

Nerve cells derived from stem cells and transplanted into mice may lead to improved brain treatments

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Scientists at the Burnham Institute for Medical Research have, for the first time, genetically programmed embryonic stem (ES) cells to become nerve cells when transplanted into the brain, according to a study published today in *The Journal of Neuroscience*. The research, an important step toward developing new treatments for stroke, Alzheimer's, Parkinson's and other neurological conditions showed that mice afflicted by stroke showed tangible therapeutic improvement following transplantation of these cells. None of the mice formed tumors, which had been a major setback in prior attempts at stem cell transplantation.

The team was led by Stuart A. Lipton, M.D., Ph.D., professor and director of the Del E. Webb Neuroscience, Aging, and Stem Cell Research Center at Burnham. Dr. Lipton is also a clinical neurologist who treats patients with these disorders. Collaborators included investigators from The Scripps Research Institute.

"We found that we could create new nerve cells from stem cells, transplant them effectively and make a positive difference in the behavior of the mice," said Dr. Lipton. "These findings could potentially lead to new treatments for stroke and neurodegenerative diseases such as Parkinson's disease."

Conditions such as stroke, Alzheimer's, Parkinson's and Huntington's

disease destroy brain cells, causing speech and memory loss and other debilitating consequences. In theory, transplanting neuronal brain cells could restore at least some brain function, just as heart transplants restore blood flow.

Prior to this research, creating pure neuronal cells from ES cells had been problematic as the cells did not always differentiate into neurons. Sometimes they became glial cells, which lack many of the neurons' desirable properties. Even when the neuronal cells were created successfully, they often died in the brain following transplant—a process called programmed cell death or apoptosis. In addition, the cells would sometimes become tumors.

Dr. Lipton solved these problems by inducing ES cells to express a protein, discovered in his laboratory called myocyte enhancer factor 2C (MEF2C). MEF2C is a transcription factor that turns on specific genes which then drive stem cells to become nerve cells. Using MEF2C, the researchers created colonies of pure neuronal progenitor cells, a stage of development that occurs before becoming a nerve cell, with no tumors. These cells were then transplanted into the brain and later became adult nerve cells. MEF2C also protected the cells from apoptosis once inside the brain.

"To move forward with stem cell-based therapies, we need to have a reliable source of nerve cells that can be easily grown, differentiate in the way that we want them to and remain viable after transplantation," said Dr. Lipton. "MEF2C helps this process first by turning on the genes that, when expressed, make stem cells into nerve cells. It then turns on other genes that keep those new nerve cells from dying. As a result, we were able to produce neuronal progenitor cells that differentiate into a virtually pure population of neurons and survive inside the brain."

The next step was to determine whether the transplanted neural

progenitor cells became nerve cells that integrated into the existing network of nerve cells in the brain. Performing intricate electrical studies, Dr. Lipton's investigative team showed that the new nerve cells, derived from the stem cells, could send and receive proper electrical signals to the rest of the brain. They then determined if the new cells could provide cognitive benefits to the stroke-afflicted mice. The team executed a battery of neurobehavioral tests and found that the mice that received the transplants showed significant behavioral improvements, although their performance did not reach that of the non-stroke control mice. These results suggest that MEF2C expression in the transplanted cells was a significant factor in reducing the stroke-induced deficits.

Source: Burnham Institute

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