Researchers find molecular trigger for brain inflammation

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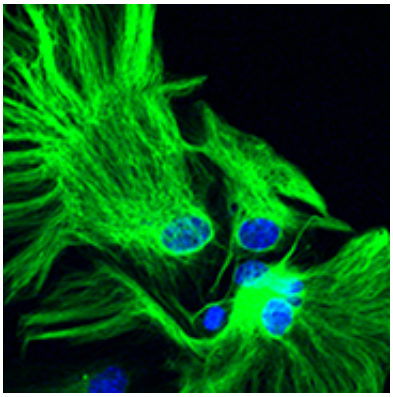

The green represents glial fibrillary acidic proteins in a mouse astrocyte. Credit: Ting Lab

Brain inflammation is a key component of multiple sclerosis, Alzheimer's, Parkinson's, ALS, and most other major neurodegenerative diseases. How inflammation starts, how it's sustained, and how it contributes to these diseases is not well understood, but scientists from the University of North Carolina School of Medicine have just found some important clues.

In a study published in the *Journal of Experimental Medicine*, UNC researchers led by Jenny Ting, PhD, the William R. Kenan Distinguished Professor of Genetics, identified key molecules that drive brain inflammation in a mouse model of multiple sclerosis – molecules that

are present at abnormally high levels in the brains of humans with the disease.

The findings show that these inflammatory molecules are ripe targets for further study and potential targets for future multiple sclerosis treatments. The research may also lead to a better understanding of Alzheimer's, traumatic brain injury, stroke and other diseases that involve neuroinflammation.

"We need to better understand brain inflammation at the molecular level in order to treat neurodegenerative conditions," said Ting, who is also a member of the UNC Lineberger Comprehensive Cancer Center. "Our study shows how two proteins that control inflammation are crucial to a particular kind of brain inflammation."

The study began as an investigation of LPC (lysophosphatidylcholine), a fat-related signaling molecule that researchers have suspected stokes harmful brain inflammation in multiple sclerosis and other central nervous system diseases.

In initial experiments, study co-lead authors – UNC postdoctoral researcher Haitao Guo, PhD, graduate student Leslie Freeman, and former graduate student Sushmita Jha, PhD (now an assistant professor at the Indian Institute of Technology Jodhpur) – found evidence that LPC triggers the inflammatory activation of mouse immune cells through two proteins called NLRP3 and NLRC4.

NLRP3 and NLRC4 are components of the so-called innate immune system – a network of infection-fighting molecules and cells evolutionarily older than the better-known adaptive immune system's T-cells, B-cells, and antibodies. Like other NLR-family proteins, NLRP3 and NLRC4 appear to have evolved to detect molecular patterns associated with certain microbes. The two proteins trigger inflammation

in response to these microbes.

There is evidence, too, that NLR-family proteins can trigger inflammation in response to non-microbial signals related to tissue damage. LPC is suspected to be one such kind of signal, and it is this sort of non-microbial tissue inflammation that researchers think is involved in neurodegenerative diseases.

In previous studies, NLRP3 was shown to be a factor in brain inflammation in multiple sclerosis and Alzheimer's disease. But no one had reported a brain inflammation role for NLRC4 in neurodegenerative diseases involving animal models.

To investigate that possibility, Freeman, Guo, and Jha examined mouse astrocytes and microglia – resident brain cells that can perform immune functions in the nervous system. These cells are usually the main sources of inflammation in neurodegenerative diseases. Ting's team found that LPC could induce an inflammatory response in these brain cells, as well, in a way dependent on NLRP3 and NLRC4.

The researchers then worked with a mouse model of multiple sclerosis. They used a chemical called cuprizone to induce brain inflammation. This chemical also helped them strip the fatty layer surrounding nerve fibers. They found that the usual inflammatory activation of astrocytes and microglia, along with the stripping of nerve fibers, was greatly reduced when the mice lacked the genes for both NLRP3 and NLRC4.

"Essentially, we saw a profound reduction of the inflammatory disease in these mice," Guo said. "And where just one of those genes was absent, we didn't see as pronounced a reduction of inflammation."

Underscoring the likely clinical relevance of these findings, the group found high levels of NLRC4 in astrocytes and microglia from the brain-

inflamed mice, as well as in biopsied brain tissue from multiple sclerosis patients. Affected mouse and human brain tissue also showed abnormally high levels of an LPC cell receptor protein called G2A.

"This is direct evidence of the importance of NLRC4 and NLRP3 in astrocytic and microglial inflammation, and we showed that this damage-associated molecule called LPC triggers the inflammation," said Guo.

More information: Leslie Freeman et al. NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes, *The Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20150237

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