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Protein Distinguishes Fetal and Adult Stem Cells

In a discovery that fills a critical gap in the understanding of stem cells, researchers have discovered a protein that fetal, but not adult, blood-forming stem cells need to replenish themselves. Finding regulatory pathways specific to fetal blood-forming cells could help scientists understand childhood leukemias and generate blood-forming cells for bone marrow transplants, said the researchers.

Howard Hughes Medical Institute investigator Sean J. Morrison and colleagues at the University of Michigan published their findings in an online publication in the journal *Cell* on July 26, 2007.

Stem cells are immature cells that give rise to multiple cell types, while also replenishing themselves through a process of self-renewal. Blood-forming, or hematopoietic, stem cells generate red and white blood cells of many types.

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- Sean J. Morrison

"As we have identified genes that regulate stem cell self-renewal, we have found big differences among stem cells at different stages of life," said Morrison. "Stem cells in different tissues at the same stage of life are more alike than stem cells at different stages of life in the same tissue."

A notable difference between stem cells at different stages of life, Morrison said, is that they often use different mechanisms to self-renew. "We had found that there were adult-specific mechanisms, which implied that there had to be some fetal-specific mechanism," he said. "But no one had found a gene that regulated self-renewal in fetal but not adult hematopoietic stem cells. That means there was a hole in our understanding of the mechanisms that maintain stem cells."

Morrison and his colleagues had long been comparing gene expression patterns in hematopoietic stem cells at different developmental stages. They had found a small number of genes whose activity varied at different stages. One of these was called *Sox17*. *Sox17* was known to regulate the formation of cells in early embryos that go on to develop into endodermal tissues like pancreas and the endothelium of blood vessels. But it was not known to have any role in hematopoietic stem cells, Morrison said.

When the researchers knocked out *Sox17* in mice, the animals failed to develop a hematopoietic system. “That told us the gene was important, but at that point we didn't know whether *Sox17* was required in the stem cells to maintain themselves, or whether it was required at some earlier stage of development to form the stem cells in the first place.”

So they engineered mice in which they could eliminate *Sox17* only in certain cells or at certain stages of development. They found that knocking out the gene in fetal mice whose hematopoietic systems had already formed caused hematopoietic stem cells to disappear.

Further studies revealed that *Sox17* was critical for the maintenance of the stem cells. What's more, the researchers' experiments showed that the gene functions within the stem cell itself, rather than being required in the external environment that supports the stem cell.

Deleting the gene in adult mice, on the other hand, had no effect on the hematopoietic system. The researchers found that *Sox17* was switched off as hematopoietic stem cells matured from highly active fetal stem cells to more slowly dividing adult stem cells.

“Thus, in *Sox17*, we have found an important new player in fetal stem cell regulation that no one had implicated before,” said Morrison. “It fills a big hole in our understanding of the mechanisms that regulate the maintenance of fetal but not adult blood-forming cells.”

Understanding fetal stem cell renewal could aid in understanding birth defects and childhood cancers, said Morrison. “For example, this finding raises the possibility that one mechanism underlying childhood leukemias may be abnormal upregulation of *Sox17*,” he said. “It is only a hypothesis that we are testing at this point, but we won't be surprised if we find childhood leukemias in which *Sox17* expression is through the roof.”

Sox17's key role in stem cell self-renewal also means that researchers might be able to manipulate the gene to grow hematopoietic stem cells from embryonic stem cells for bone marrow transplants, said Morrison. Clinicians have had limited success in culturing embryonic hematopoietic stem cells for such purposes, he said, even though they could be a highly useful source of cells for transplant.

Morrison and his colleagues now plan to trace the regulatory pathways that *Sox17* governs. “This gene may be broadly required for many different aspects of fetal/neonatal stem cell identity,” he said. “We will be looking broadly at the mechanisms downstream of this gene to see how many different aspects of fetal stem cell function it controls. It will be exciting to find out, because relatively little is known about the regulation of stage-specific stem cell properties,” he said.