How does a worm build a throat? Tackling the 'organ formation puzzle'

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(PhysOrg.com) -- Mention worms to most people, and they probably think of fishing, gardening, or trips to the vet. Mention them to Susan E. Mango, and she begins telling you how “absolutely beautiful” they are, how she marvels at their development from single cells into the six chromosome, 20,000 gene organisms upon which she has built a career that in just the past years included a MacArthur “genius” award and an appointment as a Harvard professor of molecular and cellular biology.

Regardless of the kinds of visions the mention of worms conjure, Mango

is convinced that, in time, they will reveal a few important ideas about the ways in which entire human organs are formed.

“The notion that you can track individual cells in them is just phenomenal,” she says. Her team observes how one cell becomes two, two become four, and so on, focusing on how pools of cells in the mature worm do things in a cohesive fashion, forming an organ such as the throat - the worm organ Mango studies.

Mango and her team are hardly the first to make use of these tiny creatures, the worms known in the world of biology as C. elegans.

"I don’t know if you have ever seen one under the microscope,” Mango tells a visitor to her new laboratory at 16 Divinity Avenue. “It’s just amazing looking at them,” she adds.

In the early 1970s neurobiology was the buzz word, and only a few scientists had begun digging around in the world of worms. Worm jokes abounded, and so did general skepticism that C. elegans was of any practical use. Yet John E. Sulston, recipient of the 2002 Nobel Prize in Medicine “sat down patiently and persistently at the microscope - this is before imaging technology existed and one could make videos and all that,” Mango says. “He just sat there, and watched worms develop, going from one single cell into an entire organism. He tracked down every single dividing cell to its fate, to what it would become,” she continues. “It was incredible to be able to do that… but this is what is nice about worms.”

The body of C. elegans is always transparent, and its embryo undergoes a developmental process known as “stereotypical cleavage,” a pattern of cell division with a timing and orientation that can be tracked easily in a research laboratory. “So you can say, ‘okay, we know this cell will eventually be part of the gut,’ which is what we study,” Mango explains.

She and her team can then ask questions, for instance, how does a cell transform from a pluripotent state, in which it can become any cell type in the body, to its final cellular fate, as a gut cell.

“With C. elegans (the worm), the whole process is very fast and you can watch it as it happens,” Mango says, explaining that she is impatient, and would “like to be able to do an experiment, get a result, think about it, and set up the next experiment right away. With other experimental organisms, like the mouse, you can’t do that. You have to figure it all out all ahead of time. I can’t. But this is a good rhythm for me.”

Lately Mango and her team have been watching the nuclei of embryonic worm cells. The cells are tiny structures about half a micrometer deep (a micrometer is 1/1000 of a millimeter), containing all the worm’s genetic information (DNA), and clues about the process of plasticity whereby a cell commits to a defined type.

"Isn’t that amazing, how drastically its nucleus changes?” Mango asks, pointing at an image comparing two developmental stages of a worm’s embryo in terms of the appearance of its cells’ nuclei. “As you can see, over time, the nucleus gets much more organized and then it partitions. Certain regions are kind of stuffed away into something called heterochromatin,” Mango explains. The reorganization of the genetic material inside a cell’s nucleus occurs during development, and Mango believes it could be the process that controls the potential of a cell to be “plastic.”

“Maybe what happens,” Mango hypothesises, “is that over time, cells crumple up and store away all the genetic material and genes they don’t need access to anymore having had already followed a particular path. But we don’t know,” she says. “We need to understand what controls these transitions.”

Mango's passion for puzzling through a problem began in high school. "I enjoyed looking at things from different angles," she says. From trying to distinguish a fake Rembrandt from a real one, which she did while working at a museum for a year after college, the daughter of a Byzantine historian and a translator now ponders different kinds of problems:

What happens to a cell nucleus during development? How does a worm build a throat from scratch? For that matter, what is an organ?

Mango defines an organ as a collection of many different cell types. "Their unifying principle is that they need to get some job done. Like your eye, your kidney, or your liver," the researcher says. "Those are solid organs where you have some structure…but people also talk about skin as an organ. So even though the general concept is simple, drawing the line, saying 'this is the organ and here it ends,' can be a lot more complicated."

To help delineate the organ puzzle, Mango and her team have set out to find what the animal itself 'thinks' an organ is or isn't. "We want to understand how an animal organizes itself," she says. To do so, the team must figure out the identity of 'the columns' that make up an organ's 'building'. "If you can take a single gene, delete it, and in that way cause a clean removal of all the cells in your kidney, to me it's pretty convincing that the gene is essential to make the kidney," she says.

Which brings us back to the worm's throat, a part of its gut. "Before we started doing this there wasn't any basis to say that an animal would see the whole throat as a throat, as a thing, as an entity," says Mango.

Pointing their microscope at the transparent body of a worm, Mango's team searched for the pharynx - and couldn't find it. They had found a mutant worm in which a gene they eventually called pha-4, usually

associated with the pharynx, was missing.

“So we thought: 'there is one gene, this single gene pha-4, that when mutated, prevents a whole organ from forming,'” Mango recounts. “It was so beautiful, such a simple, clear phenotype and it suggested that this gene, pha-4, has a critical role for making the pharynx, and not just one of its cells but all the pharyngeal cells.” Moreover, the gene showed no effect on cells not destined to become part of the pharynx. Its effect was specific. It was so specific that Mango and colleagues called it the “organ identity gene or selector gene.”

What Mango’s team had discovered is that a organ isn’t simply a collection of cells in a pattern labeled as such by observers, but rather “a unit of organization for the animal.”

Knowing that the pha-4 gene was central to producing a pharynx, the next question for the lab was “How does it work? How does it… pop out an organ at the end?"

Instead of it turning on a second gene that would turn on some third gene that would turn on yet another gene -- like a busy little assembly line miraculously producing a pharynx -- the gene pha-4 seems to have a global role targeting most other genes involved in the formation of the organ-to-be.

“You can imagine that an organ has to turn on many different genes in order to make all its tissues (for instance, the muscles, nerves, epithelium, and glands in the pharynx). Some genes come on and begin their work earlier than others,” Mango explains. “So...pha-4… is sitting down on hundreds of genes.”

pha-4 uses its binding preference like a conductor’s baton to direct genes to activate. As a consequence, when pha-4 is taken away, “the cells don’t

become what they should, and the organ doesn't form," the researcher explains.

It was the mutant worm what started Mango asking how an organ forms. Since Mango's discovery, researchers have found genes with similar functions in the eye and the pancreas. The gene pha-4's existence has been confirmed in creatures from simple life forms to humans. Its is a most basic of biological roles.

Is it possible that there's a gene associated with the formation of each organ? "It's possible, but we haven't found these 'organ identity genes' for all organs," Mango says.

For now there are more questions than answers, and however impatient Mango confesses to be, she has all the patience in the world for coming up with new ones. How do early things happen early in development? How do later things happen later? When does pha-4 find its targets? What's happening in a developing worm's embryo over the course of time? Can we watch this in other living animals?

"If you're going to build an organ, just like building a house, you need to start at the beginning and then progress," Mango says. "You wouldn't put the plumbing after you've put up the walls in your new house, right?"

Another important question Mango has yet to answer is what she plans to do with the half-million that come with the MacArthur honor. "Sometimes I dream about starting in some new research direction, totally off the wall," Mango says, "In truth, I haven't done anything specific with it yet." If her research record is any example, she'll find an answer soon.

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