



Current Topics

R Genes Help Legumes Choose Their Symbionts

Resistance genes play a key role when legumes choose their nitrogen-fixing bacterial partners, according to Hongyan Zhu at the University of Kentucky in Lexington and his collaborators there, at the University of Missouri in Columbia, and at Chongqing University in China. Simply put, by letting some bacteria in and keeping others out, *R* genes help control legume-rhizobia symbiotic specificity. Details appear in the October 26, 2010 *Proceedings of the National Academy of Sciences* (107:18735–18740).

Such cross-kingdom collaborations demand that the two species tolerate each other amid plant-host immune responses that exclude other bacteria. By investigating two soybean genes that regulate bacterial interactions, *Rj2* and *Rfg1*, these researchers discovered that symbiotic specificity is controlled by a member of the nucleotide-binding site/leucine-rich repeat (NBS-LRR) resistance gene family, which are known for their ability to confer protection against pathogens.

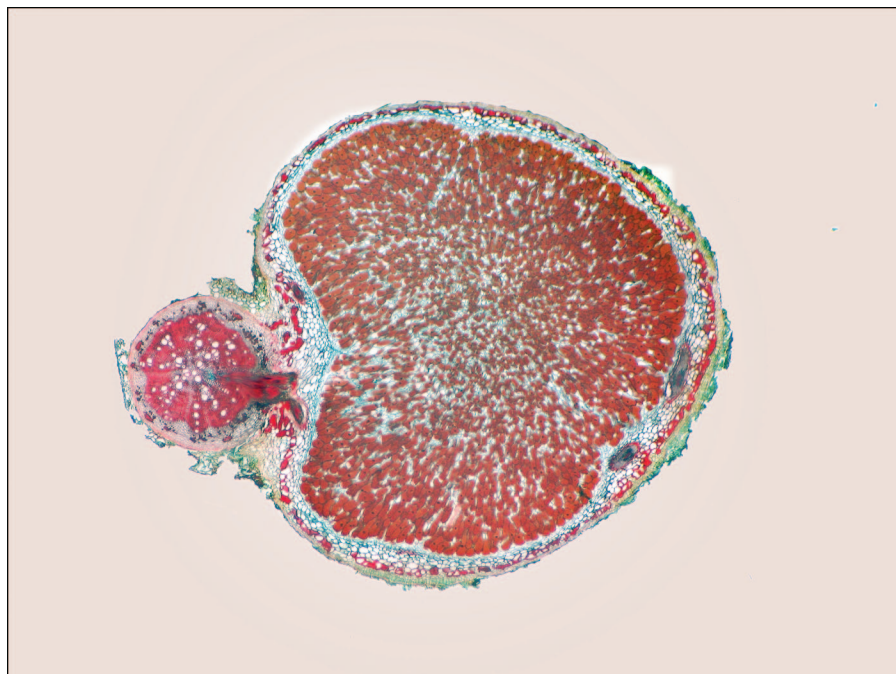
As part of symbioses, some rhizobia form root nodules—a specialized plant organ that provides an environment for specific bacteria to convert atmospheric nitrogen into ammonia, which plants use for growth. “Successful nodulation requires a fine-tuned exchange of molecular signals between host plant and its bacterial symbionts,” says lead investigator Shengming Yang at the University of Kentucky. “While Nod factors are the best-known bacterial signals, rhizobia also use surface polysaccharides and

effector proteins to modulate their host range.”

Bacterial surface polysaccharides of pathogens and symbionts play major roles in the evasion or suppression of host defense responses. “Many, but not all, rhizobial strains possess a type III secretion system (T3SS), which delivers effectors directly into host cells,” Yang says. However, unlike those of bacterial pathogens, rhizobial effectors sometimes function as facilitators superimposed on the Nod-factor signaling pathway. Nonetheless, when host plants recognize rhizobial effectors, the effect is negative. Thus, bacteria that cannot circumvent legume *R* genes will not trigger nodule formation.

