Study identifies protein that triggers lupus-associated immune system activation

6 April 2015

Massachusetts General Hospital (MGH) investigators have identified an inflammatory molecule that appears to play an essential role in the autoimmune disorder systemic lupus erythematosus, commonly known as lupus. In their report being published online in *Nature Immunology*, the researchers describe finding that a protein that regulates certain cells in the innate immune system - the body's first line of defense against infection - activates a molecular pathway known to be associated with lupus and that the protein's activity is required for the development of lupus symptoms in a mouse model of the disease.

"This study is the first demonstration that the receptor TREML4 amplifies the cellular responses transmitted through the TLR7 receptor and that a lack of such amplification prevents the inflammatory overactivation underlying lupus," says Terry Means, PhD, of the Center for Immunology and Inflammatory Diseases in the MGH Division of Rheumatology, Allergy, and Immunology. "Our preliminary results suggest that TREML4-regulated signaling through TLR7 may be a potential drug target to limit inflammation and the development of autoimmunity."

Lupus is an autoimmune disorder characterized by periodic inflammation of joints, connective tissues and organs including heart, lungs, kidneys and brain. TLR7 is one of a family of receptors present on innate immune cells like macrophages that have been linked to chronic inflammation and autoimmunity. Animal studies have suggested that overactivation of TLR7 plays a role in lupus, and a gene variant that increases expression of the receptor has been associated with increased lupus risk in human patients. The current study was designed to identify genes for other molecules required for TLR7-mediated immune cell activation.

The MGH-based team conducted an RNA-interference-based genome-scale screen of mouse macrophages, selectively knocking down the expression of around 8,000 genes, and found that TREML4 - one of a family of receptors found on granulocytes and monocytes - amplifies the response of innate immune cells to activation via TLR7. Immune cells from mice lacking TREML4 showed a weakened response to TLR7 activation. When a strain of mice genetically destined to develop a form of TLR7-dependent lupus was crossbred with a strain in which TREML4 expression was suppressed, offspring lacking TREML4 were protected from the development of lupus-associated kidney failure and had significantly lower blood levels of inflammatory factors and autoantibodies than did mice expressing TREML4.

Means notes that identifying the potential role of TREML4 in human lupus may lead to the development of drugs that could prevent or reduce the development or progression of lupus and another autoimmune disorder called Sjögren's syndrome, which also appears to involve TLR7 overactivation. Future studies are needed to better define the molecular mechanism behind TREML4-induced amplification of TLR7 signaling and to clarify beneficial reactions controlled by TREML4 - for example, the immune response to influenza virus, which the current study found was inhibited by TREML4 deficiency.

"Given that only one new drug has been approved for lupus patients in the last 50 years, there is a pressing need for more specific and less toxic drugs to treat it and other autoimmune disorders," says Means, who is an assistant professor of Medicine at Harvard Medical School.

More information: The receptor TREML4 amplifies TLR7-mediated signaling during antiviral responses and autoimmunity, DOI: 10.1038/ni.3143

Provided by Massachusetts General Hospital