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PRESS RELEASE

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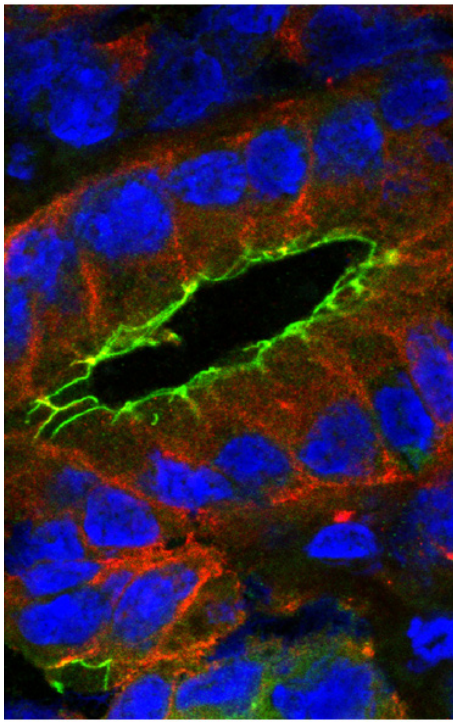
Staphylococcus aureus Achilles' heel

A human cell protein modulates bacterial virulence



Intestinal cells in which PLEKHA7 protein is marked in green, another component of the *adherens junctions* in red, and nuclei in blue. © Sandra Citi

Staphylococcus aureus is both a transient skin colonizer and a formidable human pathogen, ranking amongst the leading causes of skin and soft tissue infections, as well as severe pneumonia. Scientists attempt to work out new strategies to fight against this pathogen, of which numerous strains are now resistant to antibiotic treatments. One of the bacterium's most impressive weapons is α-toxin, which provokes the destruction of human cells. An international project led by the Stanford University School of Medicine in California, in collaboration with the University of Geneva (UNIGE) in Switzerland, allowed to identify the components of our cells that modulate the virulence of this toxin, in particular the PLEKHA7 protein. By eliminating expression of the latter, cells gained the ability to recover from α-toxin injury, and mice lacking PLEKHA7 exhibited improved healing from bacterial skin infection as well as enhanced survival of pneumonia. The results, which pave the way to new potential therapies, are published in the journal *PNAS*.

The invasive power of *Staphylococcus aureus* is largely due to α-toxin, which destroys cells by piercing their membranes. The *adherens junctions*, which tie neighboring cells to one another and thus contribute to the formation of our tissues, were discovered to play an important role in the spreading of this infection. «Our results indicate that several components of the *adherens junctions* are involved in controlling the virulence of α-toxin, to varying degrees», explains Lauren Popov, PhD student at Stanford's School of Medicine and senior author of the study. The leading role is assumed by PLEKHA7, a protein discovered by the team of Sandra Citi, professor at the Department of Cell Biology of the Faculty of Science at UNIGE and co-director of the study.

A potential therapeutic target

To determine the importance of PLEKHA7 in modulating *Staphylococcus aureus* virulence, the biologists infected cells that do not express the gene coding for this protein. They observed that these cells gained the ability to recover from α-toxin injury. «Moreover, by infecting mice genetically deprived of PLEKHA7 with a multiresistant bacterial strain (MRSA), we observed improved healing from bacterial skin infection, as well as enhanced survival of pneumonia», reveals Manuel Amieva, professor of microbiology

and immunology and of pediatrics at Stanford's School of Medicine and co-senior author of the study.The researchers are trying to understand how PLEKHA7 controls the action of α-toxin. One of their hypotheses is that this protein could aggravate bacterial toxicity by transmitting signals inducing cells' self-destruction. «Since PLEKHA7 controls disease severity in both skin infection and lethal pneumonia, we suggest to target this non-essential component of the *adherens junctions* as a potential therapy to reduce the virulence of MRSA strains», conclude the authors. Following the discovery of PLEKHA7's importance during infections due to *Staphylococcus aureus*, several approaches are currently explored to find a way to inhibit this protein and limit bacterial spreading.

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