RESEARCH ADVANCES

Sepsis Drug Shows Promise against Influenza in Rodents

Carol Potera

Eritoran, a candidate drug developed by Eisai Inc. of Japan for treating sepsis, unexpectedly shows promise as a treatment for influenza when tested in rodents, according to Stefanie N. Vogel at the University of Maryland, Baltimore, and her collaborators. “For years people have focused on attacking the influenza virus,” she says. “Our data show that you can get remarkable results by focusing on the host response rather than the virus.” Details appeared online May 23, 2013 in Nature (doi:10.1038/nature12118).

Earlier, Vogel learned that Toll-like receptor 4 (TLR4) knockout mice resist influenza infections. Eritoran is a synthetic antagonist of lipid A, and acts by preventing lipopolysaccharide (LPS) from binding to the mammalian MD2-TLR4 receptor complex. On its own, LPS, or endotoxin, is a major component of the outer membrane of many gram-negative bacteria, and its presence in mammalian hosts can trigger inflammatory illnesses or, more acutely, sepsis in the blood.

From her observations of how TLR4 knockout mice respond to influenza and her knowledge of eritoran’s mode of action, Vogel and her collaborators decided to test whether eritoran can prevent influenza-induced deaths in mice. After animals were infected with the mouse-adapted influenza strain called PR8 and then treated with eritoran two days later, 90% of them survived. In contrast, only 10% of mice survived infections with that viral strain and follow-up treatment with a placebo. Those treatments with eritoran protect the influenza-infected mice against acute inflammatory lung damage, while also lowering viral titers and levels of cytokines such as interferon. Eritoran treatments similarly protect cotton rats that are infected with human influenza strain H3N2, she says.

“Eritoran could be repositioned as an intravenous drug to treat severe influenza infections in hospitalized patients,” says Steven Opal of Brown University in Providence, R.I. Opal led the phase 3 clinical trial of eritoran for sepsis, whose findings appeared in the March 20, 2013 Journal of the American Medical Association (doi:10.1001/jama.2013.2194). In the clinical trial, eritoran performed no better than a placebo, prompting Eisai in 2011 to drop plans to pursue marketing authorization of eritoran for treating sepsis patients in the United States, Europe, or Japan.

Influenza patients could benefit from intravenous eritoran, in particular those with primary influenza pneumonia caused by highly virulent avian influenza H5N1, or avian influenza H7N9, which has no current vaccine, Opal continues. In the phase 3 trial, he adds, “A one-week course of eritoran was given in very high doses to very sick patients with sepsis, and its safety record is excellent.”

“It may help that very clinically ill people with sepsis were safely given eritoran without significant negative effects,” Vogel says. “Hopefully, eritoran
will find a niche somewhere else in the treatment of human disease.”

Carol Potera is a freelance writer in Great Falls, Mont.

RESEARCH ADVANCES

Anti-Inflammatory Drug Has Activity Blocking Virulence Factors

David C. Holzman

In a quest for alternatives to antibiotics, Menachem Shoham of Case Western Reserve University in Cleveland, Ohio, and his collaborators identified—and repurposed—the anti-inflammatory agent diflunisal to target a key transcriptional regulator that controls expression of virulence genes in methicillin-resistant Staphylococcus aureus (MRSA), without killing the pathogen or inhibiting its growth. This approach, called anti-virulence therapy, could prevent this pathogen from causing disease without generating antibiotic resistance. “Since all bacteria employ quorum sensing mechanisms, this approach is in principle valid for all bacterial pathogens,” he says. Details appeared May 20, 2013 in Antimicrobial Agents and Chemotherapy (doi:10.1128/AAC.00269-13).

Without a crystal structure for the regulatory domain of the transcription regulator, AgrA, the investigators used information describing the structure of a similar protein to compute a likely structure for AgrA. They then screened 90,000 low-molecular-weight compounds by docking each into a virtual binding pocket of the target protein. Among the 107 top-scoring compounds in vitro, they identified diflunisal, a nonsteroidal anti-inflammatory agent that officials of the Food and Drug Administration licensed for general use more than four decades ago.

“The study is intriguing as it shows that we may find valuable new treatment options in our large libraries of existing compounds,” says Hanne Ingmer of the University of Copenhagen in Denmark, who was not involved in the research.

“Targeting global virulence regulators is often problematic, because they don’t regulate all virulence determinants in the same fashion,” says Michael Otto of the National Institute of Allergy and Infectious Disease at the National Institutes of Health (NIH) in Bethesda, Md., who praises Shoham’s approach. “While inhibiting Agr—as the drugs in the present paper do—leads to decreased expression of toxins, this also leads to upregulation of surface proteins, such as protein A—which are necessary for other virulence aspects of S. aureus.” Examples, he says, include tissue attachment, biofilm formation, and evasion of antibody-based host defense. Additionally, he says, “Whether the in vitro effect translates to real inhibition of infection, at least in animals, is not clear.”

Although diflunisal awaits testing as a virulence blocker in animal studies, other antivirulence agents that target single virulence factors appear to be effective when tested in animals at protecting them in some cases or reducing the severity of MRSA in other cases, according to Shoham. Anti-virulence approaches need to be tested for unintended consequences, “especially since targeting the accessory gene regulator function is associated with increased expression of other potent S. aureus virulence factors,” says Juliane Bubeck Wardenburg of the University of Chicago in Chicago, Ill. Those other factors include

MINITOPIC

Images, Synthesis of Ribosome; Insights, Target Improvement

Recent efforts to better understand ribosomes, the seat of protein synthesis, offer insights not only into how they function but also how to block those functions with antibiotics or other agents when necessary. Examples include:

• The 54 proteins and 3 synthetic RNA molecules from *Escherichia coli* ribosomes can now be assembled in vitro to transcribe proteins from messenger RNA (mRNA) molecules, providing a potential new means for developing novel antibiotics to target ribosomes, according to Michael Jewett of Northwestern University in Evanston, Ill., George Church of Harvard University in Cambridge, Mass., and their collaborators. Details appeared June 25, 2013 in *Molecular Systems Biology* (doi:10.1038/msb.2013.31).

• New images help to explain how elongation factor G acts like a ratchet, preventing ribosomes from slipping backward while moving along mRNA molecules and synthesizing proteins, according to Arto Pulk of the University of California, Berkeley, and Jamie Cate at nearby Lawrence Berkeley Laboratory. Details appeared June 28, 2013 in *Science* (doi: 10.1126/science.1235970). Closely related articles on bacterial ribosomes can be found in the same issue of *Science*.

• Two promising experimental inhibitors of prions that bind to ribosomes apparently target its protein-folding activity, identifying this function as a potential route to treating Creutzfeldt-Jakob disease in humans, scrapie in sheep, or similar prion-associated diseases, according to Suparna Sanyal of Uppsala University in Uppsala, Sweden, and her collaborators. Details appeared June 28, 2013 in the *Journal of Biological Chemistry* (doi: 10.1074/jbc.M113.466748).