Researchers find new mechanism that controls immune responses

12 February 2015

UT Southwestern Medical Center researchers have identified a common signaling mechanism to produce interferon - one of the main proteins used to signal the immune system when the body needs to defend itself against a virus, tumor, or other diseases.

The findings are important for understanding the body's immune defense system, searching for compounds to turn the immune system on or off, and they may help combat autoimmune diseases, in which overactive immune cells attack healthy tissues.

"Our work reveals a common mechanism by which three distinct pathways lead to the production of type-I interferons," said Dr. Zhijian "James" Chen, Professor of Molecular Biology and in the Center for the Genetics of Host Defense at UT Southwestern, and a Howard Hughes Medical Institute (HHMI) Investigator. "Ultimately, we believe that understanding this mechanism will facilitate the design and development of medications to treat human diseases such as lupus."

The findings appear online in the journal *Science*.

The results show how a protein called interferon regulatory factor 3 (IRF3), which controls the production of type-I interferons, is activated and how this pathway is tightly controlled. The failure of this control system can lead to autoimmune disorders such as systemic lupus erythematosus, which causes joint pain and swelling, and can damage the brain, heart, lungs, kidneys, and digestive track. Lupus affects more than 1.5 million Americans, and is more common in young and middle-aged women than in men.

A normal function of interferons is to defend the body against infections from viruses, bacteria and parasites. Previous research has identified specific pathways that induce interferons in response to distinct infectious agents, but how these different pathways converge on IRF3 to induce interferons was not understood.

Dr. Chen and his team studied a protein called MAVS, which they discovered in 2005 and showed that it is an adaptor protein essential for interferon induction by RNA viruses such as influenza virus. In the new study, they found that MAVS is modified by the addition of a phosphate group (phosphorylated) by an enzyme called TBK1 when cells are infected by a virus and that this modification is important for IRF3 activation.

Upon closer examination, they found the amino acid sequence that is phosphorylated in MAVS is very similar to those of two other adaptor proteins, STING and TRIF, which mediate interferon induction in response to DNA viruses and bacteria, respectively. Further research confirmed that all three adaptor proteins are phosphorylated at the common sequence motif and that this phosphorylation allows each of the adaptor proteins to bind IRF3, thereby facilitating IRF3 phosphorylation by TBK1. The phosphorylated IRF3 becomes activated to induce type-I interferons.

"Although TBK1 is required for IRF3 activation, TBK1 alone is not sufficient. Phosphorylation of the adaptor proteins provides a 'license' for TBK1 to phosphorylate IRF3," said Dr. Chen, who holds the George L. MacGregor Distinguished Chair in Biomedical Science. "This hitherto unrecognized mechanism ensures that type-I interferons are produced only when a proper adaptor protein is engaged in cells that are infected by pathogens."

Provided by UT Southwestern Medical Center