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New class of antibiotics effective against drug-resistant bacteria discovered in fungi

A peptide identified in a fungus found in northern European pine forests possesses as much power as penicillin as well as vancomycin, according to an international team of researchers.

Reporting in the October 13 issue of Nature, a team from Denmark-based biotech company Novozymes, and researchers from Georgetown University Medical Center and the David Geffen School of Medicine at UCLA, say they have isolated "plectasin," the first defensin ever found in fungi. The research was performed at Novozymes laboratories in Denmark.

Defensins are peptides, miniature protein molecules that are produced by a wide range of animals to protect themselves against infection. Humans have defensins in their white blood cells and in their skin, for example, but it is believed that this new fungal defensin, plectasin, is more potent and targets certain bacteria more specifically.

Indeed, when plectasin was tested in the laboratory and in animals, it proved to be highly effective against the bacteria Streptococcus pneumoniae, and Streptococcus pyogenes, including strains that are now resistant to conventional antibiotics. These bacteria are responsible for such diseases as meningitis, community-acquired pneumonia, strep throat, life-threatening sepsis, and flesh destroying skin infections.

The discovery of plectasin has implications for the development of defensins as a treatment against many common, and deadly, infections, and may initiate a new era of antibiotic discovery and development, said study co-author Michael Zasloff, M.D., Ph.D., Professor in the Departments of Surgery and Pediatrics at Georgetown University Medical Center.

Zasloff says that the field of antibiotic development has not changed much since 1929 when Alexander Fleming realized that the fungal "bread mold" Penicillium, which had landed by chance in a Petri dish produced a substance that eliminated colonies of staphylococcal bacteria.

"Most antibiotics used by humans are produced by fungi and certain soil bacteria," he said. "Using our existing tools of discovery, we have failed to uncover any new classes of antibiotics from these sources over the past decade. However, by utilizing a new genetic approach that allowed the team to discover plectasin, we now know that a whole class of antibiotics has been overlooked."

"This finding (plectasin), and the existence of about 200,000 additional species of fungi, opens up a vast universe to explore for novel peptide antibiotics," said co-author Robert Lehrer, M.D., Distinguished Professor of Medicine at the David Geffen School of Medicine at UCLA. Plectasin, if proven safe and effective in humans, could be on the market by 2012, said Lehrer.

Zasloff and Lehrer are known internationally as experts in antimicrobial peptides - the class of antibiotics that plectasin falls within - and in this study they collaborated with Novozymes, a Danish biotech company that led the research. Zasloff and Lehrer are the only two scientists from U.S. universities on the team of 20 researchers who co-authored the research paper.

All life forms have to defend themselves against microbial invaders – bacteria, fungi, viruses – and to do this, they produce antimicrobial defensin peptides. In humans, defensins are made by specific white blood cells and immune cells that later engulf foreign invaders, and by the skin and mucous membranes, in order to kill microbes before they invade protective barriers.

Researchers believe that fungi have a similar system of defense, especially since these plant-like organisms live off rotting matter, said Zasloff. "They must compete with other organisms, like bacteria and viruses, which also want to consume the same meal. In addition, they need to defend themselves from being eaten by the microbes which surround them."

But he said no one had been able to find defensins in fungi using traditional research techniques, which involved growing fungi in liquid cultures and then testing the culture to see if it contained any antibiotic molecule.

The research team instead used the latest genetic science to search for the defensins they thought fungi must have. Selecting the Pseudoplectania nigrella species of fungus may have been serendipitous, Lehrer said, but the Novozymes team used state-of-the-art biotechnology to intercept ,and interpret its genetic messages and exhibited tremendous skill in producing plectasin efficiently, economically, and in large amounts." "I started working on antimicrobial peptides over three decades ago, said Lehrer, and my laboratory

first described human defensins in 1985. So, the discovery of plectasin makes me feel like a grandfather."

Further examination revealed that this defensin, plectasin, resembles defensins found in spiders, scorpions, dragonflies and mussels - thus suggesting that the defensins found in insects, molluscs and fungi arose from a common ancestral gene, the researchers say. Based on this information, the scientists now believe that defensins appeared in living things more than a billion years ago.

The investigators then turned to the National Center for Antimicrobials and Infection Control, the Danish equivalent of the U.S. Centers for Disease Control, to test plectasin in the laboratory for antimicrobial activity against a broad spectrum of bacteria. It showed potent activity against several species of Gram-positive bacteria, and was especially active against S. pneumoniae (the leading cause of pneumonia), including all known clinical strains and those that are now resistant to conventional antibiotics. "That is important because increasing bacterial resistance to conventional antibiotics threatens the future of many antibiotics in current use," Zasloff said.

"In mouse studies, plectasin showed extremely low toxicity, and was as effective as vancomycin and penicillin in curing the animals of experimental peritonitis (inflammation of the lining of the abdominal cavity, which can be deadly) and pneumonia caused by S. pneumoniae, the researchers report.

"Although the precise mechanism by which plectasin exerts its antimicrobial activity is still under investigation, it may work by a mechanism that is very different from traditional antibiotics, Zasloff said.

"As a group, defensins exhibit activity against many types of bacteria, fungi, protozoa, and even viruses. It is entirely possible that fungal defensins will be discovered that could be developed against all of these human pathogens," Zasloff added.

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