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 phosphorodiimidate 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...
RESEARCH ADVANCES

For Cells, Mistakes Repairing DNA Speed Evolution

Marcia Stone

Bacterial cells mutate rapidly and specifically—not merely randomly—in response to stress, says Susan Rosenberg at Baylor College of Medicine in Houston, Tex., who seeks to tweak the core principles of evolution—namely, that evolution-driving mutations arise randomly, constantly, gradually, and independently of selective environments. “Stress-induced mutations are different; they’re controlled by [specific] stress-response programs that invite error-prone DNA-break repair and are only activated when cells are maladapted to their environments—in other words, are stressed.” She spoke at a Presidential Research Seminar, sponsored by Memorial Sloan-Kettering Cancer Center in New York, N.Y., last October.

“Stress-induced mutations quickly increase genetic diversity, enabling subsets of resistant cells to survive and perpetuate their genotype, thereby saving the strain from extinction,” Rosenberg continues. Starved Escherichia coli cells, for example, activate the RpoS stress response that allows error-prone polymerases to repair double-strand DNA breaks. The resulting mutation flood accelerates evolution, Rosenberg contends. She speculates that RpoS-promoted mutagenic break repair evolved because of its value as an evolutionary engine.

Error-prone DSB-repair proteins appear to trigger stress-induced mutations in circumstances other than starvation and in organisms other than E. coli. “We know that RpoS programs are induced by osmotic, pH, temperature, and oxidative stresses,” says Rosenberg. “We also have evidence that when confronted by antibiotics, E. coli activates RpoS-encoded DSB-repair proteins similar to those used by starved cells, and that pathogenic Salmonella induces RpoS-dependent mutations in response to bile, a membrane irritant.” Additionally, Pseudomonas aeruginosa biofilms display a DSB-repair, protein-generated diversity that she suspects arises by the same mechanisms.

The ability of cells to change rapidly when stressed is also important to tumor progression in hypoxic environments because it provides a way for malignant cells to develop resistance to anti-cancer therapies, according to Rosenberg. She calls for the development of “anti-evolution” drugs that block stress-promoted cellular adaptation to host-instigated stressors. These new agents could be combined with conventional antibacterial, antifungal, and anti-cancer drugs, all of which should be classed together as “anti proliferatives,” she says. Details of her arguments appeared August 22, 2012 in Bioessays (34: 885–892; doi:10.1002/bies.201200050).

“Rosenberg and colleagues identify specific mechanisms enabling bacteria to switch into a hypermutable state, turning up the frequency with which adaptive mutations occur,” says Lance Price at George Washington University in Washington, D.C., who was not involved in this research. “More specifically, they explain how the hypermutable state is regulated. It’s very cool.

“However, this still feels Darwinian because while the responses to stressors may be specific, the mutations themselves appear to be randomly generated,” Price continues. “Importantly, the intrinsic ability of bacteria to quickly deal with stress helps explain why exposure to subtherapeutic doses of some antibiotics leads to such rapid evolution of resistant mutants and why the practice has proved so dangerous in