Understanding mutation leads to promising new treatment for autoinflammatory diseases

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(Medical Xpress)—St. Jude Children's Research Hospital scientists have not only solved the mystery of how mutations in the SHP-1 gene lead to a variety of inflammatory and autoimmune disorders, but have also identified a drug that protected against an inflammatory skin disease in a mouse model.

Researchers discovered something else: Different forms of the protein interleukin-1 (IL-1) take different routes to fuel inflammation. That finding overturned the widely held assumption that the alpha and beta versions of IL-1 work through the same pathway. The research appeared in the June 13 edition of the scientific journal *Nature*.

"These are thrilling results because we showed that blocking a single molecule, in this case IL-1 alpha, protected 100 percent of the mice

from developing an inflammatory disorder that is very close to the human disease. These results are a stepping stone that leads to the clinic," said the study's corresponding author Thirumala-Devi Kanneganti, Ph.D., an associate member of the St. Jude Department of Immunology.

The SHP-1 protein protects against unneeded and unwanted inflammation by switching off the signaling system that governs the release of molecules called cytokines. These molecules drive inflammation. Although mutations in SHP-1 have been linked for decades to a variety of inflammatory and autoimmune disorders, including lupus and multiple sclerosis, until now the mechanism responsible was unknown.

To find the answer, researchers turned to a new SHP-1 mutant mouse model of the inflammatory human skin disorder neutrophilic dermatosis. The disease is characterized by skin inflammation and sometimes painful skin abnormalities, including ulcers. Corticosteroids, the centerpiece of current treatment, are associated with serious side effects.

Kanneganti and her colleagues showed that SHP-1 mutations work through an unexpected mechanism. The system features the RIP1 kinase and IL-1 alpha in prominent roles. Kinases are signaling molecules that can start the inflammatory process. The scientists found the SHP-1 mutation led to signaling through RIP1, which resulted in the release of IL-1 alpha and other cytokines that promote and sustain inflammation. Deleting either RIP1 or IL-1 alpha prevented excessive inflammation and inflammation-related tissue damage in the mutant mice and restored normal wound healing.

The experimental drug necrostatin 1 also protected mutant mice from inflammation-driven tissue damage, researchers reported. The drug was designed to block RIP1 activity.

Deleting other protein complexes and cytokines that control or fuel inflammation had no impact on the inflammation or disease symptoms in the mice, said first author John Lukens, Ph.D., a postdoctoral fellow in Kanneganti's laboratory. That list included the molecules caspase 1, IL-1 beta and RIP3, which works with RIP1 to trigger a form of programed cell death that triggers inflammation.

Researchers noted that when IL-1 alpha was deleted, messaging through a protein complex called NF-kB also declined. NF-kB is a master regulator of inflammation. That observation offers further insight into the disease process, suggesting RIP1 and IL-1 alpha are in a feedback loop that fuels inflammation.

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