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Parasites that live inside cells use loophole to thwart immune system

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St. Jude Children's Research Hospital scientists have discovered a mechanism by which intracellular pathogens can shut down one of the body's key chemical weapons against them: nitric oxide. The researchers found that the microbes block nitric oxide production by subverting the biochemical machinery used by immune cells called macrophages to produce the chemical.

Macrophages are the battle tanks of the immune system, attacking and consuming bacteria and parasites, shredding them with enzymes and poisoning them with nitric oxide. However, some pathogens, such as those that cause tuberculosis and toxoplasmosis, have evolved to live and proliferate within macrophages themselves. To do so, these intracellular pathogens deploy an arsenal of weapons to avoid and counterattack macrophage's own weapons.

In their study that appears in the advance online publication of the journal *Nature Immunology*, St. Jude researchers focused on the role the microbes play in activating the macrophages to make an enzyme called arginase. The arginase enzyme occurs naturally in macrophages, but is normally only expressed under very specific circumstances, including when macrophages might make too much nitric oxide.

"Although the findings are basic, they suggest that it might be feasible to develop drugs to block such pathogens' biochemical subversion, restoring nitric oxide production and empowering macrophages to attack the invaders," said Peter Murray, Ph.D., an associate member of the St.

Jude departments of Infectious Diseases and Immunology.

Previously other researchers had shown that pre-activating arginase in macrophages grown in the culture dishes can block nitric oxide production in macrophages by breaking down the chemical arginine, which the macrophages need to make nitric oxide. "However, no one had really explored the possibility that intracellular pathogens could directly exploit arginase-activation as a defense until now," said Murray, the paper's senior author.

To discover whether pathogens could be induced to mount such a defense in macrophages, the St. Jude team studied the arginase-inducing activity of the microorganisms that cause tuberculosis and toxoplasmosis, as well as a relative of tuberculosis, Mycobacterium bovis, that is used as a live vaccine.

Studies in macrophages in the culture dish and in mice demonstrated that these microbes did trigger arginase production and that this triggering suppressed nitric oxide production in macrophages. The researchers also traced the biochemical mechanism by which the organisms triggered arginase—finding that the microbes hijack the machinery by which the macrophages recognize invading pathogens.

Also working with mice, the researchers tested whether shutting down arginase might enhance the ability to battle tuberculosis. They found that mice genetically engineered to lack arginase only in their macrophages showed superior resistance to tuberculosis and toxoplasmosis.

"Our findings reveal that these pathogens have evolved to exploit a biological loophole in the immune system," Murray said. "This discovery offers two important insights. It reaffirms the notion that pathogens have an incredibly diverse way of manipulating their hosts. And it reveals a new pathway by which a pathogen can induce an enzyme that is normally

not present in those macrophages and use the induction of that enzyme to its advantage."

Murray emphasized that the findings are basic, and that the researchers can only speculate about possible clinical implications at the moment. "However, we believe it could be possible to develop targeted drugs to specifically inhibit pathogens' ability to induce arginase in macrophages," he said. Such drugs might suppress such diseases as tuberculosis and toxoplasmosis by increasing the ability of macrophages to make nitric oxide. Researchers believe that the drugs could work in combination with existing treatments for tuberculosis and parasites—dealing the diseases a therapeutic one-two punch.

Source: St. Jude Children's Research Hospital