“It’s possible that some rhizobia

and pathogenic bacteria share a common set of virulence effectors to facilitate host invasion, thereby presenting the host with the dilemma of choosing to form a symbiotic alliance or mounting a disease-resistance strategy,” Zhu says. “A second possibility is that some hosts have evolved *R* genes to selectively interact with some strains of rhizobia and exclude others.” He cites the predominance of the soybean *Rj4* allele, which protects the host against nodulation by phytotoxin-producing strains of *Bradyrhizobium elkanii*. “Much remains to be learned about how *R* genes condition plant-microbe interactions in natural ecosystems,” says Zhu. One immediate benefit of their findings, he adds, is “the potential to develop unique strat-



Soybean root nodule cross section showing root parts on the left and the nitrogen-fixing bacterial aggregates on the right (magnification, ~5X). Researchers are clarifying the factors controlling the formation and maintenance of these symbioses. (Image © Garry DeLong/Photo Researchers, Inc.)

Polio Outbreaks—Some Deadly—Frustrate Eradication Hopes

Several recent polio outbreaks not only frustrate efforts to eradicate this disease, but also raise concerns about the emergent lethality of polio viruses circulating in central Africa, particularly the Republic of Congo, according to officials of the World Health Organization (WHO). Officials reported 184 cases of acute flaccid paralysis and 85 deaths from the outbreak in that country late in 2010. The virus appears to have entered Congo, which reported its last indigenous case 10 years earlier, from neighboring Angola, according to genomic sequencing analyses of virus isolates. What accounts for the nearly 50% mortality rate of this polio outbreak, however, remains to be determined. Meanwhile, a separate outbreak of polio in Central Asia and the North Caucasus Federal Region in Russia led WHO officials last year to declare that the risk of further spread “continues to be high.” Although polio vaccination campaigns launched by health officials in Tajikistan, which experienced 458 cases and is considered the “epicenter” of the outbreak in this region, appear to be working effectively, other neighboring countries are still considered at risk.

egies that enhance symbiotic nitrogen fixation in crop legumes.”

The resistance genes study is “very, very important because it provides the first demonstration of the role of *R* genes in symbiosis,” says Paola Bonfante, who studies plant-fungus relationships at the University of Torino in Italy. Two current questions in fungal symbiosis research are how 80% of plants accept arbuscular mycorrhizal fungi (AMF) despite active, albeit weak, immune defenses and how successful fungal symbionts down-regulate plant immunity genes, she says. “It will be important to see the dynamics of *R* genes during AMF reactions with their host plants.”

Some AMFs Bonfante is investigating host their own symbionts—“gram-positive endobacteria living inside the fungi, which are living inside plant roots,” she says. These bacteria split from their sister groups more than 400 million years ago, colonizing fungal hosts before the main AMF lineages separated and “thus offer a great tool to investigate evolutionary

mechanisms,” she adds. She also notes that “*Candidatus glomeribacter* endosymbionts possess T3SS, and we are now wondering about its impact on the fungal immune system.” See the July 2010 issue of *ISME J.* for details.

Marcia Stone

Marcia Stone is a science writer based in New York City.

β -Lactamase Inhibitor NXL104 Helps Overcome Resistance of Pathogens

When used with ceftazidime or other β -lactam antibiotics, NXL104, a potent inhibitor of β -lactamase enzymes, becomes a powerful combination against a wide range of β -lactamase-producing bacterial pathogens in vitro, according to David Livermore and his colleagues at the Health Protection Agency in London, United Kingdom. That particular combination also delivers a powerful one-two punch against infections in mice caused by pathogens that are resistant

to a range of carbapenem antibiotics, according to Andrea Endimiani and Robert Bonomo of the Louis Stokes Cleveland VA Medical Center and Case Western Reserve University, both in Cleveland, Ohio, and their collaborators. Details from these two studies appear in the January 2011 *Antimicrobial Agents and Chemotherapy* (55:82–85 and 55:390–394).

Put more specifically, combining NLX104 plus ceftazidime is particularly effective in vitro against *Klebsiella pneumoniae* strains carrying *K. pneumoniae* carbapenem (KPC) resistance genes, Livermore reports. Further, combining NXL104 with the antibiotic aztreonam proves effective against a wide range of carbapenemase-producing strains, including those carrying the Verona imipenemase (VIM) and the recently identified New Delhi metallo- β -lactamase (NDM) (see *Microbe*, December 2010, p. 506).

