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Golden Armor: UCSD Scientist's Discovery Suggests New Way To Fight Antibiotic-Resistant Staphylococcus Infections

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Researchers at the UCSD School of Medicine and Children's Hospital and Health Center, San Diego have discovered that "Staph" bacteria use a protective golden armor to ward off the immune system, a finding with the potential to lead to new treatments for serious infections now increasingly resistant to standard antibiotics.

The research, which is featured on the cover of the July 17, 2005 issue of *The Journal of Experimental Medicine*, focused on the major human pathogen *Staphylococcus aureus* and the characteristic yellow-orange color for which it is named ("aureus" is Latin for "golden").

Among the deadliest of all disease-causing organisms, "Staph" is the leading cause of human infections in the skin and soft tissues, bones and joints, abscesses and normal heart valves. Staph especially flourishes in the hospital setting, producing bloodstream and surgical wound infections. The spread of antibiotic resistant strains of Staph, referred to as methicillin-resistant *Staphylococcus aureus* or MRSA, has reached epidemic proportions and poses a major threat to the public health.

The UCSD team proved for the first time that the golden pigment that coats the surface of Staph is not just for decoration; rather, the molecules that give the bacteria its golden hue also help it resist killing by neutrophils, white blood cells with a front line role in immune defense against invading microbes.

Staph's coloration reflects the production of molecules called carotenoids, similar to those present in carrots and other colorful vegetables and fruits. Dietary carotenoids have long been touted for their antioxidant properties with hope that they could slow aging or fight off cancer. The scientists found that pathogenic Staph took advantage of the antioxidant effects of its carotenoid pigment to extend its own life, by inactivating chemicals deployed by neutrophils that are lethal to most bacteria. The UCSD team used a molecular genetic approach for their studies, knocking out the genes for carotenoid synthesis to generate a mutant strain of Staph that appeared white in color instead of the normal gold.

"We found that the nonpigmented Staph mutant became much more susceptible to oxidants such as hydrogen peroxide and singlet oxygen produced by neutrophils," said George Liu, M.D., Ph.D., a research fellow in the UCSD department of pediatrics who spearheaded the studies. "Without its golden pigment, the Staph lost its ability to survive in human neutrophils or blood, and could no longer form an abscess when injected into the skin of experimental mice."

The investigators proved that the antioxidant effects of the Staph pigment were the key factor in virulence by repeating experiments in blood from a human patient with chronic granulomatous disease (CGD), an inherited disorder in which neutrophils cannot produce oxidants and infections are common, as well as in mice engineered to possess the same genetic mutation. Without the oxidant assault, the ability of the nonpigmented strain to resist neutrophil killing and produce disease was equal to the golden Staph.

The power of the antioxidant pigment in promoting bacterial survival was further established extending the protective properties to a different bacteria. Pigment-producing genes of Staph were cloned into a normally colorless strain of Streptococcus ("Strep") bacteria that then turned yellow in color. The Strep expressing the golden carotenoid pigment became more resistant to oxidant and neutrophil killing, and produced larger ulcers when injected into the skin of normal mice.

"The discovery of the critical role played by golden pigment in protecting against infection provides an novel target for treatment of serious Staph infections including those produced by antibiotic-resistant MRSA," said senior author Victor Nizet, M.D., UCSD associate professor of pediatrics and an infectious diseases physician at Children's Hospital, San Diego. "Instead of attempting to kill the bacteria directly with standard antibiotics, a treatment strategy to inhibit the Staph pigment would disarm the pathogen, making it susceptible to clearance by our normal immune defenses"

Liu is the recipient of a Howard Hughes Medical Institute Fellowship and a Burroughs Wellcome Fund Career Award. This study was also financed by grants from the National Institutes of Health and the Edward Mallinckrodt, Jr. Foundation to Nizet.

Co-authors contributing to the study were Anthony Essex, UCSD graduate student in biomedical sciences; John Buchanan, Ph.D., UCSD research scientist in pediatrics; Vivekanand Datta, M.D., UCSD graduate student in molecular pathology; Hal Hoffman, M.D., UCSD assistant adjunct professor of pediatrics and medicine; John Bastian, M.D., staff immunologist at Children's Hospital, San Diego, and Joshua Fierer, M.D., UCSD professor of medicine and pathology.

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