

Accelerated Cure Project for MS

January
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Accelerating research towards a cure for multiple sclerosis

Unlocking the Mystery of Remyelination

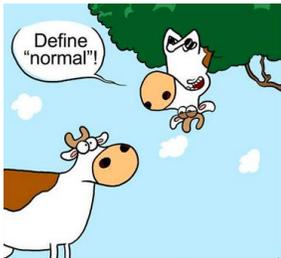
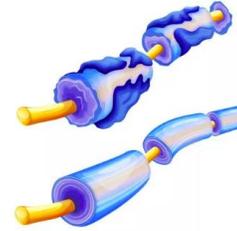
Myelin is a fatty substance that coats the nerve fibers of the central nervous system (CNS), the brain and spinal cord. It insulates the nerves and helps speed the conduction of electrical impulses along the spinal cord to and from the brain. Multiple sclerosis (MS) is a disease that causes the immune system to attack, or erode, the myelin inside the CNS. This disrupts the signals from the brain to the rest of the body. These damaged areas in the myelin sheath, seen with magnetic resonance imaging (MRI), are called plaques or lesions. Virtually all bodily functions depend on the transmission of nerve signals. When MS disrupts these pathways, multiple symptoms can occur. For example, depending on where the damage occurs, a person with MS may experience a variety of symptoms, including numbness, pain, vision loss, cognitive impairment, trouble with bowel and bladder function, difficulty with speech, or paralysis.



Cell signaling is part of the communication process that governs the basic activities of cells. Cell to cell signaling involves the transmission of a chemical signal from a sending cell to a receiving cell. These chemical signals, which are proteins or other molecules produced by a sending cell, are often secreted from the cell and released into the extracellular space. They then float over to neighboring cells. Not all cells can “hear” a particular chemical message. In order to detect a signal (or be a target cell), a neighbor cell must have the right receptor for that signal. When a signaling molecule binds to its receptor, it alters the shape or activity of the receptor, triggering a cascade of biochemical reactions inside the cell, called a signaling pathway. After the first

molecule in the pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function is carried out.

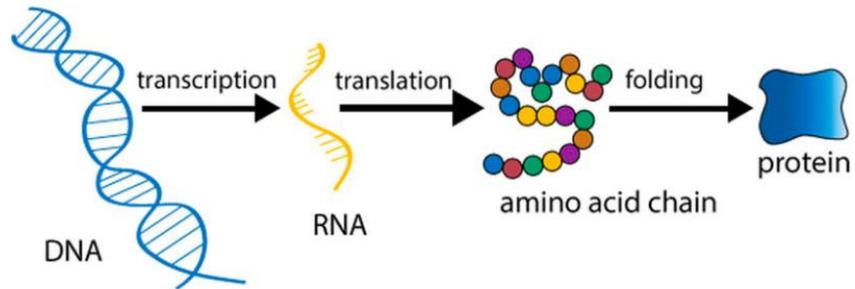
[Glial cells](#) (also called glia) are non-neuronal cells in the CNS, accounting for 90 percent of the brain's cells and more than half its volume. They surround neurons and provide support for and insulation between them. [Oligodendrocytes](#) (OD) are a type of glial cell responsible for production of myelin. They are primarily found in the brain, but also in smaller numbers in the spinal cord. ODs are formed from [oligodendrocyte progenitor cells](#) (OPCs), also known as oligodendrocyte precursor cells. OPCs have "stem cell-like" properties, such as the ability to differentiate into specific cell types and the ability to self-renew. Remyelination is the process of generating OPCs to form ODs, which then create new myelin sheaths. This regenerative process occurs in two major phases – OPC migration and differentiation. OPCs migrate to the damaged axon and then differentiate into mature ODs, which can wrap damaged axons with new myelin sheaths.



While it is a vast improvement, the myelin formed from remyelination is structurally abnormal. These nerve coverings are typically shorter and thinner than usual and, as a result, have reduced conduction velocity compared to normal myelinated axons. This is often observed in MS patients by physical exam or evoked potentials.

