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Researchers implicate unique cell type in multiple sclerosis

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Researchers at the National Institutes of Health have found evidence that a unique type of immune cell contributes to multiple sclerosis (MS). Their discovery helps define the effects of one of the newest drugs under investigation for treating MS – daclizumab – and could lead to a new class of drugs for treating MS and other autoimmune disorders.

In these disorders, the immune system turns against the body's own tissues. Ongoing clinical trials have shown that daclizumab appears to help quiet the autoimmune response in MS patients, but its precise effects on the legions of cells that make up the immune system are not fully understood.

The new study, published in *Science Translational Medicine*, shows that one effect of daclizumab is to thin the ranks of lymphoid tissue inducer (LTi) cells. These cells are known to promote the development of lymph nodes and related tissues during fetal life, but their role during adulthood has been unclear. The new study marks the first time that LTi cells have been implicated in any human autoimmune disorder.

"While further study is required to confirm the role of LTi cells in autoimmunity, our results point to the cells as a promising target for the development of new drugs to treat autoimmune disorders," said Bibiana Bielekova, M.D., an investigator at NIH's National Institute of Neurological Disorders and Stroke (NINDS).

Dr. Bielekova and her team found that among MS patients participating

in clinical trials of daclizumab, the number of LTi cells was elevated in patients not receiving daclizumab compared to those on the drug. Patients receiving daclizumab also had reduced signs of inflammation in the cerebrospinal fluid (CSF) that surrounds the brain. And the researchers found that daclizumab appears to steer the body away from producing LTi cells, in favor of another cell type that counteracts autoimmunity.

In MS, the immune system attacks myelin, a material that insulates nerve fibers running throughout the brain and spinal cord. This typically leads to vision loss, and other sensory changes such as numbness and tingling, weakness, and fatigue. The disorder affects approximately 400,000 people in the United States. In about 85 percent of patients, MS starts as a relapsing-remitting form, in which symptoms come and go. Many patients eventually develop secondary progressive MS, in which symptom flare-ups are followed by worsening disability. Many medications are available to decrease the number of flare-ups, but no medication is effective at slowing the course of progressive MS.

The newer, sophisticated drugs for relapsing-remitting MS target key cells and molecules responsible for triggering and maintaining autoimmunity. Cytotoxic T cells, the immune system's specialized mobile infantry, are known to lead the attack. Antibodies, the immune system's guided missiles, appear to help reinforce it.

Daclizumab is a lab-engineered antibody, or monoclonal antibody, that alters signaling by interleukin-2 (IL-2), a key factor that mobilizes T cells. In a large clinical trial (NCT00109161), it has shown promise as an add-on therapy for patients taking the approved MS drug interferon-beta. Another ongoing trial (NCT00390221) is investigating whether or not daclizumab is effective as a stand-alone therapy for reducing relapses in MS.

The drug was designed to suppress T cell responses to IL-2, and it does so – but Dr. Bielekova had found previously that this suppression is indirect and depends on other immune cells. For example, one effect of daclizumab is to stimulate the non-specialized counterparts of T cells, called natural killer cells. These cells in turn suppress T cell activity.

In their new study, Dr. Bielekova and her team discovered that daclizumab's stimulatory effect on natural killer cells is paired with an inhibitory effect on LTi cells. They found evidence that the drug, via its effects on IL-2 signaling, acts on a type of stem cell. The drug appears to decrease the likelihood that this stem cell will develop into LTi cells, and sway it toward becoming natural killer cells.

"This helps explain why natural killer cells are activated and their numbers are expanded by daclizumab therapy," Dr. Bielekova said. Meanwhile, she said, the drop in LTi cells was "intriguing" in itself, given the cells' role in lymph node development.

Lymph nodes – found conspicuously in the armpits, neck and groin – are patches of tissue where T cells and antibody-producing B cells set up camp. Inside the nodes, T cells and B cells are found in clusters called lymphoid follicles, where they wait for a signal that the body is under siege from infection. In autoimmune disorders, abnormal lymphoid follicles can develop and contribute to the autoimmune response. Secondary progressive MS, in particular, is associated with abnormal lymphoid follicles in the connective tissues (or meninges) surrounding the brain. These are believed to contribute to chronic brain inflammation in MS, eventually leading to shrinkage of the brain.

Dr. Bielekova and her team reasoned that daclizumab, by suppressing LTi cells, should reduce the growth of lymphoid follicles. Since it is not possible to visualize these follicles in the live brain, the researchers measured the effects of daclizumab on markers of inflammation in the

CSF. They found that CXCL13, a protein linked to lymphoid growth, and the IgG index, a measure of antibody production, decreased by an average of 50.4 percent and 13.5 percent, respectively, in trial participants who took the drug for six and half months.

"To our knowledge, no other MS therapy reduces IgG index," Dr. Bielekova said.

She cautioned that these data provide only an indirect link between LTi cells and brain inflammation in MS. If further research confirms that the cells play an important role in MS or other autoimmune disorders, "pursuing the development of new drugs to selectively inhibit LTi cells could be a useful therapeutic strategy," she said.

More information: Perry, JSA and Han, S et al. "Inhibition of LTi cell development by CD25 blockade is associated with decreased intrathecal inflammation in multiple sclerosis." *Science Translational Medicine*, published online August 1, 2012. DOI: 10.1126/scitranslmed.3004140

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