

Killing bacteria isn't enough to restore immune function after infection

September 10 2008

A bacterial molecule that initially signals to animals that they have been invaded must be wiped out by a special enzyme before an infected animal can regain full health, researchers at UT Southwestern Medical Center have found.

Using a genetically engineered mouse model, the team found that simply eradicating the infection-causing bug isn't enough to restore an animal's immune function. Lipopolysaccharide, or LPS, the dominant bacterial "signal" molecule that heralds the invasion, must also be inactivated. The findings are to appear online Sept. 11 in *Cell Host & Microbe*.

"We think this is the first evidence that killing the causative agent of a bacterial infection isn't enough for an animal to recover fully," said Dr. Robert Munford, professor of internal medicine and microbiology, and senior author of the study. "You've got to get rid of this molecule that the host is responding to or else its immune system remains suppressed."

By sensing and responding to LPS, animals mobilize their defenses to attack and kill the bacteria. This immune response also causes inflammation in the host. For a few days after the infection begins, however, an animal's ability to sense the bacteria is turned down, presumably to prevent further inflammation. In the current study, the researchers found that mice didn't recover from this "tolerant" period unless the LPS was inactivated by acyloxyacyl hydrolase, an enzyme discovered in 1983 by Dr. Munford and Dr. Catherine Hall, now an assistant professor of internal medicine at UT Southwestern.

Dr. Mingfang Lu, instructor of internal medicine and lead author of the current study, said the team also found that prolonged tolerance was immunosuppressive, reducing the animal's ability to stave off another bacterial infection.

Dr. Lu said that how long an animal remains in this tolerant state varies from animal to animal. "But mice that can't make the enzyme acyloxyacyl hydrolase seem to stay tolerant forever, leaving them unable to fight additional infections," she said.

For the study, researchers injected LPS or a common bacterium that makes LPS into the abdomens of two types of mice: ones that could produce the acyloxyacyl hydrolase enzyme and ones that could not. Two weeks later they injected the mice with a deadly strain of *Escherichia coli* – which can cause loss of water and salts, damage to blood vessels, and bleeding in humans – to gauge how prolonged tolerance influences the animal's internal defense mechanisms.

Though almost all of the mice with the enzyme survived, 90 percent of those without the enzyme died. "Being tolerant, or unable to respond normally, made them more susceptible to the *E coli* we injected them with," Dr. Lu said.

Dr. Munford said they don't have any evidence that this finding is applicable to humans, who also make the enzyme, but it is possible.

"One theory is that there is variability among humans in the production of acyloxyacyl hydrolase," he said. "We don't know this yet, but if it's true, then the presence or absence of the enzyme might contribute to the length of immunosuppression after serious bacterial infections. It might even be reversible if we could provide the enzyme or figure out a way for people to make more of it."

The team's next step is to investigate further how LPS continues to stimulate the host's immune cells for such long periods of time if it does not get degraded. They also hope to use this animal model to understand better on a molecular scale exactly what happens during post-infection immunosuppression.

Source: UT Southwestern Medical Center

Citation: Killing bacteria isn't enough to restore immune function after infection (2008, September 10) retrieved 4 May 2024 from <https://medicalxpress.com/news/2008-09-bacteria-isnt-immune-function-infection.html>

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