 neurons that form a compact circuit controlling rhythmic contractions of the pharynx(23,28).

Invariant cell lineages enable naming and tracing each neuron to founder cells(29,31). Early connectomes showed mostly unidirectional chemical synapses with abundant electrical ones synchronizing motor circuit (24,32). Modern connectomics employs advanced electron microscopy, automated imaging, and reconstruction algorithms to reanalyze data and uncover new synapses(8,33), while high-resolution imaging, genetic labelling, and single-cell RNA sequencing yield molecular neuronal atlases and a "homeobox code" of transcription factors(8,34,35). NeuroPAL enables multicoloured live neuron labelling, and optogenetics, calcium imaging, and microfluidic devices interrogate circuit dynamics and behaviour in real time, establishing *C. elegans* as a premier system for linking genes, circuits, and behaviour (36–39).

Despite its small neuron count, *C. elegans* uses most major vertebrate neurotransmitters, including acetylcholine, GABA, glutamate, serotonin, dopamine, octopamine, and tyramine, enabling complex signalling (40,41). Acetylcholine is the primary excitatory transmitter at neuromuscular junctions and interneuronal synapses, essential for viability; *cha-1* mutants lacking choline acetyltransferase die as larvae, while reduced levels cause slow growth, uncoordination, and resistance to inhibitors, with *unc-17* encoding the vesicular transporter crucial for motor function(42,43). GABA acts as an inhibitory neurotransmitter in locomotion from 26 ventral cord motor neurons (DD/VD classes); *unc-25* mutants lacking glutamic acid decarboxylase show a "shrinker" phenotype, with *unc-47* and *unc-46* aiding vesicular transport and localization (44–46).

Dopamine from eight mechanosensory neurons (via formaldehyde-induced fluorescence) acts as a modulatory signal, influencing locomotion and egg-laying, with *cat-2* tyrosine hydroxylase mutants impairing area-restricted searching (47–49). Serotonin from at least eight neuron types (immunostaining/fluorescence) stimulates egg-laying/pharyngeal pumping, inhibits locomotion/defecation, and is required for male mating; relevant genes include *bas-1*, *cat-4* (biosynthesis), and *goa-1* (G_{α} signalling)(50,51). Glutamate has excitatory and inhibitory roles: in the pharynx, motor neuron M3 uses glutamate-gated chloride channels (*avr-15*) to hasten muscle relaxation, and *avr-15* mutants are ivermectin-resistant; in the soma, AMPA-type *glr-1* drives excitatory signalling in command interneurons, and *glr-1* loss impairs

mechanosensory and chemosensory behaviours (52–54). Other neurotransmitters such as octopamine and tyramine are also present. Octopamine, for example, inhibits egg laying. In addition, peptidergic signalling via FMRFamide like neuropeptides further modulates neural circuits. However, some mammalian transmitters, such as epinephrine, norepinephrine and histamine, have not yet been identified in the worm(55–57).

Locomotion in *C. elegans* arises from alternating dorsal-ventral body wall muscle contractions, with cholinergic A/B motor neurons providing excitation and GABAergic D neurons inhibition on the opposite side, yielding sinusoidal bending. Navigation behaviors like chemotaxis and thermotaxis depend on amphid sensory neurons, e.g., AWC detecting odorants for attraction/repulsion and AFD sensing temperature gradients (44,58,59). Interneuron networks integrate sensory inputs before motor output. The semi-autonomous pharyngeal nervous system (20 neurons) coordinates feeding muscle contractions(60).

Despite its simplicity, *C. elegans* displays a rich behavioral repertoire, including locomotion, foraging, feeding, defecation, egg-laying, mating, and sleep-like states, and both non-associative and associative learning (e.g., odor-food pre-exposure boosts attraction) (25,61). It integrates cues for long-term memory via vertebrate-homologous genes/pathways, with calcium imaging and optogenetics revealing neuronal activity patterns underlying behavioral plasticity from basic circuits(62).

Although *C. elegans*' nervous system is a powerful model, it differs from mammalian brains: neurons are unmyelinated, glia few/simple, no blood–brain barrier, and lacking transmitters like norepinephrine/histamine. The circuitry is largely hardwired, with little neurogenesis after development(55,63–65). Nevertheless, the simplicity of the system is an advantage for dissecting fundamental principles. Future work combining connectomics, single-cell genomics, and advanced imaging will continue to refine our understanding of neural circuits. As the first metazoan with a completely defined connectome, *C. elegans* will remain a cornerstone of neuroscience research and a bridge between genes, circuits, and behaviour.

