Researchers block bacterial communication system to prevent deadly staph infections

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The advantage of the new vaccine is that it would work not only on current bacterial resistant stains but also would not induce the potential for new bacterial resistance because, rather than killing bacterial cells, it blocks their communication system, preventing the shift from harmless to virulent, thus allowing the body's natural defenses to combat the bacteria.

The work was published in the October 29 issue of the journal *Chemistry and Biology*.

Staph and other infections are becoming increasingly deadly because many strains of the bacteria that cause disease develop resistance to the array of antibiotics used to control them. A Centers for Disease Control (CDC) report released last week estimated that more than 94,000 Americans were infected in 1995 by a drug-resistant staph "superbug" called methicillin-resistant Staphylococcus aureus (MRSA), and more than 18,000 Americans died that year during hospital stays involving this type of infection.

The bacterial infection process is dependent on a sort of chemical conversation between individual bacterial cells, referred to as quorum sensing. In their free-living state, bacteria are typically easy to kill and non-virulent. The shift to virulence is dependent on small molecules emitted by bacteria known as autoinducers, because bacteria sense when concentrations of these autoinducers are high enough to suggest a large number of other bacteria are present.

“Bacteria basically sense they have enough of their buddies around to allow them to say, 'OK, we're in a favorable environment to start turning on certain genes,'“ says team leader Professor Kim Janda, director of the Worm Institute for Research and Medicine at Scripps Research and a vaccine expert who has worked on the development of vaccines for obesity and drugs of addiction, among other problems.

The genes turned on by quorum sensing may encode proteins harmless to their hosts, but they can also code for the toxins and other products arising from bacterial infections that cause disease. Sequestering autoinducers in some way could therefore block quorum sensing and, hence, the establishment of infections. The scientists predict that such a strategy would not lead to resistance in bacteria because it wouldn't kill the cells. Bacteria would simply remain in an inert form because they would be tricked into “thinking” not enough other cells were present to shift into their virulent mode.

Bacteria use a variety of genetic mechanisms in quorum sensing. The Scripps Research team focused on Gram-positive bacteria, whose quorum sensing is controlled by four basic types of autoinducers tied to a circuit known as the accessory gene regulator. Based on the known structure of one of these autoinducers, the team designed a molecule known as a hapten that, when conjugated with specific proteins using well-established procedures, induces the production of antibodies by the immune system.

The Janda group intentionally designed the hapten to be stable enough to work well as a potential treatment, and ultimately chose to pursue work with one of the haptens that proved the most stable. Past research by other groups has involved successfully blocking quorum sensing using molecules that essentially plug the keyholes on cell surfaces that allow bacteria to sense autoinducers, but such strategies have been hampered by the inherent instabilities of the molecules involved.

Next, the team isolated and studied the antibodies produced in mice injected with the hapten, called AP4. Subsequent experiments revealed that one of these antibodies in particular, when administered to mice infected with Staphylococcus aureus, was highly effective at binding with and sequestering the targeted autoinducer, and to a lesser extent with a second autoinducer. This activity proved to effectively block quorum sensing and infection in the mice.

Resistance to S. aureus, a common form of Staph infection has become a major concern in hospitals, and, as the recent CDC report indicates, outside of medical settings as well. As a result, says Janda, “I think the impact of this approach could be really huge, because our approach side steps the resistance problem with common antibiotic treatments.”

Janda says the antibody AP4-24H11 could one day be given to humans as a passive vaccine to block infections as it did in mice. The AP4 hapten could also be applied as an active vaccine that would induce production of antibodies to block quorum sensing. He says such vaccines could, for instance, be given to patients entering the hospital for surgery to prevent infection by Staph bacteria. This would not, however, probably be an effective treatment against infections that have already progressed, because in such cases the damage from quorum sensing would already have been done.

Janda and his colleagues, including Junguk Park, Gunnar Kaufmann and Richard Ulevitch, chairman of the Scripps Research Department of Immunology, are already working to design related haptens that will induce antibodies effective against all the autoinducers used by Gram-positive bacteria, which might one day be administered as a vaccine cocktail to prevent infection by a wide range of bacteria. The group is seeking a pharmaceutical partner to fund further tests with AP4 and AP4-24H11 in animal models and, if all goes well, to carry a vaccine through human clinical trials.

Source: Scripps Research Institute