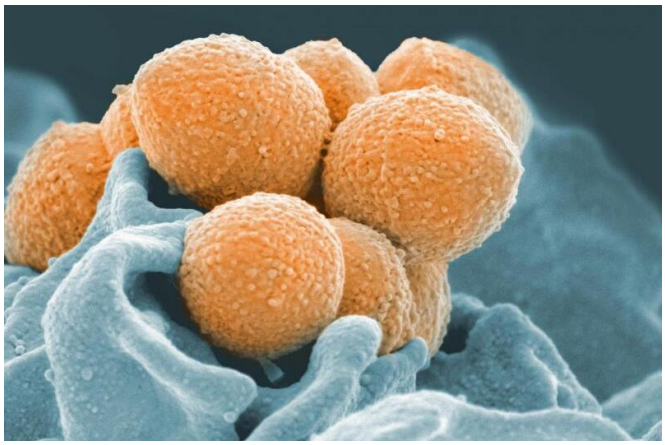
Discovery raises hopes of preventing streptococci infections

18 October 2019, by Grant Hill



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

Researchers at the University of Dundee have discovered an enzyme they believe could be key to preventing Group A Streptococcus infections that cause more than 500,000 deaths worldwide each year.

Group A Streptococcus can lead to illnesses such as strep throat, scarlet fever, sepsis and toxic shock syndrome as well as several long-term autoimmune diseases with high mortality rates.

Working with colleagues at the University of Edinburgh and the Russian Academy of Sciences, the Dundee researchers found an enzyme that is required to produce a carbohydrate on the surface of the streptococcal bacterium which enables it to infect humans and animals.

The team, led by Dr. Helge Dorfmueller, is based is based in the Division of Molecular Microbiology at the University's School of Life Sciences. Their research reveals new opportunities to inhibit this enzyme and, ultimately, fight Group A Streptococcus infections. The fact this enzyme works through a novel mechanism of action that can also be found in other streptococcal species increases the impact and relevance of this finding.

Dr. Dorfmueller said, "Strep throat is the most common Group A Streptococcus infection and can often be fought by the body's immune system. Unfortunately, the very same bacterium also causes a plethora of severe and potentially fatal illnesses, such as sepsis and toxic shock syndrome.

"We knew that the carbohydrate coating was an essential component of Group A Strep, but we wanted to find out more about how this worked. What we have now shown is that the enzyme initiates the synthesis of the bacterial coating.

"Surprisingly, we also found that this enzyme fulfils the same function in many other types of streptococci. This includes Group B Streptococci, that can cause severe infections in newborns, and Group C and G Streptococci that cause similar disease as Group A, including bacteraemia and endocarditis, in humans and animals."

The newly discovered enzyme, called ?-D-GlcNAc-?-1,4-L-rhamnosyltransferase, is not present in humans or animals, therefore providing a novel opportunity for drug discovery programmes.

Antimicrobial resistance is a global problem, and existing antibiotics fail to work in around 20 percent of cases of strep throat. The long-term aim of the Dundee team is to aid the development of a new class of antimicrobial drug that could completely inhibit or reduce the enzyme's activity. The next step towards this goal will see them work with the University's Drug Discovery Unit to develop compounds that could target this enzyme.

The research was jointly led by Ph.D. student Azul Zorzoli and Ben Meyer, a former postdoc in Dr.

Dorfmueller's lab. Azul explained, "If you picture a tennis ball, this carbohydrate would be the furry layer that covers the ball. This layer is an essential structural component of the cell and is used by the bacterium to facilitate infection. In our recent study, we show how this protein initiates the production of this carbohydrate through a mechanism never described before.

"Our research provides the opportunity to target this enzymatic step for drug discovery. For instance, these findings can become a cornerstone to potentially develop a new compound to inhibit streptococci, leading to novel therapeutic strategies. Because this step is exclusive to bacteria, compounds targeting this enzyme should have minimal off-target effects, making it an excellent candidate as an antimicrobial drug."

The research was funded by the Wellcome Trust and the Royal Society. It has been highlighted as the Editor's pick in the edition of the *Journal of Biological Chemistry* published today.

More information: Azul Zorzoli et al. Group A, B, C, and G Streptococcus Lancefield antigen biosynthesis is initiated by a conserved ?-D-GlcNAc-?-1,4-L-rhamnosyltransferase, *Journal of Biological Chemistry* (2019). DOI: 10.1074/jbc.RA119.009894

Provided by University of Dundee

APA citation: Discovery raises hopes of preventing streptococci infections (2019, October 18) retrieved 29 November 2021 from https://phys.org/news/2019-10-discovery-streptococci-infections.html

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