The rapid life cycle and transparent body of *C. elegans* make it a powerful system for studying aging, as wild-type hermaphrodites live only two to three weeks under laboratory conditions yet exhibit many hallmarks of aging seen in higher animals (Figure1). These hallmarks include chronological deterioration in the pharynx, intestine, and nervous system due to genetic and environmental factors, allowing systematic manipulation(66,67). Like aging mammals, *C. elegans* shows declining physiological functions, such as reduced pharyngeal pumping (from ~300 contractions/min in young adults to cessation by ~day 12 of adulthood), slower and less coordinated locomotion eventually halting(68,69). Chemosensory functions, defecation, and orientation to cues also deteriorate, accompanied by rapid reproductive decline. Morphological changes include pharyngeal enlargement and disorganisation, a thickened cuticle, disorganised body wall muscles, intestinal bacterial accumulation, and parallel germline/somatic gonadal degeneration(66,69,70). At the cellular level, aging features autofluorescent lipofuscin granules, increased DNA damage, and decreased metabolic activity, while declines in pharyngeal pumping and locomotion strongly correlate with lifespan, serving as useful biomarkers(66,68,71).

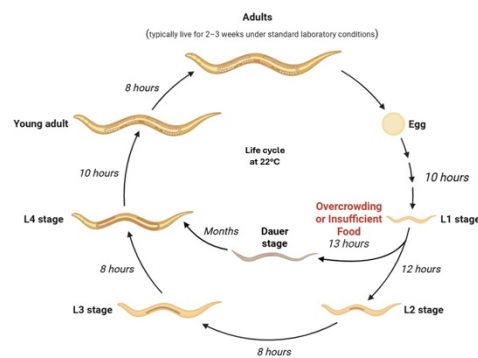


Figure 1: Life cycle and developmental progression of *C. elegans* at 22°C, including dauer formation under adverse conditions.

Genetic analysis of long-lived mutants revealed insulin/IGF-1 signalling as a central lifespan regulator; mutations reducing signalling through the insulin receptor homologue *daf-2* or downstream phosphatidylinositol 3-kinase *age-1* double hermaphrodite lifespan. Under low IIS, the FOXO transcription factor *daf-16* translocates to the nucleus, inducing genes enhancing stress resistance, metabolism, protein homeostasis, and autophagy (72–74). Many longevity pathways converge on *daf-16*; e.g., co-regulator HCF-1 inhibits it, while JNK-1 promotes nuclear localisation under stress. Epigenetic modifiers like histone demethylase *utx-1* modulate IIS: *utx-1* RNAi extends lifespan in a *daf-16*-dependent manner. Environmental factors (temperature, nutrients) influence IIS, interacting

Nervous System Category	Key Components	Primary Function or Behavior	Neurotransmitters Involved	Cell Counts and Connectivity
Somatic Nervous System	Nerve ring, nerve cords (ventral, dorsal, lateral, sublateral), head/tail ganglia, and sensory dendrites.	Locomotion, navigation (chemotaxis/thermotaxis), mechanosensation, egg-laying, and mating.	Acetylcholine, Glutamate, GABA, Dopamine, Serotonin, Octopamine, Tyramine, and Neuropeptides.	282 neurons; the adult hermaphrodite nervous system overall forms ~5,000 chemical synapses and ~600 gap junctions.
Pharyngeal Nervous System	Compact circuit embedded within the pharyngeal muscle.	Regulation of rhythmic pharyngeal pumping, feeding, and muscle relaxation.	Glutamate, Serotonin, and Acetylcholine.	20 neurons; operates as a semi-autonomous circuit.

Table 1: Summary of the structural organization, functional roles, and neurochemical signaling in the *C. elegans* somatic and pharyngeal nervous systems.

Aging and longevity

with genetics to determine lifespan.(74,75). Another conserved pathway is mTOR; its inhibition, genetically or pharmacologically, extends lifespan and regulates autophagy by clearing damaged proteins/organelles (76,77).

