istered antibiotics,” Moir says. These inhibitors are also effective in vitro against other gram-negative pathogens with this apparatus, including *Yersinia* and *Chlamydia* species.

Antibodies also can block T3SS, protecting mice against lethal infection, according to Paul Warrener of MedImmune in Gaithersburg, Md., who spoke during the 2012 ICAAC in San Francisco. He and his colleagues developed a monoclonal antibody against the PcrV protein of the injectosome complex, which blocks exoenzymes being injected in vitro and protects mice against pneumonia. A similar antibody is being evaluated in clinical trials.

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**RESEARCH ADVANCES**

**Neutralizing Vacuoles of *C. albicans* Can Tame Its Virulence**

Carol Potera

When the vacuoles of *Candida albicans* cells are made less acidic, this fungal pathogen becomes less virulent and potentially more manageable as an infectious agent, according to Rajini Rao of Johns Hopkins University School of Medicine in Baltimore, Md., and her collaborators. Details appeared July 24, 2013 in the *Journal of Biological Chemistry* (doi:10.1074/jbc.M113.494815).

Mutants of *C. albicans* that lack V-ATPase, a proton pump, are avirulent and cannot form filaments needed for infection, Rao says. V-ATPase also plays a role in protein processing, metabolite transport, biofilm formation, and other cellular activities. Faced with these many functions of V-ATPase and its several subunits, she and her collaborators focused on two isoforms of subunit a, called VPH1 and STV1. “Mutations that knock out all V-ATPase activity would not provide insight into what specific function is critical for virulence,” she explains.

Acidifying vacuoles of this yeast depends exclusively on VPH1. When Rao and her group evaluated mutants lacking either VPH1 or STV1, they found that VPH1 is critical for forming hyphae, which are critical for virulence. These filaments are reduced by up to 85% in mutants lacking VPH1 and which cannot acidify vacuoles. The importance of this subunit for virulence was further tested in experiments involving mice. Thus, injecting wild-type *C. albicans* as well as mutants lacking STV1 into mice kills nearly all of them within a week. In contrast, mice injected with mutants lacking VPH1 remain healthy.

These findings validate V-ATPase and vacuolar acidification as a potential drug target, according to Rao. “Drugs known to alter the pH of vacuoles could render *Candida* harmless while potentially posing little risk to infected patients,” she says. “The next step is to screen drugs already approved for humans to find others that block vacuole acidification.”

Rao and her collaborators learned several years ago that amidarone, a drug for treating heart arrhythmia, can block acidification of fungal vacuoles. Moreover, she says, the antifungal drug fluconazole, which blocks ergosterol biosynthesis, also impairs V-ATPase and makes fungal vacuoles less acidic.

When *C. albicans*-infected mice are treated with amidarone by itself, the animals show modest improvement. However, when amidarone is combined with fluconazole, the infection is reduced more effectively than when such mice are treated by fluconazole alone. Details of these experiments appeared June 3, 2010 in *PLoS Pathogens* [doi:10.1371/journal.ppat.1000939].

“This is the first significant attempt to dissect the importance of vacuolar acidification for *C. albicans* virulence,” says microbiologist David S. Perlin of New Jersey Medical School/Rutgers in Newark, N. J. “Because we have very few classes of antifungal drugs, exploring this virulence target is worthwhile.”

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

**Novel Antimicrobial Candidates**

Recent reports on novel antimicrobial candidates include several compounds that are active against drug-resistant strains of bacterial pathogens:

