Turning on cell-cell communication wipes out staph biofilms

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University of Iowa researchers have succeeded in wiping out established biofilms of Staphylococcus aureus (staph) by hijacking one of the bacteria's own regulatory systems. Although the discovery is not ready for clinical application, the findings offer insight into a dispersal mechanism for staph biofilms and might help identify therapeutic targets.

Biofilms are communities of bacteria that grow on moist surfaces, including heart valves, bone and medical implants. Encased in self-produced slime and highly resistant to antibiotic therapy and the body's own immune defenses, biofilm infections represent a tough and dangerous medical problem. The findings were published in the journal *Public Library of Science – Pathogens* (*PLoS-Pathogens*) on April 25.

"We have shown that activating the cells' communication system, also known as quorum sensing, in established biofilms causes the biofilms to disperse rapidly," said Alexander Horswill, Ph.D., UI assistant professor of microbiology and senior study author. "This is the first report of an existing dispersal pathway in Staph aureus. If we can tap into this mechanism, then that might lead to better treatments."

Quorum sensing is the mechanism bacteria use for cell-to-cell signaling. This communication system allows bacteria to react to environmental changes in order to survive and thrive. In Staphylococcus aureus, the quorum-sensing system is turned on by autoinducing peptides (AIPs), small molecules that contain an unusual cyclic structure and are shaped

like a ring with a tail.

Previous research, including work done at the UI, suggested that this quorum-sensing system was involved in biofilm detachment, but it was difficult to test the idea because there was no good way to make AIPs.

That is where Horswill's expertise came in. In earlier research he had developed an enzymatic approach for manufacturing cyclic peptides. Using this chemistry, he was able to prepare large quantities of the pure AIPs, which allowed the team to conduct biofilm dispersal experiments.

"Figuring out how to synthesize these signal molecules so that we could do the dispersal experiments was a real breakthrough," he said. "We used this new method to make AIP, added it directly to established biofilms and watched them blow apart. And that's when the excitement started."

Having established that activation of the quorum-sensing system in established biofilms triggers dispersal of the biofilm, the UI team has started to investigate the details of the mechanism. In particular, they discovered the mechanism depended on the presence of active proteases -- enzymes that break down proteins.

"If we can learn more about how the system works, then that might suggest new therapeutic targets," said Blaise Boles, Ph.D., UI postdoctoral research fellow.

Importantly, Horswill and Boles also showed that bacteria released from the biofilm were once again susceptible to antibiotics, which raises possibilities for improving treatments for chronic biofilm infections.

"Current treatment for endocarditis -- a potentially life threatening infection where a staph biofilm forms on heart valves -- involves weeks of intravenous antibiotics, and sometimes requires surgery," Boles

explained. "One thing we'd like to test is whether we can treat biofilms in models of diseases like endocarditis by turning on quorum sensing."

Horswill added that he plans to start a collaborative effort with Jose Morcuende, M.D., Ph.D., UI associate professor of orthopaedics and rehabilitation, to investigate the dispersal of staph biofilms from both allograft bone and medical implant materials.

The findings also may have implications for treating biofilms of emerging antibiotic resistant staph strains, including methicillin-resistant Staphylococcus aureus (MRSA).

Although the team has not tested their dispersal methods on MSRA, Horswill notes that the MRSA stains are quite similar to the lab strains he and Boles tested and have quorum-sensing systems that are even more active than those of the lab strains. This suggests that MRSA might be particularly sensitive to approaches that manipulate quorum sensing.

Moving a basic discovery into medically relevant experimental models is an example of translational research of the type supported and encouraged by the new Institute for Clinical and Translational Science at the UI.

Source: University of Iowa