Novel small molecule drug may help to ease symptoms in lupus sufferers

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Lupus, a chronic autoimmune disease, has proved difficult to treat, but a new international study co-led by a Rush University Medical Center researcher suggests that a drug starting through the pipeline could ameliorate or even eliminate the symptoms in most sufferers.

The study, published March 6 in the prestigious *Journal of Clinical Investigation*, showed that certain compounds that bind to a small region of a critical protein called CD11b can lessen the inflammation that occurs in systemic lupus erythematosus (SLE) and its renal complication lupus nephritis (LN), says Vineet Gupta, PhD, professor and vice chair for Research and Innovation at Rush University Medical Center and director of Rush's Drug Discovery Center. While an approved treatment is still years away, these novel compounds have great potential to treat and even cure lupus and its complications, says Gupta, who was a co-lead investigator in the five-year, multi-center investigation. Jochen Reiser, MD PhD, a Rush nephrologist and chair, Department of Internal Medicine, and other Rush researchers also participated in the study.

"This is the first time anyone has shown that you can use small molecules to activate CD11b and lessen systemic inflammation in an autoimmune disease," Gupta says. "We have identified a new druglike compound that reduced the disease burden" in a rodent model, and had corresponding results in human blood cells. The compound and its beneficial action were discovered in the Gupta Laboratory at Rush.

Nine out of 10 lupus sufferers are women, and most of them are women

of color. The disease comes on in young adulthood, and can "flare" up into an array of distressing and damaging symptoms that include painful inflammation, fatigue and skin rashes. Environmental factors may make the disease worse. Lupus can damage organs; kidney disease is a common complication, often called lupus nephritis. Present treatments include broad strategies, such as anti-inflammatories and steroids that aim to reduce symptoms and slow organ damage. However, these treatments are not very effective, have many side effects and cannot be used long-term.

What causes lupus remains a mystery and both environmental and genetic factors play a role. Lupus results from a disruption in the system that protects the body against infection, throwing defenders—antibodies and immune cells—against the body's own tissues. Mutations in several genes are associated with the increased risk for developing lupus, particularly a gene called ITGAM, Gupta says. About 15 to 20 percent of lupus patients have ITGAM mutations, although not everyone who has the ITGAM mutation in their genome develops the disease, Gupta says. A focus of this study was to investigate role of the genetic mutations in ITGAM. ITGAM is an important player in the immune system. When the ITGAM gene is expressed as a protein in cells it is called CD11b. A newly recognized job of this molecule is to monitor toll-like receptors (TLR), which can sniff out the signature molecules of microbes and other pathogens. TLRs can signal to the cells to produce interferon I (IFN I) to fight an infection, but Interferon I can cause damaging inflammation if deployed inappropriately, Gupta says. Using samples from 171 lupus patients, the team discovered that patients carrying ITGAM mutations had higher levels of IFN I in their blood, suggesting that ITGAM mutations are directly linked to a bad immune signature and a lupus biomarker. This is because mutated CD11b is defective; it fails in its job of suppressing the activity of TLRs, which then may signal the production of Interferon I even though there's no infection to be fought, causing inflammation and other lupus symptoms,

Gupta says. This also suggested to the investigators that if CD11b's activity could be enhanced, it might lead to an effective drug therapy for lupus.

The new compound the JCI study investigates "binds to CD11b and activates it, and by doing so enhances the ability of CD11b to suppress TLR signaling. More importantly, it binds to the normal and the mutant CD11b equally well, and forces them in an active state. The compound does not negatively impact the body's ability to fight infection, but it can reduce inflammation in the setting of an autoimmune disease. It's a much more targeted approach that makes it ultimately more effective," Gupta says.

The JCI study used a rodent model, with mice that had been genetically modified to dependably develop lupus as they aged. Administration of the new drug significantly reduced lupus and its symptoms in mice, including their renal disease. Investigators also tested the effects of the compound on immune cells from blood obtained from human subjects carrying the ITGAM mutation and observed that the compound can override the genetic defect. "Our studies suggest that CD11b activation should be explored as a novel therapeutic strategy for SLE, particularly as a personalized approach for patients carrying specific ITGAM genetic mutations." says Gupta.

More information: Mohd Hafeez Faridi et al. CD11b activation suppresses TLR-dependent inflammation and autoimmunity in systemic lupus erythematosus, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI88442

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