Deadly bacteria may mimic human proteins to evolve antibiotic resistance

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Deadly bacteria may be evolving antibiotic resistance by mimicking human proteins, according to a new study by the Translational Genomics Research Institute (TGen).

This process of "molecular mimicry" may help explain why bacterial human pathogens, many of which were at one time easily treatable with antibiotics, have re-emerged in recent years as highly infectious public health threats, according to the study published May 26 in the journal *Public Library of Science (PLoS) One*.

"This mimicry allows the bacteria to evade its host's defense responses, side-stepping our immune system," said Dr. Mia Champion, an Assistant Professor in TGen's Pathogen Genomics Division, and the study's author.

Using genomic sequencing, the spelling out of billions of genetic instructions stored in DNA, the study identified several methyltransferase protein families that are very similar in otherwise very distantly related human bacterial pathogens. These proteins also were found in hosts such as humans, mouse and rat.

Researchers found methyltransferase in the pathogen Francisella tularensis subspecies tularensis, the most virulent form of Francisella. Just one cell can be lethal. Methyltransferase is a potential virulence factor in this pathogen, which causes Tularemia, an infection common in wild rodents, especially rabbits, that can be transmitted to humans

though bites, touch, eating or drinking contaminated food or water, or even breathing in the bacteria. It is severely debilitating and even fatal, if not treated.

Similar methyltransferase proteins are found in other highly infectious bacteria, including the pathogen Mycobacterium tuberculosis that causes Tuberculosis, a disease that results in more than 1 million deaths annually. The study also identified distinct methyltransferase subtypes in human pathogens such as Coxiella, Legionella, and Pseudomonas.

In general, these bacterial pathogens are considered "highly clonal," meaning that the overall gene content of each species is very similar. However, the study said, "The evolution of pathogenic bacterial species from nonpathogenic ancestors is … marked by relatively small changes in the overall gene content."

Genomic comparisons were made with several strains of the bacteria, as well as with plants and animals, including humans. The methyltransferase protein also was found to have an ortholog, or similar counterpart, in human DNA. Although the overall sequence of the orthologs is highly similar, the study identifies a protein domain carrying distinct amino acid variations present in the different organisms.

"Altogether, evidence suggests a role of the Francisella tularensis protein in a mechanism of molecular mimicry. Upon infection, bacterial pathogens dump more than 200 proteins into human macrophage cells called 'effector proteins.' Because these proteins are so similar to the human proteins, it mimics them and enables them to interfere with the body's immunity response, thereby protecting the pathogen," Dr. Champion said.

"These findings not only provide insights into the evolution of virulence in Francisella, but have broader implications regarding the molecular

mechanisms that mediate host-pathogen relationships," she added.

Identifying small differences between the pathogen and human proteins through Next Generation genome-wide datasets could help develop molecular targets in the development of new drug treatments, she said.

Provided by The Translational Genomics Research Institute