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In the war against diseases, nerve cells need their armor

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In a new study, researchers at the Montreal Neurological Institute (MNI), McGill University, and the Université de Montréal have discovered an essential mechanism for the maintenance of the normal structure of myelin, the protective covering that insulates and supports nerve cells (neurons). Up until now, very little was known about myelin maintenance. This new information provides vital insight into diseases such as Multiple Sclerosis (MS) and other progressive demyelinating diseases in which myelin is destroyed, causing irreversible damage and disrupting the nerve cells' ability to transmit messages.

The research, published recently in the *Journal of Neuroscience*, is the first to identify a role for the protein netrin-1, previously characterized only in the developing nervous system, with this critical function in the adult nervous system. This research was funded by the MS Society of Canada and the Canadian Institutes of Health Research.

Netrin-1, a protein deriving its name from the ancient Indian language, Sanskrit, word for 'one who guides,' is known to guide and direct nerve cell axons to their targets. In the molecular biological studies conducted by the team, they found that blocking the function of netrin-1 and one of its receptors in adult neural tissue causes the disruption of myelin. "We've known for just over 10 years that netrin is essential for normal development of the nervous system, and we also knew that netrin was present in the adult brain, but we didn't know why.

It is fascinating that netrin-1 has such a vital role in maintaining the

structure of myelin in the adult nervous system," says Dr. Tim Kennedy, a neuroscientist at the MNI and the senior investigator of this study, "continuing to pursue the implications of that are incredibly exciting." "Our mission is to find a cure as quickly as possible and enhance quality of life," says Karen Lee, assistant vice-president of research programs for the MS Society of Canada. "We are pleased to be involved in funding work that supports our mission and feel that this research takes us closer to understanding the players and processes that could aid in remyelination."

The results of this study, a collaboration between Dr. Kennedy's laboratory, clinician-scientists in the Neuroimmunology group at the MNI headed by Dr. Jack Antel, and Dr. Adriana Di Polo's laboratory at the Université de Montréal, are especially significant in Canada which has one of the highest rates of Multiple Sclerosis (MS) in the world with approximately 1,000 new cases of MS diagnosed each year. "This is an exciting new area of research that could lead to new treatment strategies and ultimately improve the life of the people who suffer from MS. We are proud to be funding this collaborative research between basic and clinician-scientists," said Dr. Rémi Quirion, Scientific Director of the CIHR Institute of Neurosciences, Mental Health and Addiction.

MS is a disease of the central nervous system in which myelin is destroyed. Understanding the factors involved in maintaining myelin and promoting remyelination, offers new therapeutic targets and avenues for the treatment of MS. As described by Dr. Jack Antel, "Current MS therapies aim to block inflammation. In order to protect and restore myelin it is essential to to understand the molecules involved in these processes. This is the new era of the neurobiology of MS." The team is taking the investigation further by teaming up with the MS clinic and doctors at the MNI, providing access to a huge amount of patient data, and enabling them a broader clinical perspective.

Importantly, this newly discovered mechanism implicates a cascade of protein molecules that have not been known to be involved in myelination. The study was carried out in mice and using in vitro cell cultures. The investigators found that myelin develops normally, but then begins to come apart. Interestingly, in some respects this mirrors what happens in some demyelinating diseases like MS, where myelin forms and may be stable for years, but is then disrupted and begins to fail.

Specifically, the new findings show that netrin-1 and its receptor are needed to hold paranodal junctions in place, and thereby maintain the structure of myelin. The paranodal junction is a highly specialized region of contact where an oligodendrocyte cell attaches itself to the nerve cell's axon. This juncture acts as a molecular fence, which organizes and segregates the distribution of key proteins along the nerve cells axon and plays an imperative role in the proper conduction of electrical signals along the length of the nerve cell. When the function of netrin-1 and its receptor is disrupted, the organization of this adhesive junction comes apart, disrupting the function of nerve cells in the brain and spinal cord.

Source: Montreal Neurological Institute and Hospital