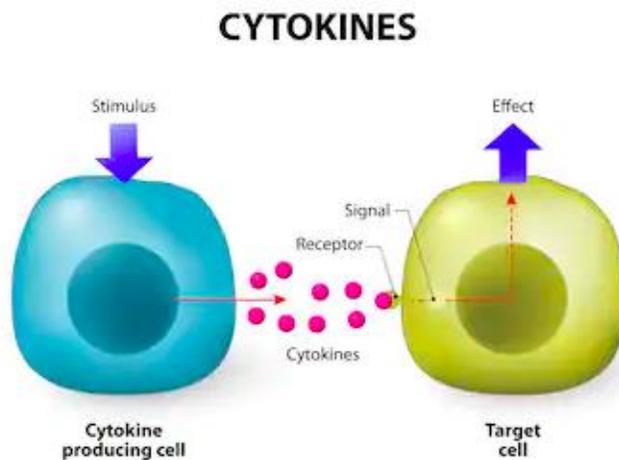
Remyelination is a very complex process with a myriad of contributing elements. Listing all of them would require an entire scientific volume. To name a few, a number of signaling pathways are known to impact OPC differentiation. The [LINGO1](#), [Hyaluronan](#) and [Wnt](#) pathways have an inhibitory effect (therefore hindering remyelination). The [RXR](#) pathway has a beneficial effect, which accelerates remyelination. The [Notch1](#) pathway affects remyelination in both directions. On the one hand, it inhibits OPC differentiation. On the other, it also appears to facilitate OPC migration. A variety of other factors influence this regenerative process. One such factor is [Reticulon 4](#) (also known as neurite outgrowth inhibitor, or Nogo). Nogo is a protein known to inhibit neuronal growth. There are three variants – Nogo A, B, and C, each with a unique function. Blocking Nogo-A during a demyelinating attack is thought to help to protect or restore damaged neurons. Researchers in Switzerland recently [found](#) that antibodies against Nogo-A enhanced neuronal regeneration and remyelination in two animal models of MS. Another protein thought to inhibit neuronal growth is [EphrinB3](#). A recent [study](#) reveals EphrinB3 also inhibits OPC differentiation. In a rat model of MS, investigators demonstrated infusion of EphrinB3 inhibits remyelination and masking EphrinB3 using antibodies promotes remyelination.

[Gene expression](#) is another important factor in remyelination. [DNA](#) (deoxyribonucleic acid) determines the structure and function of every cell and is responsible for characteristics being passed on from parents to their children. DNA is transcribed into [RNA](#) (ribonucleic



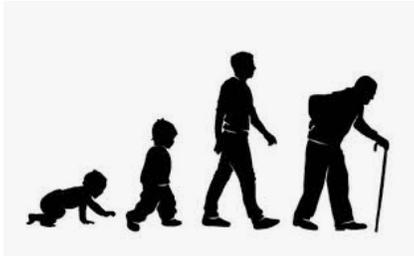
acid), which is then [translated](#) into a sequence of amino acids, the building blocks of proteins. Proteins make many of the structures and all of the enzymes in a cell or organism. [Transcription](#) is the process where a gene's DNA sequence is copied (or transcribed) into an RNA molecule. Proteins called [transcription factors](#) play a central role in regulating transcription. They can activate or repress the transcription of a gene, which determines whether the gene functions (is "turned on") at a given time. Gene expression is currently a hot topic in MS research. A number of transcription factors have been shown to be important in remyelination. Recently, investigators at the University at Buffalo discovered a transcription factor called [PRRX1](#) in human OPCs. They found that activating the PRRX1 gene disrupted myelin repair by blocking OPC proliferation, thereby disabling myelin production. As more genes involved in myelin regeneration are found and cross-linked more will be understood about the process.

The immune system is the body's defense against infections and other intrusions. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade [body systems](#) and cause disease. In MS, abnormal activity of the immune system results in inflammation, which in turn causes myelin damage. The current clinical therapies for MS primarily focus on inhibiting the immune response. [Cytokines](#) are a group of proteins secreted by cells of the immune system that act as chemical messengers to help control the immune system and fight disease. They are cell-signaling molecules that help cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. [Chemokines](#) are a type of cytokine that stimulate movement of cells. Scientists believe chemokines play a role in both the migration and differentiation of OPCs.



