Scientists identify compounds for stem-cell production from adult cells

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In the study, the scientists screened known drugs and identified small molecules that could replace conventional reprogramming genes, which can have dangerous side effects. This new process offers a new way to generate stem cells from fibroblasts, a general cell type that is abundant and easily accessible from various tissues, including skin.

The study was published in the November 6, 2008 edition (Volume 3, Issue 5) of the journal *Cell Stem Cell.*

"Our study shows for the first time that somatic or general cell types can be reprogrammed with only two genes and small molecules, and that these small molecules can replace one of the two most essential reprogramming genes," said Sheng Ding, a Scripps Research scientist and Associate Professor in the Department of Chemistry, who led the study with colleagues from Scripps Research and the Max Planck Institute for Molecular Biomedicine in Germany. "In this case, we replaced the Sox2 gene, which had previously always been regarded as absolutely essential for the reprogramming process."

The SOX2 gene encodes a transcription factor that plays a critical role in the regulation of embryonic stem cells.

"This proof-of-principle study leads us one step closer to the ultimate reprogramming of general cells to pluripotent cells in a completely chemically defined manner without genetic manipulation," he said. "In conjunction with our earlier published studies, it offers definitive proof

that we can make cell reprogramming technology much more practical than it has been."

Ding went on to suggest that this drug discovery approach could be used to identify additional small molecules, which could not only provide insights into the reprogramming process, but also become useful in in vivo stem cell biology and, ultimately, the development of novel therapeutics.

This kind of chemical approach to the generation of useful stem cells offers more precise control over the process, the study said, and has distinct advantages over the genetic manipulation of oncogenes that could introduce harmful genomic changes.

Better Results

The new study builds on an earlier study published by Ding and his colleagues in the June 5, 2008 issue of the journal Cell Stem Cell. That study showed for the first time that small, drug-like chemicals could help turn mouse brain cells back into pluripotent stem cells, while reducing some major drawbacks of a breakthrough technique discovered two years ago by Japanese researchers to produce pluripotent stem cells, once derived only from embryos.

The new study identified two small molecule compounds that improved reprogramming efficiency and that could effectively compensate for Sox2: BIX and BayK.

For the first time, the new study showed that BIX, an inhibitor of enzymes involved in regulating gene expression, enables fibroblast cell reprogramming in the absence of Sox2 gene overexpression. However, by itself, BIX's reprogramming efficiency is relatively low.

"As a result, we performed a second screen to find a compound that would synergize with BIX to further increase the reprogramming efficiency of general cells" Ding said. "Besides providing an improvement in reprogramming, we believed that these newly identified molecules might lead to discovery of different reprogramming mechanisms."

The second screen identified BayK, a calcium channel agonist, which was selected because it had no observable reprogramming activity on general cells in the absence of BIX. In addition, BayK was not known to affect the cell directly at the epigenetic level—changes in gene expression without any DNA or DNA-associated packaging protein modification—but rather at the cell signal transduction level.

The scientists found that when transduced general cells were treated with both BIX and BayK, a significant increase in the number of pluripotent cells resulted compared to transduced general cells treated with BIX alone. In vitro and in vivo characterizations confirmed that transduction of only two factors with simultaneous treatment with small molecules BIX and BayK was sufficient to reprogram general cells to become pluripotent stem cells.

The fact that BayK doesn't act on its own, but needs the presence of BIX to exert its effect suggests that cells that are already undergoing a form of reprogramming, perhaps caused by injury, might be more susceptible to it.

"Needless to say, more work needs to be done to understand the precise mechanism by which BayK affects the reprogramming process," Ding said. "It's interesting to find that a small molecule, which acts on signaling pathways that have not been linked to pluripotency and reprogramming previously can significantly enhance reprogramming efficiency. So far, it's the first small molecule of its type to show such an

effect. This might allow us to ultimately reprogram the target cell in a more specific manner, without impacting healthy cells systemically in an in vivo setting."

Source: Scripps Research Institute