Finding a new way to manage infections

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(Medical Xpress)—Waging an immunological war against a pathogen is not the body's only way to survive an infection. Sometimes tolerance, or learning to live with an invader, can be just as important. In tolerance the body lessens or repairs the damage that the pathogen causes.

Tolerance is a relatively new concept in immunology, and the details of how it works are still fuzzy. But a research team, led by Howard Hughes Medical Institute investigator Ruslan Medzhitov, has found that in mice that were coinfected with influenza virus and bacteria causing pneumonia , decreased tolerance—specifically, the downregulation of genes that respond to stress and promote tissue repair—made a deadly difference. Their research results appeared in *Science Express* on April 25, 2013.

According to Medzhitov, an immunobiologist at Yale School of Medicine, tolerance complements the immune system's fight against infection. "They're both important," he says, "and in different settings, one may be more important than the other. But they generally operate together." The mechanism by which an organism uses tolerance to survive infection can vary according to the type of pathogen and where in the body, for example, the lungs, the blood, or the digestive system, it causes infection.

To explore the balance between tolerance and immune response in a situation that has high clinical relevance, Medzhitov's team studied mice that were infected with influenza virus and Legionella pneumophila bacteria, which cause pneumonia. Bacterial pneumonia often follows

influenza infection in humans, usually from strains of bacteria that inhabit the nose and throat, and more than 65,000 people in the United States die from coinfection with influenza and bacterial pneumonia each year.

When Medzhitov's mice were given a dose of the bacteria or a dose of the virus alone, their bodies fought the infection and they survived. However, when they were given the same doses of virus and bacteria within three days—and only when they received virus first, then bacteria—all of the mice died. A longer time between the infective doses allowed the mice to survive the subsequent bacterial infection.

Medzhitov considered several reasons why a combination of virus and bacteria might be so lethal. Perhaps the mice had decreased immunological resistance because of some sort of synergy between the pathogens, or the bacteria may be secreting something virulent. It was also possible that the immune response to the infections was too strong and caused collateral damage to healthy tissue.

When he explored each possibility, however, none explained the lethality of the coinfections. Populations of virus and bacteria in the mice remained steady, showing that the immune systems of the mice were able to control growth of the pathogens. Mice that had genetically modified immune function or that received medicines to block inflammation also died, so an exaggerated immune response was not the culprit. The researchers also tested attenuated bacteria that were unable to secrete known virulence factors, and the mice still died; however, mice exposed to an inactive form of the virus were able to survive the bacteria, so something about active viral infection was needed.

A clue about tolerance came from analysis of fluid from the lungs, which showed that the mice had epithelial tissue damage and necrosis. The researchers looked at gene expression profiles in these tissues and

compared them with the gene expression profiles of lung tissue from mice infected with just one of the pathogens. They found that genes involved with tissue repair and stress response—two important features of tolerance—were specifically downregulated in the coinfected mice, which could not repair the lung damage caused by the infections.

"Something about the double infection prevented those genes from being engaged," Medzhitov says. "Mechanistically, we don't know what it is yet. We can imagine several scenarios, but it's something that we will be investigating in the future."

If the mice died because they were unable to repair lung damage, he reasoned, then something that stimulates lung repair should rescue coinfected mice from an otherwise certain death. The researchers gave coinfected mice the drug amphiregulin, a growth factor that stimulates epithelium, and found that it improved the survival of the mice.

There are many questions that need to be addressed before this treatment approach can be used in the clinic for patients with multiple respiratory infections, Medzhitov cautions. "We still need to find out which repair pathway is optimal, and in humans the pathway may be different from that in mice," he says. Even so, his proof of the concept that improved tolerance through boosted tissue repair can rescue the mice holds promise for patients who are particularly vulnerable to infections, such as infants and the elderly.

"We know a lot about how the immune system fights infections through resistance, but we know almost nothing about tolerance," Medzhitov says. "The practical aspect of that situation is that all of our attempts to manage infectious disease are currently based on one strategy."

The resistance strategy works fine in most cases. But for coinfections of HIV and tuberculosis, for example, or for other dangerous infections

that are not easily managed with medicines and can't yet be prevented with vaccines, something more is still needed, he says.

"As more investigators and clinicians appreciate the contribution of tolerance to survival, we hope that this will change," Medzhitov says. "There may be novel infection management approaches that come out of continuing basic research."

More information: Abstract: Mechanisms of Host Defense

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