The human worm

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IT IS a voracious predator that devours anything it can fit in its mouth. In the two weeks of its adult life, it produces up to 350 offspring. It moves with a surprisingly graceful sinuosity. It even socialises, after a fashion. Yet its entire body has only 959 cells, while the cells in a human body are numbered in their trillions. You have probably never seen it, although it or its close relatives may well browse on the soil-dwelling bacteria in your garden.

The internal structure of Caenorhabditis elegans

Enlarge image

This extraordinary creature is the nematode worm Caenorhabditis elegans, and it is about to make history as the first multicellular organism whose entire genetic sequence is known. By the end of this year, when they aim to finish reading all 100 million of the As, Ts, Gs and Cs that spell out its genetic code, scientists will finally have within their grasp the complete recipe needed to make an animal. A very small animal, yes□C. elegans is only a millimetre long□but far from insignificant in the quest to find out not only where genes are but what they do. To understand many of the mechanisms fundamental to complex life□how cells send and receive signals, how they know where to go and what sort of cell to become during development, how, when and why they die, why they age□we probably need look no further than this tiny creature known to insiders as The Worm.

In the 1960s, Sydney Brenner at the Medical Research Council's Laboratory of Molecular Biology (LMB) in Cambridge was the first to choose C. elegans as a model animal to study the genetic control of development and the nervous system. "Sydney had an eye to select a really superb little experimental system, and it took off in a much larger way than he expected," says John Sulston, a former colleague of Brenner's who now jointly heads the worm genome project. The worm seems tailor-made for lab research. Most of the worms are hermaphrodites, making it easier to maintain mutant strains. C. elegans grows readily in laboratory Petri dishes, reaches maturity in only three days, and produces lots of offspring. Mutants are easy to create and identify for genetic analysis.

By the late 1980s, Sulston and his colleagues had documented the full developmental history of every one of the worm's 959 adult cells, and others had mapped the approximate location of many of its genes. They began sequencing its entire genome in 1990. Today Sulston heads the Sanger Centre at Hinxton near Cambridge, which with the Genome Sequencing Center at Washington University in St Louis leads the world in human genome sequencing. "I think the success of the worm has been critical in pushing the Human Genome Project along," says Bob Waterston, director of the St Louis lab, which has been an equal partner on the worm sequence since the project began. "Five years ago people were saying the technology is not powerful enough. When we began to sequence a million bases [of the worm genome] a month, they had to sit up and take notice."

So what will the complete C. eleganssequence tell us? "The genome is a plan for the full biology of the organism," says Robert Horvitz, who worked on the cell lineage with Sulston at the LMB and now runs a large worm lab at the Massachusetts Institute of Technology in Boston. "For example, you don't want to study one member of a family of genes□you want to study all of them. Even with 80 per cent of the genes, you could be missing something."

The worm has at least 18 000 genes. Scientists have no idea what half of them do, but the other half belong to known gene families or closely match genes discovered in other organisms. Well over 50 per cent of known human genes have a match in the worm, although that fraction may be artificially high because researchers sequencing human genes tend to choose genes already known from other organisms. But the big message reinforced by the worm sequencing project is that many fundamental biological processes are conserved right the way through evolution. "That's been the revolution of the past ten years of biology," says Julie Ahringer, who works on early development in C. elegans at Cambridge University. "We now know that all animals are put together in very similar ways□humans, flies, worms and everything."

What is going to take some explaining is the sheer number of genes that C. elegans possesses□many more than are known from the fruit fly Drosophila melanogaster, for example, even though an entire worm has fewer cells than a fly has in its eye. "That it's got so many genes comes as a surprise, but in a way it's an agreeable surprise because there's a lot to understand there," says Jonathan Hodgkin of the LMB. For example, the largest gene families in the worm all make regulatory proteins. These are proteins that alter the activity of another protein, either directly or by binding to the DNA and altering how much protein is made. The question is, what are they regulating?

That's the problem that now faces Ahringer in her work on the early worm embryo. She and her lab are working with a gene called vab-7 that must be active at a critical point in development to ensure that the skin and muscle cells in the back half of the worm arrange themselves in neat rows. The protein made by vab-7 is a transcription factor, a regulatory protein that acts at the level of DNA. She is now searching for other genes that interact with vab-7 to map the whole pathway.

In her search she is making use of a new tool called RNA-mediated inhibition, or RNAi, which has added a further dimension to the worm's almost unbelievable convenience as a laboratory animal. It involves injecting the gonads of individual hermaphrodite worms with double-stranded RNA corresponding to the sequence of the gene you want to suppress. Exactly what the RNA does is a mystery, but worms treated in this way, and their offspring, look for all the world like mutants in which the gene has been turned off. Once the whole genome is available, it will be possible to suppress any of the worm's genes in this way, either alone or with others.

Job sharing

By screening worms with a mild vab-7 mutation, Ahringer found an unrelated gene that enhances vab-7's effect. Turning to the genome database, she searched for genes with a similar sequence to this new gene. She found one more, making a new gene family with just two members in the worm. (Each also has a human counterpart.) Using RNAi, she quickly learnt that if she inactivated one gene, muscle and skin cells were disorganised, while inactivating the other merely shortened the tail slightly. But inactivating both left all the embryo's tissues disorganised. Standard genetic techniques, which involve making mutations at random and selecting the ones that seem interesting, could never have uncovered this kind of shared function among genes. "RNAi has really transformed the field. Almost everyone is using it," Ahringer says.

