Scientists provide groundbreaking new understanding of stem cells

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In findings that could one day lead to new therapies, researchers from The Scripps Research Institute have described some striking differences between the biochemistry of stem cells versus mature cells.

The study, led by Scripps Research Associate Professor Sheng Ding and Senior Director of the Scripps Research Center for Mass Spectrometry Gary Siuzdak, was published in an advance, online edition of the prestigious journal *Nature Chemical Biology* on May 2, 2010.

In the research, the team used a unique approach to better understand stem cells, which have the ability to change or "differentiate" into adult cell types (such as hair cells, skin cells, nerve cells). Understanding how stem cells mature opens the door for scientists and physicians to manipulate the process to meet the needs of patients, potentially treating such intractable conditions as Parkinson's disease and spinal injury.

"In the past, scientists trying to understand stem cell biology focused on genes and proteins," said Ding. "In our study, we looked at stem cell regulation in a different way—on the biochemical level, on a functional level. With metabolomics profiling, we were able to look at naturally occurring small molecules and how they control cell fate on a completely different level."

The new paper describes parts of the stem cell "metabolome"— the complete set of substances ("metabolites") formed in metabolism, including all naturally occurring small molecules, biofluids, and tissues.

The scientists then compared this profile to those of more mature cells, specifically of nerve cells and heart cells.

When the results were tallied, the scientists had found about 60 previously unidentified metabolites associated with the progression of stem cells to mature cells, as well as an unexpected pattern in the chemistry that mirrored the cells' increasing biological maturity.

Ripe for Discovery

The study of metabolomics is relatively new, having emerged only over the past decade or so.

"One of the most interesting aspects of metabolomics is how little we know," commented Siuzdak. "We don't know what the vast majority of metabolites are, or what they do. It is an area ripe for discovery."

Research in metabolomics is made possible by a variety of special techniques and equipment. In the current study, the team used liquid chromatography-mass spectrometry (LCMS), which draws on two more traditional techniques to provide scientists with the ability to chemically analyze virtually any molecular species. The group then analyzed the resulting data using an open-access bioinformatics platform XCMS, a now-popular technique developed by Siuzdak and colleagues described in a 2006 article in the journal Analytical Chemistry. The XCMS software allows researchers to identify and assess metabolite and peptide features that show significant change between sample groups—in this case mouse stem cells versus mature cells.

The most difficult part of untargeted metabolomics studies is analyzing the results and characterizing metabolites, according to Research Associate Oscar Yanes of the Siuzdak lab, the new paper's first author.

Nevertheless, Yanes shifted though the data on stem cells and identified an unexpected pattern: stem cell metabolites had highly unsaturated structures compared with mature cells, and levels of highly unsaturated molecules decreased as the stem cells matured. Highly unsaturated molecules, which contain little hydrogen, can easily react and change into many other different types of molecules.

"The study reveals an astounding cellular strategy," commented Yanes. "The capacity of embryonic stem cells to generate a whole spectrum of cell types characteristic of different tissues (a phenomenon referred to as plasticity) is mirrored at the metabolic level."

"We were not expecting these results," said Siuzdak, "although in retrospect it makes sense that stem cells (which can form almost any cell) have metabolites that are chemically flexible."

Confirming their observations, the researchers found that by chemically blocking the usual route to saturation—oxidation—they were able to prevent stem cells' normal progress into mature heart and nerve cells. Conversely, when specific oxidized metabolites were introduced into the culture, stem cell differentiation was promoted.

Ding notes the study also provides a new perspective on fatty acids similar to those found in fish oil and other nutriceuticals.

"In the past, people focused on the fact that fatty acids were important to create cell membranes, the scaffolding of our cells," said Ding. "But in our study, we show that different fatty acids don't just play a role in constituting cell membranes, but also have functions in directing cell fate."

Provided by The Scripps Research Institute