Molecule regulates production of antibacterial agent used by immune cells

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Ravi Ranjan. Credit: Joshua Clark

Researchers have discovered how a protein molecule in immune cells promotes the production of nitric oxide, a potent weapon in the cells'

arsenal to defend the body from bacterial attack. The protein may offer a target for reining in the inflammatory response, which must be able to fight infection without damaging tissue.

The study was published in the *Journal of Innate Immunity*. NFATc3 is one of several related protein molecules known to play a role in regulating genes in the T and B cells of the immune system. Ravi Ranjan, research scientist at the University of Illinois at Chicago College of Medicine, who is first author on the paper, said he and his collaborators wanted to know if NFATc3 also had any function in macrophages—specialized killer cells that hunt down, engulf and destroy marauding bacteria.

Macrophages kill using chemicals, including nitric oxide, that they synthesize in response to infection. Macrophages are also important in reducing the inflammation in sepsis, an out-of-control reaction to infection that can cause organ failure and death.

When the researchers exposed macrophages to chemicals that signal a bacterial infection, they found that NFATc3 increasingly bound to genes that boost the production of nitric oxide synthase—the enzyme that makes nitric oxide. The binding of NFATc3 suggests the molecule is turning on those genes and upping the production of nitric oxide. Macrophages deficient in NFATc3 produced much less nitric oxide synthase under the same conditions.

"Without the ability to synthesize inducible nitric oxide synthase, a macrophage would be missing a key element of its chemical weaponry," Ranjan said. "We would expect these cells to be much less effective at killing bacteria and attenuating sepsis."

To test this hypothesis, the researchers then induced sepsis in mice that lacked the ability to make NFATc3. As expected, lung tissue from these

mice had a much higher bacterial load than the lung tissue of septic mice that could produce NFATc3.

"Our study demonstrates that NFATc3 is required for macrophages to effectively fight infection, because without it, they can't make their primary bactericidal agent—nitric oxide," Ranjan said. The immune system must strike a balance between fighting infection and going overboard as it does in sepsis and actually causing harm, Ranjan said.

"An overproduction of nitric oxide can actually contribute to lung injury even as it helps clear bacterial infections," he said.

"An NFATc3 inhibitor, given as a drug to people in septic shock, may be a way to attenuate the harmful effects that come with an overproduction of nitric oxide." Other authors on the paper are Dr. Gye Young Park, assistant professor of clinical medicine, and Dr. Lei Xiao, assistant professor of medicine, both in the division of pulmonary, critical care, sleep and allergy at UIC; Manjula Karpurapu, Jing Deng, Sangwoon Chung, Yong Gyu Lee and Dr. John William Christman of the Ohio State University Wexner Medical Center; and Myungsoo Joo of Pusan University, Korea.

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