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MS patients have higher spinal fluid levels of suspicious immune molecule

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A protein that helps keep immune cells quiet is more abundant in the spinal fluid of patients with multiple sclerosis (MS), further boosting suspicion that the protein, TREM-2, may be an important contributor to the disease.

More of an immune-control protein might seem like a boon to MS sufferers, whose symptoms are caused by misdirected immune attacks on the protective lining that coats nerve cell branches. But researchers at Washington University School of Medicine in St. Louis found the extra TREM-2 was not in the right place to reduce aggression in immune cells, a revelation that could eventually lead scientists to new pharmaceutical targets for MS prevention.

"Previously, TREM-2 had only been seen on the surface of immune cells; in the new study, we found it floating freely in spinal fluid," says lead author Laura Piccio, M.D., Ph.D., postdoctoral fellow. "This is only speculation for now, but these 'free agent' copies of TREM-2 could be making it harder for the TREM-2 that is attached to immune cells to keep the cells' aggressiveness under control."

Piccio explains that TREM-2 is a receptor protein, which means that another molecule activates it. Scientists don't currently know what that other molecule is, but the "free agent" TREM-2 in the spinal fluid could be binding to the molecule, reducing the chances that it will bind to and activate TREM-2 attached to immune cells. If Piccio and her colleagues can confirm their theory, the TREM-2 in the spinal fluid or its unknown

partner could become targets for new MS treatments. The findings appear in the journal *Brain.*

Epidemiologists estimate that 400,000 people in the United States have MS. Symptoms, which often strike in episodic bursts, include bladder and bowel dysfunction, memory problems, fatigue, dizziness, depression, difficulty walking, numbness, pain and vision problems. The disease is more common among Caucasians than any other group and affects two to three times as many women as men.

TREM-2 first came to MS researchers' attention because of Nasu-Hakola disease, a rare genetic disorder that involves a mutation in the gene for TREM-2. Among other symptoms, Nasu-Hakola causes loss of the same protective sheath around nerve cell branches that is damaged by MS.

One place where the TREM-2 protein commonly appears is the macrophage, an immune cell that performs a variety of functions, including cleaning up debris and emitting inflammatory signals that escalate immune attacks. Macrophages come in two classes: one that promotes inflammation and one that suppresses it. TREM-2 is present only on the anti-inflammatory macrophages.

Prior experiments had shown that activation of the TREM-2 receptor can help reduce immune inflammation and promote phagocytosis, a process that lets cells consume things. In the context of the central nervous system, researchers think this allows macrophages to consume dying nerve cells and to perform "housekeeping functions," such as shutting down inflammatory processes.

"The main thing we knew about MS and the function of TREM-2 before this study was that blocking TREM-2 in a mouse model of MS made their conditions worse," says senior author Anne Cross, M.D., professor

of neurology and head of the neuroimmunology section.

After Piccio identified TREM-2 in the spinal fluid, she compared that form of the protein in patients with various types of MS, patients with other inflammatory diseases of the central nervous system, and patients with non-inflammatory central nervous system diseases. To ensure that the soluble TREM-2 wasn't seeping into the patients' spinal fluid from the bloodstream, they also analyzed TREM-2 levels in blood.

While there were no differences in blood levels, the soluble form of TREM-2 was significantly higher in the spinal fluid of MS patients.

Scientists are trying to develop a mouse line where the TREM-2 gene has been disabled to learn more about the protein's contributions to the immune system.

Source: Washington University School of Medicine

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