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Biological Model : *Caenorhabditis elegans*

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A B S T R A C T

The soil nematode, *Caenorhabditis elegans* is widely used as model organisms for nearly every aspect of biology. Various disciplines employ *C.elegans* as model organisms such as Biology, Neuroscience, Toxicology as well as Ecology. Commonalities of the genetic pathways in *C.elegans* with other organisms along with humans led to significant discoveries in a wide variety of research fields, including development, signal transduction, cell death, and ageing.

Introduction

A model organism is a biological but non-human species that is commonly studied by the scientists to realize some biological phenomena, with the probability that discoveries made in the organism model will provide insight into the workings of other organisms. Model organisms are *in vivo* models and are widely used to research human disease when human testing would be unfeasible or unethical (Muller and Grossniklaus, 2010).Most model organisms share a set of common characters that make them amenable to study in the laboratory. They are generally small, easy, and economical to culture in the lab, and reproduce quickly and can be manipulated in the laboratory. The best genetic model organisms have small genome sizes, and many can reproduce sexually, allowing researchers to cross-breed individuals of different genotypes, and have short generation time. These organisms can undergo mutation in their DNA that may result in a change in a certain characteristic, and these mutants allow scientists to study certain diseases. Examples of model organisms used to study genetics are yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*), nematode (*Caenorhaditis elegans*), western clawed frog (*Xenopus tropicalis*), mouse (*Mus musculus*), and zebrafish (*Danio rerio*). The nematode, *Caenorhabditis elegans* shares a common ancestor with humans that lived in the pre-Cambrian era, i.e. 500-600 million years ago. This ancestor is also known as the urbilaterian ancestor, as it is the relative of bilaterally

symmetric, multicellular organisms on the planet, including invertebrates and vertebrates. Most of the genes and genetic mechanisms that govern modern organismal development, including those involved in human development and disease were present in the urbilaterian ancestor and are shared by existing animals, including humans and nematodes.

Caenorhabditis elegans as biological model

Caenorhabditis elegans is one of the most intensively used model organisms in biological studies. It is a multicellular eukaryotic organism under family: Rhabditidae, Order: Rhabditida, class: Chromodorea, Phylum: Nematoda, Kingdom: Animalia. *C.elegans*, is a free-living nematode inhabiting organic matter rich environments like rotting fruits and stems in many parts of the world. In 1900, Maupas named it *Rhabditides elegans*; in 1952, Osche placed it in the subgenus *Caenorhabditis* and in 1955, Dougherty raised it to the status of genus. The different *Caenorhabditis* species, *C. briggsae*, *C. remanei*, *C. japonica* and *C. brenneri* occupy various nutrient and bacteria-rich environments.

Key features of this nematode include its small body size, anatomical simplicity (>1000 cells), easy to culture, short life cycle, large size of progeny, cheap to maintain, transparent, invariant cell lineage, small genome (only 20 times that of *Escherichia coli*), and present no biohazard.

The virtues of *C. elegans* for genetic analysis include that it is small size (1.5 mm long adult), easily grown in the laboratory on agar plates, on non-pathogenic *Escherichia coli*, reproduces quickly to produce approximately 300 offspring within a reproductive cycle of only 3.5 days at room temperature. The natural *C. elegans* mode of inbreeding by the self-fertilizing hermaphrodite combined with the ability to cross hermaphrodites with males offered advantages, in which crossing can be manipulated at will. *C.elegans* lacks a respiratory and a circulatory system. *C.elegans* has a simple but sophisticated nervous system (White *et al.*, 1986). In the hermaphrodite, comprise 302 neurons, whose pattern of connectivity, also known as a connectome (neuronal 'wiring diagram') has been completely mapped out in the year 2012. Researchers have explored the neural mechanisms responsible for several interesting behaviors including chemotaxis, thermotaxis, mechano transduction, and mating behavior. *C. elegans* possesses gut granules in the intestine which emit a brilliant blue fluorescence. Recent chemical analysis has identified the blue fluorescent material contain as a glycosylated form of anthranilic acid (AA), which is derived from tryptophan by action of the kynurenine pathway. AA is antibacterial and used in defense against invading pathogens and also provides photo protection (the bursts of AA fluorescence involve the conversion of damaging UV light to relatively harmless visible light).This compound can also serve a role as a natural, endogenous marker of organism death (Coburn and Gems, 2013).

