

The Molecular Perspective on Stem Cells

Researchers are deciphering the complex molecular pathways that regulate stem cells, with an eye toward future therapies.

December 2009 -- [Erika Matunis](#) readily admits that her research probably sounds esoteric to most laypeople. By now, after 15 years in her field, she is used to seeing quizzical looks and raised eyebrows when she tells acquaintances that she studies the molecules that regulate stem cells in the fruit fly testis.

Matunis is one of several basic scientists at Hopkins who are elucidating such nitty-gritty details about stem cells.

While the majority of researchers studying stem cells use mammalian systems, it's a challenge to understand how the cells behave within these tissues. On the other hand, model organisms such as fruit flies are more easily studied, and the regulation of stem cells in these simpler organisms is in many ways similar to that in mammals, Matunis notes. "If you better understand the fundamental mechanisms of stem cells, then you can begin to manipulate those mechanisms," she says, and those efforts could lead to new therapies for cancer, diabetes, Alzheimer's disease and a raft of other conditions.

For Matunis, no fundamental mechanism is more intriguing than the point at which a stem cell divides to yield two different daughter cells. In the fly testis, which contains nine such cells, when a stem cell divides, one daughter cell is a facsimile of its parent, which replenishes the supply of stem cells; the other is a slightly differentiated entity, which will, through more divisions, give rise to a sperm cell. Matunis's research can be distilled to two basic questions: What preserves the primordial nature of the first cell? What induces differentiation in the second?

Several studies have indicated that in the *Drosophila* testis, two proteins—JAK and STAT—play critical roles in the first task, ensuring that a stem cell remains a stem cell. In a recent study, Matunis added one more piece to scientists' knowledge. Not only do JAK and STAT help to preserve stem cell identity, she found, the proteins can also instruct differentiated cells—cells on their way to becoming sperm—to dedifferentiate by reverting back to their primordial, stem cell state. Dedifferentiation occurs in a variety of different stem cell populations, perhaps as a way to replenish a supply depleted by aging or damage, says Matunis, whose study appeared last August in the journal *Cell Stem Cell*.

Elsewhere, at the [Institute for Cell Engineering](#), neuroscientist [Nicholas Gaiano](#) is addressing his own set of questions about stem cell biology using a different system, the embryonic brain. Here, Gaiano aims to identify and tease apart the different signaling pathways that instruct neural stem cells to remain in a perpetually plastic undifferentiated state or differentiate into neurons, glia and other specialized cells.

Extensive research by Gaiano and other researchers has shown that a protein called Notch plays a fundamental role in these processes. Notch signaling, they demonstrated, inhibits neuronal differentiation. However, says Gaiano, “our understanding of the process was rudimentary, at best.”

One perplexing question involved the issue of cellular heterogeneity. As brain development proceeds, neural stem cells give rise to more of themselves, as well as to a second group of more neuronally differentiated cells called intermediate neural progenitors. These two cell types exist alongside each other. How did Notch contribute to the generation and maintenance of these two different types of cells?

To examine this question, Gaiano generated a transgenic mouse line that expresses a green fluorescent protein in cells where the Notch signaling pathway is activated. His studies have shown that Notch signaling occurs in both neural stem cells and progenitor cells, but that the signaling takes place through two different molecular pathways.

“Although we have a good idea how the neural stem cells utilize Notch signaling, precisely how the intermediate progenitor cells do so remains a black box,” says Gaiano. “To differentiate into a neuron, many different signals are involved, and it will be very important to figure out how those signals interact with Notch.”

One answer may come from the lab of [Valina Dawson](#). She and graduate student Zhirkai Chi have identified a protein that appears to counteract or hinder the work of Notch. “It botches the job,” says Dawson. So we named it Botch.” While Notch tells stem cells, “Remain as you are,” Botch intercepts the message, in effect releasing the brakes that stop a stem cell from differentiating.

Could scientists somehow exploit this mechanism for use in neural stem cell therapies? “We don’t know if it will have therapeutic benefit,” says Dawson, noting that the research is preliminary. “But we’re able to ask questions about neurons that we never could before.”

–*Melissa Hendricks*