Another new tool has been developed by people working with the yeast genome (sequencing completed in 1996) and is now being adapted for the complete worm genome by Stuart Kim at Stanford University in California. It comprises a DNA microarray or "chip"□a grid of dots of DNA, each representing a gene. All 6000 yeast genes fit on one chip 2 centimetres square, though the worm genome might need a larger array. Researchers then use a fluorescent dye to label mRNA□a messenger molecule produced by active genes□from a worm that has been grown in particular conditions, or is at a certain stage of development, or has a mutation. Placed in contact with DNA chips representing the whole genome, the fluorescent RNA molecules selectively bind to their corresponding DNAs, providing a snapshot of the genes that are active at that moment. Just by looking at the different patterns of spots, you can see at a glance how turning off a particular enzyme, for example, affects the expression of all the other genes.

With techniques such as these, and given the similarity between many worm genes and genes from

other species, biologists are suddenly seeing C. elegans as a short cut to understanding other organisms. The worm genome is especially useful because worm researchers have brought about a revolution in the way sequence data are made available to the scientific community. They broke with the tradition that no data should be released before publication in a scientific journal, and instead place each day's raw sequence, virtually straight from the machine, onto a website with free access to all. Today this is standard practice for publicly funded sequencing projects, hugely accelerating the rate at which others can use the data. "The accessibility has been an enormous advantage," says Waterston. "It's drawing an incredible number of people into worm biology."

With the whole sequence on a database accessible via the Internet, finding a worm relative of a human gene, for instance, now takes just a few minutes at the keyboard. "I get lots of e-mails, phone calls and faxes from people saying the best match to the gene they've cloned is in C. elegans," says Horvitz. And it's easy to find out what that gene does in the worm. Researchers can make double-stranded RNA from the worm counterpart of a human gene to see the effect of suppressing its activity. They can even insert the human gene in place of the worm gene and see if it functions normally□or, if the human gene is known to cause a disease, find out what exactly goes wrong in the worm cells. "Worms are wonderful little test tubes for people who work in higher organisms," says Cynthia Kenyon, who studies the biology of ageing at the University of California at San Francisco.

Long live worms

Kenyon and her colleagues have isolated 23 different mutant worms that live more than twice as long as the normal two or three weeks and have identified several of the underlying genes. Recently she found that one gene, daf-2, can control the rate of ageing throughout the whole animal even if it is turned on in only a few cells. And daf-2 has a counterpart in humans that makes a receptor for insulin and insulin-like growth factor (IGF-1). What this means in terms of human ageing is unclear. But, says Kenyon, laboratory rats that are chronically underfed live longer than rats allowed to eat all they want□and their insulin levels are lower□which suggests that the receptor may also help to determine lifespan in mammals.

The worm has yielded similar parallels between genes that control programmed cell death, or apoptosis. This is a hot topic: cells may become cancerous because they fail to die when they should, and degenerative diseases could some day be treated by turning off cell death genes. Sulston and Horvitz have found that certain cells in the worm embryo always die during normal development. Horvitz later identified mutants in which these cells survive in the adult, and he has pinpointed a number of genes that control the death mechanism. At least five have counterparts that control cell death in humans.

Scientists armed with the worm's complete genome may even be able to learn some of the secrets of human behaviour. Last May, Hodgkin reported that strains of C. elegans collected in the wild showed two distinct behaviours when placed in a laboratory dish full of Escherichia coli bacteria, their standard laboratory diet. Some strains moved quickly until they encountered other worms, then "clumped" into writhing heaps. Others moved more slowly and studiously ignored each other, spreading out over the whole surface. In September, Mario de Bono and Cornelia Bargmann at the University of California at San Francisco traced the origin of the two behaviours to a single amino acid difference in one receptor protein. And yes, the protein does have a human counterpart: a receptor for a neurotransmitter, neuropeptide Y, that is involved in eating, mood, memory and blood pressure.

It is too soon to jump to conclusions about the control of human social behaviour, but Hodgkin finds the result intriguing. "What this work does is to give you an entry point into understanding what one might think of as a fairly sophisticated piece of behaviour. And maybe because we understand so much about the nervous system of C. elegans and have all these tools available, one can work out in detail everything that's going on there."

But Hodgkin cautions that even the most sophisticated laboratory analyses may never lay bare all the worm's secrets. "We grow C. elegans in the lab, and we feed it E. coli, which is a bacterium that

it never ever encounters in the wild, so it's living in a totally unnatural environment," he says. "And yet we have the impertinence to suggest that we're maybe going to understand everything about it by having its 100 million base pairs. It ain't so! There are so many things going on out there in the wild that undoubtedly we are never going to see in the lab, but which are crucially important to how the whole organism lives and interacts with its environment."

The ranks of scientists working in nematode research have swelled from their small, friendly beginnings when the sequence began to roll out of the machines in St Louis and Cambridge. If you add in all those human biologists who have started collaborations with worm people, the number reaches tens of thousands. This vindicates the view Sulston always held, that even if the project was expensive, it would ultimately be good value for money. He is currently trying to close the last few intractable gaps in the worm genome sequence. "It's worth pursuing to the end," he says. "I have no doubts at all about that. It's going to go on being mined forever and it's delivering more value every year."

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