Study spotlights potential culprit in relapses of multiple sclerosis

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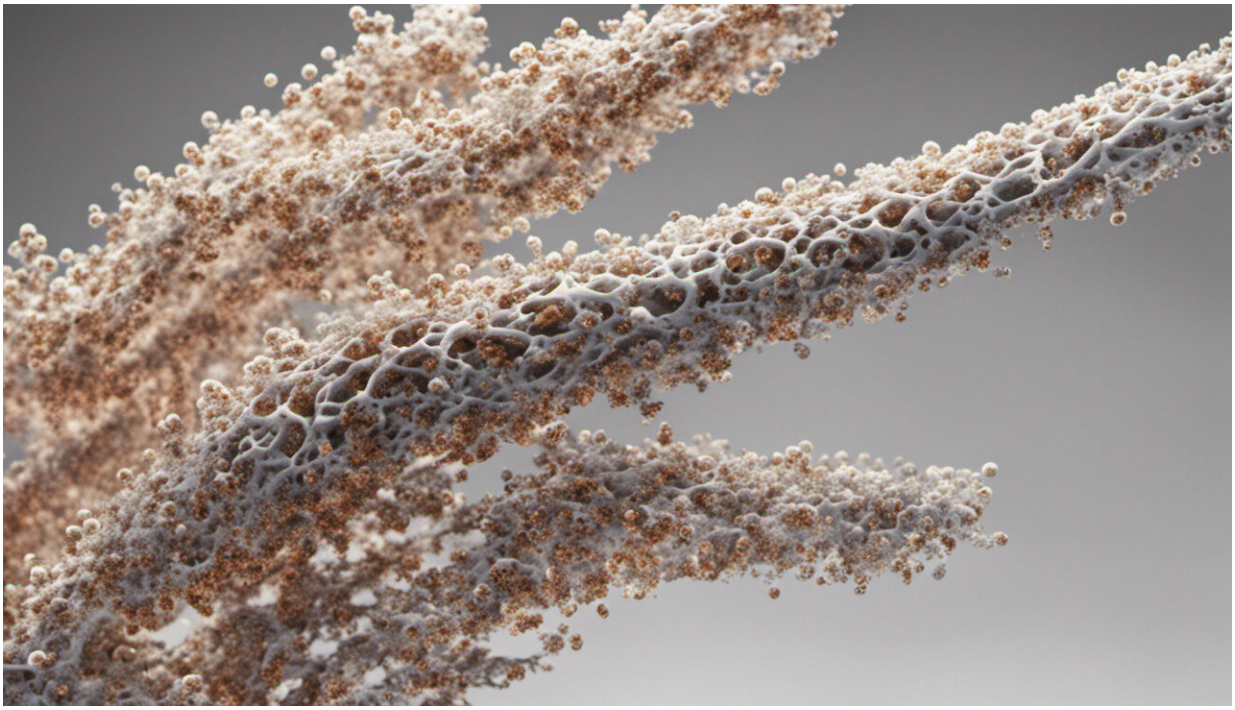

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A recent study led by the University of Nebraska–Lincoln has implicated a leading suspect in two open medical cases: the common recurrence of multiple sclerosis and the fuzzy thread tying MS to mononucleosis.

And Nebraska virologist Luwen Zhang believes the team's method of

interrogation might just assist the eventual detainment of the culprit.

Years of research suggest that getting mononucleosis—the fatigue-inducing "kissing disease" caused by the Epstein-Barr virus—multiplies the risk of later developing multiple sclerosis, the neurological disorder that often impairs movement, vision and speech. The latter develops when the body's own immune system attacks and erodes the protective sheath, or myelin, that coats nerve fibers in the brain and spinal cord, slowing or blocking electrical pulses sent via the exposed fibers.

Though the causes of the mono-MS link have remained unclear, a promising lead has recently emerged. Both mononucleosis and multiple sclerosis patients exhibit elevated levels of the white blood cells known as B lymphocytes, which crank out the antibodies that help combat viruses and other foreign invaders. That overabundance is fueled by the Epstein-Barr virus, which infects the B lymphocytes and allows them to proliferate unchecked in much the same way that cancerous cells do—drawing the ire of the immune system in the process.

To investigate the role of the virus-infected B lymphocytes, Zhang and his colleagues injected mice with virus-laden cells from a human patient with multiple sclerosis. The team then observed the rodents for MS-like symptoms: a limp or paralyzed tail, the partial or complete paralysis of limbs. The mice showed no such effects, suggesting that an overabundance of the infected B lymphocytes is not, by itself, enough to trigger the neurological disease.

But Zhang suspected that the B lymphocytes might yet have a part in the process. So the researchers later injected the mice with a protein that normally resides on the surface of the myelin sheath and is an apparent target of the immune system before the onset of multiple sclerosis. The mice began exhibiting paralysis of the tail and limbs; once those symptoms had waned, the team again injected the B lymphocytes alone.

This time, the mice showed essentially the same symptoms as they had when exposed to the myelin protein. When the supply of infected B lymphocytes subsided, so too did the symptoms.

That waning and waxing of MS-like symptoms resembled the cycle of remission and relapse seen in about 85% of human patients, Zhang said. The similarity suggests that the overabundance of B lymphocytes could be at least partly to blame for those relapses, he said. The fact that infected B lymphocytes from people without multiple sclerosis managed to incite the same symptoms further supported the team's hypothesis.

"Nobody knows the exact mechanisms behind these relapses," said Zhang, professor of biological sciences and member of the Nebraska Center for Virology. "This over-proliferation of the B cells seems to be a factor. It's not a causative factor, but it promotes multiple sclerosis formation in our mouse model."

Given that the over-proliferation is also seen in the mononucleosis that often precedes multiple sclerosis, Zhang said it represents a worthy subject of interrogation for researchers pursuing MS therapies.

Working with a mouse model similar to the one demonstrated by the Nebraska team could be a good start, he said. The team found that it could predict the timing and severity of the MS-like symptoms in its mice by accounting for when the infected B lymphocytes were administered. And that, Zhang said, could assist the early testing of pharmaceutical drugs designed to limit the common relapses. The greater the predictability and control of the MS-like symptoms, the more precisely and confidently researchers can measure the potential effects of a given drug.

"That's what I'm thinking is the true importance of this work—that it gives us a way to test different drugs," Zhang said. "It creates more

potential for treatment."

The team reported its findings in the *Journal of Medical Virology*.

More information: Pascal Polepole et al. Epstein Barr virus-immortalized B lymphocytes exacerbate experimental autoimmune encephalomyelitis in xenograft mice, *Journal of Medical Virology* (2020). DOI: 10.1002/jmv.26188