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Gene Profiling Reveals the Essence of 'Stemness'

An extensive genetic comparison of different types of stem cells and terminally differentiated cells has revealed that hundreds of genes are likely to be involved in shaping the characteristic properties of stem cells. The studies show that embryonic, neural and hematopoietic (blood-cell-forming) stem cells seem to share a common genetic program that may be important for stemness.

These initial gene-profiling studies provide basic information about the nature of stem cells that should aid long-term efforts to induce stem cells to differentiate into cells that can be used to replace tissue damaged by disease or trauma.

Howard Hughes Medical Institute investigator [Douglas A. Melton](#) and Miguel Ramalho-Santos, Soonsang Yoon, Yumi Matsuzaki, and Richard C. Mulligan at Harvard University described their findings in an article in the September 12, 2002, issue of *Science Express*, which provides rapid electronic publication of select articles that will appear in the journal *Science*.

"There has been a great deal of excitement about the possibility that adult stem cells are entirely plastic, that is, they are able to become any tissue in the body," said Melton. "However, there have been questions about whether such conclusions were correct. This led us to wonder if we could figure out whether stem cells were, in fact, all similar. And a related and critical scientific question is what genes or genetic programs are important for stem cells to have their special properties, or 'stemness.'"

To get at the answers to those questions, Melton and his colleagues developed experiments to survey thousands of genes in different kinds of stem cells and mature cells to determine if there are patterns of gene activity that are distinct to stem cells.

"We were quite stringent in our criteria for which stem cells to look at, choosing only those that everyone agreed were, indeed, stem cells," said Melton. The scientists compared embryonic stem cells, neural stem cells and hematopoietic stem cells -- all from the mouse. The researchers compared the patterns of gene activity in stem cells to the gene activity exhibited in

differentiated forms of these cells, including adult brain cells and bone marrow cells. Their studies identified stem-cell-specific genes that were distinct from those involved in the normal growth of mature cells.

The researchers performed their surveys by first isolating the messenger RNA (mRNA) from the cells. The presence of mRNA indicates that genes are expressed. They then used commercial DNA arrays containing some 12,000 genes to determine which genes were active in the cells. Statistical analysis of the results offered insights into the genetic programs used by stem cells, said Melton.

"First, we showed that there is a common genetic program among bona fide stem cells," said Melton. "But we also found that these three types of stem cells were not identical."

The researchers identified 216 "stemness" genes that are active in each of the three types of stem cells that were studied. An important sign that the analysis was valid, said Melton, was that the genes that were enriched in the stem cells included those that are commonly used as distinguishing markers for the cells.

Melton said the "stemness" genes they found fit into categories that reflect the activities that stem cells must perform to self-renew and differentiate. "For example, these stem cells seem to be highly enriched in gene products involved in dealing with environmental toxins, which enables them to cope with stress," said Melton. "Beyond that, they seem to have upregulated genes for receptors that enable them to receive signals from extracellular proteins. These might be important for signaling the cells to start differentiating.

While the scientists did find that the stem cells were genetically distinct from one another, there were interesting differences between stem cells and their differentiated counterparts. "One very nice happenstance was the finding that embryonic stem cells and neural stem cells are much more similar to each other than they are to their differentiated counterparts," said Melton. "This fits with a 'default model' we proposed, which is that the default fate of embryonic stem cells is to become neurons."

Comparing stem cells with their differentiated counterparts revealed genetic differences that will offer clues to developing techniques to induce stem cells to differentiate into adult cells, said Melton. "These findings provide a starting point to help people think how to cause stem cells to differentiate down specific pathways, such as becoming neurons that could rejuvenate brain tissue lost to neurodegenerative diseases," he said.

According to Melton, the findings are likely to aid the search for new types of stem cells. "For example, nobody has yet been able to identify adult pancreatic stem cells -- a central effort in our laboratory," he said. "But now we know that if we're going to isolate such cells, we should look for those

that express many of these 'stemness' genes."

Another significant development, said Melton, was that the studies revealed that the stem cells expressed large numbers of "expressed sequence tags," which mark genes of unknown function. "For young scientists, this finding is especially exciting because it shows that these stem cells express a large number of genes that no one has a clue what the gene products do," he said. What's more, said Melton, "it's easily a decade's worth of work just to define the functions of the genes that we have defined as characteristically active in these stem cells."