One step closer in explaining multiple sclerosis relapse during upper respiratory infection

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Andrew Steelman, assistant professor in the Department of Animal Sciences, the Neuroscience Program, and the Division of Nutritional Sciences at the University of Illinois. Credit: Lauren D. Quinn

For most of us, the flu is just the flu. We suffer through it for several days, and eventually bounce back. But for patients with multiple

sclerosis (MS) and other neurological diseases, the flu can trigger a cascade of immune responses that result in a full-blown relapse of the disease. In a recent study from the University of Illinois, researchers shed light on what may be happening in the brains of MS patients during upper respiratory infections.

"We know that when MS patients get upper respiratory infections, they're at risk for relapse, but how that happens is not completely understood," says Andrew Steelman, an assistant professor with appointments in the Department of Animal Sciences, the Neuroscience Program, and the Division of Nutritional Sciences at U of I. "A huge question is what causes relapse, and why immune cells all of a sudden want to go to the brain. Why don't they go to the toe?"

Steelman and his team used a strain of laboratory mice that are genetically prone to developing an autoimmune attack of the brain and spinal cord. After the mice were exposed to influenza, the research team examined changes in the mice and their brains.

First, exposure to the flu did induce an MS-like symptoms in some of the mice, even though the virus itself was not found in the brain. "If you look at a population of MS patients that have symptoms of upper respiratory disease, between 27 and 42 percent will relapse within the first week or two," Steelman says. "That's actually the same incidence and timeframe we saw in our infected mice, although we thought it would be much higher given that most of the immune cells in this mouse strain are capable of attacking the brain." Nevertheless, the team believes they are on the right track.

When they looked more closely, the researchers found an increase in glial activation in brains taken from influenza infected mice. For a long time, glia cells were considered the glue that holds neurons in place, but it turns out they do much more than that. Certain types of glia cells are

involved in calling immune cells—in this case, neutrophils, monocytes, and T-cells—to the brain.

"When glia become activated, you start to see trafficking of immune cells from the blood to the brain. We think that, at least for MS patients, when glia become activated this is one of the initial triggers that causes immune cells to traffic to the brain. Once there, the immune cells attack myelin, the fatty sheaths surrounding axons, causing neurologic dysfunction," Steelman explains.

Glia may be sending the signal to immune cells via molecules known as chemokines. The researchers found that one chemokine in particular, CXCL5, was elevated in the brains of mice infected with flu as well as in the cerebral spinal fluid of human MS patients during relapse. Another research group recently suggested CXCL5 could be used to predict relapse, strengthening Steelman's confidence in his results.

Despite knowing more about how immune cells are called to the brain during an upper respiratory infection, the team still can't explain why the immune system attacks the brain. But being able to identify a particular piece of the puzzle, such as CXCL5, could get the medical community closer to a drug intervention in the future. And there's a lot of value in that.

"MS patients have one or two relapses a year; it's thought that these relapses contribute to the progression of the disease," Steelman explains. "If we can pinpoint what's driving environmental factors such as infection to cause relapse, then maybe we can intervene when the patient has signs of sickness, like runny nose or fever. If we could inhibit relapse by 50 percent, we could theoretically prolong the time it takes for the patient to experience continual loss of function and dramatic disability."

More information: Stephen Blackmore et al, Influenza infection

triggers disease in a genetic model of experimental autoimmune encephalomyelitis, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1620415114