MS study offers theory for why repair of brain's wiring fails

July 1 2009

Scientists have uncovered new evidence suggesting that damage to nerve cells in people with multiple sclerosis accumulates because the body's natural mechanism for repair of the nerve coating called "myelin" stalls out.

The study, published today, July 1, 2009, in the print edition of "*Genes & Development*," was conducted by scientists at the University of California, San Francisco and University of Cambridge. The research was led by co-senior investigator David Rowitch, MD, PhD, a Howard Hughes Medical Institute investigator at UCSF.

The investigation, conducted in mice and in human tissue, showed that repair of nerve fibers is hampered by biochemical signals that inhibit the development of cells known as oligodendrocytes, which function as repair workers in the brain.

Oligodendrocytes form a protective sheath, known as myelin, that insulates the fibrous cables, or axons, radiating from nerve cells. In multiple sclerosis, the immune system's T cells and B cells attack oligodendrocytes, ultimately damaging the myelin sheath to the point that the electrical signals transmitted by the axons beneath it are disrupted.

Remarkably, the brain generally is able to recruit fresh, immature oligodendrocytes to the myelin sheath to repair the damage, for a time. This explains why, in the most common form of the disease, known as

relapsing remitting MS, the symptoms -- which range from tingling and numbness in the limbs to loss of vision and paralysis -- disappear or are greatly reduced, for some times months or years at a time.

Ultimately, however, the repair process falters and the disease progresses. In their study, the team set out to see if they could determine what was slowing down myelin repair. They lesioned a small region of white matter in healthy mice, then monitored the repair process, examining the tissue after five, 10, and 14 days.

To find out which genes were contributing to three key stages in the repair process - the recruitment of oligodendrocyte precursors to the site of injury, the maturation of those cells into functional oligodendrocytes, and the formation of a new myelin sheath -- they measured the activity of 1,040 genes. All of the genes they studied encode transcription factors, which regulate the activity of other genes. Their experiments showed that 50 transcription factors are working during key steps in myelin repair.

The team then honed in on a gene called Tcf4, because its expression was strong in damaged areas where repair attempts were under way.

Tcf4 is involved in a cascade of biochemical events known as the Wnt (pronounced "wint") pathway, whose importance has been well recognized in normal development of many tissues, including the brain. Until now, however, Wnt had not been linked to myelin production or repair.

"This is the first evidence implicating the Wnt pathway in multiple sclerosis," says lead author Stephen P.J. Fancy, PhD, a postdoctoral fellow in the Rowitch lab. "We consider this an exciting development in our efforts to understand why the repair process often fails in the disease."

To glean further evidence about Wnt's role, the researchers hyperactivated the Wnt pathway in the oligodendrocytes of mice, which caused a profound delay in repair. Further analysis suggested that the Wnt pathway activation was creating a roadblock that prolonged oligodendrocyte precursor development.

"While the animals eventually showed repair, it was delayed compared to normal mice," says Fancy. The researchers also tested human tissue for the presence of Tcf4, and found the protein in areas damaged by MS but not in healthy white matter. Further, the researchers examined available data from another study and found that many signaling molecules of the Wnt pathway are overactive in lesions of patients with MS.

"This is an important step that we hope will lead to targeted therapies involving the repair process," says co-senior author Robin Franklin of the University of Cambridge.

Now the team is starting to examine some of the other genes it found to be active in the myelin repair process, and is developing new mouse models to help test potential therapies that might manipulate the Wnt pathway to improve myelin repair. Given the pathway's role in so many different processes, however, Rowitch cautioned that targeting Wnt could cause unintended side effects.

The new work may also have implications for another neurological disease, periventricular leukomalacia, which can lead to cerebral palsy in extremely premature infants, says Rowitch. Recent studies by Rowitch and colleagues show a similar inability of oligodendrocytes to perform their important repair function.

"The researchers have made an encouraging finding that could open a new window into the cause of failed neural repair in multiple sclerosis," says Dr. Patricia O'Looney, Vice President of BioMedical Research at

the National Multiple Sclerosis Society. "Understanding such mechanisms should help advance the efforts to find valuable treatments for this debilitating disease."

Source: University of California - San Francisco

Citation: MS study offers theory for why repair of brain's wiring fails (2009, July 1) retrieved 6 May 2024 from https://medicalxpress.com/news/2009-07-ms-theory-brain-wiring.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.