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Strep Bacteria Uses A Sword And Shield To Win Battle Against Immune System, UCSD Medical Team Discovers

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A single gene called cylE within the important bacterial pathogen Group B *Streptococcus* (GBS), controls two factors that act together as a "sword" and "shield" to protect the bacteria from the killing effects of the immune system's white blood cells, according to researchers at the University of California, San Diego (UCSD) School of Medicine.

GBS is the leading cause of serious bacterial infections such as meningitis and pneumonia in newborns and is increasingly recognized as a serious pathogen in adult populations, including the elderly, pregnant women and diabetics.

In studies with mice and human blood samples, published in the online edition of *Proceedings of the National Academy of Sciences* the week of September 20, 2004, the UCSD scientists demonstrated the protective roles of two *cyl* E-encoded factors, one that creates the unusual orange pigmentation of GBS, and another that produces a toxin called hemolysin that kills immune system cells as they surround and attack the bacteria. These findings could lead to new therapeutic approaches that disarm the bacteria and allow the immune system to do its work.

"A crucial part of the body's defense against bacterial pathogens are white blood cells known as neutrophils and macrophages, which are able to engulf and kill most bacteria" said lead author George Liu, M.D., Ph.D., a UCSD research fellow in pediatric infectious diseases. "We predicted that the GBS bacteria had a unique ability to avoid the killing by white blood cells."

This unique ability turned out to include both the killing effects of the hemolysin toxin, and previously unrecognized antioxidant properties of the GBS orange pigment.

A major weapon that white blood cells use to kill bacteria after engulfment is the production of lethal oxidants similar to peroxide and bleach. Interestingly, the *cyl* E-dependent orange pigment belongs to the family of carotenoids, similar to the compounds that give color to vegetables such as tomatoes and carrots. The anitoxidant properties of food carotenoids have long been touted for their potential health benefits against aging, heart disease and cancer.

"Just as colorful vegetables with antioxidants are touted for their ability to protect us against aging or cancer, we discovered that the GBS bacteria is pulling the same trick to protect itself against our immune system," said the study's senior author, Victor Nizet, M.D., associate professor, UCSD Division of Infectious Diseases, and an attending physician at Children's Hospital San Diego.

A single gene (cylE) of the newborn pathogen group B Streptococcus (GBS) controls production of a hemolysin toxin that lyses human cells and an orange pigment resembling carotene that shields the bacterium from immune system killing. Images show colonies of GBS bacteria grown on agar plates.

The UCSD experiments confirmed the importance of the antioxidant role of the orange pigment, as mutant GBS without the cylE gene was 10 to 10,000 times more susceptible to white blood cell oxidants than the disease producing strain.

The new findings are based on previous research by the UCSD group and others, that showed *cyl* E controls the production of hemolysin, as well as the orange pigmentation of the gene. Removal of this gene created a mutant strain of GBS that lacked the hemolysin toxin and was plain white in color. When tested in animal models, the mutant GBS strain was unable to produce serious infections. In the current study, the scientists showed that the mutant GBS strain was rapidly cleared from the bloodstream of experimental animals and more easily killed by purified human and mouse white blood cells.

The hemolysin toxin was the "sword" that poked holes throughout white blood cells, such that in many cases the GBS actually killed the immune cell before it could kill the bacteria. However, even when hemolysin production was inhibited, the GBS continued to survive the white blood cell attack. In additional experiments, the orange pigment was found to be the "shield" that protected the bacteria. Combined, the toxin and orange pigmentation made GBS a potent warrior against white blood cell defenses and consequently a much more lethal pathogen.

"Recognizing the importance of these two properties for GBS infection suggests that novel drug treatments or vaccines that block the hemolysin or disrupt pigment production may be quite effective. Essentially, such therapies could make the GBS bacteria susceptible to elimination by the normal immune system of the newborn infant," Nizet said. Additional authors who contributed to the published study were Kelly Doran, UCSD assistant adjunct professor of pediatrics, Toby Lawrence, Ph.D., postgraduate researcher, UCSD Department of Pharmacology, Nicole Turkson, M.S., graduate student, Scripps Institute of Oceanography, and Manuela Puliti, Ph.D. and Luciana Tissi, Ph.D. from the University of Perugia, Italy.

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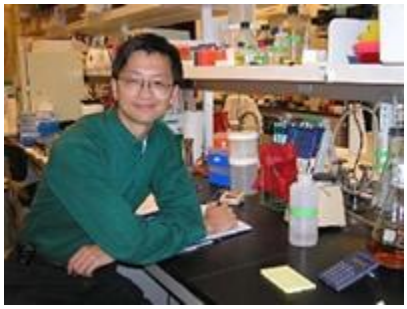

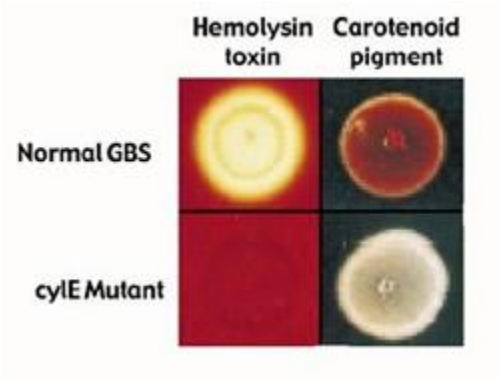
Hemolysin toxin
Carotenoid pigment
Normal GBS
cylE Mutant