Study Shows How Antibiotic Sets Up Road Block To Kill Bacteria

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(PhysOrg.com) -- Scientists have taken a critical step toward the development of new and more effective antibacterial drugs by identifying exactly how a specific antibiotic sets up a road block that halts bacterial growth.

The antibiotic, myxopyronin, is a natural substance that is made by bacteria to fend off other bacteria. Scientists already knew that this antibiotic inhibited the actions of an enzyme called RNA polymerase, which sets gene expression in motion and is essential to the life of any cell.

But until now, researchers did not know the mechanism behind how the antibiotic actually killed the bacteria.

Key to investigating this mechanism is the use of the powerful imaging technique X-ray crystallography, which allows researchers to see the fine details of the complex between the antibiotic and its target.

In the case of myxopyronin, the antibiotic binds to RNA polymerase in a way that interferes with the enzyme's ability to use DNA to start the process of activating genes so they can make proteins.

"This is the first antibiotic that we know that inhibits polymerase before it even starts RNA synthesis," said Irina Artsimovitch, a coauthor of the study and an associate professor of microbiology at Ohio State University.

The research is published online in the journal Nature.

Artsimovitch is co-principal investigator on the work along with Dmitry Vassylyev of the University of Alabama at Birmingham, who led the use of X-ray crystallography to determine the structure. Research teams from the two universities worked with staff at Anadys Pharmaceuticals Inc. of San Diego, which manufactured a synthetic form of the antibiotic used for this study.

The results of the study, and additional research planned to explore modifications of the synthetic antibiotic's structure, could lead to the development and commercial availability of a new class of antibiotic drugs.

"As a natural substance, it is what it is. If you want to design a better antibiotic, you can only do that if you know what features are important," Artsimovitch said.

Using the synthetic form of the antibiotic, called dMyx, the researchers were able to observe how it inhibits different RNA polymerases used for this work: Escherichia coli (E. coli) and Thermus thermophilus. The dMyx attaches to a site on the RNA polymerase enzyme that is near DNA. The enzyme's interaction with DNA initiates the transcription process by which genes are expressed and make proteins, essential steps for the survival of the bacteria.

The researchers observed that dMyx binding effectively halted what is called DNA melting – the separation of the two strands of the DNA double helix. This separation must occur for the enzyme to complete its task, but in the presence of the antibiotic, the enzyme instead formed a loop that blocked access of the DNA.

In the context of watching this antibiotic in action, the scientists

discovered new information about how RNA polymerase itself works. The enzyme is known to separate the double helix of DNA and use one strand to match nucleotides and make a copy of genetic material.

“We think of it as a one-step transition. RNA polymerase melts the DNA to create a bubble of 14 nucleotides, and that’s where it starts its work,” Artsimovitch said. “But what we saw was the polymerase uses two steps. It melts a little bit of the DNA, stops to check its progress, and then continues the melting further downstream.

“But the antibiotic switches it all into one state and it doesn’t allow the second step. It creates a static clash, a road block that cannot be passed.”

The scientists were able to determine that a segment of the enzyme called switch-2 refolded into a loop upon the antibiotic binding. To test the role of the switch-2 segment further, the researchers manipulated the enzyme by predicting mutations that might naturally occur as the bacteria cells tried to defend themselves against the antibiotic. These predicted mutations caused switch-2 to refold by itself, even without dMyx.

This showed that dMyx is an attractive drug candidate, Artsimovitch said. The changes the bacteria would likely make to defend against this specific antibiotic’s binding activity seem to interfere with the RNA polymerase’s ability to perform its essential task – so even while trying to mutate and become resistant, the bacteria probably would die anyway.

The scientists were able to demonstrate that the location of the dMyx binding site is different from the sites used by other antibiotics – thus, dMyx would still be active against bacterial strains already resistant to the existing drugs. Moreover, the site is so specific that this agent would not do damage to the RNA polymerase activity in healthy human cells.

“In terms of antibiotics, two things are very important: You want it to kill bacteria and you want it not to kill you,” Artsimovitch said. “For this reason, you have to use substances that inhibit only bacterial polymerase, but do not inhibit ours.”

Provided by Ohio State University

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