Earlier, Endimiani and Bonomo reported that NXL104 lowers effective minimal inhibitory concentrations (MICs) when combined with various β -lactam antibiotics. Some combinations also proved active in mice infected with *K. pneumoniae* strains expressing high levels of resistance to imipenem and ceftazidime, according to Bonomo, who notes that clinical isolates with this resistance are spreading across the United States from the east coast. Combining NXL-104 with ceftazidime to treat mice significantly increases their chances of survival with otherwise lethal infections and reduces pathogen levels, he now reports. “These [animal studies] open the door for more in-depth investigations into [NXL104], as well as novel derivatives.”

“Most impressive was the ability of the inhibitor combination [NXL104 and ceftazidime] to treat bacteria that produced three or four β -lactamases,” says Karen Bush of Indiana University in Bloomington. Carbapenems, the most powerful of the β -lactam antibiotics, are used to treat bacterial infections that resist other drugs. The re-



cent appearance of bacteria with carbapenem resistance “has created critical treatment issues in hospitals in the New York City area,” she notes. “Many of the KPC-producing strains are resistant to all antibiotics with the exception of colistin and possibly tigecycline, leaving few therapeutic options.”

Other carbapenemases, which differ from KPC and sometimes prove harder to deal with, are traveling the world within their human hosts. Thus, multidrug resistance associated with the NDM-1 enzyme is spreading rapidly, according to Robert C. Moellering, Jr., of Harvard Medical School in Boston, Mass., whose comments appear in the 16 December 2010 *New England Journal of Medicine* (363:2377–2379).

Plasmids encoding NDM-1 are being found in members of the *Enterobacteriaceae* throughout the Indian subcontinent and elsewhere in Asia, throughout much of Europe, the United States and Canada, Australia, and in Africa, according to Livermore. The major carriers of NDM-1 are *K. pneumoniae* and *Escherichia coli*, but *Acinetobacter* spp. are additional hosts, he notes. In India, the poorly regulated use of antibiotics within a huge population and a “creaky infrastructure,” which allows gut bacteria from sewage to contaminate drinking water, creates a “frightening” potential for both local and international dissemination, he warns.

Combining NXL104 with aztreonam, which proves effective when tested in rodents, will be critical for treating infections in humans that are due to NDM-1-carrying bacteria, says David Shlaes of Anti-Infectives Consulting in Stonington, Conn. Although ceftazidime is inactive against strains bearing metallo- β -lactamases such as NDM-1, aztreonam is resistant to such enzymes. NXL-104 is important “because these strains also carry serine β -lactamases which, without an added inhibitor, would result in az-

treonam resistance,” he says. However, although AztraZeneca is conducting clinical trials to evaluate ceftazidime combined with NXL-104, the combination of NXL-104 and aztreonam is not being developed commercially, according to Livermore.

David C. Holzman

David C. Holzman is the *Microbe* Journal Highlights Editor.

Food Safety Law: Focus on Prevention, Boost to FDA Authority

President Obama early in January signed the Food Safety Modernization Act (FSMA), which Congress passed days earlier during a frenzied lame-duck session (*Microbe*, February 2011, p. 54). The new law, the biggest overhaul of federal food safety legislation in decades, emphasizes the importance of preventing foodborne illness and grants significant new authority to the Food and Drug Administration (FDA). Although many stakeholders—including food-safety experts, food producers and marketers, and consumer groups—welcome the new

law, they already are voicing concerns that federal budget tightening and political maneuvering could undercut near-term efforts by FDA officials to implement some of its provisions.

“This law represents a sea change for food safety in America, bringing a new focus on prevention, and I expect that in the coming years it will have a dramatic and positive effect on the safety of the food supply,” says FDA Commissioner Margaret Hamburg. “For the first time FDA will have a congressional mandate for risk-based inspection of food processing facilities.” In addition, the new law “significantly enhances FDA’s ability to oversee the millions of food products coming into the United States from other countries.”

