Researchers pinpoint key influenza-fighting immune trigger

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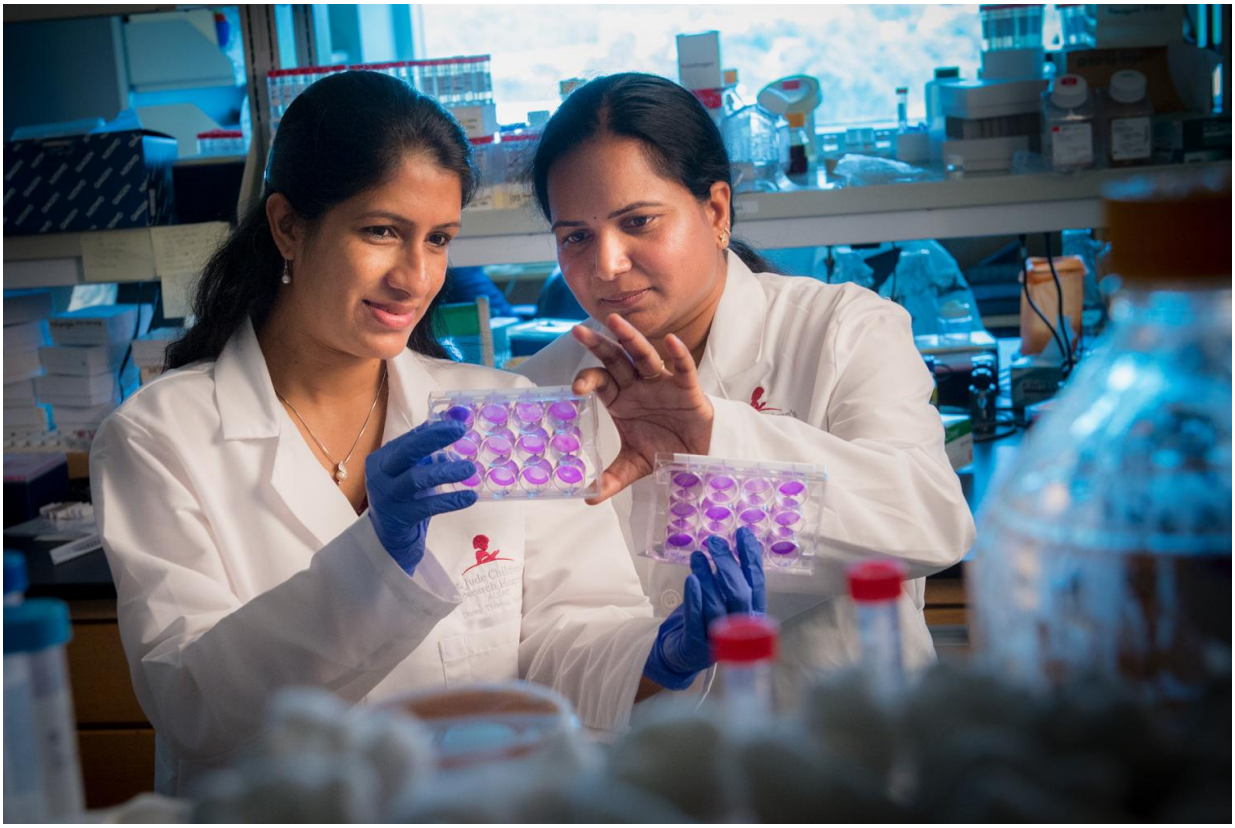

First author Teneema Kuriakose, Ph.D., a postdoctoral research associate in the Kanneganti laboratory, is pictured with Thirumala-Devi Kanneganti, Ph.D., a member of the St. Jude Department of Immunology. Credit: St. Jude Children's Research Hospital / Peter Barta

St. Jude Children's Research Hospital immunologists have identified the

protein trigger in the body's quick-reaction innate immune system that specifically recognizes the influenza virus in infected cells and triggers their death.

The researchers said that identifying this virus sensor, called ZBP1, offers the hope of developing drugs to protect against influenza's sometimes lethal complication of pneumonia. The pneumonia is exacerbated by lung inflammation and cell damage caused by overreaction of the innate immune system. Such drugs would modulate ZBP1's action—allowing the body to fight the virus by killing infected cells, but preventing that overreaction.

The team, led by Thirumala-Devi Kanneganti, Ph.D., a member of the St. Jude Department of Immunology, published their findings today in the journal *Science Immunology*. First author on the paper was Teneema Kuriakose, Ph.D., a postdoctoral research associate in the Kanneganti laboratory.

Their research sought to understand how the body's innate immune system is alerted to the presence of the virus and mobilizes to trigger infected cells to commit suicide. The innate immune system triggers the body's "emergency response" to invaders such as infections. This rapid attack gives the body's adaptive immune system time to generate antibodies that specifically target the virus or bacterium. Flu vaccines train this adaptive immune system to attack specific viral strains.

In the studies led by Kanneganti, Kuriakose and colleagues first sought to identify the specific machinery that the innate immune system uses to induce cell suicide. They identified that machinery as a biological pathway controlled by type I interferon.

Once the scientists identified that pathway, they began to search for the protein molecule that actually recognizes the virus and triggers the cell

death machinery. Their experiments used cells from genetically altered mouse strains, in which genes for particular proteins are selectively removed, to discover whether the cells lacking that protein would commit suicide when infected with influenza.

To their surprise, researchers found that cells lacking a protein called ZBP1 were completely resistant to viral-induced cell death. The finding was surprising because ZBP1 was known to sense foreign DNA in the cell, but the influenza virus uses RNA as its genetic material.

"Our discovery was totally unexpected," said Kanneganti. "We never thought we would actually identify this molecule to be important in influenza viral infection, because there is no DNA stage in the influenza life cycle." Further experiments revealed that ZBP1 was, indeed, a "master assassin" in the cell, responsible for triggering three separate cell death pathways.

In another surprise, the researchers discovered that ZBP1 was specific for recognizing influenza. The sensor did not trigger cell death in response to other similar viruses or to bacteria. This specificity is surprising, because the innate immune system is a generic emergency responder—its attack machinery evolved to thwart a wide array of invaders.

Other experiments revealed that ZBP1 acts as a protein detector, not a DNA detector, sensing telltale viral-produced proteins in the infected cell.

Moving their studies from cells to whole animals, the researchers tested the effects of knocking out the Zbp1 gene in mice infected with influenza. Because the innate immune system wasn't killing off infected cells, the mice showed an increased viral load and delayed recovery. But because the immune system wasn't able to overreact, the mice showed

reduced lung inflammation and damage to lung cells and were protected from mortality.

"Since the pathology that we saw in the mice matches what is seen in humans, we will now explore translating these findings to humans," Kanneganti said. "If we can somehow modulate the activation of this pathway, then that will help to decrease the exaggerated inflammatory response that causes mortality during influenza infection."

The timing of such drug treatment would be critical, Kuriakose said. "ZBP1 does an amazing job of killing off infected cells. But it would be very useful to modulate ZBP1 in later stages of the infection, when the uncontrolled inflammation causes damage."

Kanneganti emphasized that their discoveries have fundamental importance, because they identify a key innate immune sensor that recognizes the influenza virus and a regulator of multiple cell death pathways. These details are basic to our understanding of biological pathways of the innate immune system.

"We have shown that these molecules are important in viral infections, but now we want to test their role in other inflammatory conditions," she said. "ZBP1 is likely not dedicated to attacking only the influenza virus. Maybe it also plays other roles, and if we fully understand those roles, we can learn how to manipulate immune responses."

Provided by St. Jude Children's Research Hospital