UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

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UT Southwestern researchers create molecule that nudges nerve stem cells to mature

DALLAS – June 15, 2008 – Inspired by a chance discovery during another experiment, researchers at UT Southwestern Medical Center have created a small molecule that stimulates nerve stem cells to begin maturing into nerve cells in culture.

This finding might someday allow a person's own nerve stem cells to be grown outside the body, stimulated into maturity, and then re-implanted as working nerve cells to treat various diseases, the researchers said.

"This provides a critical starting point for neuro-regenerative medicine and brain cancer chemotherapy," said Dr. Jenny Hsieh, assistant professor of molecular biology and senior author of the paper, which appears online today and in the June 17 issue of *Nature Chemical Biology*.

The creation of the molecule allowed the researchers to uncover some of the biochemical steps that happen as nerve cells mature. It also showed that large-scale screening of compounds can provide starting points for developing drugs to treat disorders such as Huntington's disease, traumatic brain injury or cancer.

The scientists began this project as a result of a separate study in which they were screening 147,000 compounds to see which could stimulate stem cells cultivated from rodent embryos to become heart cells. Unexpectedly, five molecules stimulated the cells to transform into forms resembling nerve cells. The researchers then created a variation of these molecules, a new compound called Isx-9 (for isoxazole-9). Isx-9 was easier to use than its initially discovered relatives because it worked at a much lower concentration and also dissolved more easily in water.

"It was completely serendipitous that we uncovered this neurogenic [nerve-creating] small molecule," Dr. Hsieh said. "I think it's one of the most powerful neurogenic small molecules on the planet. In theory, this molecule could provoke full maturation, to the point that the new nerve cells could fire, generating the electrical signals needed for full functioning."

Nerve stem cells live in scattered groups in various areas of the brain. They are capable of becoming several different types of cells, not all of which are nerve cells.

In the study, rodent nerve stem cells from an area of the brain called the hippocampus were cultured with Isx-9. They clustered together and developed spiky appendages called neurites, which

(MORE)

typically happens when nerve cells are grown in culture.

Isx-9 also prevented the stem cells from developing into non-nerve cells and was more potent than other neurogenic substances in stimulating nerve-cell development. The molecule generated two to three times more nerve cells than other commonly used compounds.

Neuroscientists believed for decades that the adult mammalian brain could not grow new nerve cells. Instead, they thought, learning and memory were strictly a matter of the brain making new connections between existing cells.

It is now known, however, that the brain constantly creates new nerve cells. In the hippocampus, which is involved with learning and memory, stem cells mature into full-blown nerve cells at a rate of thousands a day, Dr. Hsieh said.

Scientists know that when a mature nerve cell sends a chemical signal called a neurotransmitter to a stem cell, the immature cell begins to mature, but they don't know what biochemical pathways or genes are involved, Dr. Hsieh said.

"The big gap in our knowledge is how to control these stem cells," she said.

Isx-9 appeared to act like a neurotransmitter-like signal on the nerve stem cells, the researchers found. By culturing the stem cells with the compound, the scientists identified a possible biochemical pathway by which stem cells begin to become nerve cells.

The researchers next plan to test Isx-9 on a large number of different combinations of RNA, the chemical cousin of DNA, to see on which genes the compound might be working. They have also applied for a patent on Isx-9 and its relatives.

Other UT Southwestern researchers involved in the study were Dr. Jay Schneider, assistant professor of internal medicine; Dr. Zhengliang Gao, postdoctoral researcher in molecular biology; Dr. Shijie Li, postdoctoral researcher in molecular genetics; Midhat Farooqi, a student in the Medical Scientist Training Program; Dr. Tie-Shan Tang, instructor of physiology; Dr. Ilya Bezprozvanny, professor of physiology; and Dr. Douglas Frantz, assistant professor of biochemistry.

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