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Identifying the Genes that Put the "Stem" in Cell

HOWARD HUGHES

A team led by Howard Hughes Medical Institute (HHMI) researchers has identified a network of hundreds of genes that keep embryonic stem cells in their characteristic malleable state, able to develop into any cell type when the time comes. The finding, based on studies of mouse cells, provides valuable insight into the way stem cells function, and could help researchers find ways to reprogram adult cells for therapeutic use.

Led by Stuart Orkin, an HHMI investigator at Children's Hospital Boston, the team published its findings in the March 21, 2008, issue of the journal Cell.

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Embryonic stem cells are the ultimate in indecision. Precursors of all the specialized cells of the body, embryonic stem cells exist in an undefined form until the time comes to head down the path toward nerve, organ, or muscle. Embryonic stem cells are distinct from other cells in two ways. First, they are pluripotent—they have the ability to develop into any cell type. Second, they are perpetually self-renewing, meaning that unlike other cells they do not die after a set number of divisions.

For years, researchers have sought to decipher the genetics behind these unique characteristics. In 2006, Orkin's team reported in the journal Nature that a set proteins that physically associate with one another regulates gene activity critical for maintaining cells in the embryonic stem-like state. These proteins, called transcription factors, bind to regulatory regions of DNA associated with specific genes and influence the genes' activity by encouraging or restricting their transcription (the first step in making a protein).

According to Orkin, the new study is a sequel to that Nature paper. "We're asking: `Well, we've got all these proteins—what are the genes they likely regulate?"

To find out, the team tagged a set of nine critical proteins with "molecular hooks" that made it possible to fish out the proteins attached to their target genes. Together, the proteins bound to roughly 6,500 genes that fell into two groups: those that the proteins kept switched off in the stem cells, and those that they switched on. However, it wasn't a simple matter of each gene being turned on or off by one transcription factor.

Instead, Orkin explained, "one class is genes that are targeted by many of the nine proteins we tested—even as many as six, seven, or eight. These cells tend to be on in embryonic stem cells, and off when the cells differentiate." Genes that were turned off in the embryonic stem cells, on the other hand, were bound by only one or two of the transcription factors.

According to Orkin, “This is the first time we've had a sense that one could distinguish these classes.” And, he said, the identity of the genes fit with the scientists' expectations of functions that need to be regulated to maintain the stem cell state. “They have to promote self renewal,” he said, “but at the same time they have to block differentiation. The two classes we see seem to more or less fit into those functions.”

Orkin said that the findings represent a “catalog of the genes bound by these factors,” which he hopes will be useful in future studies. According to Orkin, there has been a recent explosion of interest in reprogramming skin or other developed cells to act like stem cells, with the ultimate goal of treating disease. But currently, he said, the process is still essentially a “black box.” “You add genes, and the cells reprogram,” he said. “What happens in between?

“This kind of work provides the materials to get a better understanding of that process,” said Orkin. “The goal is to be able to manipulate cells in a very directed way.”