

How flesh-eating bacteria attack the body's immune system

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"Flesh-eating" or "Strep" bacteria are able to survive and spread in the body by degrading a key immune defense molecule, according to researchers at the University of California, San Diego, School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. The finding, which could aid in development of new treatments for serious infections in human patients, will be reported in the August 14 issue of the journal *Cell Host & Microbe*.

Led by senior author Victor Nizet, M.D., UC San Diego professor of pediatrics and pharmacy and an infectious diseases physician at Rady Children's Hospital, San Diego, the researchers showed that a protease known as SpyCEP (*Strep. pyogenes* cell envelope protease) – produced in large amounts by the most dangerous strains of Strep – inactivates an immune system molecule that controls the body's white blood cells ability to fight bacteria. Without signals from this molecule, white blood cells become slower and weaker, and infections can spread out of control.

"These findings may suggest a new approach to treating serious Strep infections by supporting our body's natural defense system," said Nizet.

The research focuses on the major human pathogen group A *Streptococcus*. Among the most important of all bacterial pathogens, Strep is responsible for a wide range of diseases – from simple strep throat to life-threatening conditions such as necrotizing fasciitis ("flesh-eating disease") and toxic shock syndrome.

The UC San Diego investigators examined the interaction of Strep bacteria with neutrophils, specialized white blood cells that play a front-line role in humans' immune defense against pathogenic microbes. Previous research had shown that Strep bacteria change their pattern of gene expression dramatically during the course of infection, including a massive increase in production of SpyCEP, which has the unique ability to inactivate an immune defense molecule known as interleukin-8 (IL-8). IL-8 is produced at sites of infection and serves as a signal for neutrophils to migrate out of the bloodstream and into the tissues to clear the infection.

The UC San Diego team used a molecular genetic approach for their studies, knocking out the gene encoding the SpyCEP from a pathogenic strep strain that was originally isolated from a patient suffering from necrotizing fasciitis.

"Lacking this single protease, the mutant Strep strain was easily killed by human neutrophils," said lead author Annelies Zinkernagel, M.D., a postgraduate researcher in the UCSD department of pediatrics. "In addition, the mutant Strep bacteria no longer produced a spreading infection when injected into the skin of experimental mice."

The critical role of the Strep protease was confirmed by cloning the corresponding gene into a normally non-pathogenic bacterial strain, which then became resistant to neutrophil killing. More detailed analysis demonstrated that by inactivating IL-8, SpyCEP blocked neutrophil migration across blood vessels as well as neutrophil production of "extracellular traps" used to ensnare bacteria.

The immune-blocking effects of SpyCEP produced by Strep were strong enough to allow other bacterial species to survive at the site of infection, which may contribute to mixed infections that require complex antibiotic regimens. The researchers also showed that a pathogen of fish,

Streptococcus iniae, produces its own version of SpyCEP that may contribute to recent reports of severe skin infections caused by this bacterium in fish handlers.

Nizet explained that the researchers' findings could lead to novel treatments for Strep-related diseases. "In addition to attempting to kill the bacteria directly with standard antibiotics, new treatment strategies could be targeted to inhibit the Strep protease and thereby disarm the pathogen, making it susceptible to clearance by our normal immune defenses," he said.

Source: University of California - San Diego

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