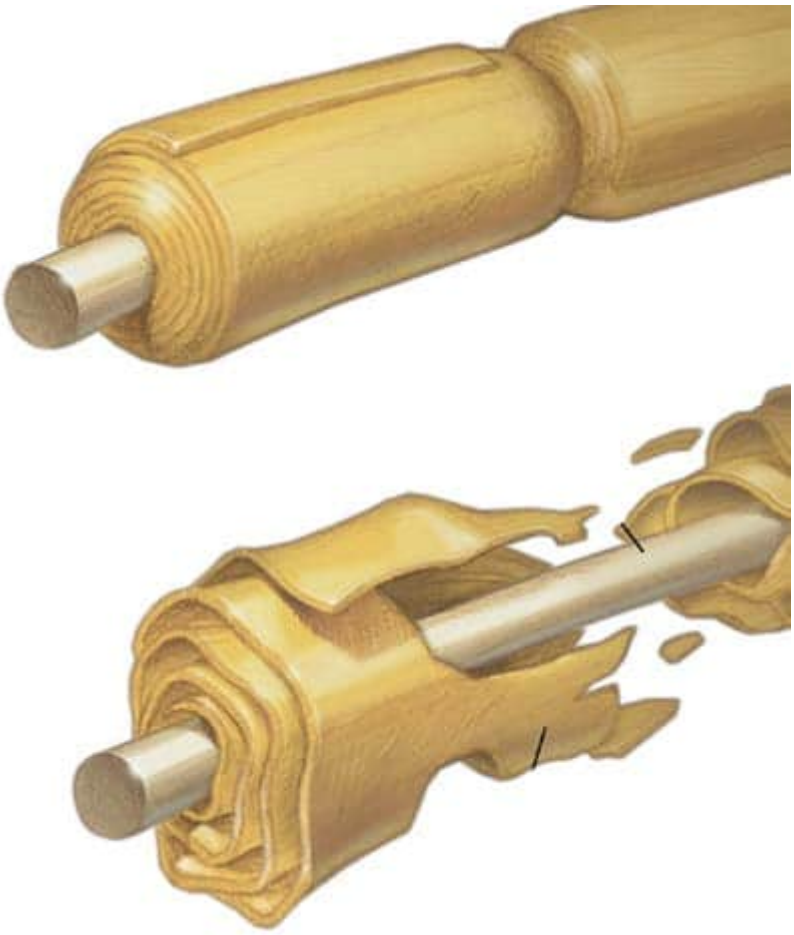
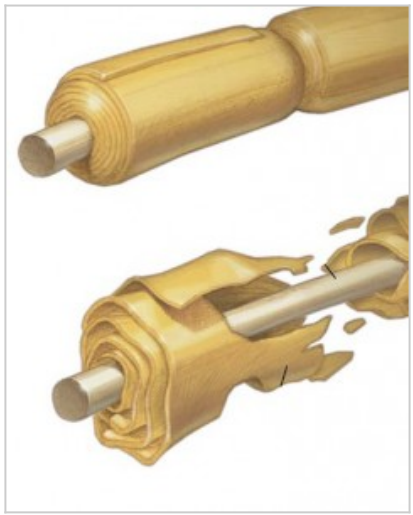
Jumpstarting myelin repair



Understanding why remyelination stops could lead to new treatments

by Mary E. King, PhD



Top image shows a normal nerve. Bottom image shows nerve affected by MS. Illustration courtesy of Mayo Foundation for Education and Research

Multiple sclerosis researchers are hot on the trail of why myelin repair sometimes works—and sometimes doesn't.

Myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord, and increases the speed of signals transmitted through the nerves, is lost in the immune attacks that are characteristic of multiple sclerosis. This immune inflammation also damages oligodendrocytes, the type of cell that manufactures and repairs myelin.

"What we know is that the adult human brain has the ability to repair myelin," says Bruce Trapp, PhD, chair of the Department of Neurosciences at the Lerner Research Institute, part of the Cleveland Clinic. He adds that this repair, called remyelination, can occur in individuals with MS, but "the problem is that remyelination often fails. One of the goals of MS research is to determine why remyelination fails in some instances and why it succeeds in others."

Dr. Trapp studies slices of brain that he obtains through a special rapid autopsy program in the Cleveland area that enables people with MS to donate their brains and spinal cords to his research at their death.

