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Multiple Sclerosis: A New Theory for Why Repair of the Brain's Wiring Fails

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

The new research, published by Howard Hughes Medical Institute investigator David H. Rowitch and colleagues in the July 2009 issue of the journal *Genes & Development*, shows that repair of nerve fibers is hampered by biochemical signals that inhibit cellular repair workers in the brain, called oligodendrocytes.

The symptoms of MS, which range from tingling and numbness in the limbs to loss of vision and paralysis, develop when nerve cells lose their ability to transmit a signal. Axons, which are the fibrous cables radiating from nerve cells, transmit impulses to neighboring neurons. They are dependent on myelin, which protects nerve cells and helps transmit their electrical signals properly. In people with MS, immune cells attack and erode this protective layer of myelin. In the early stages of the disease, damage accumulates in the myelin sheath only, but it does not affect the nerve cells themselves. Later on, axons without myelin and the nerve cells themselves die.

Although damaged myelin can usually be repaired, in some people with MS the repair effort is inefficient, said Rowitch, who is at the University of California, San Francisco. This could be because oligodendrocytes themselves might not work properly, or they may be killed off by the disease. Rowitch explained that in chronically demyelinated areas of the central nervous system, oligodendrocyte precursor cells have been found, but they appear stalled in development and never become fully functional oligodendrocytes.

Rowitch and his team set out to see if they could determine what was slowing down myelin repair. With colleagues at UCSF and the University of Cambridge in England, Rowitch destroyed a small region of white matter in the spinal cords of 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 -- the researchers 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.

“They turned on and off at particular time points associated with recognized stages of the repair process, such as recruitment of repair cells back into the lesion, early differentiation [of the precursor cells into more specialized cells], and then myelin production,” said Rowitch.

The team focused, in particular, on one of the genes called Tcf4. In damaged areas where repair attempts were under way, expression of Tcf4 was strong, Rowitch said.

Tcf4 is involved in a cascade of biochemical events known as the Wnt (pronounced “wint”) pathway. While the pathway’s importance has been recognized in normal development of many tissues, including the brain, Rowitch said Wnt had never before been linked to myelin production or repair.

To glean further evidence about Wnt’s role, the researchers hyperactivated the Wnt pathway in the oligodendrocytes of mice, testing whether this helped or hurt myelin repair. Doing so caused a profound delay in repair, Rowitch said. Upon further analysis, the researchers concluded that the Wnt pathway activation was creating a roadblock that prolonged oligodendrocyte precursor development.

“These animals did eventually show repair,” Rowitch said, “but it was delayed by about 10 days compared to normal mice.” 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 patients with MS.

Rowitch’s 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 in another disease Rowitch studies—periventricular leukomalacia (PVL), a deficiency of white matter around the brain’s ventricles, which connect to the central canal of the spinal cord. PVL usually occurs in extremely premature infants with brain injury, who often go on to develop cerebral palsy.

Although scientists had previously believed PVL resulted when oligodendrocytes were killed off by stress or toxic injury, Rowitch and colleagues at Children's Hospital in Boston recently found that, as in the MS study, oligodendrocyte precursors had been recruited to the site of white matter lesions and stood poised to repair the damage, but for some reason did not proceed.