Study finds key protein for firing up central nervous system inflammation

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Scientists have identified an influential link in a chain of events that leads to autoimmune inflammation of the central nervous system in a mouse model of multiple sclerosis (MS).

An international team of researchers led by scientists in The University of Texas MD Anderson Cancer Center Department of Immunology reported their results in an advance online publication in *Nature Medicine*.

The researchers spell out the pivotal role of Peli1 in the activation of immune cells called microglia that promote inflammation in the central nervous system in response to tissue damage or invasion by microbes.

"The major implication of discovering a signaling role for Peli1 in this animal model is that it might also be significant in the pathogenesis of MS," said senior author Shao-Cong Sun, Ph.D., professor in MD Anderson's Department of Immunology.

Microglia cells involved in multiple sclerosis

Sun and colleagues found that Peli1 is heavily expressed in microglial cells and promotes their activation and subsequent damaging immune response. Peli1 also protects that autoimmune reaction by initiating the destruction of a protein that otherwise would inhibit inflammation.

Microglia are known to be crucial to the initiation of MS, an immune system assault on nerve fibers called axons and on myelin, the protective sheath around the axons. They also were previously known to play a similar role in experimental autoimmune encephalomyelitis (EAE), an animal model of MS.

The precise mechanism of this autoimmune-stimulating effect has been unknown. Sun and colleagues fill an important gap with their Peli1 discovery.

Microglia sense tissue damage. They secrete chemokines and inflammatory cytokines in response, drawing infection-fighting T cells into the central nervous system, leading to inflammation.

Infections genetic overreaction that inflames

The authors note that microbial infections are a known environmental trigger for the onset and maintenance of multiple sclerosis and the induction of EAE in mice. Toll-like receptors that detect pathogens play a roll in MS and EAE. They were suspected of involvement in microglial activation and inflammation.

Upon sensing microbes or cell damage, toll-like receptors launch a signaling cascade that activates a variety of genes involved in inflammation and white blood cell homing to the microbes or injury site.

Peli1 is known as a targeting agent, marking proteins with molecules called ubiquitins, ensuring they are functionally modified or found by cellular protein-destruction machinery. In this case, Sun and colleagues found that Peli1 ubiquitinates another targeting agent as a signal, which in turn marks a crucial anti-inflammatory protein for destruction.

The team found:

- Mice with Peli1 knocked out were resistant to EAE. Those with Peli1 developed severe symptoms including a gradual increase in paralysis.

- Mice with intact Peli1 had high levels of microglial activation after EAE began and low levels of resting microglia. Mice with Peli1 knocked out had high levels of resting microglia.

- Expression of proinflammatory chemokines and cytokines was impaired in microglia taken from Peli1 knockout mice. Peli1 sends signal to destroy Traf3

Sun and colleagues then tracked down the role Peli1 plays in protecting one of the molecular networks that is set off when toll-like receptors detect microbes or injury. The MAPK pathway activates a variety of genes involved in inflammation and T cell response.

MAPK is kept in check by a protein called Traf3. The team found that Peli1 signals another ubiquitin ligase that in turn marks Traf3 for destruction, liberating the MAPK network.

After EAE is induced, mice with intact Peli1 have a gradual depletion of Traf3 in their microglia. Traf3 accumulated in the microglia of Peli1 knockout mice. EAE was restored in Peli1 knockout mice when Traf3 was inhibited.

Sun said the team is studying the pathway in human multiple sclerosis to replicate their findings and explore the possibilities for potentially treating MS.