Researchers Reveal Repressor Protein Blocks Neural Stem Cell Development

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Leslie Franz

A protein known to repress gene transcription at the molecular level in a variety of processes also blocks embryonic neural stem cells from differentiating into neurons, according to a study by University of California, San Diego and Howard Hughes Medical Institute (HHMI) researchers published online October 10 in *Nature.*

The research team focused on a repressor protein called SMRT (silencing mediator of retinoic acid and thyroid hormone receptor), which has been shown to repress gene expression in a number of molecular pathways. By creating a strain of "knock-out" mice missing the SMRT gene, the team was able to pinpoint significant alterations in brain development in the absence of SMRT. These findings demonstrate the important role of this protein in preventing premature differentiation of specific brain cells from undifferentiated neural stem cells *in utero*.

"By showing that SMRT prevents differentiation by maintaining neural stem cells in a basic stem cell state, we now have a target to study further how stem cells restrict themselves from differentiating," said first author Kristen Jepsen, Ph.D., an assistant research scientist at the UC San Diego School of Medicine.

The research team also noted that in the SMRT-deficient mice, the brain exhibited signs of excessive exposure to retinoic acid--naturally occurring vitamin A--which is a known teratogen (an agent which causes birth defects). This finding suggests that in addition to maintaining neural stem cells in a pre-differentiated state, the SMRT protein controls retinoic-acid induced differentiation and, when missing, abnormalities that mimic vitamin A exposure occur.

This finding provides scientists with one more important key to understanding how stem cells maintain their potential to grow into specific cells.

"Incremental steps such as this lay the groundwork for continuing studies investigating the potential of stem cells to be used therapeutically to replace damaged or deficient cells associated with disease," said Jepsen.

Co-authors of the *Nature* paper are Derek Solum, Ph.D., Tianyuan Zhou, Ph.D., Robert McEvilly, Ph.D. and Hyun-Jung Kim, Ph.D., of HHMI and UC San Diego; Christopher Glass, M.D., Ph.D., professor of cellular and molecular medicine at UC San Diego; Ola Hermanson, Ph.D. of the Karolinska Institutet in Sweden, and senior author Michael G. Rosenfeld, M.D., HHMI investigator and professor of medicine at UC San Diego.

Media Contact: Leslie Franz, 619-543-6163