Scientists produce functioning neurons from human embryonic stem cells

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Scientists with the Institute of Stem Cell Biology and Medicine at UCLA were able to produce from human embryonic stem cells a highly pure, large quantity of functioning neurons that will allow them to create models of and study diseases such as Alzheimer's, Parkinson's, prefrontal dementia and schizophrenia.

Researchers previously had been able to produce neurons - the impulse-conducting cells in the brain and spinal cord - from human embryonic stem cells. However, the percentage of neurons in the cell culture was not high and the neurons were difficult to isolate from the other cells.

UCLA's Yi Sun, an associate professor of psychiatry and biobehavioral sciences, and Howard Hughes Medical Institute investigator Thomas Südhof at the University of Texas Southwestern Medical Center were able to produce 70 to 80 percent of neurons in cell culture. Sun and Südhof also were able to isolate the neurons and determine that they had a functional synaptic network, which the neurons use to communicate. Because they were functional, the neurons can be used to create a variety of human neurological disease models.

The study results are published today in an early online edition of the peer-reviewed journal *Proceedings of the National Academy of Sciences*.

"Previously, the system to grow and isolate neurons was very messy and it was unknown whether those neurons were functioning," Sun said. "We're excited because we have been able to purify so many more

neurons out of the cell culture and they were, surprisingly, healthy enough to form synapses. These cells will be excellent for doing gene expression studies and biochemical and protein analyses."

Sun's method prodded human embryonic stem cells to differentiate into neural stem cells, the cells that give rise to neurons. When the time was right, Sun's team added protein growth factors into the cell culture that stopped the neural stem cells from self-renewing and prodded them into differentiating into neurons. To isolate the cells, Sun and her team added an enzyme that digests a sort of protein matrix that holds cells in culture together. The neurons could then be separated from the neural stem cells that had not yet differentiated, a sort of chemical round-up that isolated the neurons. The cells were then put into a cell strainer that allowed passage through of the isolated neurons.

The large number of pure neurons produced will allow Sun and her team to study their biological form and structure, the genes they express, the development of synapses and the electric and chemical communication activities within the synapse network.

"We will be able to study the cellular properties of neurons in a very defined way that will maybe tell us what goes wrong in diseases such as Alzheimer's and Parkinson's," Sun said. "We're currently creating many models of human neurological diseases that may provide the answers we're looking for. We don't know what causes prefrontal dementia, Huntington's disease or schizophrenia. The key is likely in the quality of neuronal communications. By studying the chemical and electrical transmissions, we may be able to determine what goes wrong that leads to these debilitating diseases and find a way to stop or treat it."

Sun will be among the first researchers to be able to study true neuron function.

A second important discovery in Sun's study showed that two embryonic stem cells lines derived in similar manners, and therefore expected to behave similarly when differentiating, did not. Using the same techniques to prod the two embryonic stem cells lines to differentiate, Sun found that one line had a bias to become neurons that are found in the forebrain. The other line differentiated into neurons found in rear portions of the brain and spinal cord. The finding was surprising, and significant, Sun said.

"The realization that not all human embryonic stem cell lines are born equal is critical," Sun said. "If you're studying a disease found in a certain part of the brain, you should use a human embryonic stem cell line that produces the neurons from that region of the brain to get the most accurate results from your study. Huntington's disease, for example, is a forebrain disease, so the neurons should be differentiated from a cell line that is biased to produce neurons from the forebrain."

Sun said there are ways to prod an embryonic stem cell line biased to become neurons found in the rear brain to become neurons found in the forebrain. However, there are limits to how much prodding can be done.

Sun and her team confirmed that the two embryonic stem cell lines were different through gene expression analysis – neurons that perform different functions in different parts of the brain express different genes. The cell line prone to becoming neurons found in the forebrain expressed genes typically found those neurons, while the other line expressed genes found in the rear brain and spinal cord.

Sun and her team now are studying why the two human embryonic stem cell lines have biases to become different types of neurons.

"If we knew that, we might be able to tweak or alter whatever is driving the bias so that limitation in the stem cell line could be bypassed," Sun

said.

Source: University of California - Los Angeles