Foodborne illnesses strike an estimated 48 million individuals each year in the United States, leading to several thousand fatalities, Hamburg says, citing recently updated estimates from the Centers for Disease Control and Prevention in Atlanta, Ga. Moreover, the aggregate cost for those illnesses and their collateral impact, including medical care and lost wages, could be as high as \$157 billion per

FDA Guidance for MRSA Tests; Research To Explain Staph’s Pathogenic Aptitude

Officials at the Food and Drug Administration (FDA) in January issued detailed guidance for the performance of nucleic acid-based in vitro diagnostic devices for testing clinical specimens suspected of containing methicillin-resistant *Staphylococcus aureus* (MRSA). Although agency officials say the guidance can be used to support Class II submissions for such devices, they emphasize that the current documents are not meant to establish “legally enforceable responsibilities.” Meanwhile, recent research findings help to explain why *S. aureus* is such an effective pathogen of humans. These bacteria carry a receptor that recognizes portions of the hemoglobin protein that are peculiar to humans, according to Erik Skaar and his collaborators at Vanderbilt University in Nashville, Tenn. Thus, the pathogen is particularly adept at acquiring the iron that it needs from specific human protein molecules that sequester it. Details appear in the December 16, 2010 *Cell Host & Microbe* (8:544–550).

Microbes in Unexpected Places or with Unexpected Activities

Here are several recent examples of microbes being found in unexpected niches or undertaking unexpected activities:

- Rocks within the gabbroic layer of the Earth, which lies above the mantle but is more than 1 km below sea level, provide a niche for a poorly diverse microbial community, much of it devoted to degrading hydrocarbons, according to Stephen Giovannoni of Oregon State University, Corvallis, and collaborators there and at several other institutions. Details appear in the November 5, 2010, *PLoS ONE*.
- When fed to mice, nonpathogenic strains of *Clostridium* bacteria can stimulate regulatory T cells in the gut, in turn suppressing allergies and autoimmune diseases of the host, according to Kenya Honda of the University of Tokyo and collaborators. Details appear online 23 December 2010 and in print on 21 January 2011 in *Science* (331: 337–341).
- A strain of bacteria from the mud of Mono Lake, California, appears to thrive on arsenic, perhaps substituting it for phosphate, according to Felisa Wolfe-Simon at the U.S. Geological Survey in Menlo Park, Calif., and her collaborators. Details appear online in the 3 December 2010 *Science*. (These findings are stirring considerable controversy in the scientific blogosphere.)

year, according to Caroline Smith DeWaal, who is Food Safety Director for the Center for Science in the Public Interest, a consumer advocacy organization in Washington, D.C. Recent high-profile outbreaks of foodborne illnesses helped to build broad and bipartisan support for the new law, she says. Its provisions are directed mainly at FDA, in part because public concerns about food safety focus there during outbreaks. The U.S. Department of Agriculture (USDA) shares federal responsibility for food safety, particularly through its inspections of meat and poultry.

The new law, which “marks an overall improvement,” contains several important provisions, says Michael Doyle, Director of the Center for Food Safety at the University of Georgia in Griffin. For example, giving FDA authority to issue “mandatory food recalls is new,” as is extending agency authority over food imports.

Another provision that is “new and important is that all companies will need to have food safety plans in place, except for those that are waived,” he adds, referring to smaller companies that operate only locally or with low volumes of products.

Some changes that were incorporated into the new law reflect a “shift to risk analysis and what’s the biological basis of adverse effects” that took shape during the past decade, says Robert L. Buchanan, who directs the Center for Food Safety and Security Systems at the University of Maryland, College Park. An important component of this approach is “risk ranking,” which entails figuring out “what foods present the most risk.” Complicating any effort to bring better scientific understanding to these analytic challenges, however, is the way the public seems to treat food risks, he says. “It’s fascinating; we seem to feel differently about food

than anything else. It’s almost sacred—either safe or unsafe—whereas with drugs, we recognize [gradations of] risk.”

Even before President Obama signed FMSA, some members of Congress were vowing to block its provisions by curbing FDA funds. “One of the big hurdles is that it will cost \$1.4 billion to implement FMSA,” Doyle says. Earlier versions of the legislation included user fees, but they were discarded along the way to enactment. “If FDA wants to hire 2,000 inspectors, it will require a considerable appropriation,” he says. “Time will tell.”

Jeffrey L. Fox

Jeffrey L. Fox is the *Microbe Current* Topics and Features Editor.

