Scientists use blood-brain barrier as therapy delivery system

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This image shows the high density of blood vessels in the brain and the close proximity of brain cells to those vessels. A cut-away of one blood vessel shows vessel lining cells (endothelia -- red). Davidson and colleagues transformed these cells into enzyme production factories and showed that enzyme produced there entered the brain and corrected diseased cells. Credit: Mary Moye-Rowley

The blood brain barrier is generally considered an obstacle to delivering therapies from the bloodstream to the brain. However, University of Iowa researchers have discovered a way to turn the blood vessels surrounding brain cells into a production and delivery system for getting therapeutic molecules directly into brain cells.

Working with animal models of a group of fatal neurological disorders called lysosomal storage diseases, the UI team found that these diseases cause unique and disease-specific alterations to the blood vessels of the blood brain barrier. The scientists used these distinct alterations to target the brain with gene therapy, which reversed the neurological damage caused by the diseases.

The findings, which were published Sept. 13 in Nature Medicine's Advance Online Publication (AOP), could lead to a new non-invasive approach for treating neurological damage caused by lysosomal storage diseases.

"This is the first time an enzyme delivered through the bloodstream has corrected deficiencies in the brain," said lead investigator Beverly Davidson, Ph.D., UI professor of internal medicine, neurology, and molecular physiology and biophysics. "This provides a real opportunity to deliver enzyme therapy without surgically entering the brain to treat lysosomal storage diseases.

"In addition, we have discovered that these neurological diseases affect not just the brain cells that we often focus on, but also the blood vessels throughout the brain. We have taken advantage of that finding to delivery gene therapy, but we also can use this knowledge to better understand how the diseases impact other cell types such as neurons," she added.

Lysosomal storage diseases are individually quite rare, but as a group they affect approximately 1 in 8,000 live births. The diseases are caused by deficiencies in enzymes that break down larger molecules. Without these enzymes, the large molecules accumulate inside cells and cause cell damage and destruction.

Enzyme replacement therapy has been successful in treating one form of

lysosomal storage disease called Gaucher disease. However, storage diseases that affect the central nervous system remain untreatable because it has not been possible, to this point, to get the missing enzymes past the blood-brain-barrier and into the brain.

"Our discovery allowed us to test the idea that the brain cells might be able to make use of the reintroduced enzyme to stop or reverse the damage caused by the accumulated materials," said Davidson, who also is the Roy J. Carver Professor in Internal Medicine. "In the treated mice, the affected brain cells go back to looking normal, the brain inflammation goes away and the impaired behaviors that these mice have is corrected."

To develop their gene therapy targeting system, Davidson and colleagues used a technique called phage panning to identify peptides that hone in on the blood vessels surrounding the brain. Surprisingly, they found that peptides that targeted the brain blood vessels in mice with lysosomal storage diseases were distinct from the peptides that targeted brain blood vessels in healthy mice. Moreover, the peptides that targeted blood vessels in different diseases were distinct from each other, suggesting that each disease causes specific alterations to the blood vessels.

The team modified a deactivated virus used for gene therapy so that the virus expressed copies of the unique brain-targeting peptide on its outer coat, and also carried the genetic blueprint for the missing enzyme.

The study showed that the modified virus targeted the blood vessels in the brain and caused the blood vessel cells to produce the enzyme. Most importantly, the researchers found that the enzyme was secreted into the brain tissue in sufficient quantities to correct the disease symptoms and problems.

The team was able to use this approach to treat two types of lysosomal

storage disease in mice, suggesting that the approach could be used for other types of lysosomal storage disease and possibly other neurological disorders.

Source: University of Iowa (news : web)