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How bacteria fight antibiotics

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Researchers report in two separate papers in Science this week on novel methods used by bacteria to avoid being killed by antibiotics. In one study, scientists at the Rockefeller University report that the bacterial cells known as persisters, which tolerate but do not become resistant to antibiotics, preexist in a population and that their random switching between normal and slow-growing persister states enables them to escape antibiotic killing (*Science*2004, DOI:10.1126/science.1099390).

And in an accompanying paper, Stanford University researchers demonstrate that certain antibiotics trigger the SOS response in bacteria, resulting in shutdown of DNA replication and transient dormancy, enabling survival of the antibiotic sensitive bacteria (*Science* 2004 DOI:10.1126/science.1101630). The SOS response prevents damaged DNA from being copied at cell division, said Christine Miller, lead author of the Stanford study. "It's common throughout the whole plant, animal, bacterial world," she said.

Miller and colleagues were investigating conditions that affected the dpiAB gene operon - overexpression of which results in overcoming of the replication proteins DnaA and DnaB and induction of the SOS response - while it was connected in a plasmid to a lacZ reporter gene. They found that exposure to antibiotics triggered reporter gene expression, but only the beta-lactam or penicillin group of antibiotics - which work by binding cell wall components and causing cell lysis - had this effect.

"What they discovered is an interconnection among regulatory pathways that people did not suspect talked to each other - that is, the cell wall, DNA replication, and SOS," Kim Lewis, professor of biology at Northeastern University, told us.

But Lewis, who was not involved in the study, said there was a disconnect between the observations and the model the authors propose. "The cell can do considerably simpler and more elegant things - and it doesn't, which means we don't understand something," Lewis said. "We're missing something."

Nathalie Balaban's group at the Rockefeller cultured single bacterial cells and monitored the effect on them and their progeny in the presence and absence of antibiotics. "It's a technique that's based on Steve Quake's microfluidic devices, and we just adapted it for this experiment," Balaban said. They found that the slow-growing persisters flip into normal growth mode and back again in a stochastic fashion and therefore escape antibiotic killing.

The authors write that even before antibiotic treatment, persisters could be clearly distinguished from the normal cells by their reduced growth rate. The group mathematically modeled the switching from a normal to a persister state and *vice versa*. "We have described it is as stochastic, but we don't know a specific mechanism [to account for the switch]," Balaban said.

"This is interesting, but for somebody who doesn't know why this is important, this will just stay cute and insignificant," said Lewis, whose group has already described how persisters are largely responsible for the complete tolerance of biofilms to killing by antibiotics. "That is what makes persisters so really important - because biofilms are responsible for something like 65% of all infections in the West. It's an enormous, intractable problem."

And Lewis felt the use of the term "phenotypic switch" was unfortunate and misleading. "A switch in microbiology is a very particular thing," he said. "Phenotypic switches always in all cases that have been described so far affect the genome."

Still, Denis A. Mitchison, emeritus professor at the Department of Cell and Molecular Sciences at St. George's Hospital Medical School, London, welcomed Balaban *et al.*'s findings. Mitchison, who was not involved in the study, said that when he began working on the concept of persistence 50 years ago, in the area of tuberculosis, he had grant proposals turned down because the referees thought these bacterial populations do not preexist and are the result of interaction with drugs. "This is very nice because it's providing evidence that that's not so," said Mitchison.

References

1. *Science*, [http://www.sciencemag.org/]

2. Stanley N. Cohen Laboratory at Stanford University, [http://sncohenlab.stanford.edu/]

3. Kim Lewis, [http://www.biology.neu.edu/faculty03/lewis03.html]

4. Rockefeller University Laboratory of Living Matter, [http://www.rockefeller.edu/research/abstract.php?id=88]

5. Holding C: Lab on a chip *Genome Biology*, March 16, 2004., [http://genomebiology.com/researchnews/default.asp?arx_id=gb-spotlight-20040316-01]

6. Persister cells and tolerance to antimicrobials

7. Johnston N: Debaffling biofilms *The Scientist*, 18:34, August 2, 2004., [http://www.the-scientist.com/yr2004/aug/hot_040802.html]