Sequencing Technologies Yield Novel Microbial Noncoding RNA Molecules

DNA sequencing is continuing to reveal noncoding (nc) bacterial and archaeal RNAs, many of unknown function. These efforts now include a new batch of 104 highly structured ncRNAs uncovered by Ronald R. Breaker and his colleagues at Yale University in New Haven, Conn. “These ncRNAs not only greatly expand the variety of known RNAs, they provide a starting point for the biochemical and genetic studies needed to explain their biological functions,” he says. Breaker spoke this February at a Presidential Research Seminar, a weekly series sponsored by Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, N.Y. “An additional challenge will be to determine the three-dimensional structures of the large ncRNAs and attempt to correlate them with function,” says Dinshaw Patel of MSKCC, who hosted the seminar.

Bacterial genomes contain 10 to 15% noncoding DNA sequences that, when transcribed into RNAs, endow



the cell with critical fitness advantages. Both large and small ncRNAs are structurally diverse, with some of the larger ncRNAs nearly as complex as ribosomes. Their conserved complexity and diversity along with their varied genomic locations suggest that these RNA molecules are involved in a wide range of biologic roles and activities. See *Genome Biology* (<http://genomebiology.com/2010/11/3/R31>) for details.

One of the most surprising recent findings is a cyclic di-guanosyl-5'-monophosphate (c-di-GMP)-binding riboswitch, which is linked to a self-splicing intron. Its host bacterium, *Clostridium difficile*, appears to harness this apparatus to promote protein production from a downstream pathogenicity gene, according to Breaker. Thus it seems that not all group I self-splicing ribozymes are associated with selfish genetic elements, he says. "Furthermore, because this regulatory region can read both GTP and c-di-GMP concentrations and trigger splicing accordingly, it appears to constitute a two-input gene control system." Details appear in the 13 August 2010 *Science* (329:845–848).

Breaker and his collaborators also are investigating a set of ornate large extremophilic (OLE) RNAs produced by *Bacillus halodurans*. These RNA molecules bind to an OLE-associated protein (OAP), which has several transmembrane domains. "We know that OAP recruits OLE RNA to the cell membrane, suggesting that's where most of the transcript's complex structure performs its biochemical function," Breaker says. Noting that OLEs are not only membrane-bound but also abundant in *B. halodurans*, he speculates that they enable this extremophile to adapt to its environment. "The newer and faster technologies will most likely reveal a vast number of additional ncRNAs," he adds, referring to recent improvements in DNA sequencing analysis.

Cholera in Haiti Adds to Suffering, Evokes Calls for Drug Treatment and Vaccination Plans

Although the cholera outbreak that began in Haiti during October 2010 is subsiding, its death toll exceeded 1,400 as of late November among more than 60,000 cases, according to officials of the World Health Organization (WHO). Genomic analysis indicates that the outbreak strain was introduced into the country "from a distant geographic source . . . through human activity," according to Eric Schadt of Pacific Biosciences in Menlo Park, Calif., and his collaborators there and elsewhere, whose findings appear in the January 6, 2011 *New England Journal of Medicine* (NEJM) (364:33–42). Although rehydration proves a lifesaving therapy for many individuals with cholera, Matthew Waldor of Harvard Medical School in Boston, Massachusetts, and his collaborators recently recommended that the United States stockpile cholera vaccines to deploy at the first signs of outbreaks such as the one in Haiti (see December 9, 2010 NEJM, 363:2279–2282). Meanwhile, David Sack of the Johns Hopkins Bloomberg School of Public Health, Baltimore, Md., and his collaborators, urge that antibiotics also be used judiciously during such outbreaks, noting that appropriate drug therapy "shortens the duration of illness and reduces the shedding of thousands of infectious doses" (January 6, 2011 NEJM, 364:5–7).

See the January 2011 *Molecular Microbiology* for details.

"This study shows how inexpensive next-generation sequencing is revolutionizing the field of molecular microbiology," say Wes Sanders and Alain Laederach at the University of North Carolina in Chapel Hill. "Now it is possible to characterize an entire bacterial transcriptome in a single experiment," they add. Moreover, says Eric Westhof of the Université de Strasbourg in France, "Until Breaker's group exploited the power of comparative sequence analysis—combining sophisticated automatic technology with manual intervention—the complex structures of ncRNAs remained hidden in the genome's 'dark matter' long considered nothing more than junk."

