Research reveals how a fungal infection activates inflammation

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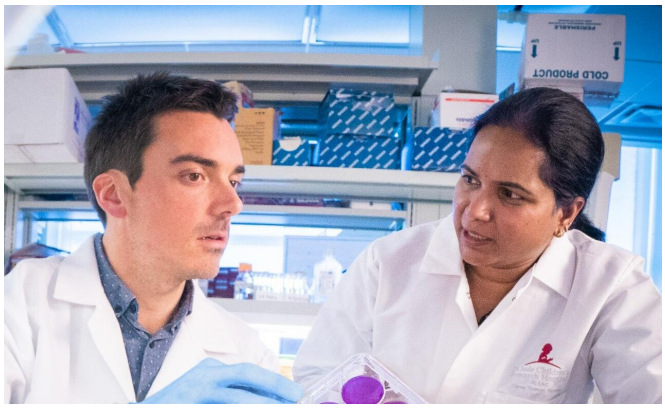

Benoit Briard, Ph.D. and Thirumala-Devi Kanneganti, Ph.D. Credit: St. Jude

Scientists at St. Jude Children's Research Hospital have identified the mechanisms behind inflammasome activation driven by infection with the fungal pathogen Aspergillus fumigatus. Fungal infection, especially with A. fumigatus, is a leading cause of infection-associated deaths in people with compromised immune systems. The work provides clues to a potential therapeutic approach for treating infectious and inflammatory disorders. The findings were published online today in *Nature*.

"Inflammasomes are important sentinels of an organism's innate immune defense system," said corresponding author and founding member of the inflammasome field Thirumala-Devi Kanneganti, Ph.D., of the St. Jude Immunology department. "Our prior work showed that fungal pathogens activate the inflammasome, but the exact mechanism of action for inflammasome engagement was unknown."

To understand these mechanisms for A. fumigatus, the scientists looked for pathogen-associated molecular patterns, which can stimulate the innate immune response by activating the inflammasome.

The scientists focused on NLRP3, the most-studied inflammasome sensor.

The research identified galactosaminogalactan (GAG), a novel fungal pathogen-associated molecular pattern. GAG is essential for A. fumigatus-induced NLRP3 inflammasome activation. The scientists showed that A. fumigatus deficient in GAG fail to induce inflammasome activation. Conversely, over-production of GAG by A. fumigatus increases inflammasome activation.

Additionally, inflammasome activation is critical for clearing A. fumigatus infections in animals. The A. fumigatus fungal strain that failed to produce GAG was more virulent in mice, while the strain that over-produced GAG was less virulent.

Similarly, inflammasome activation is protective during gut inflammation in a mouse model of colitis, an inflammatory disease. Treatment with purified GAG provided protection against colitis.

"We showed that protection against this inflammatory disease was dependent on the ability of GAG to induce inflammasome activation," said first author Benoit Briard, Ph.D., formerly of St. Jude Immunology. "These findings demonstrate the mechanism for the therapeutic potential of GAG in inflammatory diseases."

More information: Briard, B., Fontaine, T., Samir, P. et al. Galactosaminogalactan activates the inflammasome to provide host protection. *Nature* (2020). doi.org/10.1038/s41586-020-2996-z

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