Sequencing efforts miss DNA crucial to bacteria's disease causing power

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Genomic sequencing is supposed to reveal the entire genetic makeup of an organism. For infectious disease specialists, the technology can be used to analyze a disease-causing bacterium to determine how much harm it is capable of causing and whether or not it will be resistant to antibiotics. But new research at Rockefeller University suggests that current sequencing protocols overlook crucial bits of information: isolated pieces of DNA floating outside the bacterial chromosome, the core of a cell's genetic material.

"Extensive sequencing of chromosomal DNA has been performed for a variety of pathogenic organisms, but these sequences fail to uncover the presence of DNA elements in the cell's cytoplasm. As a result, the DNA profile of a pathogenic bacteria may be incomplete," says Vincent Fischetti, head of the Laboratory of Bacterial Pathogenesis and Immunology. "We have now devised a way to identify these elements."

Extrachromosomal DNA can include bacteria-infecting viruses, known as phages, and strands of self-replicating DNA, known as plasmids, often picked up from other bacteria. These phages and plasmids can easily move between bacterial cells, and scientists have known for some time that, as a result, these so-called mobile genetic elements can play important roles in virulence and antibiotic resistance.

This study focused on phages. Their activity outside the chromosomes has been poorly studied; most research has focused on phages integrated into bacterial chromosomes. Meanwhile, plasmids, which allow bacteria

to share genes among themselves, are well studied.

"So far, no one has looked across a variety of strains of bacteria, as we have done with *Staphylococcus aureus*, to find these extrachromosomal phages that have potential to play an important role in disease," says Bryan Utter a postdoc in the lab and the first author of the research published June 25 in *PLoS ONE*. *Staphylococcus* is a common bacterium that can cause serious or even fatal infections under certain circumstances.

Until now, an analysis of this scope wasn't possible, because chromosomal DNA easily fragments and contaminates the sample during the process by which researchers prepare the extrachromosomal DNA, making them virtually impossible to identify and sequence.

"To solve this problem, we borrowed a tool from phages themselves: the enzymes these viruses use to break apart a phage-infected cell to release their progeny," says Douglas Deutsch, a graduate student in the lab. These enzymes, a focus of research in the lab in the development of novel anti-infectives, are now being harnessed to gently extract the chromosomal DNA, while leaving behind any other genetic elements for analysis. Using this technique, they looked for extrachromosomal phages across 24 medically important strains of Staphylococci.

Not only did extrachromosomal phages appear widespread among these strains, but the researchers found evidence that these phages encode genes that can make the bacteria more dangerous.

For example, when the researchers decoded the complete sequence of one extrachromosomal circular phage from a disease-causing *Staphylococcus*, they identified a number of genes that may help this strain evade a host's immune system and that could readily spread to other *Staphylococcus* bacteria. The researchers are now studying what

role, if any, these viral genes play in this strain's ability to cause disease.

The implications go beyond pathogenicity. Phage elements, including those not integrated into chromosomes, are part of a bacterial system for regulating genes. For instance, some of these phage elements can activate or silence bacterial genes by moving into or out of the chromosome. Within the *Staphylococcus* strains, the researchers found both transient elements as well as those residing permanently outside the chromosomes.

"By examining the DNA outside the bacterial chromosomes, you may get a better understanding of the dynamics by which these elements may mobilize thereby controlling microbial genes," Fischetti says.

Provided by Rockefeller University

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