'Double agent' in the immune system may make us vulnerable to bacterial infections

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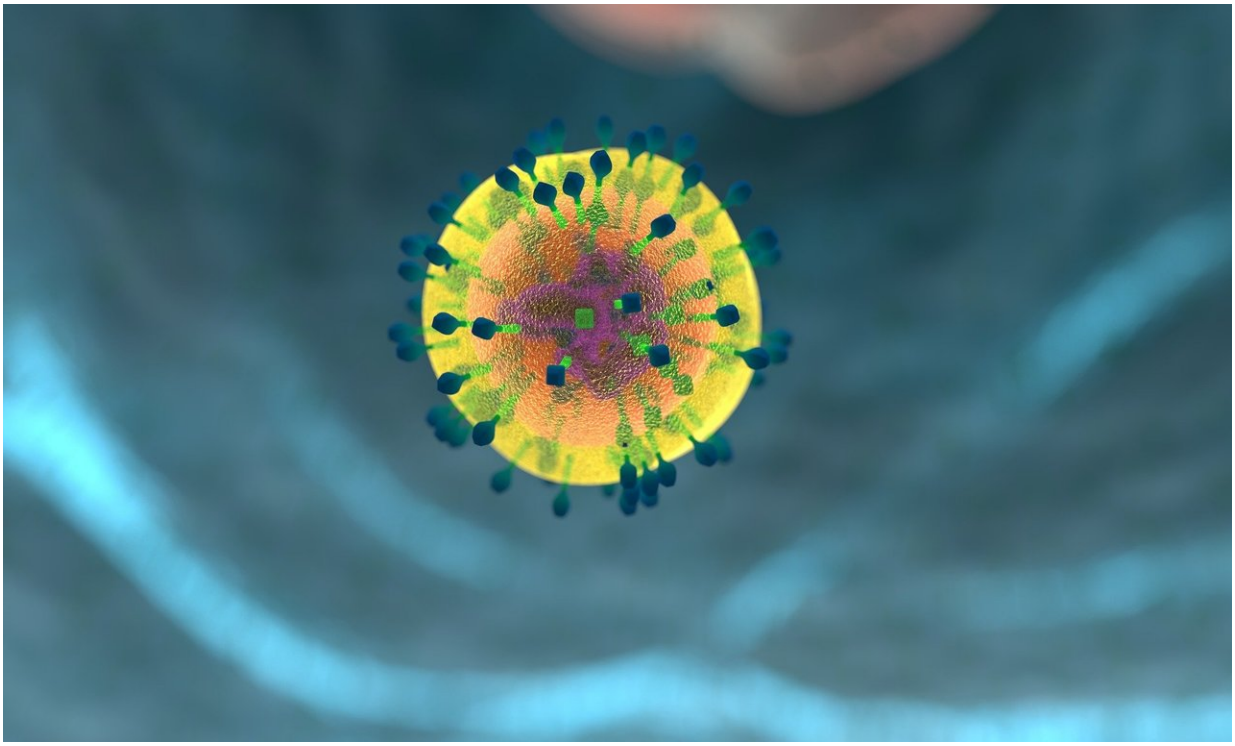

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Scientists at Scripps Research have discovered the role of an immune system double agent. This molecule, called USP18, can help curtail immune responses, but it can also open the door to bacterial infections, such as harmful listeria and staph infections.

"I call the molecule a 'wolf in sheep's clothing,' " says Namir Shaabani, Ph.D., a postdoctoral researcher at Scripps Research and co-first author of the recent *Science Immunology* study.

The researchers found that deleting the specific gene for this protein in certain immune system cells helps the body fight bacterial infections.This work, conducted in mouse models, offers a potential antimicrobial approach that could target both bacteria and viruses.

It all comes down to type 1 interferons, a type of immune molecule produced at the start of a viral infection. Interferons fight off the virus, and then their levels should drop when the threat is gone.

Study senior author John Teijaro, Ph.D., assistant professor at Scripps Research, says scientists have long wanted to understand a paradox in immunology—the question of how interferon-stimulated genes (ISGs) that usually help against viruses also dampen the host's ability to resist many bacterial infections.

For the new study, the team found that deleting a single ISG known as Usp18 in mouse dendritic cells, a type of immune cell, enhanced the body's ability to control infections with two strains of Gram-positive bacteria. They also found that normal induction of USP18 after infection impaired antibacterial responses mediated by a protein called tumor necrosis factor and accompanying reactive oxygen species generation, which help destroy bacteria in cells.

"Our results were unexpected because the absence of USP18 augments type 1 interferon signaling, which, if the current thinking is correct, should promote rather than prevent bacterial infection," says Teijaro.

Teijaro emphasizes that the study is basic biology—it illuminates the fundamental workings of the immune system—but it's worth

investigating whether USP18 can be targeted with drug therapies to treat bacterial infections. Knowing how to inhibit USP18 function could also give doctors the tools to boost interferon activity to better fight viral infections as well.

"One of our goals going forward is to test this therapeutically," says Teijaro. "We also want to expand our investigation to understand the role of USP18 in secondary bacterial pneumonia and tuberculosis infections."

There's one more potential advantage to developing therapies targeting USP18, Shaabani says. "Therapies targeting USP18 would also have the advantage of targeting the host, and not the bacteria directly, and therefore should be less susceptible to antibiotic resistance."

More information: Namir Shaabani et al, The probacterial effect of type I interferon signaling requires its own negative regulator USP18, *Science Immunology* (2018). DOI: 10.1126/sciimmunol.aau2125

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