Dietary restriction extends lifespan in *C. elegans* (e.g., eat-2) largely by activating AMPK (aak-2), which shifts energy sensing toward stress resistance, mitochondrial maintenance, and reduced mTOR/autophagy signaling, while temperature also modulates lifespan via metabolic rate(76,78–82). In addition, age-related NAD⁺ decline can be countered by boosting NAD⁺ availability, which activates the sirtuin SIR-2.1 and downstream mitochondrial stress programs that converge on daf-16/FOXO to promote longevity(83–86) Moreover, changes in germline signaling and epigenetic regulation (e.g., glp-1, utx-1, SIR-2.1, and non-coding RNAs) can extend lifespan by reprogramming gene expression and reallocating resources toward somatic maintenance, with multiple inputs converging on shared transcriptional regulators (75,85,87–90).

Metabolism and Energy

Metabolic regulation in *C. elegans* is highly conserved, with many human lipid-metabolism genes having worm counterparts and hundreds of genes controlling fat storage, mobilisation and energy production. Its short life cycle, transparency and accessible genetics, through CRISPR, RNAi and fluorescent lipid reporters, make it an efficient model for studying energy balance and metabolic disease(91). The worm regulates feeding through pharyngeal pumping controlled by chemosensory and endocrine signals, providing measurable indicators of hunger and satiety. Lipids serve as the primary energy reserve, stored in intestinal and hypodermal cells and estimated using dyes such as Nile Red and BODIPY. Under nutrient-rich conditions, worms convert excess nutrients into triacylglycerols, while during starvation or dauer they mobilise fat through lipolysis and β -oxidation. Key conserved pathways such as insulin/IGF-1, mTOR and daf-16/FOXO integrate nutrient status with growth, autophagy and lifespan, highlighting the tight coupling between metabolism and longevity(91,92).

AMPK functions as the central energy sensor, with loss of the aak-2 catalytic subunit causing rapid fat depletion and starvation sensitivity, whereas activation supports survival under low-energy conditions. During dauer, AMPK represses lipolysis to conserve energy and coordinates broader metabolic shifts(93). Another major regulator, nhr-49, the worm orthologue of PPAR α , controls β -oxidation and fatty-acid desaturation; loss of nhr-49 can lead to fat accumulation, while overexpression promotes fat utilisation. Additional factors, including the SREBP orthologue SBP-1, the seipin orthologue SEIP-1, peroxisomal β -oxidation, the glyoxylate shunt, the pentose-phosphate pathway and autophagy, further support

metabolic flexibility. Because these pathways mirror those in humans, *C. elegans* serves as a powerful platform for translational research, enabling genetic screens and drug assays that rapidly identify compounds affecting fat synthesis or oxidation and offering a practical bridge to understanding and targeting metabolic disease(91–93).

Development and Cell Differentiation

One of the most striking features of *C. elegans* is the deterministic nature of its development. A newly hatched larva contains about 550 nuclei, and roughly 260 additional somatic cells are produced during the four larval stages, following a fixed and fully mapped lineage. This complete fate map has enabled the precise dissection of how genes control development(31). Temporal progression through larval stages is regulated by heterochronic genes: loss of lin-14 causes premature skipping of L1 fates, whereas its overactivity prolongs L1 characteristics; lin-28 mutants enter adulthood early, while lin-29 mutants fail to complete the larval-to-adult transition. MicroRNAs such as lin-4 and let-7 regulate these timing genes, demonstrating for the first time that small RNAs control developmental timing in animals(94–96). Spatial patterning depends on conserved pathways including Notch, Wnt, TGF- β and EGF, which guide cell–cell signalling, polarity and fate decisions. Notch signalling through lin-12 shapes gonad and vulval development; Wnt components such as mom-2 and bar-1 establish anterior–posterior polarity; and EGF–let-23 signalling determines vulval fates. These systems parallel vertebrate signalling pathways, emphasising the worm’s relevance to broader developmental biology(97,98).

C. elegans has also clarified the genetics of programmed cell death. Exactly 131 somatic cells undergo apoptosis in a reproducible pattern, driven by the core machinery of CED-3 (caspase), CED-4 (Apaf-1-like activator) and CED-9 (Bcl-2-like inhibitor). The BH3-only protein EGL-1 initiates apoptosis by releasing CED-4 from CED-9, enabling activation of CED-3, an architecture later found to be conserved in mammals(99–101). Germline development further illustrates how simple systems reveal complex principles: hermaphrodites switch from spermatogenesis to oogenesis, males make only sperm, and this timing is controlled by somatic-gonad signals. Germ cells inherit P granules that specify germline fate, and genes such as glp-1 and pie-1 are essential for stem-cell maintenance and fertility(99–101). The worm’s transparency and small cell number allow direct imaging of divisions, migrations and morphogenesis, as well as targeted laser ablation to test lineage relationships(31). Discoveries of heterochronic genes, microRNAs and conserved signalling pathways in *C. elegans* have shaped modern developmental genetics, making the worm a foundational model for understanding how cell fates are specified and how developmental timing is genetically controlled.

