ICU
MANAGEMENT & PRACTICE

Lifeline for 'Antibiotic of Last Resort': Mechanism That Triggers Resistance to Vancomycin Identified

Gerry Wright, a professor in the Department of Biochemistry and Biomedical Sciences at McMaster University in collaboration with colleagues at the John Innes Centre in Norwich, and the University of Cambridge in the UK, have identified the specific mechanism that triggers resistance to vancomycin.

The discovery reveals new understanding about what is happening at the molecular level in vancomycin resistance. It also represents an essential first step in developing new antibiotics that can evade the sensing mechanism of bacteria and overcome resistance.

The research, funded in part by the Canadian Institutes of Health Research and the Canada Research Chairs program, is published online in the journal Nature Chemical Biology.
"Vancomycin is the antibiotic of last resort and is only given when all other treatments fail," said Wright, who holds the Canada Research Chair in Molecular Studies of Antibiotics and an endowed research Chair in Infection and Anti-Infective Research.

"For years it was thought that resistance would be slow to emerge since vancomycin works in an unusual way. But with the widespread use of the drug to treat infections caused by the hospital superbug MRSA, it has become a serious clinical problem."

MRSA is the short-form for methicillin-resistant staphylococcus aureus, a bacterial infection that is highly resistant to some antibiotics. MRSA bacteria are responsible for a large percentage of hospital-acquired staph infections, but may also be acquired in the community.

Vancomycin is used to treat enterococcal infections that develop in patients following abdominal surgery. Enterococcal bacteria first developed resistance to vancomycin in 1986 and the first case of vancomycin-resistant MRSA (VMRSA) was reported in 2002.

For 20 years, scientists around the world have debated whether bacteria sense the drug itself to trigger resistance or whether they sense the impact it has on the cell wall of bacteria.

Most antibiotics work by inhibiting an enzyme but vancomycin binds to cell wall building blocks, causing a weakness in the structure of the cell wall so the cell bursts and dies.

Some scientists believed that bacteria detect the cell wall degradation to trigger resistance. Others argued that bacteria detect the presence of the drug directly.

Wright and his team studied the vancomycin-resistance mechanism in the harmless soil bacteria Streptomyces coelicolor.

The scientists showed that bacteria detect vancomycin itself. They also conducted preliminary experiments that suggest the same mechanism exists in disease causing bacteria.

"We have finally cracked the alarm system used by bacteria, and hopefully new antibiotics can be developed that don't set it off," said Mark Buttner, a study collaborator and senior scientist at the John Innes Centre.

Marc Ouellette, scientific director of the Institute of Infection and Immunity at the Canadian Institutes for Health Research (CIHR), said the research findings shed new light on the antibiotic resistance issue.

"Thousands of Canadians die every year from antibiotic-resistant infections," Ouellette said. "This issue has long been a priority of the CIHR and this exciting work expands our understanding of how bacteria develop resistance to antibiotics. It lays the groundwork for developing new therapies to prevent and treat antibiotic-resistant infections."

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Journal Reference:
Kalinka Koteva, Hee-Jeon Hong, Xiao Dong Wang, Ishac Nazi, Donald Hughes, Mike J Naldrett, Mark J Buttner, Gerard D Wright. A vancomycin photoprobe identifies the histidine kinase VanSsc as a vancomycin receptor. Nature Chemical Biology, 2010; DOI: 10.1038/nchembio.350

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