Mélange of Microbiota, Gut Epithelial, and Immune Cells Key to Metabolic Balance

A three-way interaction involving the resident microbiota, B cells of the immune system, and the epithelial cells lining the gut is critical for maintaining host metabolic as well as critical immune system functions, according to Polly Matzinger of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md., and her collaborators. In mice, when B cells are missing or cannot express IgA antibodies, those gut epithelial cells change, taking on a more defensive posture but, in doing so, lose some of their capacity to absorb nutrients, particularly fats. This pattern in mice might help to explain several gastrointestinal disorders that occur among immunodeficient patients, the NIAID researchers note. Details appear in the December 2011 *Nature Medicine*, doi: 10.1038/nm.2505.


Atomic force microscopy (AFM) and molecular dynamic simulations provide a means for probing how tightly *S. aureus* cells bind to solid surfaces such as those found on implantable devices, according to Steven Lower at OSU. Unlike scanning and transmission electron microscopy, AFM allows one to observe single living cells in solution. However, adapting AFM to study *S. aureus* is “very challenging and we’re still working out the bugs,” he says.

*S. aureus* cells depend on bacterially produced fibronectin-binding protein A (FnBPA) to adhere to the host protein fibronectin, which coats implants, and then to form biofilms. Bonding activity with such surfaces varies among strains of *S. aureus*. Importantly, Lower says, it is highest for those strains that were collected from 26 patients with cardiac device infections (CDI) compared to commensal strains from individuals without implants and those whose implants did not carry biofilms. Control samples came from nasal swabs of healthy volunteers. “Over half of the human population has staph living in their noses at some time,” he says. Yet not every cardiac implant patient develops a biofilm and, among those that do, not every biofilm leads to systemic staph infections for the individuals carrying those devices.

Subsequent DNA sequencing analysis identified six SNPs in the gene encoding FnBPA, three of which (at positions 652, 782, and 786) are found often in the CDI samples. All three of those SNPs fall within regions of FnBPA involved in high-affinity binding to fibronectin, Lower points out. Further, isolates with 2 or 3 of the SNPs bind more tightly than do isolates with one or none of the SNPs.

A photometric adhesion assay confirmed that *S. aureus* cells that contain all three SNPs attach more firmly to a fibronectin-coated surface than do those with fewer SNPs. In silico molecular dynamic simulations suggest that the SNPs help FnBPA to form extra hydrogen bonds with fibronectin. “The different techniques gave similar answers,” Lower says.

Finding that “a single amino acid substitution within an adhesin can affect the virulence potential of a pathogen is novel and a great step forward,” says biochemist Magnus Hook of Texas A&M University Health Science Center in Houston. He considers such efforts to characterize molecular interactions between hosts and pathogens a “must.”

Whether the *S. aureus* strains associated with patients carrying cardiac implants developed SNPs before those devices were implanted or those SNPs arose subsequently is not yet known, according to the OSU and Duke researchers. If individuals are carrying strains with predisposing SNPs and are scheduled to receive implants, perhaps those individuals need to be more closely monitored or even treated prophylactically with antibiotics, the researchers suggest.

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To Amplify Infections, Chlamydia Bind, Induce a Host Cell Growth Factor

*Chlamydia trachomatis* cloaks itself with host-produced, fibroblast growth factor-2 (FGF2) while infecting human cells and then commandeers host genes to produce still more FGF2, further driving this infectious cycle, according to Joanne Engel and her collaborators at the University of California, San Francisco (UCSF). The growth factor helps to shield the pathogen against host immune defenses, the UCSF researchers say. Their findings appear in the October 2011 *PLoS Pathogens* [doi:10.1371/journal.ppat.1002285].

Expecting *C. trachomatis* to bind heparan sulfate proteoglycan molecules along the outer surface of host cells, the UCSF researchers were surprised to find the pathogen instead binds directly to FGF2. “There are not many examples of a pathogen binding directly to a growth factor,” Engel says. FGF2 binds directly to elementary bodies (EB), the spore-like form of *C. trachomatis* that binds to cell membranes. After enter-
ing host cells, EB remodel the cell membrane to establish a protective niche within which *Chlamydia* replicates.

Experiments involving HeLa cells provide evidence that EB and FGF2 interact with specificity, according to Engel. For example, adding FGF2 to such cells enables them to bind EB in a dose-dependent manner. It also enhances the ability of *C. trachomatis* to infect them. Moreover, surface-bound EB colocalize with FGF2, but not with other growth factors, including closely related FGF1 molecules, according to immunofluorescence microscopy. Treating cells with antibodies that neutralize FGF2 decreases EB binding by twofold, further confirming the specificity of the EB-FGF2 interaction.

Perhaps even more convincingly, *C. trachomatis* binding to HeLa cells induces them to make and secrete more FGF2. When HeLa cells are infected with *C. trachomatis*, FGF2 gene expression increases as much as fivefold within 24 hours. “This amplifies the infectious cascade similar to a positive feedback loop,” Engel says. She speculates that by co-opting genes for producing host cell growth factors that spread infection, *C. trachomatis* may interfere with apoptosis, which instead limits infection.

This research is “a tour de force,” says microbiologist Raphael Valdivia of Duke University in Durham, N.C. “The most surprising observation is that *Chlamydia* highjacks FGF2 to act as a sandwiching factor linking bacteria to the surface of host cells.” Moreover, inducing FGF2 to maximize infectivity is “a very clever strategy, indeed,” he adds.

Studies are being planned to learn whether *C. trachomatis* binds FGF2 in vivo, according to Engel. If this mechanism operates in infected hosts, it could become a target for therapy, directing candidate drugs to act on this host process rather than directly on the pathogen. “The advantage of this approach is that you won’t get drug resistance because you’re not targeti

**Plasma-Treated Alginate Wound Dressing Effective against MDR Pathogens**

A twist of plasma technology adds antimicrobial muscle to alginate-based dressings that are used widely for treating wounds, according to Suresh Joshi of Drexel University College of Medicine in Philadelphia, Pa. He reported recent findings during the 49th Annual Meeting of the Infectious Diseases Society of America held last October in Boston, Mass.

“Calcium or sodium alginate wound dressing has been in clinical practice for over a decade,” Joshi says. The only drawback of this dressing is that it does not have significant antimicrobial coverage to protect wounds or control pathogens.” However, treating such dressings with non-thermal [unheated], dielectric-barrier discharge plasmas has a “powerful antimicrobial effect,” he and his collaborators find. By “plasma,” he refers to a gas-like state of matter containing ionized particles.

Solutions infused with such plasmas are lethal to bacteria, generating free radicals and oxidizing species and probably causing severe oxidative stress. More recently, Joshi and his collaborators moved from in vitro experiments to determine whether plasma-treated alginate gels retain antimicrobial activity and can deliver it effectively to treat the kinds of microbial pathogens, including *Staphylococcus aureus*, *S. epidermidis*, *Acinetobacter baumannii*, *Escherichia coli*, *Candida albicans*, and *C. glabrata*, that cause wound-related infections.

Testing involved alginate gels that