Team discovers evolutionary mechanism that allows bacteria to resist antibiotics

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In research published in *Proceedings of the National Academy of Sciences*, assistant professor of biochemistry and molecular biology at Saint Louis University Mee-Ngan F. Yap, Ph.D., discovered new information about how antibiotics like azithromycin stop staph infections, and why staph sometimes becomes resistant to drugs.

Her evidence suggests a universal, evolutionary mechanism by which the bacteria eludes this kind of drug, offering scientists a way to improve the effectiveness of antibiotics to which bacteria have become resistant.

Staphylococcus aureus (familiar to many as the common and sometimes difficult to treat staph infection) is a strain of bacteria that frequently has become resistant to antibiotics, a development that has been challenging for doctors and dangerous for patients with severe infections.

Yap and her research team studied staph that had been treated with the antibiotic azithromycin and learned two things: One, it turns out that the antibiotic isn't as effective as was previously thought. And two, the process that the bacteria use to evade the antibiotic appears to be an evolutionary mechanism that the bacteria developed in order to delay genetic replication when beneficial.

The team studied the way antibiotics work within the ribosome, the site where bacteria translates the genetic codes into protein. When the bacteria encounter a potential problem in copying its genetic material, as posed by an antibiotic, it has a mechanism to thwart antibiotic inhibition by means of "ribosome stalling" that is mediated by special upstream peptide elements.

As the bacteria's ribosome copies the strings of genetic code, "ribosome stalling" at upstream elements often promotes the rearrangement of messenger RNA and activates downstream translation of the resistance gene.

Many resistant pathogens exploit this mechanism to up-regulate antibiotic resistance genes, and so survive even in the presence of antibiotics. In effect, the delay allows the bacteria to prepare a defense against the antibiotic further down the line of genetic code.

Yap found that the azithromycin-bound ribosomes do not simply stall at random residues, but only at specific sites. Intriguingly these residues seem to be the preferred stalling site in the "ribosome stalling" peptide elements that stop genetic activity.

"Here we describe, to our knowledge, the first genome-wide snapshot of ribosome distribution along messenger RNAs in *Staphylococcus aureus*," Yap said. "By globally mapping the position of stalled ribosomes in azithromycin-treated staph, we identified the proteins affected by this antibiotic.

"Our results reveal a striking similarity of stalling motifs that strongly suggests a universal stalling mechanism," Yap said. "We have identified what appears to be an evolutionary mechanism developed by bacteria to counteract the type of antibiotics that includes azithromycin, called macrolides."

Yap hopes this new understanding of how antibiotic resistance occurs will offer opportunities to improve existing drugs' effectiveness and give doctors more tools to help patients with severe infections.

More information: *Proceedings of the National Academy of Sciences*, www.pnas.org/content/111/43/15379.full

Provided by Saint Louis University

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