Stress Responses and Adaptation

Living in fluctuating environments, *C. elegans* has evolved diverse and interconnected systems to detect and respond to oxidative, xenobiotic, heat, cold, osmotic, hypoxic, pathogenic and nutritional stress. Many of these pathways are conserved in mammals, making the worm a strong model for stress biology and ageing. A central regulator is SKN-1, the orthologue of mammalian Nrf2, which controls detoxification, antioxidant defences and xenobiotic responses. SKN-1 integrates metabolic, nutrient and proteostasis signals, promoting phase II detoxification enzymes, glutathione synthesis, lipid catabolism and mitochondrial maintenance(21,102). Heat shock activates the HSF-1 pathway, inducing molecular chaperones and proteasome components essential for thermotolerance and lifespan extension. The ER and mitochondrial unfolded protein responses (UPR^{ER} and UPR^{mt}), mediated by components such as IRE-1, PEK-1, ATF-6, and ATFS-1, upregulate chaperones, proteases and metabolic enzymes to maintain protein homeostasis, with activation of ATFS-1 extending lifespan. Hypoxia activates HIF-1, which shifts physiology toward anaerobic metabolism and survival, while osmotic stress induces glycerol synthesis through *gpdh* genes to maintain hydration (103–105).

Innate immunity is another major stress pathway, centred on the conserved p38 MAPK cascade, which activates antimicrobial peptides and detoxification enzymes in response to pathogens. Regulators such as PMK-1, SKN-1 and *daf-16* coordinate stress and immune responses to ensure appropriate prioritisation between defence, repair and survival. Mild activation of immune pathways can provide cross-protection against other stresses and promote longevity. Stress can also influence future generations: parental exposure to mild heat or starvation enhances offspring stress resistance through small RNAs and chromatin modifications, demonstrating transgenerational epigenetic inheritance(106–108). Ultimately, *C. elegans* integrates environmental, metabolic and developmental cues to orchestrate adaptive responses that shape growth, reproduction and lifespan, providing a powerful system for understanding how organisms maintain homeostasis and how stress-response dysregulation contributes to disease.

Translational Relevance to Human and Mammalian Physiology

Despite its simple anatomy, *C. elegans* is a powerful translational model because many genes and pathways are conserved with humans(21,109). The worm’s transparency and fixed, small number of neurons make it ideal for the live imaging of synaptic development, vesicle trafficking, and neurotransmitter release. Key proteins required for synaptic vesicle priming and release, such as *unc-13* and *unc-18*, are highly homologous to their mammalian counterparts, allowing for the precise mapping of molecular interactions that govern neuronal communication. These foundational similarities in cellular machinery provide a robust framework for investigating more complex human pathologies(110–112).

C. elegans has also been instrumental in neurodegenerative research: transgenic animals expressing human amyloid-β, tau, α-synuclein, or polyglutamine repeats reproduce model key features of Alzheimer’s, Parkinson’s and Huntington’s diseases, enabling rapid identification of genetic modifiers and small molecules that reduce aggregation or toxicity(113–115). Metabolic disorders can also be modelled: high-glucose or high-fructose diets induce fat accumulation and shorten lifespan, while mutations in conserved regulators such as AMPK or *nhr-49* mimic aspects of human metabolic syndrome(116,117). Worms likewise provide tractable systems for mitochondrial dysfunction and proteostasis defects; mutations in mitochondrial polymerases, respiratory chain proteins or proteases cause developmental delays and neurodegeneration, and interventions such as mitochondrial UPR activation or NAD⁺ supplementation can partially rescue these phenotypes(86,104). Toxicology studies benefit from the ease of exposing worms to pesticides, pollutants and pharmaceuticals, allowing high-throughput assessment of survival, reproduction, behaviour and gene expression. Because detoxification pathways like the SKN-1/Nrf2 axis are conserved, worm assays can often predict mammalian responses(86,102,118).

