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Defining a Niche that Regulates Stem Cells

Researchers have discovered a set of regulatory cells that governs the behavior of stem cells in the fruit fly *Drosophila*. Stem cells retain the capability to divide and to develop into many types of adult cells. These studies suggest that the special properties of these regulatory cells allow stem cells to replenish themselves indefinitely.

In an article published in the October 13, 2000, issue of the journal *Science*, Howard Hughes Medical Institute investigator Allan C. Spradling and colleague Ting Xie report that they have identified the types of cells that make up the niche—a specialized cellular environment that provides stem cells with the support needed for self-renewal. Spradling and Xie characterized the niche cells that govern the production of *Drosophila* embryonic germline stem cells—those cells in the ovary that are the earliest precursors to eggs. According to the scientists, their findings offer a potentially valuable model to explore how stem cells are regulated *in vivo*.

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— Allan C. Spradling

"The idea that stem cells require niches—local environments of surrounding cells that are important for their regulation—has been around for a long time," said Spradling, who is at the Carnegie Institution of Washington. "The problem has been that mammalian stem cells have been studied by purifying them and trying to grow them in culture. So, it has been difficult to study *in vivo* the niches that surround the stem cells and to deduce the regulatory mechanisms that make these niches work."

According to Spradling, the niche environment may constitute a primary regulatory force that may be capable of reprogramming somatic cells to become stem cells. The *Drosophila* ovary represents a useful model system for studying the role of the niche in stem cell regulation, said Spradling. "Its anatomy is particularly favorable because there are only two or three stem cells in it, and as they divide, they move out in a uniform string, so you can precisely trace their activity over a long period of time. In addition, there are

few cells that make up the niche and provide important regulatory signals."

The researchers began by exploring the role of the three major cell types that surround the stem cells in the *Drosophila* ovariole—terminal filament cells, cap cells and inner sheath cells. "The key issue in our mind was whether this group of cells around the stem cells was really acting as a niche," said Spradling. "We wanted to see what would happen if a stem cell was removed from that location. Would it be possible, for example, to put another cell into that location? Would that cell be influenced by the surrounding cells to function as a stem cell?"

The scientists genetically altered individual stem cells, marking them and speeding up their progress through the niche. When the scientists measured the progress of the progeny of the marked stem cell, they detected a rapid replacement of the marked cell with "wild-type" stem cells in the niche. "This showed us that a cell can move into that spot and function as a stem cell," said Spradling.

The researchers took advantage of a special structure within the stem cells, called the fusome, so that they could learn which cells were able to replace a lost stem cell. Normally, when a stem cell divides, one daughter cell differentiates and leaves the niche, while another remains behind to repopulate the niche. When a stem cell is lost, the daughter of a nearby stem cell that would have differentiated, instead moves into the vacated niche and becomes a new stem cell.

"This finding suggests a potentially interesting reason why you would want to have a pair of stem cells in a niche," said Spradling. "They can back each other up, which potentially makes for a more longer-lasting stem cell production capacity in case every so often one of the stem cells, in effect, makes a mistake and both daughters differentiate."

Xie and Spradling also sought to learn which of the surrounding niche cells is the most important source of regulatory signals. They reasoned that a key clue to the importance of each kind of cell was whether its ratio when compared to stem cells remained constant as the flies aged.

"The terminal filament cells and the inner sheath cells changed in number and location over time," said Spradling. "However, the cap cells seem to remain the most constant, and they are in direct contact with the stem cells. Also, when we found unusual ovarioles with more stem cells, they showed a proportionate increase in the number of cap cells," he said. Taken together, these observations suggest that cap cells perform an important regulatory role, said Spradling. The work also hints that cap cells may allow stem cells to "adhere" within the niche.

The discoveries about the nature of the *Drosophila* ovariole stem cell niche could influence thinking about human stem cells, said Spradling. "These findings suggest that the stem cell itself may be less important than many investigators believe," he said. "Perhaps the stem cell has a special mechanism to keep it from differentiating, but the rest of the stem cell

regulation may be more influenced by signals from the cells that make up the niche.

"This view of a stem cell and how it's regulated makes it very easy to understand the plasticity of stem cells that has been reported in several recent experiments in mammals that were quite unexpected and exciting," he said. Additionally, Spradling's studies indicate that the signals governing stem cell differentiation appear to be conserved in *Drosophila* through embryonic and larval development. "This fact may simplify the problem of creating differentiated cells from stem cells, because you don't need a whole new collection of mechanisms," he said.