

Protein identified that serves as a 'brake' on inflammation

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Researchers have identified a protein that offers a new focus for developing targeted therapies to tame the severe inflammation associated with multiple sclerosis (MS), colitis and other autoimmune disorders. St. Jude Children's Research Hospital scientists led the study which appears today in the scientific journal *Immunity*.

Investigators showed that the protein NLRP12 works in T [cells](#) to limit production of chemical messengers or cytokines that fuel inflammation. T cells are specialized [white blood cells](#) produced to eliminate specific infectious agents and other threats. Deletion of the Nlrp12 gene led to increased cytokine production in T cells. Specially bred mice that received T cells deficient in the protein NLRP12 developed more severe symptoms of colitis and the chronic skin condition atopic dermatitis.

The results suggest how mutations in the Nlrp12 gene cause disease, which until now was unclear. "We have identified a possible mechanism of how mutations in Nlrp12 lead to atopic dermatitis and possibly other diseases in humans," said corresponding author Thirumala-Devi Kanneganti, Ph.D., a member of the St. Jude Department of Immunology. "Understanding the precise inner-workings of NLRP12 in T cells will help guide efforts to develop therapies to ease symptoms by taming inflammation driven by T cells."

Researchers also found that NLRP12-deficient mice may offer a much needed mouse model for studying the development of balance and movement problems in people with multiple sclerosis (MS).

NLRP12 belongs to a family of proteins best known for working in the [innate immune system](#) to help cells sense threats and then launch the inflammatory response to eliminate them. The innate [immune system](#) is the body's first line of defense. It works with T cells and other components of the adaptive immune system to safeguard health.

Previous research from Kanneganti's laboratory showed that rather than fueling production of the cytokines that drive inflammation, NLRP12 played a different role in the [innate immune response](#). Researchers showed that in the innate immune system, NLRP12 worked in the NF-?B signaling pathway to restrain inflammation.

The latest study showed that NLRP12 serves the same anti-inflammatory function in T cells. Investigators demonstrated that NLRP12 works through the NF-?B pathway in T cells to regulate production of interleukin 4 (IL-4) and other cytokines.

"This study provides the first evidence that NLRP12 can function in [adaptive immune cells](#) to regulate inflammation and impact various [autoimmune disorders](#)," Kanneganti said. "That's important because excessive inflammation plays a role in many human diseases, including cancer."

The findings could also advance efforts to understand and treat MS, a chronic inflammatory disorder in which T cells attack and damage the myelin sheath that insulates nerve fibers. The resulting demyelination disrupts nervous system functioning, causing MS symptoms.

Demyelination and [inflammation](#) both occur in the current [mouse model](#) of MS and result in progressive paralysis beginning in the tail. Surprisingly, the deletion of Nlrp12 in mice led to different symptoms. The mice had less paralysis, but developed problems with balance and movement, just like MS patients. Investigators linked the new symptoms

to increased IL-4 production by T cells that lacked NLRP12. When excess IL-4 was eliminated using various methods, the mice again exhibited classical paralysis rather than the other symptoms related to balance and movement.

More information: The NLRP12 Sensor Negatively Regulates Autoinflammatory Disease by Modulating Interleukin-4 Production in T Cells, dx.doi.org/10.1016/j.immuni.2015.03.006

Provided by St. Jude Children's Research Hospital

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