- Host defense peptidomimetic 4 destabilizes bacterial membranes and binds to DNA, rapidly killing gram-negative bacterial pathogens, according to Rasmus Jahnsen of the University of Copenhagen in Copenhagen, Denmark, and his collaborators there and the University of British Columbia (BC) in Vancouver, BC, Canada. Details appeared October 10, 2013 in *Chemistry & Biology* (doi:10.1016/j.chembiol.2013.09.007).
- Peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs), synthetic analogs of DNA or RNA that silence specific genes, prove to be bactericidal, have MICs in a “clinically relevant range,” and can increase survival of mice that are infected with *Acinetobacter* strains, according to Bruce Geller of Oregon State University in Corvallis and his collaborators there and at the University of Texas Southwestern Medical Center in Dallas and at Sarepta, Inc., also in Corvallis. Details appeared October 14, 2013 in the *Journal of Infectious Diseases* (doi:10.1093/infdis/jit460).
- Treating *Staphylococcus aureus* with acyldepsipeptide activates the bacterial protease ClpP, which targets misfolded proteins, making persister cells within the bacterial population susceptible again to antibiotics, according to Kim Lewis of Northeastern University in Boston, Mass., Kenn Gerdes at Newcastle University in the United Kingdom, and their collaborators. Details appeared November 14, 2013 in *Nature* (doi:10.1038/nature12790).

**NEW IN ASM JOURNALS**

**Cell Death through Apoptosis Activates Latent Herpesviruses**

David C. Holzman

Cell death programs, also known as apoptosis, can trigger herpesviruses to replicate, including any of four known human herpesviruses that can remain latent in their hosts for extended periods, according to Steven Zeichner of Children’s National Medical Center and George Washington University in Washington, D.C., and his collaborators. Because so many humans are infected by one or more herpesviruses—including cytomegalovirus, oral herpes simplex virus-1 (HSV-1) and genital herpes simplex virus-2 (HSV-2), and *Varicella zoster*, which causes chicken pox and shingles—this apoptosis-activation pathway could have broad clinical significance. Moreover, it might help to explain some of the side effects of several widely used anticancer drugs, he and his collaborators point out. Details appear in the October 2013 *Journal of Virology* (87:10641–10650).

These studies began with Zeichner following up findings that high concentrations of the antibiotic doxycycline can induce apoptosis and also activate replication by the Kaposi’s sarcoma-associated herpesvirus (KSHV). In other words, apoptosis triggers an “alternative replication pathway” for this virus, he says. Similarly, he adds, apoptosis also triggers replication of HSV-1, citing research by his former mentor, Bernard Roizman of the University of Chicago.

“We decided to test . . . several additional human herpesviruses that cause notable diseases and which have good latent infection cell line models, including human herpesvirus (HHV)-6A, -6B, and -7, and Epstein-Barr virus (EBV),” Zeichner says. Several widely used cytotoxic drugs, including doxorubicin and vincristine, act in part by inducing apoptosis of malignant cells. In doing so, they also can activate EBV, KSHV, and several additional herpesviruses, he finds. Perhaps patients being treated with such drugs, who are harboring latent herpesviruses, also should be treated with antiviral agents, he and his colleagues note.

Additionally, prednisone, a widely used steroid anti-inflammatory agent, may activate latent herpesviruses through apoptosis, according to Zeichner. For example, some patients with Kaposi’s sarcoma become worse following treatment with this drug or similar glucocorticoids. Instead of acting via immunosuppression, such drugs might be reactivating KSHV.

“It was intriguing to learn that steroids might activate herpesviruses due to apoptosis instead of immunosuppression, as is widely believed,” says Dharam Ablashi of the HHV-6 Foundation in Santa Barbara, Calif. “Perhaps herpesvirus reactivation is responsible for some of the organ failure and severe complications that occur during the late flare of symptoms that occurs in these patients.”

Zeichner’s report “does not address whether shingles may arise through this mechanism—a fascinating possibility,” Ablashi says. Oral and genital herpes may also flare due to apoptosis. In any case, understanding the mechanism of reactivation via apoptosis, he says, “will be the first step towards developing novel approaches to treat such conditions in a rational manner.”

Amid this interest, several researchers expressed doubts to the HHV-6 Foundation about whether the cell lines used for Zeichner’s study carry latent herpesviruses. Sharing those concerns, Ablashi advises Zeichner to redo his experiments with different cell lines. Although Zeichner disagrees, saying the cells that he used contain latent virus and that other researchers report similar findings, he does plan