Innate immune system protein provides a new target in war against bacterial infections

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Research led by St. Jude Children's Research Hospital scientists has identified a possible new approach to defeating bacterial infections by targeting an innate immune system component in a bid to invigorate the immune response.

In this study, researchers demonstrated that the primary function of one of the innate immune molecules is to suppress inflammation, which in turn dampens the immune response to infections and other threats. Investigators showed the protein works by inhibiting two pathways that control production of specialized molecules that fight infections. The findings appear in the current online edition of the scientific journal *Nature*.

"The beauty of this finding is that if we can generate monoclonal neutralizing antibodies against this protein, we can block bacterial infection. This discovery offers a completely new approach to fighting infections by targeting the host immune response rather than the bacterium," said Thirumala-Devi Kanneganti, Ph.D., an associate member of the St. Jude Department of Immunology, and the study's senior and corresponding author. Monoclonal antibodies are laboratory-produced versions of natural antibodies and are designed to detect specific proteins. Kanneganti laboratory is already working to develop a neutralizing antibody.

Despite the availability of antibiotics, bacterial infections continue to extract a heavy toll of suffering and death. A better understanding of how the immune system recognizes and responds to infectious agents would aid efforts to develop new, more effective treatments.

This study builds on earlier work from Kanneganti's laboratory and focuses on the NOD-like receptor protein 6 (NLRP6). NLRP6 belongs to a family of proteins that are part of the innate immune response that serves as the first line of defense. These proteins serve as sentinels working inside cells to recognize and response to infectious agents. Until now, however, nothing was known about NLRP6's role in the process.

Working in mice with and without the Nlrp6 gene, researchers tracked the immune response to different bacteria agents. This study focused on the innate immune response to Listeria monocytogenes, Salmonella typhimurium and Escherichia coli. All are bacteria that spread through food with potentially deadly results.

Surprisingly, mice without NLRP6 were far more likely to survive infection with lethal doses of the bacteria than their normal counterparts. The NLRP6-deficient mice had fewer bacteria in their livers and spleens one and three days after infection. They also had higher than normal levels of monocytes and neutrophils in circulation. Those are white blood cells known to play an important early role in combating infections. The findings suggest that mice lacking NLRP6 mount a more effective immune response.

Researchers went on to show that NLRP6 suppressed activity in pathways that trigger production of proteins called cytokines, which promote inflammation to combat the infection. The results show that NLRP6 regulates the nuclear factor-kappa B (NF-kB) and mitogen-activated protein kinase (MAPK) pathways.

"The result was entirely unexpected," said Paras Anand, Ph.D., a postdoctoral fellow in Kanneganti's laboratory and the study's first author. "This is the first member from the NLR family of proteins that inhibits rather than activates pathways involved in the innate immune response."

"NLRP6 might represent an entirely new subclass of these NLR proteins that functions to impede bacterial clearance," he said. Investigators are now studying the protein's response to other infectious agents.

Previous work on this molecule demonstrated that NLRP6 also helps to limit colitis and colon cancer. Kanneganti said the findings underscore the importance of balance to a properly functioning immune system. "This molecule helps maintain a balance between promoting and suppressing inflammation. In Colitis, NLRP6 seems to protect the host from the consequences of chronic inflammation and in the other we show it impedes bacterial clearance," she said.

Provided by St. Jude Children's Research Hospital