Central nervous system inflammation—a pathway and possible drug target

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Scientists have long known that the central nervous system (CNS) has a remarkable ability to limit excessive inflammation in the presence of antigens or injury, but how it works has been unclear. Now, Yale

researchers have identified a mechanism that offers this new insight into this protective effect. The findings were described in the April 8 journal of *Science Advances*.

Until now, the prevailing theory has been that the blood brain barrier provided the protective effect by preventing immune cells and molecules from entering the brain. However, when inflammation does occur, the brain has a way other than the blood brain barrier of slowing or stopping it, the Yale team observed

Just as humans communicate using language, cells communicate using cell surface molecules and soluble proteins. And it is a particular conversation between a protein known as HVEM (herpes virus entry mediator) and SALM5, a molecule mainly found in neuronal cells, that suppresses CNS inflammation, said senior author on the paper, Lieping Chen, MD, PhD United Technologies Corporation Professor in Cancer Research, professor of immunobiology, dermatology, and medicine (medical oncology); and co-director, cancer immunology program at Yale Cancer Center.

"We've identified a key molecular pathway that may control CNS inflammation and provide evidence that this pathway could be manipulated by a monoclonal antibody to enhance immune response," Chen said. "Also, we developed a new receptor array technology to identify the interaction between HVEM and SALM5. Both discoveries could be applied to the study of other pathways in the search for new therapies."

Chen said his team's interpretation opens the way for new drugs that can control CNS disease, including brain tumors. Specifically, using a strategy similar the anti-PD1/anti-PDL1 therapy developed in his lab many years ago to promote immune response in other human cancers.

More information: Y. Zhu et al. Neuron-specific SALM5 limits inflammation in the CNS via its interaction with HVEM, *Science Advances* (2016). DOI: 10.1126/sciadv.1500637