Interestingly, the immune system has a conflicting effect on myelin repair. [Research](#) shows acute inflammation is a key signal that activates adult OPCs to mobilize and mature (thereby facilitating remyelination), however long-term inflammation can be toxic to OPCs (which inhibits the regeneration process). Further [study](#) indicates that key cytokines responsible for the destruction of myelin may also mediate the process of myelin regeneration and repair. For example, [interleukins](#) (ILs) are thought to be involved in [both processes](#).

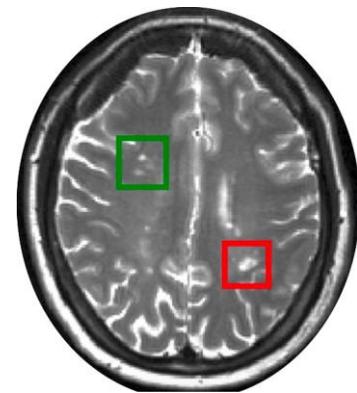
Researchers also believe the environment surrounding cells plays a key role in remyelination. MS lesions often contain myelin and OD debris. Data from a [2006 study](#) indicate this material may inhibit the differentiation of OPCs, thereby decreasing the efficiency of remyelination. Cytokines mediate the inflammatory responses that promote pathogen and debris clearance from the damaged axon.



Myelin production and repair is naturally regulated in the body and is usually efficient in a healthy CNS. A variety of factors can interfere with myelin production, including a diet high in sugar content, poor sleep quality, alcohol, nutrient deficiencies, and hormonal imbalances. Many regenerative processes become less efficient with increasing age, including remyelination. This is particularly relevant for diseases like MS, which can span decades. Aging brings about intrinsic changes in OPCs and their

signaling, both of which impact myelin repair. Compounding this aging effect, the repair process becomes increasingly incomplete in people with MS. Most, if not all, nerve function can be restored early in the disease. However, the repair process becomes less efficient over time, and disability mounts. When axons are left bare (without myelin), their conduction velocity goes down. In addition, a naked axon is much more likely to degrade completely, resulting in complete loss of function. Once a nerve fiber is degenerated, it cannot regenerate. This loss of axons because of a lack of protection is a significant factor in the debilitating effects of MS.

Although myelin repair is typically limited in people with MS, it does occur in a significant percentage of MS patients, in all stages and manifestations of the disease, including primary progressive MS. These repaired lesions are frequently referred to as [shadow plaques](#). It isn't clear what prevents remyelination in lesions that occur in early stages of the disease. Scientists believe it could relate to abnormal inflammatory activity or dysfunction of ODs. In either case, nerve repair may begin within a month or two after the damage occurs. ODs can survive a demyelinating attack and may contribute to subsequent regenerative attempts. However, decreased numbers of ODs over time (after repeated attacks) may make remyelination impossible in late stage disease. In advanced MS, myelin repair seems to only occur at the edge of MS lesions, suggesting that the forces regulating nerve repair are insufficient to reach the lesion core. In lesions containing more ODs, impaired OPC differentiation appears to be the primary obstacle to efficient myelin repair.



Brain MRI - The red box contains 1 demyelinated lesion. The green box contains 3 shadow plaques (remyelinated lesions).



[Pathology studies](#) show remyelination is found in both inactive lesions, and in lesions with ongoing demyelinating activity. One [study](#) demonstrates that older age at death and longer disease duration were associated with significantly more remyelinated lesions. According to these data there is no relationship between the capacity for remyelination and one's age of disease onset. Investigators found that the location of lesions plays a role in the remyelination process, with nerves in subcortical or deep white matter lesions more likely to regenerate than those in periventricular lesions.

Another [study](#) concludes that remyelination may be more efficient in females (who are at higher risk of developing MS) than males. This could be due to the differential effects of sex hormones on OD proliferation and maturation, as well as on the neuroinflammatory process.

All of the FDA-approved drugs are designed to slow the rate of relapse and the accumulation of disability. None of them can undo the nerve scarring that occurs in MS. Several signaling pathways and other complex factors have been shown to impact remyelination, representing possible exciting new [therapeutic targets](#). Scientists all over the world are working to better understand the intricacies of this regenerative process in order to determine how to repair myelin and restore function to those living with MS.