Some of his recent work has focused on lesions that extend across both white matter (which contains a lot of myelin and whose lesions can be seen on a standard MRI scan) and gray matter (which has less myelin and whose lesions cannot be seen on an MRI scan). By directly comparing the different portions of the same lesions, "it was very clear that gray matter has a greater repair capacity than white matter. Analyzing these lesions gives us the possibility to determine what inhibits repair and what enhances repair," he states.

Dr. Trapp and colleagues have now identified specific molecules produced in the white matter lesions that inhibit repair. If a therapy can be developed that stops the production of these molecules in the human brain, it could eventually be used in conjunction with immune-modulating therapies that inhibit damage.

Dr. Trapp will also investigate whether there are molecules in the gray matter that do the opposite—that is, promote remyelination. Perhaps, he theorizes, the slowdown in remyelination in MS is caused by both the production of molecules that inhibit repair and a reduction in the normal amounts of molecules that promote repair.

Removing a block

Larry Sherman, PhD, a professor of cell and developmental biology at the Oregon Health & Science University and senior scientist at an affiliated institution, the Oregon National Primate Research Center, was the first to identify the accumulation of a specific molecule, hyaluronic acid (HA), in areas of myelin damage in mice with an MS-like disease, called experimental autoimmune encephalomyelitis, or EAE.

“Whenever it built up in areas of the EAE mouse brain, HA seemed to prevent precursor cells from becoming new oligodendrocytes [that are] necessary for remyelination to occur,” Dr. Sherman explains. (Precursor cells are cells that can become oligodendrocytes under the right conditions.)

Further research in his laboratory revealed that the breakdown byproducts of HA, not the intact HA molecule, are responsible for slowing remyelination. In addition, the enzyme that breaks down HA is only seen in demyelinated lesions in brains from people affected by MS and in mouse brains affected by EAE, not in healthy brains. So Dr. Sherman decided to try to block the breakdown of HA by inhibiting the enzyme. His laboratory used a drug that does exactly this. When the researchers gave the drug to mice (using a different mouse model of MS), remyelination increased. “This was remarkable—not only did we see myelin coming back, but we saw evidence of functional myelin with increased speed of nerve conduction.”

Unfortunately, the drug that works in the mouse model would be too toxic to use in humans. The next phase of research, Dr. Sherman explains, is to identify other, less toxic agents that specifically block the enzyme that breaks down HA in MS lesions.

If the research team can identify a candidate medication that works in both mouse cells grown in tissue culture and in a live mouse model of MS, it will then be tested further in a novel model that looks very much like aggressive primary-progressive MS. Success would likely lead to human clinical trials, he notes.

Initial funding from the National MS Society in the form of a pilot research grant in the early 2000s, together with the Society’s continuous support since, has enabled Dr. Sherman’s current studies of remyelination.

Promoting cell survival

Sharon Way, PhD, a Society-supported postdoctoral scholar working in the laboratory of Brian Popko, PhD, of the University of Chicago Department of Neurology, is researching a different approach to increasing remyelination—by promoting oligodendrocyte survival. Scientists have previously described an important protective process for maintaining cell health in response to several different stressors, including inflammation; this process is the integrated stress response (ISR). While the biochemistry is fairly complex, the key point for

Dr. Way and her colleagues was that they might be able to harness this natural protective

process. Enhancing the ISR, Dr. Way suggests, might improve oligodendrocyte survival during the inflammatory stresses of MS. Since oligodendrocytes are critical for remyelination, this might increase myelin repair.
Dr. Way is currently concentrating on a vital component of the ISR, a specific protein called eIF2-alpha. Dr. Way's team has found that inhibiting the activity of eIF2-alpha reduces oligodendrocyte death, and boosting it increases oligodendrocyte death.

"Now that we know the eIF2-alpha step in the ISR pathway is important, we are testing different drug therapies to see if we can pharmaceutically enhance this to protect oligodendrocytes," Dr. Way explains. If a candidate drug works in mouse oligodendrocytes grown in cell culture and then in mouse models of MS, it could move into clinical trials in humans. "We are protecting oligodendrocytes from inflammation using this approach," Dr. Way continues. "Since no known anti-inflammatory agent can completely block all inflammation in MS, this could be used in conjunction with current anti-inflammatory therapy" to stop the disease progression in complementary ways.

Mary E. King, PhD, is a freelance medical writer from Boulder, Colo.

Read about other approaches to myelin repair.