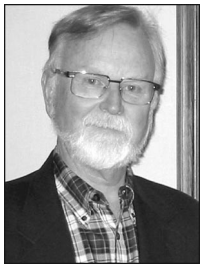
Journal Highlights

New Data on Tat System Might Lead to Novel Antibiotics



Vasil

Most secreted bacterial proteins exit the cytoplasm via the general secretory (Sec) pathway. Unlike Sec, which is powered by ATP, the more recently discovered Tat system works off of pH differences. Michael L. Vasil and coworkers at the University of Colorado show that in *Pseudomonas aeruginosa*, specific amino acids in the signal peptide of an extracellular virulence determinant play a critical role in its secretion via Tat. "Our results also demonstrate a degree of functional compatibility between the TAT systems of different bacterial species," says Vasil. "We and others have now established that the TAT system plays a vital role in the pathogenic potential of both plant and animal bacterial agents. Our data might provide a foundation to identify compounds that would abrogate TAT function, thereby leading to a novel class of antibiotics."

(A. Snyder, A. I. Vasil, S. L. Zajdowicz, Z. R. Wilson, and M. L. Vasil. 2006. Role of the *Pseudomonas aeruginosa* P1cH Tat signal peptide in protein secretion, transcription, and cross-species Tat secretion system compatibility. J. Bacteriol. 188:1762–1774.)

New Pathway for p53-Independent Apoptosis

Given that the tumor suppressor ARF stabilizes and activates p53, ARF inactivation has been commonly viewed as one of the many means of inactivating the p53 pathway, a sine qua non for mammalian tumorigenesis. Now Steven R. Grossman and coworkers at the University of Massachusetts Medical School, Worcester, show that ARF causes degradation of a transcription factor, (CtBP) that is a master repressor of pro-apoptotic genes. "CtBP degradation via ARF induced apoptosis in p53-null colon cancer cells, and the effect was rescued by replacing the lost CtBP with an exogenous cDNA allele," says Grossman. "p53-independent ARF tumor suppression may be especially relevant to the development of epithelial malignancies, which form the vast majority of human cancers."

(S. Paliwal, S. Pande, R. Kovi, N. E. Sharpless, N. Bardeesy, and S. R. Grossman. 2006. Targeting of C-terminal binding protein (CtBP) by ARF results in p53-independent apoptosis. Mol. Cell. Biol. 26:2360–2372.)

Compound Unblocks Cellular Immune Response to Hepatitis C

Malcolm

An estimated 170 million people worldwide are infected with hepatitis C virus (HCV), which in about 80% of cases leads to chronic disease. The current standard of care, pegylated alpha interferon with or without oral Ribavirin, is successful against only about half of infections from the major genotype affecting North America and Europe. Now Bruce Malcolm and colleagues of the Schering-Plough Research Institute show that a mechanism-based inhibitor of a hepatitis C protease enhances the antiviral activity of alpha interferon in replicon cells, supporting the hypothesis of S. M. Lemon and M. Gale that the NS3 protease blocks cellular immune response to the virus. "So in addition to abrogating HCV replication directly, a sufficiently potent protease inhibitor should unblock the cellular immune response, in effect 'unmasking' the infection," says Malcolm.

(B. A. Malcolm, R. Liu, F. Lahser, S. Agrawal, B. Belanger, N. Butkiewicz, R. Chase, F. Gheyas, A. Hart, D. Hesk, P. Ingravallo, C. Jiang, R. Kong, J. Lu, J. Pichardo, A. Prongay, A. Skelton, X. Tong, S. Venkatraman, E. Xia, V. Girijavallabhan, and F.G. Njoroge. 2006. SCH 503034, a mechanism-based inhibitor of hepatitis C virus NS3 protease, suppresses polyprotein maturation and enhances the antiviral activity of alpha interferon in replicon cells. Antimicrob. Agents Chemother. 50: 1013–1020.)

