Surprise: Lost stem cells naturally replaced by non-stem cells, fly research suggests

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Johns Hopkins researchers have discovered an unexpected phenomenon in the organs that produce sperm in fruit flies: When a certain kind of stem cell is killed off experimentally, another group of non-stem cells can come out of retirement to replace them.

The discovery sheds light on the tiny "environments" that stem cells occupy in animal bodies and may help explain how stem cells in tumors replenish themselves, the researchers report in the May 8 issue of the journal *Cell Reports*. Damage of the kind duplicated in the laboratory occurs naturally after exposure to radiation and perhaps also after ingestion of toxic chemicals such as those used in chemotherapy.

The research group, led by Erika Matunis, Ph.D., a professor of cell biology at the Johns Hopkins University School of Medicine, has been using the fruit fly as a model living system in which to study stem cells in their natural state. Most stem cell research is done on cells grown in the laboratory, but in real life, stem cells reside in tissues, where they are sequestered in tiny spaces known as niches. Adult stem cells keep dividing throughout life to make various kinds of cells, like new blood cells and germ cells.

Matunis's group studies such niches in fruit fly testes, the sperm-producing organs shaped like a coiled tube whose end houses a niche. In the niche are three kinds of cells: germ line stem cells, which divide to produce sperm; somatic cyst stem cells, which make a kind of cell that helps the sperm-producing cells out; and hub cells, which make signals that keep the other two kinds of cells going.

The hub cells are not stem cells; they have settled on their final form, incapable of dividing further or changing their function—or so everyone thought.

However, in a bid to figure out what happens when the somatic cyst stem cells are killed off, Matunis suggested that graduate student Phylis Hétié figure out how to best do away with them, thinking the task would be straightforward.

Instead, she says, "it took a lot of heroic, patient combinations" of different genes working together to kill the somatic cyst cells, Matunis says.

"When we finally figured out a way to kill all of the somatic stem cells, we thought that the rest of the tissue would probably just empty out," she says. In 35 percent of testes, that's just what happened. But in the rest, the somatic stem cells grew back.

This was a surprise, Matunis says, and left a puzzle: Where were the new somatic stem cells coming from?

The answer, it turned out, was another surprise: the hub cells. When the somatic stem cells were destroyed, the hub cells cranked up their machinery for cell division. The team did several experiments to be sure that the hub cells were involved, including one in which they genetically marked the hub cells and saw the mark appear in the newly formed somatic stem cells—a clear sign that hub cells had divided to make new stem cells.

Matunis notes that the new stem cells created by the hub cells aren't exactly the same as the old ones. "We thought some of them looked a little bit weird," Matunis says. Sometimes, the new cells made molecules that only hub cells normally make. As the researchers looked closer, they realized that the damaged and recovered testes were making new niches. Instead of just one pocket of stem cells, a damaged testis might have two or three.

The researchers don't know how the new niches are formed, but speculate that the original niche gets bigger as the new cells divide, then splits. The group is doing more experiments aimed at "explaining the basics of how niches work in general," Matunis says.

Matunis says the research may be useful for understanding cancer, because a lot of cancer involves cancer stem cells, also known as tumor-initiating cells. Many tumors seem to have stem cells inside them that divide to keep the tumor going. Knowing how tumor niches support the continued growth and division of stem cells might one day offer new targets for controlling such growth.

In the study, the damage was caused deliberately, but the research suggests one way that natural damage might scatter stem cells around the body.

"We're very curious to unravel the signals that are changing when we damage this niche and it undergoes these unexpected behaviors," Matunis says.

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