Enzymes act like a switch, turning antibiotic resistance on and off in enterococci

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Antibiotic-resistant enterococci are a serious problem for patients in the hospital, but little is known about how these bacteria are able to escape antibiotics. New discoveries about the ways in which enterococci turn their resistance to cephalosporin antibiotics on and off are described in a study that will be published November 1 in the online journal *mBio*. The new details about resistance could lead to new therapies for preventing and treating enterococcal infections.

Enterococcus faecalis isn't always a deadly pathogen. Normally a friendly resident of the gastrointestinal tract, in individuals who are immune compromised *E. faecalis* can turn ugly. Infecting the bloodstream, urinary tract, and surgical sites. Patients who are given cephalosporin antibiotics for other problems are also prone to opportunistic *E. faecalis infection*, since the bacterium is naturally resistant to these antibiotics and flourishes when sensitive bacteria are killed off. Cephalosporins are like a last resort for treating infections that are resistant to other, less powerful drugs, so a patient treated with cephalosporins who acquires an *E. faecalis* infection essentially goes from the frying pan (their original infection) and into the fire (*E. faecalis* infection).

But how do enterococci overcome cephalosporin antibiotics? Despite the importance of this pathogen in hospitals, scientists still know relatively little about how enterococci skirt cephalosporin attacks. Chris Kristich and his colleagues at the Medical College of Wisconsin have uncovered new details about the bacterium's ability to turn resistance on and off, a development that could lead to new therapies for enterococcal

infections.

According to Kristich, the enzyme IreK is involved in resistance to cephalosporins, since enterococci that lack it are much more sensitive to the drugs. IreK is a kinase – an enzyme that carries phosphate groups. The study coming out in mBio details new findings about another aspect of resistance control: an enzyme called IreP, which takes phosphates off of IreK, thus controlling how active IreK is in the bacterium.

"Phosphorylating IreK changes the activity of the kinase – it's a way to turn it on and off," says Kristich. "The result of that actually is to regulate the level of the kinase output – it is reflected by the level of cephalosporin resistance."

Kristich says the bacterium probably needs a way to turn resistance on and off because maintaining the cellular machinery for resistance costs the cell important resources. "We don't know exactly how [enterococci become resistant to cephalosporins]. Whatever the mechanism, it may be costly when there's no cephalosporin around," says Kristich.

The problem with enterococcal infections is not going to get better until new therapies and preventive strategies can be developed, says Kristich. Knowing more about how the bacterium can go back and forth from sensitive to resistant and back can help lead researchers to ways of controlling infections. "There's an opportunity to develop a new strategy by understanding the basis for cephalosporin resistance," says Kristich. "If we could figure out a way to make enterococci susceptible to cephalosporins, they could be used to treat or prevent these infections."

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