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A Worm is More Like a Human Than Previously Thought

Humans have more in common with the lowly worm than previously thought, according to scientists reporting in the cover article of *Molecular Cell*, published today. The findings have important implications for medicine, including the study of birth defects, cancer, and tissue engineering.

"Our studies show that animals that are very distantly related show something strikingly in common that hadn't been expected," said Joel Rothman, associate professor of molecular biology at the University of California, Santa Barbara.

Rothman's lab studies the nematode worm known as *C. elegans*, an important organism for biological research, which has also been recently embraced by the biotechnology industry to study the basis for disease processes. The nematode *C. elegans* is the most completely described animal on the planet, according to Rothman. "With this animal we can ask deep questions and get profound answers quickly and relatively cheaply," he said.

This new research shows that nature uses the same fundamental machinery to create vastly different creatures. "We found that a key regulator of early development is the same in worms and vertebrates -- animals like ourselves that possess an internal skeleton," said Rothman. And because the machinery is the same, it may be possible to learn about the causes of many human birth defects by examining how worms develop and how that development can go awry."

Post-doctoral researcher Morris Maduro and Rothman found that there is a common regulator gene that controls the formation of many of the internal organs in both nematodes and vertebrates. This gene tells early cells what to become, for example, an intestine or a muscle cell.

Early on, the embryos of most animals become divided up into three different layers -- ectoderm, mesoderm, and endoderm. As vertebrate embryos mature or develop, the mesoderm produces heart, blood and muscles, while the endoderm becomes the organs of the intestine, liver, pancreas, and lungs.

In the much simpler nematode, there are too few cells in early embryos to form actual layers. However, just one cell, which is analogous to the mesoderm layer of vertebrates, produces muscles, a feeding apparatus that resembles a heart and cells that are comparable to blood.

As with vertebrates, the endoderm of the nematode also differentiates into a gut organ.

In the *C. elegans* embryo, when there are only four cells, a single cell is selected to produce mesoderm and endoderm organs. "Despite the enormous differences, remarkably, it appears that the same genes operate at that stage to control that selection in both the worm and vertebrate animals," said Rothman.

This implies that the common ancestor from many hundreds of millions of years ago, shared by both humans and worms, used the same early regulatory machinery. The invention of groups or layers of cells that could ultimately produce heart, lungs and other key organs which allow humans to thrive as large animals, evolved from a single event during which this regulatory switch was invented.

Rothman explained that his lab identifies and studies mutant worms that are defective in early development. They then identify the genes causing those birth defects.

"Our goal is to learn about how those genes work and what can go wrong when they are broken. In this way we can hope to learn how to fix them," he said, noting that some of his work is funded by the March of Dimes Birth Defects Foundation.

The information already gathered by scientists includes mapping out the wiring of the worm's entire nervous system, or brain, and the ten thousand interconnections

between the nerve cells.

The worm develops quickly, growing from an egg to an adult in three days, as compared to mice, for example, which take several months. In addition to growing quickly, researchers can grow large quantities of the worms for study -- several thousand can be grown on a single Petri dish in a few days.

The recently mapped human genome revealed that humans have only approximately 35,000 genes, whereas *C. elegans* has over 19,000 -- not a huge difference, according to Rothman, who said most scientists were startled to learn that humans did not have many more genes.

The similarities between the number and identity of genes in humans and worms allow researchers to extrapolate from worms to humans in their genetic research. He explained that the "gene knockout" technique that is used to learn about how single genes work can take a year or more to complete using mice.

In contrast, a revolutionary technique invented a few years ago allows worm genes to be "knocked out" literally overnight, thus speeding up gene studies enormously.

("Knockout" is the way that biologists study the function of genes by removing them one at a time, and examining the outcome.)

The initial experiment that led to the discoveries described in this cover article in *Molecular Cell* took only one day to complete. "We are learning about genetic switches and how they work together to create us," said Rothman.

He said they are doing a systematic gene by gene removal to ask how the overall system works.

"It is analogous to learning about how a car works by removing its individual parts and asking what goes wrong when that part is missing," he explained. "This is teaching us an enormous amount about animal biology and ultimately human biology."

Rothman believes that the research into these genetic switches will provide a basis for tissue engineering, which will come to fruition in the next few decades.

Replacement organs such as hearts and liver may eventually be grown in the lab, starting with a small amount of tissue from the person needing the new organ.

"As we learn what the switches are, for example what tells the embryonic cells to specialize into a heart, it will ultimately become possible to turn these switches on and grow a replacement organ in the lab," said Rothman. "This is one reason why the biotech industry has committed hundreds of millions of dollars into research on simple animals like our beloved worm."

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