Research shows why one bacterial infection is so deadly in cystic fibrosis patients

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Scientists have found why a certain type of bacteria, harmless in healthy people, is so deadly to patients with cystic fibrosis.

The bacterium, *Burkholderia cenocepacia,* causes a severe and persistent lung infection in patients with CF and is resistant to nearly all known antibiotics. Cystic fibrosis is a chronic disorder characterized by a buildup of mucus in the lungs and other parts of the body, and various types of lung infection are responsible for about 85 percent of deaths in these patients.

The Ohio State University researchers have determined that *B. cenocepacia* bacteria interfere with an important survival process in cells whose job is to fight infection. This phenomenon is even stronger in CF patients, so the infection exacerbates the cell malfunction.

The research group also showed that rapamycin, an existing drug known to stimulate this cell-survival process, called autophagy, helped control *B. cenocepacia* infection in mice that serve as a model for cystic fibrosis.

The scientists also dissected the role of a molecule called p62, which plays a role in the autophagy process. They found that p62 inside macrophages, the cells that fight infection, is influential in controlling *B. cenocepacia* infection.

"This suggests that manipulating p62 levels might help patients with CF fight off the lethal infection," said Amal Amer, assistant professor of

microbial infection and immunity and internal medicine at Ohio State and senior author of the study.

The research will be presented April 22 at the American Society for Biochemistry and Molecular Biology annual meeting, which is being held in conjunction with the Experimental Biology 2012 conference in San Diego. The rapamycin findings also were published in a recent issue of the journal Autophagy.

The *B. cenocepacia* infection remains relatively rare but highly transmissible in patients with cystic fibrosis. "It's really a death sentence for the patient. The disease either progresses with propagation of inflammation and chronic destruction of lung tissue, or acute infection with severe sepsis that occurs very quickly. We don't know which patient will take which course," said Amer, also an investigator in Ohio State's Center for Microbial Interface Biology.

Amer and her colleagues had been studying autophagy in other organisms before experimenting with these bacterial cells. Autophagy allows a cell to digest parts of itself to produce energy when it is experiencing starvation.

"We were among the first to show that autophagy can actually clear infection," Amer said. "So not only is it a physiological pathway in the background all the time, but some bacteria, when they infect cells, will be engulfed by autophagy. And that helps in clearing the infection."

These cells that can use autophagy to clear infection are the macrophages, which are first-responders in the immune system that essentially eat offending pathogens.

Amer and Ohio State doctoral student Basant Abdulrahman showed that macrophages isolated from both mice and humans that carried the most

common CF mutation could not clear the *B. cenocepacia* infection. The bacterium invades the macrophage and just sits there, Amer explained, instead of being digested and cleared away.

Because autophagy was not working in these cells, the researchers tested the effects of the drug rapamycin, an immune-system suppressant that is known to stimulate autophagy, in normal animals and those with the most common CF genetic mutation.

The drug had no real effect on normal mice because they could clear a *B. cenocepacia* infection on their own, said Abdulrahman, the study's lead author and presenter of the research at Experimental Biology 2012. But in mice with CF, she said, the drug's stimulation of the autophagy process helped these mice clear the bacterial infection from their lungs.

With this strong suggestion that autophagy is a potential target for new CF treatments, the researchers set out to better understand this process in CF macrophages that are unable to fight the *B. cenocepacia* infection. And that is when they found that p62 shows promise as an even more specific drug target. Additional studies of p62's effects on this bacterial infection are in progress.

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