Disinfecting Dirty Dental Water Systems

Dental unit water systems (DUWS) used to irrigate the oral cavity can be heavily contaminated. Jimmy T. Walker of the Health Protection Agency, Porton Down, United Kingdom, and others found that over 50% of systems sampled in the European Union exceeded current American Dental Association standards, and recovered opportunistic pathogens such as legionellae and *Mycobacterium* spp., often in biofilms. They evaluated disinfectants and selected several to be studied as used in general dental practices, and found that the most effective were Dentosept and Oxygenal. "We have now been able to provide dentists with effective disinfection strategies," says Walker. "At present the European Union does not have guidelines for water quality of DUWS—this study will help inform the debate on this issue. We have now extended our research to encompass studies involving prions, their routes of infection, and potential cross-infection between patients within the dental practice."

(A. J. Schel, P. D. Marsh, D. J. Bradshaw, M. Finney, M. R. Fulford, E. Frandsen, E. Østergaard, J. M. ten Cate, W. R. Moorer, A. Mavridou, J. J. Kamma, G. Mandilara, L. Stösser, S. Kneist, R. Araujo, N. Contreras, P. Goroncy-Bermes, D. O'Mullane, F. Burke, P. O'Reilly, G. Hourigan, M. O'Sullivan, R. Holman, and J. T. Walker. 2006. Comparison of the efficacies of disinfectants to control microbial contamination in dental unit water systems in general dental practices across the European Union. Appl. Environ. Microbiol. 72:1380–1387.)

Commensal Flora Reduce *E. coli* O157:H7 and Shiga Toxin in Mouse Intestine

Shiga toxin (Stx) released during *Escherichia coli* O157:H7 infection causes a life-threatening complication, hemolytic uremic syndrome, in about 10% of infected children. The toxin is encoded on a lysogenic phage, and expressed during the lytic cycle. Alison A. Weiss of the University of Cincinnati et al. showed that mice colonized with intestinal *E. coli* that were phage resistant had lower levels of Stx following infection with *E. coli* O157:H7 than did mice with phage-susceptible *E. coli*. "Only about 10% of the kids who are infected with *E. coli* O157:H7 develop hemolytic uremic syndrome," says Weiss. "Our results suggest that kids with phage-susceptible intestinal *E. coli* may experience a higher toxin load, which could be an important susceptibility factor. We think that introduction of Stx phage-resistant intestinal *E. coli* could be developed as a probiotic to prevent disease caused by *E. coli* O157:H7."

(l–r) Strasser, Gamage, and Weiss

(S. D. Gamage, A. K. Patton, J. E. Strasser, C. L. Chalk, and A. A. Weiss. 2006. Commensal bacteria influence *Escherichia coli* O157:H7 persistence and shiga toxin production in the mouse intestine. Infect. Immun. 74: 1977–1983.)

New Nitrogen Modulating Genes and Their Regulation

The movement of ammonium across biological membranes is mediated in prokaryotes and eukaryotes by ammonium transport proteins (AMT/MEP). Having characterized two *Aspergillus nidulans* AMT/MEP genes, Meryl Davis et al. of the University of Melbourne, Australia, now outline the contributions of two additional MEP genes to ammonium uptake. "Our studies reveal that the organism can differentiate nitrogen sufficiency, limitation, and starvation as distinct physiological states, and the expression patterns of the AMT/MEP genes reflect these states," says Davis. "Remarkably, the expression of all these genes requires the transcriptional activator AreA, a global nitrogen regulator which previous studies suggest is inactive when nitrogen is adequate. Our studies show that AreA is active under repressing conditions, at least at some promoters. Our work highlights promoter-specific contexts as important in determining the activation capacity of AreA under different nitrogen conditions, and provides an excellent system for studies of this new aspect of AreA function."

Davis

(B. J. Monahan, M. C. Askin, M. J. Hynes, and M. A. Davis. 2006. Differential expression of *Aspergillus nidulans* ammonium permease genes is regulated by GATA transcription factor AreA. Eukaryotic Cell 5: 226–237.)