MINITOPIE
Deciphering cAMP: Quantitative Physiology Reveals Metabolic Controls

Quantitative modeling of Escherichia coli cellular physiology helps to reveal just how tightly cAMP signaling coordinates protein expression within such cells, according to Terence Hwa of the University of California, San Francisco, and his collaborators. Thus, for example, cAMP-dependent catabolite repression ensures that proteomic resources are directed to distinct metabolic sectors as needed, reflecting the response of such cells to different environments and available nutrients. Instead of being centered on carbon metabolism, as commonly thought, cAMP signaling “orchestrates the allocation of proteomic resources in response to different metabolic demands,” they report. This “top-down” approach to analyzing physiology within bacterial cells might well be applied “to elucidate other signaling networks.” Details appeared August 7, 2013 in Nature (doi:10.1038/nature12446).

RESEARCH ADVANCES
Unexpected Role for Heme Protein in Archaeon M. acetivorans

John Otrompke

The protein MA4561 from the archaeon Methanosarcina acetivorans is not the phytochrome-like photoreceptor that it was first thought to be, but is instead a heme-binding protein that likely acts as a reductox sensor, according to Nicole Frankenberg-Dinkel at the Ruhr-Universität in Bochum, Germany, and her collaborators. While some bacteria use heme-containing proteins as reductox sensors, M. acetivorans is the first archaeon known to do so, she says. Details appeared May 9, 2013 in the Journal of Biological Chemistry (doi: 10.1074/jbc.M113.476267 jbc.M113.476267).

Although earlier considered a phytochrome-like photoreceptor, “MA4561 is unable to bind any known chromophores of phytochrome photoreceptors, ruling out the possibility that it is a phytochrome,” Frankenberg-Dinkel says. The heme, an oxygen-binding, iron-containing porphyrin that is part of the MA4561 protein in M. acetivorans, serves a different purpose, she adds. In this microorganism it “either detects dimethyl sulfide directly, or it detects that the cell is in a not-so-good redox state, and that different nutrition sources need to be acquired to survive.”

For such reasons, she and her colleagues now call the MA4561 protein methyl sulfide methyltransferase-associated sensor (MsmS), Frankenberg-Dinkel continues, adding: “There’s an other protein of M. acetivorans, MA0863, that is highly similar to MsmS, and we’d like to find out if this is doing similar things.”

In other organisms, the heme cofactor typically attaches to proteins via electrostatic interactions, and those proteins with heme cofactors typically are used to bind oxygen or transfer electrons, Frankenberg-Dinkel continues. In this case, however, heme attaches covalently to MsmS. Only two other such examples are known so far—one involving DcrA from Desulfovibrio vulgaris and the protein GSU0303 from Geobacter sulfurreducens.

“The researchers have convincingly demonstrated that this protein contains a covalently attached heme cofactor, and present very clear evidence that the protein shows a dependency of its autophosphorylation activity on the redox state of the heme,” says Gunhild Layer at the University of Braunschweig in Germany, who is investigating the biosynthesis of heme in bacteria and archaea. “Normally, covalently attached hemes are found in the periplasm, but MsmS is localized . . . inside the cell. Furthermore, usually other proteins are required to insert a cofactor into a protein, but in MsmS this seems not to be the case, as the protein itself is able to insert the heme. Again, this is very unusual for archaea.”

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RESEARCH ADVANCES
Urine, Once Thought Sterile, Has Its Own Microbiome

Jennifer Rohn

The long-enshrined belief that urine is sterile is giving way to the notion that the urinary tract hosts a bona fide microbiome, according to several investigators who spoke during the symposium, “How Knowledge from the Human Microbiome Projects Will Change the Practice of Clinical Micro-
biology,” convened last May in Denver during the 2013 ASM General Meeting. Thus, they say, when urine specimens from healthy patients test positive for bacteria, it may no longer be acceptable for clinicians to dismiss those results as mere contamination or “asymptomatic bacteriuria.”

The microorganisms that one detects in urine depend on how it is analyzed. Because *Escherichia coli* accounts for upwards of 90% of all acute cases of urinary tract infections (UTI), clinical laboratories typically analyze urine under culture conditions that favor this well-known pathogen. Also, labs tend to reject any culture result that falls below an arbitrary threshold, which may be as high as $10^5$ CFU/ml. Further, labs typically disqualify mixed growths because they are deemed more likely to reflect contamination or to contain bacteria that are not common pathogens of the urinary tract. No wonder so many doctors have little idea what might be hiding behind “negative” culture findings from clinical lab urine analyses.

Better analytic tools not only could change those reports but also are providing a different view of what urine contains under ordinary circumstances, according to symposium participant Paul Schreckenberger of Loyola University of Chicago in Maywood, Ill. For example, after subjecting urine specimens from healthy donors to 16S ribosomal RNA gene sequencing and to analysis by matrix-assisted laser desorption ionization mass spectrometry, he says that he was amazed to find a large array of rare and exotic microbial genera, including *Aerococcus*, *Actinobaculum*, and *Alloscardovia*, many of which cannot be readily cultivated.

Deep-sequencing techniques are also helpful for uncovering microbial species in urine, says symposium participant David Relman of Stanford University in Stanford, Calif. This analytic approach uncovers remarkably complex microbial communities within the human urinary tract, whose composition can shift depending on whether the microbial community is in a pathogenic or benign mode—similar to what occurs, for example, in the gut with Crohn’s disease or in the vagina with vaginosis.

Understanding the bladder microbiome is not merely an ecological exercise. Importantly, some culture-negative patients complaining of lower urinary tract symptoms are infected, but with levels of bacterial pathogens that fall below the routine threshold set for diagnosing UTIs, according to Linda Brubaker, who is Schreckenberger’s collaborator at Loyola, and also James Malone-Lee of University College in London, United Kingdom, a pioneer in this field.

In such clinical cases, sensitive detection to determine whether pathogens are part of the mix and then deciding which individuals need antibiotics can be crucial in terms of outcome, Brubaker continues. Perhaps the urinary microbiome, even if ephemeral, is itself protective and thus antibiotic treatments sometimes might cause more harm than good, she points out. Further research to learn which microorganisms occupy this environment could help in guiding such treatment decisions.

Jennifer Rohn is a writer and research biologist based in London, England.

**RESEARCH ADVANCES**

**Gut Microbes Affect Host Responses To Two Oral Vaccines**

Carol Potera

Among their diverse activities, the microorganism of the gut apparently affects the host immune response to orally administered vaccines, say Claire Fraser, director of the Institute for Genome Sciences at the University of Maryland (UM) and her collaborators at its Center for Vaccine Development (UM-CVD) in Baltimore. After being vaccinated, cynomolgus macaques with a highly diverse gut microbiota resisted infectious challenges and dis-