

Stem cells used to create critical brain barrier in lab

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Using neural stem cells derived from the fetal brains of rats, a team of Wisconsin scientists has devised a rudimentary blood-brain barrier in the lab.

Writing this week (Dec. 19) in the online editions of the *Journal of Neurochemistry*, a group led by University of Wisconsin-Madison professor of chemical and biological engineering Eric V. Shusta describes an experiment in which nascent rat neural stem cells were used to prod blood vessel cells to assume properties of the blood-brain barrier.

The blood-brain barrier is an anatomical feature in humans and other animals that protects the brain from chemicals and other harmful agents, but also limits the ability of clinicians to administer helpful drugs. It is a feature that can succumb to diseases such as Alzheimer's or acute conditions such as stroke, which can leave the brain vulnerable.

The blood-brain barrier is a critically important structure, Shusta says. Not only does it physically block the movement of substances between blood and brain, but it also possesses active properties that enable cells to pump unwanted molecules from cells back into the bloodstream. What's more, it has a metabolic function that can alter the chemical properties of the molecules that do get through to the brain.

"It dictates traffic in and out of the brain," Shusta explains.

Demonstrating that developing brain cells can release factors that may

coax small blood vessels to exhibit the properties of the blood-brain barrier is important for a number of reasons. First, it forms a basis for understanding the mechanism that provides critical protection for the brain. Second, it may lead to insights regarding ways to overcome a barrier that frustrates neuroscientists, drug companies and clinicians who would like to sneak drugs past it to treat disease.

"What we have shown is that these neural stem cells have the ability to stimulate adult blood vessel endothelial cells to display enhanced blood-brain barrier properties," Shusta says. "This may lead to new in-vitro models of the blood-brain barrier."

That in turn may help researchers devise new therapies to treat brain disease and to form a clear understanding of how the barrier forms during the course of development.

"One of the big questions of (brain) development is how does the blood-brain barrier form and when does it form," says Shusta. "That's poorly understood."

The Wisconsin team, which includes UW-Madison School of Medicine and Public Health professor and stem cell authority Clive Svendsen, used brain stem cells grown as "neurospheres" to coax brain endothelial cells — flat cells that line blood vessels — to form a tighter, more dense barrier to small molecules that would otherwise diffuse through the blood vessel cells.

What is curious, according to Shusta and Svendsen, is that during development, brain endothelial cells form an enhanced barrier in the complete absence of astrocytes, a mature type of cell that serves as the two-by-four of the brain, but which do not appear in great numbers until birth. Astrocytes provide both structural support and are critical to the maintenance of the adult blood-brain barrier.

"One of the things we found is that the neural stem cells had a significant effect on the development of blood-brain barrier properties in the absence of astrocytes," Svendsen says. "It is possible these cells take on the role of astrocytes in early development and may be very important for establishing the initial barrier prior to the astrocytes taking over and completing the barrier."

The new work was accomplished by culturing endothelial cells in concert with the neurospheres. Somehow, the neurospheres prompted the endothelial cells to form tighter, denser cell-to-cell junctions, enhancing their ability to form a barrier and exclude small chemical molecules from passing through, a hallmark of the blood-brain barrier.

Using neural stem cells, Svendsen argues, provides a new way to assess how the barrier forms in early development, insight that might provide clues about how to mend the barrier when it is broken through disease or events such as stroke.

"Could neural progenitor cells or stem cells have a role in forming the blood-brain barrier after damage or disease? The answer seems to be yes," says Svendsen.

The team will next try to produce similar results using human endothelial cells and neural stem cells. "That would be very exciting," Svendsen acknowledges. "We don't have a good model for a human blood-brain barrier."

Development of a human model, presumably, would be of enormous interest to researchers and pharmaceutical companies as many promising drugs are composed of molecules too big to pass through the human barrier and thus cannot be used in the clinic.

Source: University of Wisconsin-Madison

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