

Researchers discover human immune system has emergency backup plan

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New research by scientists at the University of California, San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences reveals that the immune system has an effective backup plan to protect the body from infection when the "master regulator" of the body's innate immune system fails. The study appears in the December 19 online issue of the journal *Nature Immunology*.

The innate [immune system](#) defends the body against infections caused by [bacteria](#) and viruses, but also causes inflammation which, when uncontrolled, can contribute to chronic illnesses such as [heart disease](#), [arthritis](#), [type 2 diabetes](#) and cancer. A molecule known as nuclear factor kappa B (NF-κB) has been regarded as the "master regulator" of the body's innate immune response, receiving signals of injury or infection and activating genes for microbial killing and inflammation.

Led by Michael Karin, PhD, Distinguished Professor of Pharmacology, the UC San Diego team studied the immune function of laboratory mice in which genetic tools were used to block the pathway for NF-κB activation. While prevailing logic suggested these mice should be highly susceptible to bacterial infection, the researchers made the unexpected and counterintuitive discovery that NF-κB-deficient mice were able to clear bacteria that cause a skin infection even more quickly than normal mice.

"We discovered that loss of NF-κB caused mice to produce a potent immune-activating molecule known as interleukin-1 beta (IL-1β), which

in turn stimulated their bone marrow to produce dramatically increased numbers of white blood cells known as neutrophils," said Karin. Neutrophils are the body's front-line defenders against infection, capable of swallowing and killing bacteria with a variety of natural antibiotic enzymes and proteases.

The new research demonstrates that the innate immune system deploys two effective strategies to deal with invasive bacterial infection, and that the IL-1 β system provides an important safety net when NF- κ B falls short.

"Having a backup system in place is critical given the diverse strategies that bacterial pathogens have evolved to avoid bacterial clearance," said Victor Nizet, MD, professor of pediatrics and pharmacy, whose laboratory conducted the infectious challenge experiments in the study. "A number of bacteria are known to suppress pathways required for NF- κ B activation, so IL-1 β signaling could help us recognize and respond to these threats."

While helpful in short-term defense against a severe bacterial infection, the dramatic increase in neutrophil counts seen in the NF- κ B-deficient mice ultimately came at a cost. Over many weeks, these activated immune cells produced [inflammation](#) in multiple organs and led to the premature death of the animals. Long-term blockade of NF- κ B signaling has been explored extensively by the biotechnology and pharmaceutical industry as a strategy for anti-inflammatory or anti-cancer therapy, perhaps unaware of the risks suggested by this new research.

"One might contemplate adding a second inhibitor of IL-1 β signaling to protect against the over-exuberant neutrophil response," said Karin. "Unfortunately, loss of both the NF- κ B pathway and the backup IL-1 β pathway rendered the mice highly susceptible to invasive [bacterial infection](#) which they no longer cleared."

Altogether, the UC San Diego research sheds new light on the complex and elegant regulatory pathways required for a highly effective innate immune system. The scientists noted that future investigations must take into account these interrelationships in order to design novel drugs against inflammatory diseases that achieve their treatment goals while minimizing the risk of infection.

Provided by University of California - San Diego

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