A surprise mechanism uncovered in the development of lupus

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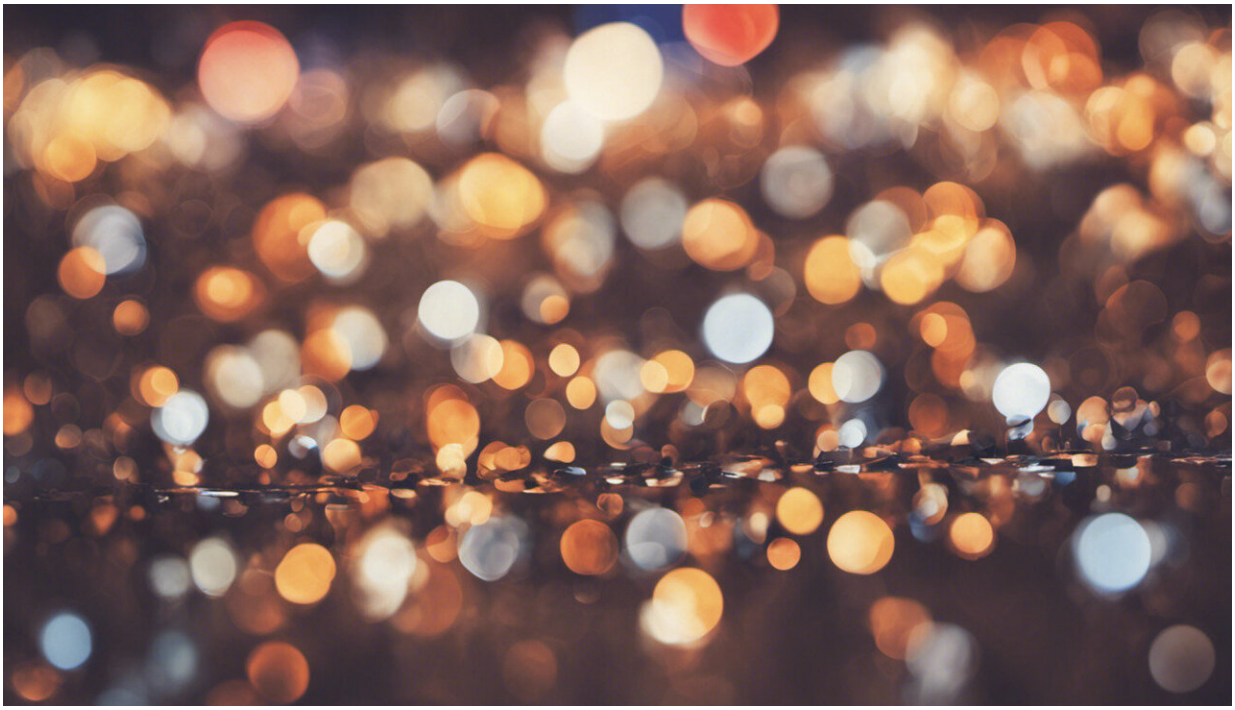

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In a study with a surprising outcome, scientists at Yale School of Medicine have discovered that an enzyme complex known for promoting natural resistance to bacteria and fungi unexpectedly inhibits the development of lupus. The finding could pave the way for development of therapeutic interventions in this debilitating disease. The study

appears online in the Oct. 24 issue of *Science Translational Medicine.*

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system attacks the body's healthy tissue rather than foreign pathogens, resulting in inflammation and damage to joints and internal organs. The etiology of lupus is not well understood, but the suspected cause is debris produced when cells die.

The Yale researchers focused on a key enzyme complex in this process known as NADPH oxidase, or Nox2, and evaluated its role in lupus pathogenesis.

Before this study, it was commonly thought that Nox2 might actively promote the development of lupus by facilitating the release of DNA from white blood cells called neutrophils in a process called NET ("neutrophil extracellular trap") generation. To test that hypothesis, the Yale team evaluated disease in lupus-prone mice that lacked the Nox2 protein. Contrary to expectations, the Nox2-deficient mice whose neutrophils failed to generate NETs not only still got lupus, but got a much worse form of the disease. Surprised by the finding, researchers realized that normal function of Nox2 inhibits the development of lupus, rather than promoting it.

They are now focusing their research on how Nox2 controls lupus. "Nox2 clearly has an important role in fighting infection and lupus is often triggered by infection. We suspect that Nox2 could be an important connection between response to infection and lupus flares," said lead author Mark Shlomchik, M.D., professor of laboratory medicine and immunobiology at Yale School of Medicine. "We now plan to explore the mechanism by which NADPH oxidase is exerting its effects. Doing so should provide additional insights into the cause of this disease."

The implication for human cases of lupus could be enormous. "We suspect that without NADPH oxidase, neutrophils may die in a way that inflames the immune system," Shlomchik explains. "This may help us develop therapies that promote NADPH oxidase function and thereby suppress disease."

Provided by Yale University