The early work of Doughtery and associates provided the concepts and methods of axenic and monoxenic cultures of *C. elegans* (Ferris and Hieb, 2015). The initiation of the research using *C. elegans* by Sidney Brenner in the 1960s resulted in a large number of worldwide research projects on this nematode. In 1963, Sydney Brenner proposed research into *C. elegans* primarily in the area of neuronal development; the ultimate goal was to determine the role of each gene involved in neural development and function (Chalfie *et al.*, 1985). In 1974, he began research into the molecular and developmental biology of *C. elegans*, which has since been extensively

used as a model organism. *C. elegans* was the first multicellular organism to have its whole genome sequenced. The project initiated by Sulston and associates to construct a physical map of the entire genome of *C. elegans* in the mid 1980s and the publication of the complete genome of *C. elegans* in 1998 contributed much to opening genomics as a discipline (Sulston *et al.*,1992; Bird *et al.*,1999). The genome contains an estimated 20,470 protein-coding genes.

The resulting genome sequence of *C. elegans* is an invaluable resource for the study of plant and animal parasitic nematodes. About 35% of *C. elegans* genes have human homologs-many *C. elegans* genes can function similarly to mammalian gene. In 2003, the genome sequence of the related nematode *C. briggsae C. remanei*, *C. japonica* and *C. brenneri* was also determined, allowing researchers to study the comparative genomics of these organisms.

It was initially proposed as a model for developmental biology because of its invariant body plan, ease of genetic manipulation and low cost of maintenance. Nematodes have affixed, genetically determined number of cells, a phenomenon known as eutely and the constancy of cell position from individual to individual have perhaps been the most unique advantages offered by this organism for the study of development. *C.elegans* is transparent, facilitating the study of cellular differentiation and other developmental processes in the intact organism. The developmental fate of every single somatic cell (959 in the hermaphrodite; 1031 in the male) has been mapped out. These somatic cells in a hermaphrodite represent a wide variety of tissues from all three germ layers, and the developmental biology of *C. elegans* has been traced from zygote to adult. In both sexes, a large number of additional cells (131 in hermaphrodite, most of which would otherwise become neurons) are eliminated by programmed cell death (apoptosis). By studying apoptosis in *C.elegans*, researchers hope to identify genes that switch on cell death in cancer cells, such as leukemia. *C.elegans* has proved to be a very useful model organism for investigating the roles of cell signaling and induction in development. Signals from neighboring cells direct gene expression and development (induction), and cell migrations around developing embryo. The related genetics in developmental biology including vulva formation, the dauer larvae pathway, programmed cell death, and underlying biochemistry apply to insects, mammals (including man), as well as nematodes and likely other organisms (Sommer and Bumbarger, 2012). Moreover, extensive research on *C. elegans* has identified RNA-binding proteins as essential factors during germ line and early embryonic development. Sulston's delineating cell lineage and the role of cell death in *C. elegans* and Horvitz's identifying a number of genes that control this programmed cell death brought new insight on the developmental biology of that nematode and all of its cells.

C. elegans has been a model organism for research into ageing (Rodriguez *et al.,* 2013; Shen *et al.,* 2018). A number of genes are responsible for longevity and senescence in nematodes have been identified (Denzel *et al.,* 2019).

A useful feature of *C.elegans* is that the function of specific genes can be disrupted by RNA interference (RNAi). Silencing the function of a gene in this way can sometimes allow a researcher to infer what the function of that gene may be. The nematode can either be soaked in or injected with a solution of double stranded RNA, the sequence of which is complementary to the sequence of the gene that the researcher wishes to disable. RNA interference (RNAi) in *C.elegans* can also be done by simply feeding the nematode

transgenic bacteria expressing RNA complementary to the gene of interest. This strategy for gene loss of function experiments is the easiest of all animal models, and thus, scientists are able to knock down 86% of the 20,000 genes in the worm, establishing a functional role for 9% of the genome (Darryl *et al.,* 2015).

