Protein lets brain repair damage from multiple sclerosis, other disorders

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A protein that helps build the brain in infants and children may aid efforts to restore damage from multiple sclerosis (MS) and other neurodegenerative diseases, researchers at Washington University School of Medicine in St. Louis have found.

In a mouse model of MS, researchers found that the protein, CXCR4, is essential for repairing myelin, a protective sheath that covers nerve cell branches. MS and other disorders damage myelin, and this damage is linked to loss of the branches inside the myelin.

"In MS patients, myelin repair occurs inconsistently for reasons that aren't clear," says senior author Robyn Klein, MD, PhD, associate professor of medicine and of neurobiology. "Understanding the nature of that problem is a priority because when myelin isn't repaired, the chances that an MS flare-up will inflict lasting harm seem to increase."

The findings appear online in The Proceedings of the National Academy of Sciences.

Mouse models typically mimic MS symptoms by causing chronic immune cell infiltration in the brain, but, according to Klein, the ongoing immune damage caused by the cells makes it difficult for researchers to focus on what the brain does to repair myelin.

For the study, Klein and first author and postdoctoral fellow Jigisha Patel, PhD, used a non-inflammatory model that involves giving mice

food containing cuprizone, a compound that causes the death of cells that form myelin in the central nervous system. After six weeks, these cells, known as oligodendrocytes, are dead, and the corpus callosum, a structure that connects the left and right hemispheres of the brain, has lost its myelin. If cuprizone is then removed from the mouse diet, new cells migrate to the area that restore the myelin by becoming mature oligodendrocytes.

Klein's investigations began with the processes triggered by dying oligodendrocytes while mice are still on the cuprizone diet. The dying cells activate other support cells in the brain, causing them to express inflammatory factors.

Klein showed that levels of a receptor for inflammatory factors, CXCR4, peaked at six weeks. If researchers continued feeding the mice cuprizone for 12 weeks, levels of the inflammatory factor and its receptor dropped significantly. At 12 weeks the mice were also unable to restore myelin, suggesting a potential connection between myelin repair and CXCR4.

"This was a surprise, because the main thing CXCR4 has been known for is its role in forming the brain, not healing the brain," Klein says. "But we did know that injury increases the number of brain cells that make CXCR4, so it wasn't an unreasonable place to look."

Klein showed that the cells destined to become oligodendrocytes and repair myelin damage, known as neural precursor cells, have high levels of the CXCR4. The cells come up to the corpus callosum from an area below the ventricles, a noncellular area filled with cerebrospinal fluid.

When scientists blocked CXCR4 from becoming activated or reduced cells' ability to make it, the mice were unable to restore myelin. Neural precursor cells stayed in the ventricle and grew in number but did not

move to the corpus callosum to begin repairs.

"Apparently the neural precursor cells have to stop proliferating before they can migrate, and CXCR4 plays a role in this change," Klein says. "CXCR4 also seems to be essential to the cells' ability to develop into mature oligodendrocytes and form myelin."

Klein plans to see if she can restore myelin repair in genetically engineered mouse models of MS with a genetically altered lentivirus that increases levels of an inflammatory factor that activates CXCR4. She also will work with Washington University colleagues to study the new model with advanced imaging techniques in an attempt to further clarify the relationship between loss of nerve cell branches and myelin damage in MS.

"We do not yet know if this myelin repair pathway is somehow damaged or impaired in MS patients," Klein says. "But I like the idea of turning on something that the brain already knows how to make by itself, allowing it to heal itself with its own molecules."

More information: Patel JR, McCandless EE, Dorsey D, Klein RS. CXCR4 promotes differentiation of oligodendrocytes progenitors and remyelination. Proceedings of the National Academy of Sciences, published online May 31, 2010.

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