Fruit-fly study adds weight to theories about another type of adult stem cell

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It turns out that an old dog - or at least an old fruit-fly cell - can learn new tricks. Researchers at the Stanford University School of Medicine have found that mature, specialized cells naturally regress to serve as a kind of de facto stem cell during the fruit-fly life cycle.

The surprising discovery counters the common belief that the ability to form new cell types or tissues wanes as a cell becomes more specialized.

"It was mind-boggling, because it went completely against what we had expected to see happening," said lead researcher Molly Weaver, PhD. "Once we figured out what was happening, however, the results were very clear." Weaver is a postdoctoral scholar in the laboratory of Mark Krasnow, MD, PhD, professor and chair of biochemistry.

Harnessing this type of developmental backtracking in adult human cells would allow researchers to explore new avenues for treating many human diseases. Although recent research has shown that human skin cells can be coaxed in a laboratory dish to generate many other types of cells, the conversion requires the use of viruses to deliver specific combinations of genes into the cells. The existence in humans of similar, naturally occurring stem cell understudies, called "facultative stem cells," has recently been proposed, but the idea remains controversial.

"In the past, many believed that cell specialization, or differentiation, was a terminal state - there was no going back or getting young again," said Krasnow, the senior author of the research. "But now, not only do

we know this reversion happens naturally, we also have a very tractable genetic system in which to study it."

The research will be published online Aug. 1 in *Science Express.*

Weaver, who is also Howard Hughes Medical Institute fellow of the Life Sciences Research Foundation, didn't start out trying to overthrow stem cell paradigms. Fruit flies, or Drosophila, have a long and illustrious history as laboratory guinea pigs. Weaver was simply investigating how the respiratory system of the fly is remodeled when the animal transforms from a tiny, grublike larva into a full-fledged, winged fly lusting after your bananas and apples.

Like all insects, fruit flies don't have lungs and their blood doesn't carry oxygen to their tissues. Instead they "breathe" through tiny openings along their bodies called spiracles. These spiracles connect to a complex system of tubes called trachea that penetrate the tissue to deliver oxygen and carry away carbon dioxide. In fruit flies, the trachea branch from a structure running the length of the animal called the dorsal trunk.

During metamorphosis, nearly all the larval cells are replaced by cells arising from structures called imaginal discs. The undifferentiated cells of these discs bide their time during the larval stage and only spring into action when the time comes to begin dividing to produce the tissues of the adult fly.

Weaver and Krasnow, who is also a Howard Hughes Medical Institute investigator, wanted to know what happened to the tracheal system during the fly's switch from squirmer to hoverer. They looked at fruit flies that had been genetically modified so that proliferating cells in the trachea expressed a highly visible green fluorescent protein, allowing the researchers to track the fate and location of the cells by looking for those that glowed green under a microscope.

Then things got interesting. Although the trachea branch from either side of the dorsal trunk, only one side has imaginal cells. The expectation has always been that these cells migrate across the dorsal trunk to repopulate both sides of the trachea with a flying-appropriate blend of cell types. But, despite spending countless hours behind a microscope, Weaver never saw any green cells making their way to the other side.

"I had about four different hypotheses to explain why I couldn't see any of these cells crossing the dorsal trunk," said Weaver. "It took quite a while to convince ourselves what was truly going on."

Further experiments that followed the fate of individual stalk cells in live fruit flies proved that a group of well-differentiated cells known as the anterior dorsal branch stalk cells were actually stepping in to repopulate the side of the trachea lacking imaginal cells. As a result, the researchers concluded that a single tissue was being remodeled by two types of multipotent cells: one, the undifferentiated imaginal cells held in reserve to repopulate the fruit fly body, and the other, a highly specialized cell that reverses its developmental course in order to give rise to different cell types.

"To find two very different kinds of progenitor cells in a single fruit-fly tissue raises the possibility that there may be more than one kind of adult stem cell in mammalian tissue," said Krasnow. "It may be that organisms use both quiescent, undifferentiated cells and more highly differentiated yet reversible facultative stem cells under different conditions."

Weaver and Krasnow plan to compare molecular and genetic characteristics of the anterior dorsal branch stalk cells and the imaginal cells in the trachea in an effort to identify how the stalk cells are able to re-attain such developmental flexibility. They have already noticed that, contrary to surrounding cells that accumulate more than two sets of chromosomes through a process called endoreplication, the stalk cells

have smaller nuclei and don't form extra sets of chromosomes-differences that may allow the stalk cells to more easily re-enter the cell cycle.

"Although it wasn't expected, Drosophila have clearly taken advantage of this biological capacity during metamorphosis," said Krasnow. "The stem cell community is debating whether every mammalian tissue relies on conventional adult stem cells of the sort already identified in bone marrow and muscle, or if instead there are facultative stem cells that can arise from differentiated cells within the tissue. Now we know that it doesn't necessarily have to be one or the other. It could be both."

Source: Stanford University Medical Center