Researchers discover a 'security chief' that sounds the alarm against infections

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Corresponding author Thirumala-Devi Kanneganti, Ph.D., pictured with first authors Ein Lee, M.D., and Rajendra Karki, Ph.D. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital scientists have identified a key molecule that serves as a "security chief" to help the immune system quickly recognize and fight infections with dangerous gram-negative bacteria like Salmonella. The research appears online today in the

journal *Cell*.

The key molecule is IRF8, a transcription factor that regulates gene expression. Researchers showed that in immune cells called macrophages, IRF8 functions like a building security chief to make sure there are enough guards on duty to spot burglaries and alert authorities.

The scientists demonstrated IRF8 works by regulating the cells' supply of proteins called NAIPs. Researchers knew NAIPs were responsible for detecting Salmonella Typhimurium, Pseudomonas aeruginosa and other gram-negative bacteria in macrophages, and activating a protein complex called the NLRC4 inflammasome. Once activated, the NLRC4 inflammasome helps launch the inflammatory response to fight the infection and trigger the inflammatory cell death (pyroptosis).

This study revealed IRF8 is also essential for an effective immune response. Researchers showed that not only can IRF8 increase expression of NAIP genes, but that the transcription factor is essential for optimal activation of NLRC4.

"This advances our understanding of how our bodies sense infectious agents, particularly toxic agents like Salmonella," said corresponding author Thirumala-Devi Kanneganti, Ph.D., a member of the St. Jude Department of Immunology. "Such knowledge is essential for finding new ways to block infections."

Kanneganti and her colleagues study the innate immune response, the body's first line of defense against infectious agents and other threats. NLRC4 is one of five major inflammasomes involved in regulating that response. NLRC4 is unique because it is activated solely to fight gram-negative bacteria, particularly Salmonella, Legionella and Pseudomonas.

"Not only is NLRC4 important for protecting against these deadly

pathogens, but mutations in NLRC4 lead to autoinflammatory diseases in humans," Kanneganti said. "Yet, very little is known about NLRC4, including its regulation."

First authors Rajendra Karki, Ph.D., a staff scientist in Kanneganti's laboratory, Ein Lee, M.D., a graduate student, and their colleagues used a variety of methods to reveal details. The specifics included evidence that IRF8 binds to regions in DNA that control the production of NAIPs.

Researchers compared normal (wild type) macrophages derived from mouse bone marrow and macrophages without functional IRF8. Without functional IRF8, the immune response to Salmonella and other infections was muted. Fewer infected cells died and production of molecules that drive the inflammatory response was also reduced.

NAIPs work by detecting different bacterial components. Investigators found evidence that without IRF8, expression of genes encoding mouse NAIPs was reduced, leading to less inflammasome activation caused by bacterial proteins.

In addition, mice that lacked the Irf8 genes were more susceptible to Salmonella than mice with one or both Irf8 genes. Without Irf8, the mice died more quickly and carried more bacteria. "The finding suggests that reduced cytokine production and reduced cell death both contributed to greater susceptibility to Salmonella infection," Karki said.

Along with discovering IRF8's role in regulating NLRC4 activation, researchers found more evidence for the specificity and redundancy of the immune system. "For example, while IRF8 was required for optimal activation of NLRC4, IRF8 was not required for activation of at least three other inflammasomes," Lee said.

And, while IRF8 was required for optimal NLRC4 activation,

researchers noted that another transcription factor SPI1 (PU.1), may contribute to transcription of NAIPs. "This shows just how uniquely the system is designed so that we are not depending on a single molecule (IRF8) to regulate everything," Kanneganti said.

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