C. elegans is increasingly used in precision medicine through humanised gene-replacement, where worm genes are swapped with human orthologues to test whether specific variants rescue mutant phenotypes, an approach applied to genes involved in mental disorders, mitochondrial disease, and lipid metabolism(119,120). Host–microbe interaction studies also thrive in this model: worms can be colonised by pathogens such as *Pseudomonas* and *Staphylococcus*, revealing innate immune pathways, microbiome influences on development and metabolism, and microbial effects on drug efficacy(107,121). The worm’s transparency allows direct imaging of colonisation and tissue responses, while bacterial genomes can be engineered to probe host pathways. Alongside biological

Physiological domain	Central focus	Main mechanisms	Physiological significance	Overall significance
Aging and longevity	Genetic and environmental regulation of physiological decline	Insulin/IGF-1 signaling (<i>daf-2</i> , <i>age-1</i> , <i>daf-16</i> /FOXO), mTOR, AMPK (<i>aak-2</i>), dietary restriction, SIR2.1/NAD ⁺	Determines lifespan duration and maintains somatic functions via proteostasis and stress resistance	Conserved nutrient-sensing pathways integrate metabolic status and environmental cues to delay multi-organ functional deterioration.
Metabolism and energy	Homeostatic control of energy balance and lipid storage	AMPK (<i>aak-2</i>) energy sensing, <i>nhr-49</i> (PPARα orthologue), <i>SIR-1</i> (SREBP), β-oxidation, and insulin/mTOR signaling	Regulates fat mobilization, starvation survival, and the transition to the dauer stage to ensure organismal fitness	Conserved metabolic circuits coordinate nutrient intake with lipid synthesis and utilization, serving as a model for human metabolic disease.
Development and cell differentiation	Deterministic cell lineage and genetic control of developmental timing	Heterochronic genes (<i>lin-14</i> , <i>lin-28</i> , <i>lin-29</i>), microRNAs (<i>lin-4</i> , <i>let-7</i>), <i>Notch</i> (<i>lin-12</i>), <i>Wnt</i> , EGF, and core apoptotic machinery (<i>ced-3</i> , <i>ced-4</i> , <i>ced-9</i>)	Ensures invariant spatial patterning, precise temporal transitions, and programmed elimination of specific somatic cells	Fixed cell lineages and conserved signaling cascades provide a foundational model for spatial patterning, microRNA regulation, and apoptosis.
Stress response and adaptation	Cellular homeostasis and transgenerational survival under environmental flux	SKN-1 (Nrf2), HSF-1, UPR ER/UPR mt (ATF5-1, IRE-1), HIF-1, p38 MAPK (PMK-1), and epigenetic chromatin modifications	Promotes thermotolerance, innate immunity, and detoxification, providing cross-protection and transgenerational resistance	Interconnected stress pathways activate adaptive transcriptional programs that prioritize defense and repair over growth.

Table 2: Summary of the major physiological domains, regulatory mechanisms, and functional significance in *C. elegans*

relevance, the worm offers practical strengths, low cost, rapid life cycle, reduced ethical constraints, and compatibility with automated, high-throughput platforms using imaging, microfluidics, and machine learning(109,116,120,122,123). Although *C. elegans* cannot model every physiological process, its advantages make it an essential complement to mammalian systems and a frequent source of early mechanistic insight.

9- Future Directions and Conclusion

Research on *C. elegans* is moving quickly, driven by technologies that connect basic biology to therapeutic insight. Single-cell multi-omics, integrated with the complete cell lineage and connectome, is revealing how gene-expression programs shape physiology and behaviour, while improved EM, long-term live imaging, optogenetics and biosensors enable causal dissection of neural circuits(124–126). Expanding gene-editing tools, CRISPR, base/prime editing, inducible systems and synthetic biology, allow precise modelling of human mutations and engineered behaviours. At the same time, focus is shifting from lifespan to health span, with quantitative readouts of movement, stress resistance, cognition, and reproduction under different diets, microbiota, and environments. Emerging work on epigenetics and transgenerational inheritance shows how histone marks and small RNAs transmit effects of stress and diet across generations, and microbiome studies using natural or synthetic communities are uncovering new host–microbe interactions(108,119,127). Cross-species validation in flies, fish, mice and human organoids will be essential, but as these tools mature, this small nematode will remain a central platform for discovering mechanisms and interventions relevant to human health and disease.

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