MICROBIOLOGY

A Possible New Approach to Combating Staph Infections

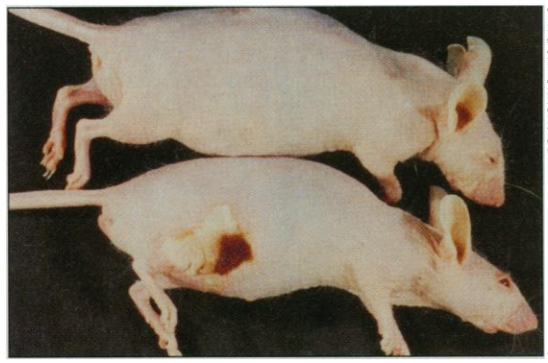
In the past 2 years, infectious-disease specialists have begun seeing one of their worst nightmares come true. They may be losing their last line of defense against the dangerous pathogen *Staphylococcus aureus*, which causes infections ranging from skin abscesses to such life-threatening conditions as pneumonia, endocarditis, septicemia, and toxic shock syndrome. Roughly one-third of the strains currently isolated from patients who acquire *S. aureus* infections while hospitalized are resistant to all antibiotics but one, vancomycin—and now resistance to that antibiotic has begun cropping up. But new research suggests an approach to combating *S. aureus* that may sidestep the organism's ability to develop resistance.

On page 438, Naomi Balaban, an infectious-disease researcher at the University of California, Davis, and her colleagues report that they can decrease the incidence and severity of *S. aureus* infections in mice by blocking the activity of a protein called RAP, which controls the production of toxins and other proteins that make the bacterium pathogenic. The work is still in its early stages and many questions remain, but it suggests that disabling RAP—perhaps by vaccinating people with the protein so that the immune system takes it out of commission, or by developing drugs that prevent it from doing its job—might keep the microbe from spreading within the body before the patient's immune system flushes it out.

Unlike conventional antibiotics, such drugs would interfere with disease without killing the organism directly, and in the absence of such selective pressures, strains resistant to anti-RAP therapies may be less likely to develop. "This opens a whole new strategy for treating or preventing one of the most serious hospital infections we contend with," says Julie Gerberding, an infectious-disease specialist at the University of California, San Francisco. "Methods that prevent disease without selecting for drug resistance could really help us—and we're going to need help soon."

Balaban discovered RAP several years ago while a postdoctoral fellow in Richard Novick's lab at New York University (NYU) School of Medicine. Her work there suggested that the protein helps *S. aureus* shift from the early stage of infection, in which the bacteria attach to host cells, to its later phase in which the organism spreads through the body, producing toxins and other molecules that destroy host tissues and cripple immune cells that might otherwise kill it. The bacteria secrete RAP, which has a molecular weight of 38,000, and as they multiply, the protein gradually builds up outside the microbial cells until it reaches a critical concentration.

At this point, it apparently sends a signal to the bacteria that culminates in the production of another regulatory molecule called RNAIII. (RAP stands for RNAIII activating protein.) This RNA then turns on the genes that produce toxins and other proteins needed for *S. aureus* to cause disease.



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RAPping staph. *S. aureus* infection causes a skin lesion in a control mouse *(bottom)* but not in the mouse vaccinated with the protein RAP *(top)*.

Because RAP plays such a critical role in *S. aureus* pathogenicity, Balaban thought it would be a good target for *S. aureus* prevention strategies.

In one set of experiments, the researchers inoculated mice with RAP purified from supernatants of *S. aureus* cultures. The vaccinated animals developed antibodies to RAP, and these mice fared much better than controls when the researchers injected *S. aureus* under the animals' skins. Seventy percent of the controls developed skin lesions, compared to 28% of those inoculated with RAP, and more of the control mice died than did the RAP-inoculated ones.

Because it takes weeks to mount an immune response, such a vaccine would most likely benefit those whose risk of infection can be anticipated, such as diabetics and dialysis and surgery patients, as well as firefighters and military personnel. But another strategy might help those who are already sick.

While Balaban was at NYU, she discovered that a mutant—and nonpathogenic—*S. aureus* strain produces a small peptide that blocks RAP's ability to turn on RNAIII production. Exactly how it does this is unclear, but recently the Balaban team determined the amino acid sequence of the peptide, called RIP for RNAIII-inhibiting peptide, and found that it resembles a stretch of RAP near the larger protein's amino terminus. This suggests, Balaban says, that RIP might bind to the same molecule that RAP does when it triggers RNAIII production, preventing the larger molecule from acting.

To see whether RIP inhibits infection by a pathogenic *S. aureus* strain, the team added the peptide to *S. aureus* and then injected the mixtures into mice. A smaller percentage of the animals injected with the RIP-pretreated bacteria developed lesions, compared to mice that received control bacteria. Jean Lee, a microbiologist at Harvard Medical School in Boston, points out, however, that "there's a big leap between preincubating the bacteria with RIP and treating the animal after it has an infection."

If RIP and RAP act as postulated, it may be possible to design small-molecule drugs that block RAP activity and thus *S. aureus* pathogenicity. But Balaban's former colleague Novick has questioned whether RAP does act as the researchers originally proposed. He and his colleagues have since identified a much smaller peptide that activates RNAIII and have suggested that Balaban's 38-kilodalton protein may have been contaminated with the real activator—the peptide.

In response, Balaban says her current work shows that an *S. aureus* strain lacking the gene for the peptide Novick identified still produces RAP that activates RNAIII perfectly well. She suggests that the peptide Novick identified and RAP both activate RNAIII, and they likely function in the same pathway. Otherwise, interfering with RAP alone would not diminish *S. aureus* pathogenicity. Novick agrees that his experiments do not rule out this possibility.

Several additional uncertainties also remain, such as whether anti-RAP strategies will be effective against other conditions caused by *S. aureus*, such as septicemia, and even whether the bacterium will find its way around treatments directed against RAP. "I bet on the bacteria in all cases," says Barbara Iglewski, a microbiologist at the University of Rochester School of Medicine and Dentistry in New York. "I'm sure they'll figure out a way around this [vaccination strategy]." Still, she says such new strategies are needed: "The fact remains that we've run out of good drugs and we need alternative approaches. Let's try to keep one step ahead of the bacteria."

–Evelyn Strauss

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