Johannes Huebner's interest in intestinal bacteria and their sweet-sour capsule

Enterococci have a Janus-like character in that they can have positive and negative effects on human health. Some Enterococcus species are common commensal organisms in human intestines and other species are used in raw-milk cheese where they enhance flavour development. On the negative side, enterococci are also a common cause of hospital-acquired infections. Prof. Dr. Johannes Huebner from the Freiburg University Medical Centre is looking into how these bacteria interact with their host cells, amongst other issues. He is hoping that the bacteria's capsular polysaccharides might at some point in the future be used as a vaccine, opening the door to new treatment options for often difficult-to-treat enterococcal infections.
Enterococci would appear to be a magnet to resistance genes. Some species of the Gram-positive bacteria of the genus Enterococcus are found in the human intestines where they communicate with each other and with other bacterial species. When they come into contact with antibiotic-resistant relatives, they dock to them and take up the useful antibiotic resistance genes by way of a tubular bridge. "Enterococci were the first bacteria to become resistant to all standard antibiotics, including vancomycin which was discovered in the 1950s and is generally used to treat infections that are resistant to all other antibiotics," said Prof. Dr. Johannes Huebner, head of a group of researchers in the Department of Infectious Diseases at the Freiburg University Medical Centre. "The antibiotic resistance of enterococci has become a major problem in hospitals. There are regular enterococci outbreaks in the USA, and this is increasingly also happening in European hospitals. As enterococci are so resistant to common antibiotics, it is difficult to eradicate such outbreaks."

Highly complex polysaccharide structures

The gene transfer described above causes the rapid spread of resistances among enterococci. So the question that needs to be dealt with is how to effectively treat enterococcal infections that are resistant to common antibiotics. Hüblner and team's objective is to develop an immunotherapy against enterococcal infections. As the efficacy of older antibiotics wanes and the supply of new ones declines, the pharmaceutical industry is experiencing a paradigm shift from antibiotics development to the development of innovative biologics such as vaccines. This would greatly benefit immunocompromised cancer patients and intensive care patients who are at a particular risk of contracting infections caused by multi-resistant bacteria.

Prior to returning to Freiburg in 2004, Prof. Huebner spent seven years in the USA heading up a research group at the Harvard Medical School in Boston, which was working on multi-resistant enterococci. Huebner focuses mainly on molecules in the cell wall of Gram-positive bacteria, which are known as capsular polysaccharides. These high-molecular polysaccharide chains form a layer around the bacteria, attach to a host cell and play a key role in protecting them against attacks by
the human immune system. "If we could find specific structures in this capsule to which the human immune system has a particularly effective reaction, we would be able to develop a vaccine against multi-resistant Enterococcus species," said Hübner.

This is not an easy task as research into capsular polysaccharides is a science in its own right: the isolation, purification and characterisation of the complex polysaccharide structures is far more complicated than for proteins. Huge quantities of sample material are necessary to produce enough bacteria to analyse. Huebner's team needs to grow between six and twenty litres of bacterial suspension in flasks. The suspension is then centrifuged, the bacteria destroyed with enzymatic methods and the liquid filtered. "We are the only group of researchers in the world working on enterococcal polysaccharides," said Huebner adding, "but we also need to work in cooperation with other researchers, such as researchers from the Research Center Borstel who carry out spectroscopic MRI analyses."

Goal number one in the development of a vaccine

The researchers from Freiburg have already isolated and characterised a large number of capsular polysaccharides using chemical methods such as gel chromatography. The cell walls of enterococci contain a large number of teichoic acids, lipoteichoic acids, capsular polysaccharides and carbohydrates that are covalently linked to proteins or fatty acids. The scientists have already managed to clarify the function of some of these substances. For example in 2006, the researchers were able to show that a lipoteichoic acid that they had previously discovered is involved in the
defence of antibacterial peptides. This function is important in the intestines where it protects other intestinal symbiotic microorganisms and regulates the composition of the intestinal flora. However, this particular compound also has the potential to protect pathogenic enterococcal species.

Huebner's team is also focusing on a capsular polysaccharide that they believe has great potential as a vaccine. Working with a relatively large pharmaceutical company, Huebner and his team are currently working on the development of such a vaccine. They are investigating which regions of this particular polysaccharide are well suited for triggering an immune reaction. In addition, they are also coupling the polysaccharides with proteins in an attempt to induce the immune system to produce memory cells for the combined antigens. This would enable the immune system to react immediately to dangerous enterococci even years after vaccination.

Bacteria reach out into the skies

Huebner’s team is also focusing on other microbiological issues. Working with a team led by Prof. Dr. Elisabeth Grohmann, the researchers are investigating how enterococci manage to become resistant to antibiotics so quickly. The project focuses on the mechanisms that enable bacteria to exchange genes with one another. The researchers are also interested in the genes that mediate the bacterial resistance to numerous antibiotics. Another collaborative project, initiated around a year ago by several German and Mexican research partners, is focusing on the increasing antibiotic resistance of enterococci in wastewater in Mexico City. The city, with its 20 million inhabitants, discharges all its wastewater into a valley in the Mexican desert where a green oasis is prospering. The water drains away and collects in groundwater aquifers which supply the city with drinking water. The city’s wastewater contains antibiotics and thousands of different bacterial species. The teams are looking into the question as to whether the number of antibiotic-resistant bacteria is increasing. What risk is attached to microorganisms that are returned to Mexico City along with the water?
Another of Huebner’s team’s projects is being carried out in collaboration with the European Aerospace Agency (ESA) and other partners. Grohmann, Huebner and other researchers are investigating why bacteria form biofilms on the surface of the sensitive construction elements of the International Space Station ISS. It is very difficult to get rid of the complex microbial communities once they are there. “In future, we will investigate whether gravity affects the formation of biofilms and whether hitherto unknown genetic programmes are involved,” said Huebner. Although the researchers have no ambition to travel into space, the project is highly ambitious in itself.

Further information:

Prof. Dr. med. Johannes Huebner
Dept. of Infectious Diseases, Internal Medicine II
Freiburg University Medical Centre
Hugstetter Str. 55
79106 Freiburg
Tel.: +49 (0)761/ 270 - 18 280
Fax: +49 (0)761/ 270 - 32 130
E-mail: johannes.huebner(at)uniklinik-freiburg.de

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