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Interferon could be a key to preventing or treating multiple sclerosis

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Multiple sclerosis (MS) results when the body's own defense system attacks nerve fibers in the brain and spinal cord. Now scientists led by John Russell, Ph.D., at Washington University School of Medicine in St. Louis have shown that interferon-gamma plays a deciding role in whether immune cells attack and injure the central nervous system (brain and spinal cord) in mice.

Interferon-gamma is an immune system protein that helps the body defend itself from invaders. In their latest research, which appeared in the October issue of the *Journal of Experimental Medicine*, the researchers show that interferon-gamma determined whether activated immune cells — previously primed to go after nerve cells — would actually cause nerve damage in experimental mice.

The researchers found that in the cerebellums and brainstems of the mice, interferon-gamma was protective. However, in the spinal cord, interferon-gamma had the opposite effect, permitting nerve cell damage.

"Some studies show that the most serious cases of MS in people occur when the immune system specifically targets the cerebellum, a part of the brain responsible for sensory perception, coordination and movement control," says Russell, professor of developmental biology. "Our study suggests that researchers need to look at the amount of interferon-gamma produced in the cerebellum and other brain regions in people with MS."

The researchers studied mice genetically engineered to be physiologically "blind" to interferon-gamma — the mice had none of the usual receptors on their cells that recognize and respond to interferon-gamma. So in these mice it was as though interferon-gamma didn't exist.

In the interferon-insensitive mice, immune cells primed to attack nerves and then injected into the mice's veins were able to get into the cerebellum and brain stem and initiate nerve cell damage leading to MS-like disease.

In comparison, in mice with normal interferon-gamma recognition, immune cells were prevented from entering the brain and causing problems. The exact mechanism to account for this is still under study.

"Down the road, we would like to investigate whether we can prevent disease in the cerebellum in mice if we promote interferon production in that brain region," Russell says. "One way to do that would be to use gene therapy to insert a gene that would increase interferon in the mice's brains. Then we would test the mice to see if they gained protection against MS-like disease."

In contrast to its protective role in the brain, in the spinal cord interferon-gamma helped instigate nerve damage. In mice with intact interferon-gamma recognition, activated and injected immune cells were able to enter the spinal cord and cause injury. In mice without interferon recognition, the immune cells were unable to initiate spinal cord inflammation, and no damage occurred.

"Our research shows that certain characteristics inherent in different regions of the brain and spinal cord can provoke immune attacks on nerve cells," Russell says. "An understanding of the mechanisms involved in immune system invasion of the nervous system may allow development of better models for determining prognosis and treating

many neurological diseases such as multiple sclerosis."

This latest research bolsters Russell's central hypothesis about MS and related disorders, which goes against some widely held assumptions. He holds that in physiological circumstances that ultimately lead to MS, the central nervous system itself allows or even aids immune system attacks.

"A scientifically popular view of how MS occurs is that the immune system somehow gets armed against normal brain antigens and attacks neurons," Russell says. "In that view, brain cells have a passive role. But in this and previous research, we've shown that there's a 'conversation' between the immune system and the central nervous system and that molecular signals passed between them are involved in the development of MS-like disease in mice."

Source: Washington University School of Medicine