Investigators figure out how to block new antibiotic resistance gene

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A new antimicrobial-resistance gene, VCC-1, a ß-lactamase gene, has been discovered in benign close relatives of virulent Vibrio cholerae, which causes cholera. Now, a team of Canadian researchers has found a way to block the VCC-1 enzyme, which disables that resistance gene. The research is published February 19th in *Antimicrobial Agents and Chemotherapy*, a journal of the American Society for Microbiology.

VCC-1 was first found in Canada, by investigators from the Public Health Agency of Canada, on frozen shrimp that had been imported from India, and sold in a Canadian grocery store. A handful of other ß-lactamase resistance genes have also emerged from India. ß-lactamase genes code for enzymes that can break down ß-lactams, which are a critically important class of antimicrobials.

The investigators identified the gene in a non-toxogenic strain of Vibrio cholerae. Since then, VCC-1 has also been found in non-toxogenic V. cholerae off of the German coastline. The danger is that it's a short jump for a gene from non-toxogenic V. cholerae to its toxogenic siblings.

"We noticed that VCC-1 belongs to the same class of [antibiotic resistance] enzymes that avibactam is active against," said lead author Brian Mark, Ph.D., Professor, Department of Microbiology, University of Manitoba. The US Food and Drug Administration had recently approved Avibactam. "I said, 'lets try avibactam'," and sure enough, it blocks the enzyme quite potently," said Dr. Mark.

To see how avibactam did so, Dr. Mark and his collaborators used X-ray crystallography, a method of visualizing the three-dimensional structure of molecules at the atomic level.

The X-ray crystallography showed that the avibactam molecule has a protuberance that fits snugly into a pocket on VCC-1, "the same pocket that VCC-1 uses to break down the antibiotic," said Dr. Mark.

After that, "We went back to the original strain, the Vibrio the VCC-1 was originally found in," said Dr. Mark. "We grew it up, and demonstrated that if you try to kill this bacteria with carbapenem [an important beta lactam antimicrobial], it is very resistant, which is alarming, as this is a front line, last resort antibiotic, and here it is sitting on shrimp that people are eating. But if you add avibactam to the carbapenem, it becomes really potent, because you blocked the VCC-1 which was enabling the resistance."

The US Food and Drug Administration recently approved combination drug containing avibactam and the antibiotic, ceftazidime. Should a patient enter a clinic ill with a pathogen carrying VCC-1, knowledgeable physicians will be ready.

Provided by American Society for Microbiology

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