Scientists identify a mechanism of epidemic bacterial disease

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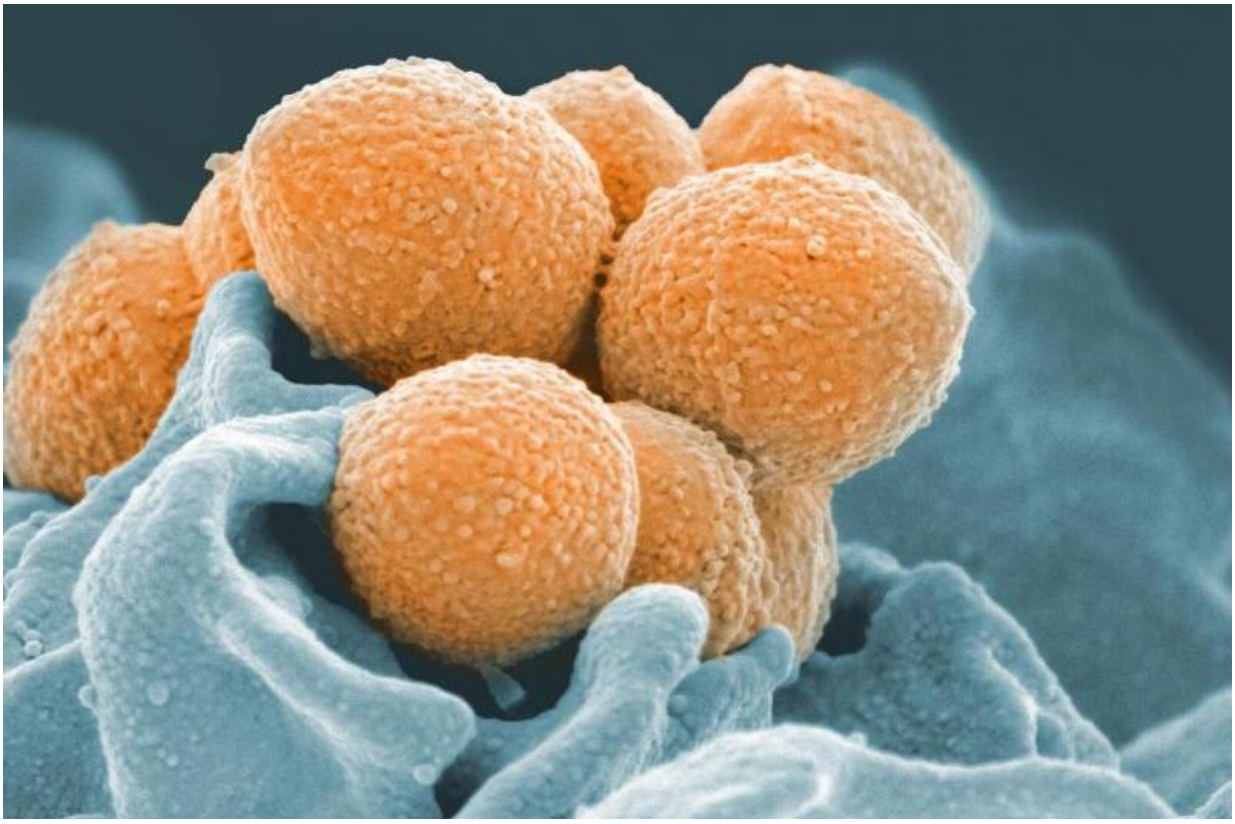

A scanning electron microscope image of Group A Streptococcus (orange) during phagocytic interaction with a human neutrophil (blue). Credit: NIAID

Through identification of increased toxin production by epidemic forms of group A *streptococcus* (the "flesh-eating" bacterium), for the first time

scientists are able to pinpoint the molecular events that contribute to large intercontinental epidemics of disease. The study was based on sequencing almost 5,000 group A *streptococcus* genomes collected over decades.

Researchers from Houston Methodist Research Institute, Houston Methodist Hospital, institutions in Finland and Iceland, and the U.S. National Institute of Allergy and Infectious Diseases report their discoveries and implications for future studies of epidemic diseases in an upcoming *Journal of Clinical Investigation* (early online).

According to James M. Musser, M.D., Ph.D., principal investigator of the study and chair of the Department of Pathology and Genomic Medicine at the Houston Methodist Research Institute , the collaborative research showed, at the precise nucleotide level, genetic changes that contributed to large epidemics of group A *streptococcus* (GAS).

"These findings now give us the opportunity to begin to develop new translational medicine tools and strategies," said Musser. "We can use this information to develop novel therapeutics, advanced diagnostic techniques and new ways to prevent, or dampen, epidemics."

According to the World Health Organization, GAS causes more than 600 million cases of human disease every year. The majority of cases are group A *streptococcus* pharyngitis, more commonly known as strep throat. But group A strep is also the major cause of preventable childhood heart disease caused by rheumatic fever and rheumatic heart disease. On the far end of the infection severity spectrum, group A *streptococcus* also causes necrotizing fasciitis ("flesh-eating" disease), an infection with a high mortality rate.

The collaborating team of international scientists found that group A *streptococcus* was an excellent model organism to study the molecular

basis of epidemic bacterial infections. Researchers have known for more than a century that this pathogenic bacterium can cause epidemics, but no one has been able to fully address the cause. Now with next generation sequencing, scientists are able to sequence the entire genome of the bacteria, just as is done in humans. Group A *streptococcus* was selected as the model organism for study due to the availability of comprehensive strain samples collected over decades, and its relatively small genome, which allows the genome of thousands of strains to be completely sequenced relatively rapidly.

The researchers' original hypothesis, which turned out to be correct, was that changes in the genetic make-up of the GAS pathogen had underpinned new epidemics. To address this hypothesis, the collaborating international team sequenced the genome of thousands of disease-causing strains, precisely defining every base pair mutation in the strains.

"The surprise was that the changes involved alterations in the genes encoding two potent toxins that contribute to human infections," said Musser, who is director for the Center for Molecular and Translational Human Infectious Disease Research at Houston Methodist.

The researchers found that in the epidemic form of group A *streptococcus*, which can manifest as necrotizing fasciitis, or "flesh-eating" disease, there were two significant and crucial changes within the regulatory region of the epidemic strains. The regulatory region identified controls how two key toxin-encoding genes are transcribed and the toxic proteins made. These specific genetic changes result in the creation of single nucleotide polymorphisms, or SNPs.

Musser's team found that two of those SNPs result in significantly increased production of two important toxins that harm humans called streptolysin O and NAD-glycohydrolase. The third SNP creates a form

of one of those toxins that becomes more active than the original form. All three of these SNPS contributed to building a pathogenic organism that is a more virulent machine capable of causing epidemics.

"Think about the thermostat in your house that controls temperature. If you want to make your house hotter, or if group A *streptococcus* wants to make itself 'hotter,' that is, more virulent, it turns up the heat by making more of these two toxins that harm human cells," said Musser.

Musser and team are hopeful findings from their model study will allow other infectious disease researchers to use analogous strategies that focus on other pathogens, like Staphylococcus aureus (the leading cause of skin and soft-tissue infections), and antibiotic-resistant bacteria such as *Klebsiella pneumonia* or *Escherichia coli*.

Provided by Houston Methodist