Protein proves to be vital in immune response to bacteria

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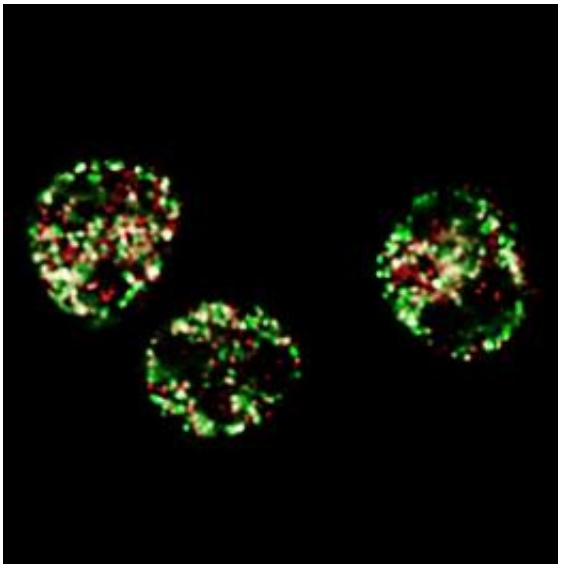

Bacteria blocker. Granulocytes, a type of white blood cell, are shown from a healthy individual. After exposure to a mycobacterium, these immune system cells secrete the protein ISG15, shown in green, to help fight the bacterial infection. ISG15 was found to be vital to stopping the spread of mycobacteria, which cause diseases like tuberculosis.

(Medical Xpress) -- A team of researchers led by scientists at Rockefeller University have discovered that a protein once thought to be mainly involved in antiviral immunity is in fact more important in fighting bacterial infections and could provide new mechanisms for treating diseases like tuberculosis, which is increasingly becoming resistant to antibiotic medication.

A mutation in the gene that codes for the protein ISG15 was found to increase susceptibility to infection by mycobacteria, a group of bacteria that cause a range of disorders, the most common of which are tuberculosis and leprosy.

"We were very surprised by this," says Dusan Bogunovic, a postdoctoral associate in the St. Giles Laboratory of Human Genetics of Infectious Diseases at Rockefeller and lead author on the study, which appeared in Science in August. "There were about 300 articles published on ISG15 before this, and I'd say 295 of them looked at viral disease. This connection to bacterial infection wasn't known."

The studies Bogunovic refers to tested only viruses and used mouse models - scientists can't knock out the ISG15 gene in humans to see what happens. But the lab, headed by Senior Attending Physician Jean-Laurent Casanova, tapped into their database of 300 people with what's known as Mendelian susceptibility to mycobacterial disease, a rare disorder that predisposes individuals to become severely ill from exposure to mycobacteria, even weak strains that would not affect healthy people. Whole exome sequencing revealed that ISG15 was mutated in three children whose diseases had no known cause. ISG15 proved to be a new genetic link to the disease, which has several other genes attributed to it.

"What's interesting here, in addition to finding a new genetic mutation that causes susceptibility to mycobacterial disease, is that while these children became very, very sick from a bacterium that would not harm you or me, they had normal reactions to viral infection," says Bogunovic. "They've seen flu, chicken pox, and they're fine. So it turns out that this gene is essential for immunity against bacteria. It could be important in fighting viruses, but it's not essential."

ISG15 is a protein involved in a cascade of protein-cell interactions that

help drive the immune system to eliminate a pathogen from the body. In studies spanning two and a half years, Bogunovic and colleagues worked out the protein's function. They found it was secreted by granulocytes, a type of white blood cell, and that it prompted another white blood cell, called a natural killer cell, to release interferon-gamma, a protein crucial to fighting mycobacterial infections.

To test whether this genetic mutation was, in fact, causing mycobacterial disease among the three children, Bogunovic exposed samples of their blood to a tuberculosis vaccine routinely given to children in Europe and elsewhere. Using a mild form of the tuberculosis bacterium, the vaccine exposes children to the disease and prompts the immune system to fight it off and remember it, reducing the chances of getting sick from full-blown tuberculosis in the future. The patients in this study had low levels of interferon-gamma in response to the vaccine, indicating their immune systems weren't fighting it. When Bogunovic added the ISG15 protein to the blood samples, interferon-gamma levels shot up. This and other tests proved that the genetic mutation was causing the children's immune deficiency.

"We know interferon-gamma is vital to fighting tuberculosis, and now we know that ISG15 is one of the proteins that brings it into action," says Bogunovic.

That means the proteins could be used in a treatment for tuberculosis and other mycobacterial diseases, rather than antibiotics. It's an approach in line with the growing field of personalized medicine, whereby a patient's genetic makeup is considered alongside clinical and environmental information to produce more effective treatment.

"Of course we are not there yet," says Bogunovic. "But this is an indication that we might not have to rely on antibiotics one day."

In the meantime, Bogunovic and his fellow lab members will continue to investigate ISG15's cell-signaling functions - they're currently looking for its receptor - and to search for more genetic errors that lead to mycobacterial disease.

More information: Mycobacterial Disease and Impaired IFN-γ Immunity in Humans with Inherited ISG15 Deficiency, by Dusan Bogunovic et al., *Science* online: August 2, 2012. www.sciencemag.org/content/ear … cience.1224026.short

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