

Studies pinpoint key targets for MRSA vaccine

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Each approach dramatically reduced the virulence of staph infections in mice. The combination may protect people from MRSA infections and provide lasting immunity to this virulent and drug-resistant organism, which has become the leading cause of death from infectious disease in the United States.

Since the 1960s, development of a staph vaccine has been a priority for the medical profession--but less so for the pharmaceutical industry, which has veered away from vaccine research. Previous attempts at a MRSA vaccine have failed. In the last decade, however, as staph increased its ability to resist multiple antibiotics and drug-resistant strains came to dominate the community setting, the search for a protective vaccine has moved to center stage.

One of the challenges in creating a vaccine is the ability of this germ to short-circuit the host's defenses. Most bacterial infections trigger an immune counter-attack designed to rid the body of the microbe and prevent subsequent infections. Most vaccines rely on this same strategy. Staph, however, has evolved its own tools to blunt the immune response.

"Staph aureus is the world champion of immune suppression," said the senior author of both studies, Olaf Schneewind, PhD, professor and chair of microbiology at the University of Chicago. This allows the organism to persist long enough to escape the blood stream and settle into various tissues, where it builds a protective capsule, replicates and soon spreads in greater numbers to additional sites.

"Even when the infection can be cleared with antibiotics and surgery, the patient has no immunity," he said. "So these infections often recur."

An effective vaccine requires finding the right targets: proteins key to the disease process and exposed on the cell surface. Schneewind and colleague Dominique Missiakas, PhD, associate professor of microbiology at the University, began by assembling a library of all 23 surface proteins made by staph and created new strains with a mutated version of each protein. So each strain was normal except for one disabled surface protein. When they exposed mice to these mutant microbes, two sets of potential vaccine targets emerged.

One, known as protein A, is a cell-surface molecule that binds to receptors on B cells, the white blood cells that produce antibodies. Protein A is the key to staph's ability to evade immunity. It shields the bacteria by "cross-linking" two receptors on the B cells. This triggers cell death. So mice confronted with a staph infection do not make antibodies against the bacteria.

In the August 17, 2010, issue of the *Journal of Experimental Medicine*, Schneewind's team tested a way around that obstacle. They found that staph with a mutant

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version of protein A, unable to short-circuit B cells, did stimulate an immune response. Mice exposed to the "non-toxic" version of protein A were able to mount an effective immune response, killing bacteria, -- including the virulent strain known as USA300, the current source of about 60 percent of staph infections. The vaccine enabled these mice to reduce tissue damage and prevent, or at least delay, death.

"I believe," said Schneewind, "that protein A may be the key to making a staphylococcal vaccine."

The second target was a set of two clotting factors, coagulase and von Willebrand factor binding protein (vWbp), that the bacteria use to assemble protected niches within various tissues where they can replicate.

When the bacteria leave the blood stream, they settle into various organs, such as the kidneys. In this setting, they use these clotting factors to build a protected environment, called an abscess, where they can multiply. After several days, these abscesses rupture, spilling a new load of bacteria into the bloodstream where they can disseminate to uninfected tissues.

Bacteria that lacked functional versions of these two clotting factors were unable to form abscesses or persist in infected tissues. In the August 2010 issue of *PLoS Pathogens*, Schneewind and colleagues show that by generating antibodies to these two clotting factors and transferring them to infected mice, they could protect those mice from a staph infection.

The also made and tested an anti-coagulase vaccine by injecting purified versions of the clotting factors from a different kind of bacteria (*E. coli*) into mice and allowing the mice time to produce antibodies. About two weeks later they injected the mice with staph. Even when injected with the USA300, mice vaccinated with both antigens had far fewer abscesses and survived longer.

"The establishment of abscess lesions can be blocked with antibodies specific for coagulases," the authors conclude. "These data further corroborate the concept that Coagulase and vWbp should be considered for staphylococcal vaccine development."

Studies testing the ability of a vaccine combining both approaches are underway.

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