Researchers Discover Key Mechanism to Emergence of Deadly Strep Bacteria

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The incidence of serious strep infections has risen dramatically in the last three decades, and this increase is largely attributed to the spread around the globe of a single strain of strep known as the invasive M1T1 clone. Researchers at the University of California, San Diego (UCSD) School of Medicine and the University of Wollongong in Australia have discovered that, 30 years ago, a virus infected the strep bacteria – creating a deadly strain of "flesh-eating" bacteria that has evolved to produce serious human infections worldwide.

"Just like a computer virus might come in and reprogram your hard drive, this virus reprogrammed the genetic machinery of the M1T1 strep into a more virulent form," said senior author Victor Nizet, M.D., UCSD Professor of Pediatrics and Pharmacy. "The consequences of this event on human health are still being felt three decades later."

The research, reported in the July 15 advance online publication of the journal *Nature Medicine*, focuses on the major human pathogen group A *Streptococcus* ("strep".) Among the most important of all human infectious disease agents, strep is responsible for a wide range of diseases, ranging from simple throat and skin infections to life-threatening invasive conditions such as necrotizing fasciitis ("flesh-eating disease") and toxic shock syndrome. Strep is estimated to cause over 700 million infections each year; over 650,000 of these are dangerous invasive forms.

The UCSD-Australian research team sought to identify what special characteristics make the invasive M1T1 strep clone so virulent for humans. They observed that during the early stages of a simple skin infection, a small subpopulation of the strep bacteria hijack a protein called plasminogen from the human bloodstream. The bacteria attach the protein to their own surface, and then activate it into a protease – an enzyme that digests proteins and is capable of destroying cells and tissues – thus allowing the bacteria to break out and spread through the body.

Applying the pressure of natural selection, the human immune system normally would clear a localized infection. But in the case of the M1T1 strep clone, natural selection instead favors the emergence of the invasive mutants. The researchers found that a specific genetic mutation in the

M1T1 strep clone controls the shift to this invasive form – a property which they traced to an event that occurred about 30 years ago when a virus known as a bacteriophage infected the strep bacteria and introduced a new gene. The new gene allowed the bacteria to resist clearance by the human immune system.

"Our study provides a model of how natural selection, exerted by the human immune system, can generate hypervirulent bacterial variants with an increased risk of producing invasive infections," said lead author Mark Walker, Ph.D. a Professor of Biological Sciences at the University of Wollongong. "In the case of the invasive strep clone, a bacteriophage provided the bacterium a genetic advantage that turned a relatively benign pathogen into a potential deadly disease agent."

A gene present on the bacteriophage acquired by the M1T1 strep encodes an enzyme that allows the bacteria to escape being trapped and killed by neutrophils – white blood cells that play a front line role in human's immune defense by pathogenic microbes. The same genetic mutation that allows the strep bacteria to acquire plasminogen and activate it throughout the body also increases production of the bacteriophage-encoded enzyme that blocks neutrophil killing. When neutrophils of the immune system are summoned to clear a simple strep infection, they apply a natural selective pressure favoring the genetic mutation.

"The mutation allows the bacteria not only to survive neutrophil killing, but to spread and destroy tissues, as is seen in necrotizing fasciitis and other severe forms of strep infection," said Walker.

The research team used genetically engineered mice expressing human plasminogen and infected them with M1T1 strep clone, discovering that the bacteria routinely mutated to the invasive form, then spread throughout the body to produce a fatal infection. When the researchers eliminated the single bacteriophage gene encoding the neutrophil resistance factor, the M1T1 strep strain lost its ability to undergo the dangerous mutation and could no longer spread to produce severe infection. Ancestral strains of the M1T1 strep, isolated before the acquisition of the bacteriophage, also failed to undergo the mutation to produce serious disease.

The collaborative study was initiated during Prof. Walker's Australian-American Fulbright Commission Senior Scholar Award sabbatical in Dr. Nizet's laboratory, and financed by grants from the National Institutes of Health, the National Health and Medical Research Council of Australia, and the Department of Employment Science and Technology (Australia) International Science Linkages Program. Co-authors contributing to the study were Andrew Hollands, Martina Sanderson-Smith, Jason Cole, Joshua Kirk, Anna Henningham, and Jason McArthur of the University of Wollongong; Katrin Dinkla and Gurshan Chhatwal of the Helmholtz Centre for Infection Research in Braunschweig, Germany; Rita Kansal and Malak Kotb of the University of Tennessee-Memphis; Ramy Aziz of the University of Cairo, Egypt; Amy Simpson, UCSD Medical Student, and John Buchanan, UCSD Assistant Research Scientist in Pediatrics.

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