Researchers identify enzyme that contributes to development of lupus

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Researchers at Beth Israel Deaconess Medical Center (BIDMC) have identified an enzyme that is significantly elevated in mouse models of systemic lupus erythematosus and in blood samples of patients with lupus. Published online today in *The Journal of Clinical Investigation*, the new findings demonstrate that inhibition of the SHP-2 enzyme can significantly diminish lupus symptoms - including skin lesions, enlarged spleen and kidney failure - and suggest that development of a SHP-2 inhibitor drug could offer a new therapeutic approach for this often debilitating disease.

Systemic lupus erythematosus is a chronic autoimmune disease that causes widespread inflammation and tissue damage to organ systems throughout the body. There is no cure for the disease, which primarily strikes young women in their 20s and 30s and affects an estimated 1.5 million individuals in the United States and at least 5 million worldwide.

"SHP-2 can lead to an overproduction of cytokine molecules," explained senior author Maria Kontaridis, PhD, Interim Director of the Basic Cardiology Research Program in the CardioVascular Institute at BIDMC and Assistant Professor of Medicine at Harvard Medical School (HMS). "In patients with lupus, we know that cytokines trigger inflammation, contribute to immune cell dysfunction, and lead to organ damage."

Kontaridis, whose mother battled lupus for more than 25 years - has spent more than a decade studying genetic mutations in a class of enzymes known as protein tyrosine phosphatases. Her previous work has

revealed that mutations in these proteins alter cellular signaling pathways, leading to the development of a group of rare congenital heart diseases known as RASopathies. Several years ago, after learning that more than 50 children with a RASopathy disorder called Noonan syndrome had also developed lupus, Kontaridis hypothesized that there might be a correlation between phosphatase activity and systemic autoimmunity.

Preliminary tests of lupus mouse models revealed that SHP-2 enzyme activity was elevated four-to-six-fold compared with a group of control mice. "We then validated this finding in humans by examining blood cells isolated from lupus patients and found SHP-2 activity was also significantly higher than normal," said first author Jianxun Wang, PhD, a postdoctoral fellow in the Kontaridis laboratory and an Instructor in Medicine at HMS.

The investigators next conducted a series of biochemical analyses to identify the mechanisms by which SHP-2 is involved in the development of lupus and made use of a novel inhibitor of the SHP-2 enzyme to show that its inhibition could lead to the amelioration of the disease. "The mice were remarkably changed as a result of the drug treatment," said Kontaridis. "The animals' lifespans were increased, characteristic skin lesions were eliminated, the enlarged spleens were reduced in size - and most remarkably - the kidneys were normalized."

When the investigators went on to study what was happening at the molecular level, they discovered that SHP-2 predominantly affected the proliferation of double-negative T cells, candidate markers of immune dysregulation.

"We know these T cells are responsible for the secretion of specific cytokines, and we think these cytokines are what induce the infiltration of inflammatory cells into the target tissues in animal models of lupus,"

said Kontaridis. "We identified two specific cytokines regulated by SHP-2 in lupus - IL17 A/F and interferon gamma - both of which we think mediate the pathogenicity of SLE and cause the disease-associated inflammation and organ damage."

"Treatment of patients with SLE has lagged behind other conditions and, unfortunately, is still limited to the use of immunosuppressive drugs," said George Tsokos, MD, Chief of Rheumatology at BIDMC and a coauthor on the paper. "The identification of novel targets such as this one shows promise that the development of a small molecule drug inhibitors, such as for SHP-2, will allow for the initiation of clinical trials in patients with lupus."

"My own mother's 26-year long battle with lupus motivated me and inspired this investigation," said Kontaridis. "Our findings, and others like this, give great hope that one day soon there will be newer and better treatment options available for the millions of patients that suffer with this disease."

More information: Jianxun Wang et al, Inhibition of SHP2 ameliorates the pathogenesis of systemic lupus erythematosus, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI87037

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