MedicalXpress

Scientists make big discovery in antibiotics research

July 21 2015, by Mark Johnson, Milwaukee Journal Sentinel

Scientists seeking to develop the next generation of antibiotics may have found a crucial clue within the human body: a protein that distinguishes between our cells and those of invading microbes, according to a study led by researchers at the University of Wisconsin-Madison.

The discovery is important because antibiotics, credited with saving millions of lives since their discovery in 1928, have been under increasing attack from bacteria that have developed resistance to them. Infections caused by these resistant bacteria are now responsible for about 23,000 deaths a year in the U.S.

The new study, which appears in the journal *Nature Structural and Molecular Biology*, suggests that the protein intelectin could hold the key to a new kind of antibiotic. The protein is found mostly in the human gut and the lungs, places especially vulnerable to invaders. Intelectin levels rise in response to an infection.

"This has the potential to change the game in terms of how we combat microbes," said Laura Kiessling, the UW professor of chemistry and biochemistry who led the study. The project also involved work by UW bacteriology professor Prof. Katrina T. Forest as well as scientists at the Scripps Research Institute in La Jolla, Calif., and Emory University School of Medicine in Atlanta.

"This is an extremely exciting proposition as it could provide a new pathway of drug discovery against ... pathogens that have significant

socioeconomic impact and impose a heavy burden on our health systems," said Mark von Itzstein, director and principal research leader at the Institute for Glycomics at Griffith University in Australia.

Von Itzstein, who did not take part in the study, said antibiotic resistance "is at staggering levels ... there are strains of worrying bacteria that we can now barely treat and these are becoming killers."

Kiessling and her colleagues are now trying to modify the protein to make it recruit the immune system to eliminate bacteria. The next step will be to test the protein's microbe-fighting effectiveness in mice.

Although the paper does not claim intelectin kills microbes by itself, Kiessling said researchers have found several lines of evidence suggesting that it may help clear away the microbes. The protein is found not only in humans, but in many other creatures, including horses, sheep, goats, eels and frogs.

"All of these different species have to fight off bacteria," Kiessling said.

Developing frog embryos produce a large amount of intelectin, a period when they would be especially susceptible to bacteria.

Kiessling, a 1999 winner of a MacArthur Foundation "genius grant," focuses in her lab on examining the role of carbohydrates found on the surfaces of cells. The new paper represents two years of work that began when a student in her lab, Darryl A. Wesener, became interested in intelectin. Another student, Kittikhun Wangkanont, determined the protein's structure.

Scientists have known about intelectin for a while. Genetic variations in the protein have been linked to asthma and Crohn's disease, a form of inflammatory bowel disease. The protein is also a marker for tumors and

is found in higher levels in diabetes.

"But it wasn't really clear what it did," Kiessling explained.

Her lab examined how the protein responded to both human cells and microbial cells. The scientists exposed intelectin to arrays of carbohydrates found on the surface of human cells, then to arrays of the carbohydrates found on microbial cells.

They found that the protein bound to the carbohydrates on the microbial cells, but not to those on the human cells. This means that the protein is able to distinguish between cells that are part of ourselves and cells that are not.

"I think this is a really interesting paper," said Jeff Gildersleeve, a senior investigator at the National Cancer Institute, who was not involved in the study. He said that while the protein has been known, the way that it binds to other cells was not known.

Intelectin is also folded in a distinctive way, giving it an unusual structure, Gildersleeve said. The way a protein is folded determines the way it functions.

The new study provides scientists with their first picture of intelectin.

In the human gut, intelectin is secreted into a kind of No Man's Land that exists between the epithelial cells that line the stomach and our collection of microbes, known as the microbiome.

"We think it's going to help rid us of any bad actors that get into our gut or into our lungs," Kiessling said.