Research team finds possible clue to progression of multiple sclerosis

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Wayne State University School of Medicine researchers, working with colleagues in Canada, have found that one or more substances produced by a type of immune cell in people with multiple sclerosis (MS) may play a role in the disease's progression. The finding could lead to new targeted therapies for MS treatment.

B cells, said Robert Lisak, M.D., professor of neurology at Wayne State and lead author of the study, are a subset of lymphocytes (a type of circulating white blood cell) that mature to become plasma cells and produce immunoglobulins, proteins that serve as antibodies. The B cells appear to have other functions, including helping to regulate other lymphocytes, particularly T cells, and helping maintain normal immune function when healthy.

In patients with MS, the B cells appear to attack the brain and spinal cord, possibly because there are substances produced in the nervous system and the meninges — the covering of the brain and spinal cord — that attract them. Once within the meninges or central nervous system, Lisak said, the activated B cells secrete one or more substances that do not seem to be immunoglobulins but that damage oligodendrocytes, the cells that produce a protective substance called myelin.

The B cells appear to be more active in patients with MS, which may explain why they produce these toxic substances and, in part, why they are attracted to the meninges and the nervous system.

The brain, for the most part, can be divided into gray and white areas. Neurons are located in the gray area, and the white parts are where neurons send their axons — similar to electrical cables carrying messages — to communicate with other neurons and bring messages from the brain to the muscles. The white parts of the brain are white because oligodendrocytes make myelin, a cholesterol-rich membrane that coats the axons. The myelin's function is to insulate the axons, akin to the plastic coating on an electrical cable. In addition, the myelin speeds communication along axons and makes that communication more reliable. When the myelin coating is attacked and degraded, impulses — messages from the brain to other parts of the body — can "leak" and be derailed from their target. Oligodendrocytes also seem to engage in other activities important to nerve cells and their axons.

The researchers took B cells from the blood of seven patients with relapsing-remitting MS and from four healthy patients. They grew the cells in a medium, and after removing the cells from the culture collected material produced by the cells. After adding the material produced by the B cells, including the cells that produce myelin, to the brain cells of animal models, the scientists found significantly more oligodendrocytes from the MS group died when compared to material produced by the B cells from the healthy control group. The team also found differences in other brain cells that interact with oligodendrocytes in the brain.

"We think this is a very significant finding, particularly for the damage to the cerebral cortex seen in patients with MS, because those areas seem to be damaged by material spreading into the brain from the meninges, which are rich in B cells adjacent to the areas of brain damage," Lisak said.

The team is now applying for grants from several sources to conduct further studies to identify the toxic factor or factors produced by B cells

responsible for killing oligodendrocytes. Identification of the substance could lead to new therapeutic methods that could switch off the oligodendrocyte-killing capabilities of B cells, which, in turn, would help protect myelin from attacks.

The study, "Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro," was published in the May 2012 edition of the *Journal of Neuroimmunology* and was recently featured in a National Multiple Sclerosis Society bulletin. Other WSU researchers involved in the study include Joyce Benjamins, Ph.D., professor and associate chair of neurology; Samia Ragheba, Ph.D., assistant professor of neurology and immunology & microbiology; Liljana Nedelkoskaa, research assistant in neurology; and Jennifer Barger, research assistant in neurology; as well as researchers at the Montreal Neurological Institute and McGill University in Montreal. The research was supported by a National Multiple Sclerosis Society Collaborative MS Research Center Award, the Canadian Institutes of Health Research and the Multiple Sclerosis Society of Canada.

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