MINITOPIC

Revising Sepsis Treatment

Here are several examples of psychiatric drugs being evaluated for their unexpected anti-infective activities, and another look at a drug for treating sepsis:

- The antidepressant sertraline (Zoloft) can inhibit the fungal pathogen Cryptococcus neoformans, according to Matthew Sachs of Texas A&M University and his collaborators. It is even more potent when used with the antifungal agent fluconazole when tested in mice, they note. Details appear in the July 2012 Antimicrobial Agents and Chemotherapy 56:3758–3766.

- Another antidepressant fluoxetine (Prozac) shows inhibitory activity against a variety of RNA enteroviruses, including the coxsackievirus, according to Paul Krogstad of the University of California, Los Angeles and his collaborators. Details appear in the July 2012 Antimicrobial Agents and Chemotherapy (doi:10.1128/AAC.00983-12).

- Although manufacturer Eli Lilly withdrew the antisepsis drug Xigris (drotrecogin alfa) in 2011 because of concerns over safety, its clinical use leads to about an 18% reduction in deaths from severe sepsis, suggesting it should be brought back to market, according to Andre Kalil of the University of Nebraska Medical Center and Steven LaRosa of Beverly Hospital in Beverly, Mass. Details appear in the July 17, 2012 Lancet (doi:10.1016/S1473-3099(12)70157-3).

RESEARCH ADVANCES

Vaccine Candidate Blocks Pseudomonas aeruginosa by Targeting Mucosal Immunity

Carol Potera

A new candidate vaccine, one that triggers a T-cell response and mucosal immunity rather than relying on B cells producing protective antibodies, appears promising against Pseudomonas aeruginosa when tested in mice, according to Gregory Priebe, an intensive care specialist at Boston Children’s Hospital in Boston, Mass., and his colleagues at nearby Harvard Medical School.

Priebe and his collaborators used bioinformatics to evaluate P. aeruginosa proteins, an approach that “usually focuses on finding antibody targets” such as outer membrane and secreted proteins, he says. Instead of choosing any of those proteins, however, they went with PopB, a highly conserved component of the type III bacterial secretion system that injects toxins into target host cells and plays an important role in pathogenesis. More importantly in this context, PopB proves also to be a potent stimulator of the Th17 lineage of T helper cells in infected hosts. Those cells, in turn, secrete the cytokine interleukin-17 (IL-17) to enhance mucosal immunity. “That’s what’s different about our approach,” he says.

Mice immunized with purified PopB and an adjuvant generate strong Th17 immune responses against P. aeruginosa. For example, after PopB-immunized mice are inoculated with an otherwise lethal P. aeruginosa strain, called ExoU+ PAO1, 62% of them survive, compared to 20% of those that were immunized with another type of vaccine, according to Priebe. Notably, no antibodies were involved in protecting these PopB-immunized mice, he says. Details appear in the June 21, 2012 American Journal of Respiratory and Critical Medicine (doi:10.1164/rccm.201202-01820c).

“The killing action is somewhat indirect,” Priebe says, referring to the mucosal immune response of the PopB-immunized mice against P. aeruginosa. Th17 cells produce IL-17 in response to the bacteria, attracting host neutrophils, the main type of white blood cells that kill the pathogen. Other T-cell based vaccines typically act by inducing cytotoxic T lymphocytes (CTL) that kill pathogens directly. However, CTL vaccines “generally work on viruses, not bacteria,” he says.

Patients with cystic fibrosis (CF) and those on hospital ventilators are especially susceptible to P. aeruginosa infections, and such infections are increasingly resistant to antibiotics. A vaccine to prevent such infections, particularly among individuals with CF who tend to become chronically infected with this pathogen, would help to offset antibiotic treatment failures. Not content with the efficacy of this new candidate vaccine, Priebe is developing conjugate vaccines that combine PopB with different polysaccharides to induce hosts to make antibodies as well as to develop a mucosal immune response.

Standard antibody-based vaccines do not protect well against this pathogen, yet it is difficult to identify mediators of mucosal immunity. The method that Priebe used to identify Th17-stimulating antigens “changes the paradigm for identifying vaccine candidates not predicted by antibody reactivity, and it could easily be applied to detect T cell-stimulating antigens in any system,” says Joanna Goldberg, a professor of microbiology, immunology, and cancer biology at the University of Virginia, Charlottesville.

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