# Antibiotics as active mutagens in the emergence of multidrug resistance

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Multidrug resistant bacteria such as Methicillin-resistant Staphylococcus aureus (MRSA) pose a major problem for patients, doctors, and the pharmaceutical industry. To combat such bacteria, it is critical to understand how resistance is developed in the first place. It is commonly thought that an incomplete course of antibiotics would lead to resistance to that particular antibiotic by allowing the bacteria to make adaptive changes under less stringent conditions.

However, new research from Mike Kohanski, Mark DePristo, and Jim Collins at Boston University and the Howard Hughes Medical Institute shows that low doses of antibiotics can produce mutant strains that are sensitive to the applied antibiotic but have cross-resistance to other antibiotics. Their findings shed light on one of multiple mechanisms that may contribute to the emergence of multidrug resistant bacterial strains or so called "superbugs".

The study, published in the February 12th issue of *Molecular Cell,* a Cell Press journal, builds on earlier observations from this group that antibiotics produce reactive oxygen species (ROS) in bacteria. At high doses, ROS ultimately kill the bacteria, but at low doses they can lead to mutations. To test the hypothesis that low dose antibiotics might contribute to drug resistance through increased mutagenesis, they first confirmed that each of the antibiotics tested actually increased mutations in a manner that was dependent on the ability of the bacteria to produce reactive oxygen species.

This indeed proved to be the case, so they turned their attention to examining cross-resistance to other antibiotics. While each of the antibiotics tested (ampicillin, norfloxacin, kanamycin, tetracycline and chloramphenicol) is capable of some degree of cross-resistance, quite strikingly, ampicillin appears to give rise to the widest range of resistance. Surprisingly, the bacteria remained sensitive to the applied antibiotic. The observed resistance in each case is dependent on the ability of the bacteria to produce ROS, similar to the ability to produce mutations.

The researchers confirmed the link between antibiotic cross resistance and antibiotic-induced ROS by sequencing the bacterial genes known to cause resistance to each antibiotic, and in most cases they found mutations in the expected genes that would lead to the production of proteins that help the bacteria to endure the antibiotics (such as multidrug efflux pumps).

Importantly, this mutagenic mechanism occurs not only in laboratory strains of Escherichia coli and Staphylococcus aureus, but also in a clinical isolate of Escherichia coli showing that it is likely a general survival mechanism for bacteria. According to Collins, "our work shows that low levels of antibiotics can serve as active mutagens rapidly leading to multidrug resistance".

These findings have important implications in terms of both how antibiotics are administered and the potential benefits of combining antibiotic treatment with inhibitors that prevent the formation of ROS or that prevent the bacteria from generating mutations.

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