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ANTIBACTERIAL DRUGS

Antibody–antibiotic conjugate tracks down hidden *S. aureus*

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Staphylococcus aureus generally resides outside host cells, but it can also infect cells such as phagocytes and thus disseminate around the body and cause chronic or recurrent infections in tissues distant from the initial site of infection. The antibiotics that are currently used to treat *S. aureus* infections only target extracellular, planktonic bacteria, so the effects of targeting intracellular *S. aureus* are not known. In a new study, Lehar *et al.* develop an antibody–antibiotic conjugate (AAC) that binds to the *S. aureus* cell wall and releases the antibiotic moiety upon entry into host cells.

Lara Crow/NPG

First, the authors compared the infectivity of intracellular methicillin-resistant *S. aureus* (MRSA) with that of planktonic bacteria. In medium containing vancomycin (one of the antibiotics used to treat MRSA infections), planktonic MRSA was rapidly sterilized, whereas MRSA in peritoneal cells survived and could even infect co-incubated osteoblasts. Mice injected with MRSA-infected immune cells developed higher bacterial burdens than did mice injected with an equivalent dose of free bacteria. These findings indicate that bacteria can 'escape' antibiotics by hiding in host cells, and that these intracellular bacteria can thus be more virulent than free bacteria.

To combat these hiding bacteria, the authors designed an AAC containing an antibody that would bind to the bacterium, and an antibiotic that would be released only after entry of the opsonized bacterium into a mammalian cell. The authors screened a panel of 40 patient-derived *S. aureus*-specific antibodies against several strains of *S. aureus*; an antibody specific for sugar modifications of wall-techoic acid (WTA; a type of glycopolymer on the outer layer of Gram-positive bacteria) showed binding to all tested strains. For the antibiotic moiety, the authors used a rifamycin derivative (a rifalogue), which could kill dormant antibiotic-resistant bacterial cells (known as 'persister' cells), non-replicating but viable cells, and intracellular MRSA. To allow intracellular release of the rifalogue from the AAC, the authors attached it to the WTA-specific antibody using a linker that could be cleaved by the lysosomal enzyme cathepsin D.

The AAC, but not the antibody alone or a non-cleavable version of the AAC, killed bacteria in macrophages, suggesting that the construct worked as intended. Moreover, unlike a mixture of rifampicin and the antibody alone, the AAC markedly reduced the transfer of bacteria from infected peritoneal cells to non-infected osteoblasts in the presence of vancomycin. Mice injected with vancomycin and intracellular MRSA developed colonies of the bacteria in the brain, but these colonies did not develop in mice treated with vancomycin and the AAC. Furthermore, a single dose of the AAC 24 hours after infection prevented colonization of the kidneys, whereas treatment with vancomycin, the unconjugated rifalogue, the unconjugated WTA-specific antibody or the non-cleavable AAC beginning at the same time point did not.

Overall, this study shows that targeting intracellular *S. aureus* — for example with this AAC — may be a clinically relevant and effective way of preventing colonization and reducing the risk of developing chronic infections.

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