Stem cell study reveals cells' capability in mouse brain tissue repair

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UCSF scientists have determined that adult stem cells in a specific region of the mouse brain have a built-in mechanism that allows the cells to participate in the repair and remodeling of damaged tissue in the region.

As the cells are also present in the human brain, the same capacity or potential may exist in humans, the researchers say. If they do, it is possible that the cells' behavior could be enhanced to treat tissues damaged throughout the brain by disorders such as stroke and traumatic injury.

The study, reported in the December 15 issue of *Cell*, was led by Chay T. Kuo, MD, PhD, a UCSF postdoctoral fellow in the laboratory of senior investigator Yuh-Nung Jan, PhD.

Kuo is one of 16 UCSF CIRM Stem Cell Scholars – up and coming young scientists funded by the California Institute for Regeneration Medicine, established by California voters in 2004 to allocate $3 billion over 10 years to support stem cell research.

"The results were very surprising," says Kuo. "Our results show that neural stem cells in mice have the ability to sense damage in their environment that leads to their subsequent proliferation to help restore local tissue integrity. If we can figure out how this happens, and determine that it occurs in human neural stem cells, we may be able to increase the effect and harness it for therapeutic use."

Understanding this proliferative capacity during environmental change is critical, he says, as adult neural stem cells in this region may sometimes proliferate out of control to form brain tumors. This possibility has been reported and is being explored by scientists in the UCSF Institute for Regeneration Medicine and UCSF Department of Neurological Surgery.

The scientists focused their study on postnatal neural stem cells that lie next to the lining of the brain's lateral ventricles, or cavity, in a region known as the subventricular zone (SVZ). In 1999, the lab of study co-author Arturo Alvarez-Buylla, PhD, UCSF Heather and Melanie Muss Professor of Neurological Surgery, discovered that cells in this region known as astrocytes function as adult neural stem cells in mice (Cell, June 11, 1999) and later discovered similar cells within the human brain (Nature, Feb. 19, 2004). The cells are recognized as a major source of adult stem cells in the mammalian brain.

Scientists have known that neural stem cells play a key role in both embryonic and postnatal mice, driving the development of specialized cells within the brain such as neurons, astrocytes, oligodendrocytes, and ependymal cells. And they have identified many of the molecular pathways that control neural stem cell behavior in embryonic mice.

But relatively little was known about the molecular programs that control neural stem cells in the postnatal mouse, or how neural stem cells may respond to tissue damage -- two key questions for scientists exploring the potential of these cells to treat disease.

To shed light on these issues, Kuo and his colleagues genetically engineered neural stem cells and ependymal cells in the SVZ of newborn mice in such a way that they lacked two key proteins, named Numb and Numblike.

These proteins are known to play a critical role in maintaining neural

stem cell function in embryonic mice, but scientists have not known their actual function. They suspected that the proteins might be active in the SVZ of postnatal mice as well. If so, they reasoned, preventing the proteins' synthesis might inhibit the cells' local activity and, in so doing, reveal their postnatal function. At the same time, if the cells' activity was inhibited by the absence of the proteins, there could be tissue damage in the SVZ, providing a model for exploring the way in which the neural stem cells responded to it.

The strategy paid off.

Kuo and his colleagues' examination of postnatal mouse brains on autopsy seven and 14 days after the genetic modification revealed that absence of proteins Numb and Numblike led to severe brain ventricle enlargement. This defect resulted from damage of ependymal cells, which form the epithelial lining of the brain ventricles, and of neuroblasts, which evolve into neurons. Thus, it was evident that, as in embryonic mice, the proteins play a crucial role in the maintenance of cells in the region, and revealed a previously unknown function for them in assuring ependymal layer integrity.

Wholly unexpected, however, was the fact that damage to the left ventricular wall was substantially repaired when these sick mice were examined six weeks later. As a result of a known limitation of the genetic engineering technique that Kuo employed – some neural stem cells escaped gene deletion, thus allowing the Numb protein they synthesized to remain intact – some neural stem cells had continued to function. Faced with damage in the region, these cells had responded, mediating the rebuilding of ventricular wall lining and establishing a modified neural stem cell environment.

The scientists do not know the precise mechanisms by which the stem cells carried out their response. But it was astonishing, says study senior

investigator Jan, who is , a Howard Hughes Medical Institute investigator, the Jack and DeLoris Lange Endowed Chair in Molecular Physiology and professor of physiology and biochemistry at UCSF.

"The holes that had formed in the brain ventricular wall had largely been repaired. These adolescent mice looked quite good. The finding shows that the brain has the ability to repair itself and that it is more plastic than previously appreciated."

The model Kuo devised, says Jan, will provide a powerful tool for studying the response of neural stem cells of the SVZ to damage caused by such conditions as stroke and trauma.

It can also be used to test the impact of deleting various genes from neural stem cells of the SVZ. The results, he says, would contribute to scientists' understanding of the full pathway of genes needed to prompt differentiation of neural stem cells both in the brain and in the culture dish. In this sense, he says, "the deletion of Numb and Numblike was a test case."

In collaboration with other UCSF neuroscientists, as well as neurosurgeons, Kuo is currently exploring whether neural stem cells of the SVZ can respond to damage outside the ventricle region and, if so, whether inflammation in the traumatized area prevents the stem cells from restoring the tissue.

And he wonders whether the epilepsy that can occur in stroke and trauma patients, often years after the injury, results from unsuccessful attempts by the progeny of neural stem cells to make synaptic connections with other cells in the damaged region.

Numerous other UCSF labs are also investigating neural stem cells in the SVZ of the embryonic and postnatal brain, with an eye toward

developing therapies for Parkinson's, epilepsy and ALS, says Arnold Kriegstein, MD, PhD, the John G. Bowes Endowed Chair in Stem Cell and Tissue Biology and director of the UCSF Institute for Regeneration Medicine.

And like the neural stem cells they study, these scientists are collaborating, making connections aimed at building new material. "As such," says Kriegstein, "their work demonstrates the power of synergy."

Source: University of California - San Francisco