Biomedical engineers find chink in bacteria's armor

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Biomedical researchers at Boston University's College of Engineering may have discovered the path toward developing better drugs capable of defeating so-called "superbugs," bacteria that have developed resistance to common antibiotics. The researchers have discovered a previously unknown chain of events occurring in bacteria that opens to door to new avenues of research.

Currently, three classes of bactericidal antibiotics are used to target different bacterial functions: inhibiting DNA replication; blocking protein-building; or halting construction of cell walls. Research from the laboratory of Professor James Collins found the three classes more alike than anyone realized, and the commonalities may be the bugs' downfall.

Collins and colleagues' article, "A Common Mechanism of Cellular Death Induced by Bactericidal Antibiotics," appears in the September 7 issue of *Cell*.

The researchers discovered a common process, or pathway, that was triggered by all three types of antibiotics. "There's an underlying pathway beyond the drug interacting with the target," said graduate student and lead author Michael Kohanski, "and the endpoint of this pathway is excessive free radical production."

Free radicals -- such as hydroxyl or superoxide radicals -- are molecules that carry a free, or unpaired, electron like a weapon. "They'll damage DNA, proteins, lipids in the membrane, pretty much anything. They're

equal opportunity damagers," said Kohanski.

This hidden pathway and resultant free radical overload appears to help current antibiotics do their job, but is not always enough to kill all bacteria by itself. Collins' group theorizes that if this effect can be amplified, or if the cell's genetic defense against it can be weakened, no bacteria could withstand its effect and the emergence of antibiotic-resistant bacteria could be limited.

"Importantly, we showed that if you can inhibit or block the bacterial defense mechanisms to hydroxyl radical damage, you can potentiate or enhance the lethality of bactericidal antibiotics. This highlights the value of taking a network biology approach to antibiotics and provides a framework for creating new classes of drugs," said Collins.

"What we think is happening is the cell is getting a signal that says, 'There's something wrong with our energy production system and we need to make more energy.' But, there's really nothing wrong. The cell becomes confused, turns on too many processes at once and it's overwhelmed," said Kohanski.

Previous work by Kohanski and co-lead author Dan Dwyer, a postdoctoral researcher in Collins' lab, revealed the first hints that this underlying pathway exists. In studying bacterial response to a quinolone, an antibiotic that inhibits DNA replication, they noted a surprising change in genes responsible for energy production and iron uptake.

In the current study, the researchers used DNA microarray studies to see if all three classes of bactericidal antibiotics triggered this process. Across the board, they noted increased gene activity along the intracellular assembly lines that make energy for the bacterial cell, just as in the earlier study. They began to deduce the details of the new pathway.

Cells produce free superoxide radicals naturally in oxygen-rich environments, but when they unnecessarily ramp up energy production to a frantic pace – such as when triggered by antibiotics – more radicals get churned out than the cell's safety measures can mop up. The superoxide radicals then pull iron from other components of the cell, and this iron rapidly stimulates production of toxic levels of hydroxyl radicals.

"It's really amazing that despite the diversity of targets, you have everything funneling into this common pathway, where there's a global meltdown occurring," said Dwyer. "There's almost no way for the cell to recover from this. It shows you how potent these molecules are to damaging and killing the cell."

In addition to potentially making bacteria more vulnerable to current drugs, this finding may revitalize development of antibiotic drugs sidelined because of narrow differences between therapeutic and toxic doses. Such drugs might re-enter the pipeline, if this free-radical producing pathway is exploited to lower the therapeutic dose, making formerly dangerous drugs safer.

Source: Boston University