Multiple sclerosis blocked in mouse model

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Scientists have blocked harmful immune cells from entering the brain in mice with a condition similar to multiple sclerosis (MS).

According to researchers from Washington University School of Medicine in St. Louis, this is important because MS is believed to be caused by misdirected immune cells that enter the brain and damage myelin, an insulating material on the branches of neurons that conduct nerve impulses.

New insights into how the brain regulates immune cell entry made the accomplishment possible. Washington University scientists had borrowed an anti-cancer drug in development by the company ChemoCentryx simply to test their theories.

"The results were so dramatic that we ended up producing early evidence that this compound might be helpful as a drug for MS," says Robyn Klein, MD, PhD, associate professor of pathology and immunology, of medicine and of neurobiology. "The harmful immune cells were unable to gain access to the brain tissue, and the mice that received the highest dosage were protected from disease."

ChemoCentryx is now testing the drug in Phase I safety trials. The study is published in The *Journal of Experimental Medicine*.

Klein and her colleagues discovered a chemical stairway that immune cells have to climb down to enter the brain. Immune cells that exit the blood remain along the vessels on the tissue side, climbing down from

the meninges into the brain where they can then cross additional barriers and attack myelin on the branches of neurons.

"The effect of immune cell entry into the brain depends on context," Klein says. "In the case of viral infection, immune cell entry is required to clear the virus. But in autoimmune diseases like multiple sclerosis, their entry is associated with damage so we need to find ways to keep them out."

The stairway is located on the tissue side of the microvasculature, tiny vessels that carry blood into the central nervous system. The steps are made of a molecule called CXCL12 that localizes immune cells, acting like stairs that slow them down so that they can be evaluated to determine if they are allowed to enter the brain. Klein's lab previously discovered that the blood vessel cells of the microvasculature display copies of this molecule on their surfaces.

Klein also found that MS causes CXCL12 to be pulled inside blood vessel cells in humans and mice, removing the stairway's steps and the checkpoints they provide. In the new paper, she showed that blocking the internalization of the molecule prevented immune cells from getting into the brain and doing harm.

Work by another lab called Klein's attention to CXCR7, a receptor that binds to CXCL12. She showed that the receptor is made by the same cells in the microvasculature that display CXCL12. They watched the receptor take copies of CXCL12 and dump them in the cells' lysosomes, pockets for breakdown and recycling of molecules the cell no longer needs.

"After it dumps its cargo in the lysosome, the receptor can go right back to the cell surface to pull in another copy of CXCL12," Klein says. "There likely exists an equilibrium between expression and disposal of

CXCL12. Some of the proteins expressed by the immune cells in MS patients affect CXCR7 expression and activity, disrupting the equilibrium and stripping the steps from this immune cell stairway we're studying."

Klein contacted researchers at ChemoCentryx, who were developing a blocker of the CXCR7 receptor as a cancer treatment. When they gave it to the mouse model of MS, immune cells stopped at the meninges.

Klein also found that immune factors could cause microvasculature cells to make more or less of CXCR7, ramping up or down the number of steps on the chemical stairway. She is currently investigating additional immune factors that impact on CXCR7 activity within the blood vessel cell. Whether a given factor promotes or suppresses the receptor may also differ depending upon what part of the brain is being considered.

"One of the biggest questions in MS has been why the location, severity and progression of disease varies so much from patient to patient," Klein says. "Getting a better understanding of how these factors regulate immune cell entry will be an important part of answering that question."

More information: Cruz-Orengo L, Holman DW, Dorsey D, Zhou L, Zhang P, Wright M, McCandless EE, Patel JR, Luker GD, Littman DR, Russell JH, Klein RS. CXCR7 influences leukocyte entry into the CNS parenchyma by controlling abluminal CXCL12 abundance during autoimmunity. *The Journal of Experimental Medicine*, Feb. 7, 2011.

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