MedicalXpress

Researchers unlock an immunity 'black box'

April 18 2017

A research team led by St. Jude Children's Research Hospital immunologists has revealed a previously unknown immune machinery that goes awry to trigger the inflammatory disease neutrophilic dermatosis. Neutrophilic dermatoses are a heterogeneous group of autoinflammatory skin disorders that include Sweet's syndrome, pyoderma gangrenosum, and subcorneal pustular dermatosis and may occur with cancers such as leukemia as well as infections or inflammatory bowel disease.

Mapping the biological machinery underlying the disease's inflammation is important because there are no drugs that specifically target the wide array of similar autoinflammatory diseases. Autoinflammatory diseases occur when the hyperactive innate immune system attacks the body.

Currently, the only treatments for such disorders are strong immunosuppressive drugs that also render patients susceptible to infection.

The study was led by Thirumala-Devi Kanneganti, Ph.D., a member of the St. Jude Department of Immunology. The findings appear today in the journal *Immunity*. First authors were Prajwal Gurung, Ph.D., a postdoctoral fellow in the Kanneganti laboratory, and Gaofeng Fan, Ph.D., of Cold Spring Harbor Laboratory.

Abnormalities in the PTPN6 gene have been implicated in human diseases such as pyoderma gangrenosum, multiple sclerosis, leukemia and psoriatic arthritis.

The researchers used a strain of gene-altered mouse in which the activity of a protein encoded by the Ptpn6 gene was "dialed down." The mice developed inflammatory skin disease similar to neutrophilic dermatosis in humans. Like humans with the disorder, the mice appear normal when first born, but as they age, they developed the inflammatory disease.

How does disease ensue in the Ptpn6 mutant mice? What are the key pathways that are regulated by the Ptpn6 gene? Kanneganti and her colleagues previously discovered in a seminal study published in Nature that IL-1 alpha is the key master regulator that provokes uncontrolled immune response in the Ptpn6 mutant mice. But the machinery linking Ptpn6 and IL-1 alpha was a "black box," Kanneganti said.

To map the machinery, the researchers took a genetic approach and painstakingly produced mice defective in Ptpn6 that additionally lacked candidate genes in the pathway. Here, the researchers knew that if the Ptpn6 mutant mice crossed with the mouse deficient in a candidate gene do not develop disease, they would be able to identify the gene that triggers aberrant inflammation and disease. After creating some 50 different combinations with different candidate genes, the researchers pieced together the puzzle of the immune machinery underlying the inflammation.

The picture they revealed further confirmed that IL-1 alpha is a master immune switch that activates the machinery. In addition, they also identified several key molecules including RIPK1, TNF, TAK1 and SYK that drive inflammation and tissue damage.

"This is quite an important finding," Kanneganti said. "IL-1 alpha was discovered more than 45 years ago, but we have not known how it is regulated and how it functions. And our lab is one of the very few in the country studying IL-1 alpha."

The finding of IL-1 alpha's role, as well as many other molecular switches in the immune machinery, will offer multiple targets for developing drugs to switch off the uncontrolled immune response in inflammatory diseases, Kanneganti said. "In this particular study, we have identified several prime drug targets for molecules involved in the pathway, especially IL-1 alpha," she said.

Another important finding is how different "cellular compartments" interact to trigger autoinflammatory disease. While the abnormal Ptpn6 gene functions in the bone marrow—a major source of disease instigating innate immune cells—the IL-1 alpha master switch functions in the skin.

"This told us that cross talk between cells is really critical in mediating this disease," Kanneganti said. "It gives us important information about how the immune system works both to drive autoinflammatory disease and to fight infection. And it illustrates why we could not have studied this process in a cell culture system but needed to study it in a mouse model."

Finally, the study unraveled how the Ptpn6 gene regulates IL-1 alpha mediated aberrant inflammation and disease. The researchers identified that Ptpn6 inhibited activation of a critical tyrosine kinase called SYK to modulate activation of a central adaptor protein MyD88, a previously unknown signaling node. Given the central role of MyD88 in inflammation, these data are relevant not only to neutrophilic dermatosis but also to several other inflammatory diseases and will spur several new studies.

More information: Prajwal Gurung et al, Tyrosine Kinase SYK Licenses MyD88 Adaptor Protein to Instigate IL-1α-Mediated Inflammatory Disease, *Immunity* (2017). DOI: 10.1016/j.immuni.2017.03.014

Provided by St. Jude Children's Research Hospital