Stem cell research reveals myelin repair capacity

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**Improved brain recovery in mouse models shows possible treatment pathways for diseases like cerebral palsy, multiple sclerosis**

(SACRAMENTO, Calif.) — Using genetically engineered stem cells, UC Davis researchers have identified brain cell interactions that offer a possible pathway to developing therapies for human myelin diseases such as cerebral palsy and multiple sclerosis.

Wenbin Deng

In [a study published today in *Cell Reports*](http://www.cell.com/cell-reports/fulltext/S2211-1247%2816%2930410-7), [Wenbin Deng](http://www.ucdmc.ucdavis.edu/biochem/faculty/deng/)and his colleagues present data showing that immature astroglial transplants, derived from human-induced pluripotent stem cells (iPSCs), are highly protective against white matter brain injury – which can occur from lack of oxygen following a stroke or in childbirth – and can improve spatial learning and memory function in mouse models.

“This work has far-reaching implications in understanding the pathogenesis of white matter injury and is an important step toward developing treatment strategies based on astrocyte replacement,” said Deng, principal investigator of the study and associate professor in the [UC Davis Department of Biochemistry and Molecular Medicine](http://www.ucdmc.ucdavis.edu/biochem/).

The white matter of the brain underlies the thinner outer layer of gray matter on the brain’s surface. White matter chiefly contains axons, the long projections of neurons whose cell bodies are contained in the gray matter. The axons are surrounded by myelin – white insulating sheaths that are essential to the efficient transmission of nerve impulses.

Astrocytes (also known as astroglia) are star-shaped cells in the brain and spinal cord that are present in both gray and white matter. Originally thought to have merely a structural support function, astrocytes are now understood to be important regulators of neuron development and function. They are believed to act on oligodendrocytes, which are myelin-producing cells.

Astrocytes undergo a long maturation process during development. After an injury to the brain, such as may result from oxygen deprivation from a stroke or during birth, early or immature astrocytes are believed to protect oligodendrocytes, allowing them to proliferate and continue to produce myelin. But mature astrocytes are thought not to have these protective qualities, and if they are predominantly present, nonfunctional scars form in brain tissue after injury.

Because of the neuroprotective effects of immature astrocytes, the research team explored their potential to play a role in repair following injury.

The UC Davis researchers first generated immature astrocytes from human iPSCs and induced some to mature. They then compared the effects of immature astrocytes and mature astrocytes on myelin-producing oligodendrocytes. In cell culture, they found that immature astrocytes were much better able to promote proliferation of oligodendrocytes than the mature astrocytes. In addition, the investigators for the first time identified a factor secreted by immature astrocytes, tissue inhibitor of metalloproteinase-1 (TIMP-1), as important to astrocytes’ effects on oligodendrocytes.

The researchers next implanted immature astrocytes in mouse models of white matter damage from low blood flow. After four days, they observed that the density of myelinated axons was significantly higher in mice that received the astroglial implant that secreted TIMP-1.

If TIMP-1 secretion by astrocytes was inhibited before implantation, the positive effects on myelination did not occur, further implicating this factor as important to immature astrocytes’ protective influence.

The team next concentrated the factors collected from the immature IPSC-derived astrocytes – including TIMP-1 – and delivered them intra-nasally (through the nose) to the mouse models, which the researchers found was a sufficient pathway to promote proliferation of oligodendrocytes in the brain.

The investigators also studied how implanting immature astrocytes after brain injury affected spatial learning and memory.  Using a Morris water navigation test, they found that treated mice performed significantly better than the control group without implanted astrocytes.

“We believe that the human iPSC technology may one day be applied to patients and change the standard of care for treating central nervous system disorders in which myelin loss plays an important role,” Deng said. “We are hopeful that his could lead to a promising therapy for premature brain injury, cerebral palsy, multiple sclerosis, spinal cord injury, white matter stroke and many neurodegenerative diseases.”

The paper is titled, [“Human iPSC-Derived Immature Astroglia Promote Oligodendrogenesis by Increasing TIMP-1 Secretion.”](http://www.cell.com/cell-reports/fulltext/S2211-1247%2816%2930410-7)

Joining Deng in the study were first author Peng Jiang, along with Chen Chen, Xio-Bo Liu, David E Pleasure, all from UC Davis, and Ying Liu, from the University of Texas Health Science Center. Shenglan Li assisted with gene expression analysis.

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