Brenner also chose *C.elegans* as it is easy to grow and can be frozen. When subsequently thawed they remain viable, allowing long-term storage. A 15% glycerol solution is used for the freezing of *C.elegans*. Samples are cooled at 1^0 C per minute. Freshly starved young larvae survive freezing best. About 35 to 45% of the worms stored in liquid nitrogen survive. The worms can also be stored at -80^0C for over ten years, but survival is not as great as for worms stored (25 years) in liquid nitrogen at -196°C (Mikus *et al.,*2016).

C. elegans used as a model system to elucidate the toxicology, as well as, in environmental toxicology. *C. elegans* genetics clearly provides an advantage in toxicology tests as toxin effects can be directly linked to gene activities allowing for determination of sublethal effects (Martinez-Finley and Aschner, 2011). Studies have been primarily concerned with finding lethal endpoints of metals and organic compounds in single species cultures, aqueous solution, soil and sediment dose bioassays (Sochova *et al.,*2006). An exciting recent application of the *C. elegans* genetic model is to address ecology and evolution questions of broad concern to biologists. Examples of applications include a *Yersinia pestis* - *C. elegans* model to show biofilm-mediated interactions between bacteria and predatory invertebrates (Darby *et al.,* 2002), the advantage of sexual reproduction to increase developmental flexibility (male or hermaphrodite) of progeny under changing resource conditions (Prahlad *et al.,*2003), that starvation stress induces adult diapause as a means of survival and dispersion (Angelo and Van Gilst, 2009; Kim *et al.,*2019) and modification of foraging strategies in response to environmental conditions (Boender *et al.,*2011).Other examples of recent use of the *C. elegans* model include showing that growth at high densities resulted in genetic changes to pheromone receptors (McGrath *et al.,*2011) and that sexual reproduction in *C. elegans* allows coevolution to survive against the pathogen *Serratia marcescens* (Morran *et al.,*2011). Even though, *C. elegans* is a suitable model for multiscale analysis from molecular to organism/population level, the range of *C. elegans* studies in environmental toxicology have been focused mostly on organism-level endpoints, such as mortality behavior, growth, or reproduction.

In 2002, the Nobel Prize in Physiology or Medicine was awarded to Sydney Brenner, H. Robert Horvitz, and John Sulston for their work on the genetics of organ development and programmed cell death in *C. elegans*. The 2006 Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig C. Mello for their discovery of RNA interference in *C. elegans*. In 2008, Martin Chalfie shared a Nobel Prize in Chemistry for his work on green fluorescent protein; some of the research involved the use of *C. elegans*. *C. elegans* made news when specimens were discovered to have survived the Space Shuttle *Columbia* disaster in February 2003. Later, in January 2009, live samples of *C. elegans* from the University of Nottingham were announced to be spending two weeks on the International Space Station, in a space research project to explore the effects of zero gravity on muscle development and physiology. Descendants of the nematode aboard *Columbia* in 2003 were launched into space on *Endeavour* for the STS-134 mission. Although these works does not include plant and soil nematology, it brings much attention to nematodes.

The early and ongoing research achievements on the model nematode *C. elegans* have provided a valuable resource for biology and genetics. While the *C. elegans* model now serves as an immense resource for investigating systems and genes in parasitic nematodes as well as plant nematodes (Meneely *et al.,* 2019). Major technical advances, such as the cloning and physical mapping of the entire *C. elegans* genome, the development of transposon-tagging, reverse genetics, germ-line DNA transformation, genetic mosaics, and laser microsurgery, are essential to maintain and expand the usefulness of this model (Corsi *et al.,* 2015). The most comprehensive collection of methods and information resources for analysis of *C. elegans* is found in compilation of Epstein and Shakes in 1995 (Epstein and Shakes, 1995). Knowledge gained in one area of research ultimately connects with research in other areas. Recent years have seen increasing adoption of *Caenorhabditis elegans* in experimental evolution in every aspects of biology.

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