New clues to myelination could help identify ways to intervene in neurodegenerative diseases

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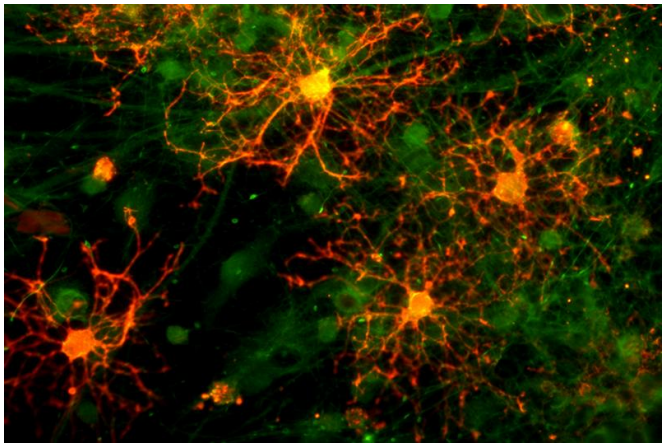

Cell culture containing oligodendrocytes with cortical neurons. Immature oligodendrocytes (bright yellow) interact with neurons (orange) during the first steps of the myelination process. Credit: Pablo Paez

Researchers at the University at Buffalo have identified a critical step in myelination after birth that has significance for treating neurodegenerative diseases like multiple sclerosis, in which myelin is lost or damaged. Myelin is the protective coating that neurons need to function.

The preclinical research, published online in October in the *Journal of Neuroscience*, concerns oligodendrocytes, the cells that make myelin, and the progenitor cells that are their precursors.

The work involved the study of voltage-operated calcium channels, which are responsible for initiating many physiological functions.

How myelin-making cells mature

"Our findings show that these calcium channels modulate the maturation of oligodendrocytes in the brain after birth," said Pablo M. Paez, PhD, an assistant professor in the Department of Pharmacology and Toxicology in the Jacobs School of Medicine and Biomedical Sciences at UB and a research scientist with the Hunter James Kelly Research Institute (HJKRI) at UB, where most of the work was done.

"That's important because it's possible that the activity of this calcium channel can be manipulated pharmacologically to encourage oligodendrocyte maturation and remyelination after demyelinating episodes in the brain," he said.

Within two weeks after birth, the researchers found, the maturation of oligodendrocytes and myelination will proceed so long as calcium channels are functioning properly. In their experiments, mice from whom these calcium channels were removed had abnormal oligodendrocyte maturation, which prevented normal myelination.

Based on these findings, Paez said it appears that in these animals, the inability to develop myelin normally persists into adulthood, suggesting that the expression of voltage-operated calcium channels during the first steps of myelination is essential for the brain's normal development.

"If we can further enhance our understanding of how these oligodendrocyte precursor cells mature, then it may be possible to stimulate them to replace myelin in diseases like multiple sclerosis," he said.

"Demyelination—the loss of myelin—impairs the ability of nerve impulses to travel from nerve cell to nerve cell," Paez explained. "That can lead to deficits in motor, sensory and/or cognitive function. While remyelination occurs in many multiple sclerosis lesions, this becomes increasingly less effective over time and eventually fails."

The results are of particular interest, he noted, because many therapies are already on the market that target calcium channels for cardiovascular disorders and other diseases.

"The pharmacology of these calcium channel blockers is very well-understood, so an understanding of how they influence myelination could potentially bring us closer to new therapies more rapidly than some other therapeutic possibilities," said Lawrence Wrabetz, MD, professor of neurology and biochemistry and director of the HJKRI.

Scientists at the HJKRI conduct research to better understand myelin, the fatty insulator that enables communication between nerve cells. The researchers study how damage to myelin occurs, and how that damage may be repaired. The institute, part of UB's New York State Center of Excellence in Bioinformatics and Life Sciences, was established in 1997 by Buffalo Bills Hall of Fame quarterback Jim Kelly and his wife Jill after their infant son Hunter, was diagnosed with Krabbe Leukodystrophy, an inherited fatal disorder. He died in 2005 at the age of eight.

More information: V. T. Cheli et al. Conditional Deletion of the L-Type Calcium Channel Cav1.2 in Oligodendrocyte Progenitor Cells Affects Postnatal Myelination in Mice, *Journal of Neuroscience* (2016). DOI: 10.1523/JNEUROSCI.1770-16.2016

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