Breaker will be speaking at an ASM-sponsored conference on RNA regulation in bacteria, 7–11 March 2011, in San Juan, Puerto Rico. See <http://www>

[.asm.org/index.php/meetings/2010-asm-conference-on-regulating-with-rna-in-bacteria.html](http://www.asm.org/index.php/meetings/2010-asm-conference-on-regulating-with-rna-in-bacteria.html).

Marcia Stone

Three Crenarchaeotes, All Hyperthermophiles, Form Biofilms

In the absence of other microbial species, three closely related hyperthermophilic crenarchaeotes—*Sulfolobus acidocaldarius*, *S. solfataricus*, and *S. tokodaii*—form biofilms, according to Sonja-Verena Albers and her collaborators at the Max Planck Institute for Terrestrial Microbiology in Marburg, Germany. Although other investigators report finding archaea within bacterial biofilms, these experiments appear to be the first in which archaeal species propagate biofilms on their own, she says. Details appear in the

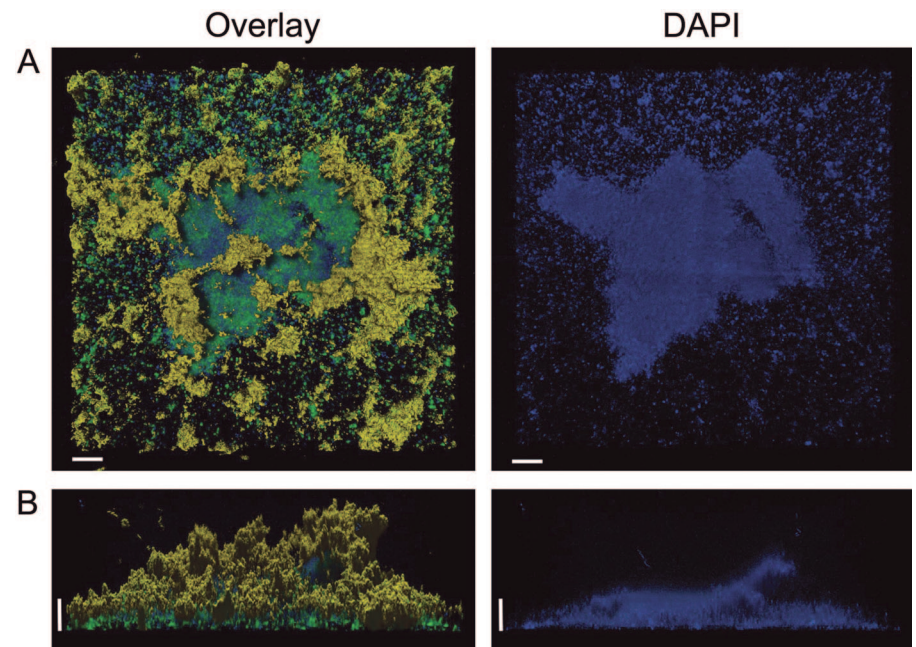
November 2010 *PloS One* (DOI: 10.371/journal.pone.0014104).

All three of these acid-loving *Sulfolobus* species are found in geothermally active environments, and they grow optimally at 75–85°C and in the acidic pH range of 2–3. Earlier, while collaborating with Wolfram Zillig at the Max Planck Institute for Biochemistry in Martinsried, Albers noticed that such *Sulfolobus* form microcolonies. “This indicated that these strains might be able to form biofilms,” she says.

These archaeal biofilms differ from those that bacteria form, according to Albers and her collaborators. “Bacterial biofilms form carpet-like structures; in contrast, *S. acidocaldarius* [cells] form tower structures and secrete a large amount of extracellular polysaccharides,” they report. Curiously, the biofilms that these three crenarchaeotes form differ from one another, likely reflecting differences in their responses to localized environments that they encounter in hot springs, according to Albers and her collaborators. “*S. solfataricus* and *S. tokodaii* are always isolated from the middle of solfataric hot springs, whereas *S. acidocaldarius* is mainly found in the crust at the sides of hot springs,” they point out.

Simulating hot-spring conditions in the lab proves challenging, particularly when adapting analytic methods to very high temperatures, according to Albers and her collaborators. For instance, they had to find a way of covering their microliter plates to slow evaporation rates while still allowing enough oxygen through the covering to enable growth of the aerobic strains that they were studying, she says, adding: “Then we had to build a metal container, that we filled with a layer of water at the bottom and which could be sealed for the incubation in the high-temperature oven.”

