C. elegans as a model organism

Olivier Cinquin, May 2009
Lecture plan

- Nematodes
- How C. elegans came to be a model organism
- Features that make C. elegans a good model organism
- Highlights of some success stories; cell lineage, RNAi
- Has the original goal been achieved?
Different sorts of worms

Acoelomate

Flatworm

Body covering (from ectoderm)
Tissue-filled region (from mesoderm)
Digestive tract (from endoderm)

Coelomate

Annelid

Body covering (from ectoderm)
Tissue-filled region (from mesoderm)
Digestive tract (from endoderm)
Coelom

Pseudocoelomate

Nematode

Body covering (from ectoderm)
Tissue-filled region (from mesoderm)
Digestive tract (from endoderm)
Pseudocoelom
Nematodes are everywhere

In short, if all the matter in the universe except the nematodes were swept away, our world would still be dimly recognizable, and if, as disembodied spirits, we could then investigate it, we should find its mountains, hills, vales, rivers, lakes, and oceans represented by a film of nematodes. The location of towns would be decipherable, since for every massing of human beings there would be a corresponding massing of certain nematodes. Trees would still stand in ghostly rows representing our streets and highways. The location of the various plants and animals would still be decipherable, and, had we sufficient knowledge, in many cases even their species could be determined by an examination of their erstwhile nematode parasites.

(Nathan Cobb)
Why should we care about nematodes?

- Medicine: >1 billion people infected with helminths (Hotez et al, 2008); ascariasis #1 neglected tropical disease (Hotez et al, 2007); not so deadly but considerable burden; poverty-promoting (Hotez & Ferris, 2006)

- Almost no new drug in the past 25 years (Kaminsky et al, 2008)

- Agriculture (both plants and livestock); drug resistance is becoming a problem

- Model system
What does C. elegans look like?

From wormclassroom.org

Rene Garcia
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A model for what?

“Choosing the right organism for one’s research is as important as finding the right problems to work on” (S. Brenner)

Brenner asked different questions with different model organisms (phages, C. elegans, and Fugu)
The historical context

- DNA double helix (1953)

Jacob & Monod (1961): “The discovery of regulator and operator genes, and of repressive regulation of the activity of structural genes, reveals that the genome contains not only a series of blue-prints, but a coordinated program of protein synthesis and the means of controlling its execution”

Storage and retrieval of genetic information: problem solved, by using tractable experimental systems. How are complex computations performed?

From http://www.mun.ca/biochem/courses/3107
Sydney Brenner’s vision

Letter to Max Peruz (1963): It is now widely realized that nearly all the "classical" problems of molecular biology have either been solved or will be solved in the next decade. [...] I have long felt that the future of molecular biology lies in the extension of research to other fields of biology, notably development and the nervous system. [...] The great difficulty about these fields is that the nature of the problem has not yet been clearly defined, and hence the right experimental approach is not known. [...] The experimental approach I would like to follow is to attempt to define the unitary steps of development using the techniques of genetic analysis. Our success with bacteria has suggested to me that we could use the same approach to study the specification and control of more complex processes in cells of higher organisms. [...] I would like to tame a small metazoan organism to study development directly.

C. elegans
Short history of C. elegans studies

Another nematode model system

Ascaris used for cell and developmental biology in the 19th and 20th centuries

Boveri (1888b)
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Important C. elegans features

- Small, reproduces fast, easy to maintain
- Transparent; imageable by electron microscopy (popular at the time); specific cells can be ablated (big improvement over hot needles)
- Fixed number of cells (Dougherty & Calhoun, 1948)
- Hermaphrodites and males: good for quick inbreeding and crosses (Dougherty & Calhoun, 1948)
- Small total cell number; simple nervous system (Brenner, 1974)
- Behavioral and morphological mutants, easy to identify (eg Nigon & Dougherty, 1950, Brenner, 1974)
C. elegans life cycle

From wormatlas.org
Mutants

From wormclassroom.org
Genes and chromosomes can now be marked fluorescently.
**Important unpredicted C. elegans features**

- Surprising conservation of signaling pathways in particular and genes in general (but also many nematode-specific genes and diversity within the phylum Nematoda; “as many different domains in Nematoda as have been predicted in the rest of Metazoa to date”, Wasmuth et al, 2008; see also Thomas et al, 2008)

- Syncytial gonad and transgenes

- RNAi: susceptibility to feeding and soaking RNAi appears exceptional even in nematodes

- Freezing

- Mutagenesis easier than for related species

- A large community, providing critical knowledge and tools; John Sulston and Bob Horvitz co-recipients of the Nobel prize. Nucleating a new community of successful scientists around an appropriate model system is perhaps Sydney Brenner’s greatest achievement.
C. elegans drawbacks

- No immortal cell lines
- Germline transgenes difficult (but getting easier with more recent techniques)
- No practical homologous recombination; often multiple alleles for a same gene, and need to figure out which are true nulls (but partial loss of function can also be an advantage).
What has been achieved?

C. elegans has been a gold mine. Non-exhaustive list:

- cell death: cell death as a cell fate and suicide; identification of the role of caspases; C. elegans viable even without cell death, apoptotic cells easily identifiable, whole lineage known
- cell division (embryos), asymmetric division
- ageing; identification of mutations that increase lifespan
- characterization of the Notch signaling pathway; stem cell niche (more about that later)
- mechanism of RNAi
- miRNA, heterochronic genes
- cell fusion (seam cells)
- sex determination, dosage compensation
- neurons: reproducible synapses
- meiosis
- sperm signals
- chemotaxis
- pathogenesis
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The lineage

Experimental tour de force

Reproducible between animals (which made it possible to compile)

Cells of a same organ can be far apart in the lineage; "There is hardly a shorter way of giving a rule for what goes on than just describing what there is." (Brenner, 1993)

This is only half the story: soma vs germ line
More live imaging:
Germ line I

Wolke et al (2007)
More live imaging: Germ line II

Wild Type Ovulation

Miller et al (2001)
More live imaging: Embryo

RNAi

- Interesting history: techniques don’t always work the way we rationalize them
- Useful tool for countless studies, small and large scales
- C. elegans used to dissect the mechanism of RNAi; still an active research field
- C. elegans lucky choice: works by feeding; unusual even for nematodes (Felix, 2008)
Short history of RNAi

- Antisense can suppress gene expression by transfection of DNA or direct RNA injection (1980s)
- Translation block in vitro


- Use of injected antisense mRNA to silence genes.

- Fire et al (1998): dsRNA is the species that must be injected for silencing

- The idea of regulatory role for mRNAs dates back to 1960s and 1970s (reviewed by Morange, 2008)

Investigating the mechanism of RNAi

- Mutagenesis
- Screen for worms that resist RNAi against an essential gene (Tabara et al, 1999)
- Probably a lot more to be discovered (e.g. activation of transcription by RNA?)
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Has the original goal been achieved?

“‘We tend to talk loosely about genetic programs and we should be careful about the implications of this language even when used metaphorically’ (Brenner, interview with Lewin, 1984)

“‘How genes might specify the complex structures found in higher organisms is a major unsolved problem of biology.’ This is still true today.” (Brenner, Nobel lecture)

“I believe that the whole of systems biology is a waste of time. [...] Systems biology [...] claims to release people from thinking. [...] Systems biologists [...] came out of the people who did the sequencing, they came out of people working with yeast. [...] Systems biology [...] does not have to pose any hypothesis.” (Brenner, interview with de Chadarevian, 2009)

Terminology issue; systems biology is not about vaguely hoping to make sense of high-throughput data acquired indiscriminately