New approach for attacking lupus identified

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Investigators at Hospital for Special Surgery have identified two new targets for drugs aimed at controlling lupus. If companies are able to develop drugs that hone in on these targets, patients may be able to control their disease with few side effects.

“The study identifies very good therapeutic targets, and what needs to be done is identify better candidate drugs,” said Lionel Ivashkiv, M.D., director of Basic Research at Hospital for Special Surgery in New York City. He led the study, which was published online in *Nature Immunology* on December 16 and will appear in print in February.

Because abnormally high levels of interferon-alpha can lead to lupus, researchers have developed drugs that block interferon. These drugs, however, have immunosuppressive side effects that can leave patients vulnerable to various illnesses and infections, some of which can be deadly. Currently, these drugs are being tested in clinical trials. If researchers are able to develop drugs for the newly identified drug targets, patients may be able to avoid these immunosuppressive effects.

Interferons have two major functions. First, they protect against viruses and second, they regulate immune responses, strengthening immune responses and playing a role in autoimmunity. Different proteins, called STATs, mediate the two functions of IFN. STAT1 mediates the autoimmune and inflammatory functions, and STAT2 mediates the virus protection function.

“What we were interested in understanding is how you can regulate the

balance between activating the inflammatory effects and the antiviral effects," Dr. Ivashkiv said. "We thought if we could control the functions of the interferons, that would lead to new therapeutic approaches where you could block specifically some of their functions, but not others."

The investigators discovered that calcium specifically increases activation of STAT1 by interferons, and thus turned their attention to calcium. The researchers tested whether two kinase enzymes in the calcium-signaling pathway, CAMK and Pyk2, could be manipulated to control STAT1. In studies involving mice, the investigators showed that blocking these calcium-signaling pathways with a drug called KN-93 regulated the amount of STAT1, but not STAT2 activation.

"What we found was that these kinases that are regulated by calcium actually regulate the strength of activation of STAT1 by the interferons, but they do not regulate the strength of activation of STAT2," said Dr. Ivashkiv. "The idea was if you block these signaling pathways, would you block the STAT1 part, which controls the inflammatory/deleterious effects and preserve the antiviral part. We tested that in an animal model of lupus and we were able to show, in vivo, that you can suppress STAT1 activation by inhibiting the calcium-dependent kinases."

The researchers say that their work has identified a new therapeutic approach for attacking lupus. "What the companies are trying to develop are, basically, antibodies against the interferons. The concern there is that if you block the interferon completely, patients may become very immunosuppressed and unable to handle viral infections," Dr. Ivashkiv said. "Our idea is that if you block these calcium pathways, you could block the deleterious effects of the interferon, but maintain the antiviral effects."

Lupus is an autoimmune disease that can affect various parts of the

body, including the skin, joints, heart, lungs, blood, kidneys and brain. Inflammation, considered the primary feature of lupus, is characterized by pain, heat, redness, swelling and loss of function. In most people, the disease affects only a few organs and symptoms are mild, but in others, the disease can cause serious and even life-threatening problems. According to the Lupus Foundation of America, an estimated 16,000 Americans develop lupus each year.

Source: Hospital for Special Surgery