The researchers from the Max



Confocal laser scanning microscopic picture of a 5-day *S. acidocaldarius* biofilm. Cells were stained with DAPI, ConA, and IB4; left side shows an overlay of all channels; the right side, only the DAPI channel. Bars are 20 μm . (Image by Andrea Koerdt and Sonja Albers.)

Planck Institute are continuing to analyze proteomic and transcriptomic data gathered while observing two-day-old biofilms of the three *Sulfolobus* species. “We are most interested in which regulators switch cells to the biofilm mode of growth,” Albers says. “Archaea do not use cyclic-di-GMP, which in bacteria is a main player in this process. Rather, archaea, have to use other mechanisms. Moreover, no quorum sensing molecules have been identified in archaea, and that is again an important issue that has to be addressed.”

“Information about archaeal and/or extremophilic biofilms is very limited,” says microbiologist Gemma Reguera of Michigan State University in East Lansing. “Crenarchaea, in particular, are known to be part of environmental biofilms, yet their ability to form biofilms had not been documented, at least not with this level of detail. This research team optimized every single assay meticulously. The result is a beautifully crafted paper with high-quality, reproducible data, and outstanding microscopy to char-

acterize biofilm components and structure.”

Barry E. DiGregorio

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Metabolite from Tooth Decay Bacterium Curbs Yeast Oral Pathogen

A secondary metabolite from *Streptococcus mutans* can prevent the yeast *Candida albicans* from becoming pathogenic, according to Robert Cichewicz, a natural products chemist at the University of Oklahoma (UO) in Norman, and his collaborator, Fengxia Qi, a dental researcher at the UO Health Science Center in Oklahoma City. They consider that metabolite, which they call mutanobactin A, a promising lead for agents to treat *Candida* infections such as thrush, which can erupt in the oral cavity.

Indeed, both microorganisms occupy the human mouth, where *S. mutans* can be a major contributor to tooth decay. Qi, part of a team that



sequenced the genome of *S. mutans* UA159, noticed that it carries a gene encoding a molecule whose structure resembles the peptide antimicrobials bacitracin and gramicidin. Moreover, that gene was part of a cluster, or genomic island, that appears to encode other secondary metabolites. “Most predominant oral microbial species do not make secondary metabolites,” Cichewicz says. When they looked more deeply into the cluster, they learned that the gene Qi had identified encodes a hybrid nonribosomal peptide/polyketide compound that protects *S. mutans* from oxidative damage and is necessary for biofilms to form under conditions similar to those in the mouth. The name “mutanobactin” reflects its origin in *S. mutans* and the gene cluster homology to bacteriocin biosynthetic pathways. Details appear in the September 2010 *Applied and Environmental Microbiology* (76:5815–5826.).

“The shift from a compact yeast shape to a filamentous state is believed to be critical for *Candida* to become harmful,” Cichewicz says. Additional experiments verify that, while mutanobactin A prevents *C. albicans* from forming tangled mats of intertwined mycelia, it is not active against a panel of 30 other types of microorganisms, he notes. According to structural analysis by members of his group, the yeast-inhibiting metabolite from *S. mutans* contains a 1,4 thiazepan-5-one ring system, an unusual feature in a natural product. Additional mutanobactin derivatives B and C are also being investigated. Details appear in the December 15, 2010 *Organic & Biomolecular Chemistry* (8: 5486–5489).

“Dentists and chemists don’t often work together, but this interaction gave us the chance to find an amazing compound,” Cichewicz says. “I’ve done natural product research for 15

years, and this is one of the best compounds I’ve run across that has a real possibility of becoming a drug.”

A fascinating property of mutanobactin A “is that it’s a modulator of activity and doesn’t kill the yeast, but keeps it from going into a virulent stage of its life cycle,” says Art Edison, a professor of biochemistry and molecular biology at the University of Florida in Gainesville. Indeed, it acts similarly to quorum sensing agents, adding to its appeal as a candidate drug because, like them, its use should not put selective pressure on an organism to develop resistance. The UO studies also highlight the value in understanding interactions between species. “But it’s a long, hard road to commercialize a new drug,” Edison says.

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