Scientists grow critical nerve cells

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After years of trial and error, scientists have coaxed human embryonic stem cells to become spinal motor neurons, critical nervous system pathways that relay messages from the brain to the rest of the body. The new findings, reported online Jan. 30, 2005 in the journal Nature Biotechnology by scientists from the University of Wisconsin-Madison, are important because they provide critical guideposts for scientists trying to repair damaged or diseased nervous systems.

Motor neurons transmit messages from the brain and spinal cord, dictating almost every movement in the body from the wiggling of a toe to the rolling of an eyeball. The new development could one day help victims of spinal-cord injuries, or pave the way for novel treatments of degenerative diseases such as amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. With healthy cells grown in the lab, scientists could, in theory, replace dying motor neurons to restore function and alleviate the symptoms of disease or injury.

Much sooner in the future, the advance will allow researchers to create motor neuron modeling systems to screen new drugs, says study leader Su-Chun Zhang, an assistant professor of anatomy and neurology in the Stem Cell Research Program at the Waisman Center at UW-Madison.

Scientists have long believed in the therapeutic promise of embryonic stem cells with their ability to replicate indefinitely and develop into any of the 220 different types of cells and tissues in the body.

But researchers have struggled to convert blank-slate embryonic stem cells into motor neurons, says Zhang. The goal proved elusive even in simpler vertebrates such as mice, whose embryonic stem cells have been available to scientists for decades.

One reason scientists have had difficulty making motor neurons, Zhang believes, may be that they are one of the earliest neural structures to emerge in a developing embryo. With the ticking clock of development in mind, Zhang and his team deduced that there is only a thin sliver of time - roughly the third and fourth week of human development - in which stem cells could be successfully prodded to transform themselves into spinal motor neurons.

In addition to the narrow time frame, it was also critical to expose the growing stem cells to an array of complex chemical cocktails. The cocktails constitute naturally secreted chemicals - a mix of growth factors and hormones - that provide the exact growing conditions needed to steer the cells down the correct developmental pathway. "You need to teach the [embryonic stem cells] to change step by step, where each step has different conditions and a strict window of time," says Zhang. "Otherwise, it just won't work."

To differentiate into a functional spinal motor neuron, the stem cells advanced through a series of mini-stages, each requiring a unique growing medium and precise timing. To start, the Wisconsin team generated neural stem cells from the embryonic stem cells. They then transformed the neural cells into progenitor cells of motor neurons, which in turn developed in a lab dish into spinal motor neuron cells.

The newly generated motor neurons, according to Zhang, exhibit telltale electrical activity, a sign that the neurons, which normally transmit electrical impulses, were functional.

The spinal motor neuron cells have survived in culture in the lab for more than three months, says Xuejun Li, an assistant scientist in Zhang's group, and the lead author of the study.

To determine the exact recipe for motor neuron growth, Li foraged labs worldwide to obtain the growth factors and other natural chemicals needed to guide cells from one stage of motor neuron development to another. But once past a certain point, Li found that the cells kept veering off toward different cellular destinies. After hundreds of unsuccessful variations of growth factors and morphogens, Li was struck by an idea: Why not apply a chemical known to be necessary for a later stage of neuron development to a much earlier step in the process?

The hunch paid off and turned out to be the final piece of the puzzle.

The discovery, says Zhang, demonstrates that human stem cells do not necessarily differentiate in linear fashion, as scientists always believed. Rather, a series of complex overlapping changes may well be the developmental norm in higher vertebrates such as humans.

"We cannot simply translate studies from animal to humans," says Zhang.

The next step, Li says, will be to test if the newly generated neurons can communicate with other cells when transplanted into a living animal. The team will first test the neurons in chicken embryos.

While the new results are promising and provide access to critical cells that may one day be used in therapy, it will likely be many years before they can be tested in humans, Zhang says.

Source: University of Wisconsin-Madison