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SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Location, Location, Location: Environment Influences Virulence Phenotypes of *Legionella pneumophila*

The Dot/Icm type IV secretion system (T4SS) of *Legionella pneumophila* is thought to be essential for virulence phenotypes because *dot/icm* mutants are defective when broth stationary-phase cultures infect eukaryotic hosts. Bandyopadhyay et al. (p. 723–735) showed that defective entry, delay of phagosome acidification, and intracellular multiplication of *dot/icm* mutants are reversed when stationary cultures are incubated in water or encysted in amoebae, mimicking environmental niches of the Legionnaires' disease bacterium. A second T4SS, the Lvh T4SS, was implicated in the reversal. These results suggest that alternative virulence mechanisms may be uncovered for other environmental pathogens by experimentally mimicking their environmental niches.

Comparative Genomics Reveals a Genomic Island in Pathogenic *Leptospira*

Virulence mechanisms and, more generally, the fundamental understanding of the biology of the causative agents of leptospirosis remain largely unknown. Bourhy et al. (p. 677–683) report that a 54-kb genomic island of *Leptospira interrogans* serovar Lai can form a circular plasmid. This study hypothesizes that the novel genes from this genomic island have been horizontally transferred from other leptospires, thus contributing to genome plasticity and evolution of pathogenic species.

Liver-Stage Malaria Vaccine Undergoes Initial Immune Response Studies

Many malaria vaccines are close to reaching the stage of human clinical trials. A recombinant protein based on *Plasmodium falciparum* liver-stage antigen 1 (LSA-1) is the first hepatic-stage malaria recombinant protein to be produced under conditions to enter this pipeline. In anticipation of this study by Brando et al. (p. 838–845), the cellular and humoral immune responses to this new vaccine candidate in three strains of mice with two adjuvants, AS01B and AS02A, being evaluated for licensure for human use, are studied. A/J and BALB/c mice, but not C57BL/6J mice, mount antigen-specific responses to the vaccine formulations.

Chlamydia pneumoniae-Induced Toll-Like Receptor 2-Mediated Macrophage Foam Cell Formation Is Reversed by a Liver X Receptor Agonist

Although numerous studies have associated *Chlamydia pneumoniae* with atherosclerosis and cardiovascular diseases, the mechanisms that lead to macrophage foam cell formation, a hallmark of early atherosclerosis, remain unclear. Cao et al. (p. 753–759) demonstrate that *C. pneumoniae* elicits foam cell formation predominantly via Toll-like receptor 2 (TLR2). Enhancing cholesterol efflux in the presence of the liver X receptor (LXR) agonist GW3965 significantly decreased foam cells induced by *C. pneumoniae* or ligands specific for TLR2 and TLR4. These findings suggest that activation of the LXR signaling pathway may reduce these potentially atherogenic processes and that drugs such as GW3965 may have therapeutic potential.

Understanding the Impact of Schistosomiasis on Liver Protein Expression

Schistosoma mansoni eggs initiate an intense immune response in the liver that results in granuloma formation and fibrosis. To understand the impact of this process on liver function, Harvie et al. (p. 736–744) used proteomics to compare liver protein expression in mice at 8 weeks postinfection. This study revealed a greater than fivefold decrease in proteins associated with normal functions (e.g., citric acid, fatty acid, and urea cycles) and a threefold to ninefold increase in stress and structural proteins. These findings also highlighted distinct differences in the expression patterns of several immune response-associated proteins, reflecting altered isoforms or posttranslational modifications.

Making a Link between Phagocytosis and Cytokine Production

Macrophages are a major source of cytokines upon interaction with bacteria through specific receptors such as Toll-like receptors (TLR). Surprisingly, *Staphylococcus aureus* can activate macrophages even in the absence of TLR2 and TLR4, revealing the presence of another activation pathway. Kapetanovic et al. (p. 830–837) demonstrated the importance of phagocytosis in the absence of TLR2 for tumor necrosis factor and interleukin-10 production. In addition, using transfection models, they identified the contribution of the intracellular receptor Nod2 as well as a modulating role of Nod1. These findings highlight the intracellular sensing of *S. aureus* after phagocytosis as an alternative activation pathway to TLR2 involved in the induction of cytokines.

Modification of the Structure of Peptidoglycan as a Strategy for Evading Innate Immunity

Nucleotide-binding oligomerization domain proteins (NOD1 and NOD2) are pathogen recognition receptors that sense the breakdown products of peptidoglycan (PGN). Wolfert et al. (p. 706–713) have shown that a number of synthetic muropeptides can induce tumor necrosis factor alpha (TNF-α) gene expression without significant TNF-α translation in a NOD1- or NOD2-dependent manner. This translation block was lifted when the muropeptides were coincubated with lipopolysaccharides. Surprisingly, amidation of the α-carboxylic acid of isoglutamic acid of several diaminopimelic acid-containing muropeptides led to loss of activity. Many pathogens modify carboxylic acids of their PGN by amidation, which reinforces our finding that this type of modification is a strategy for evading host innate immunity.

Can *Chlamydia trachomatis* Blovar-Specific Interactions with Host Proteins at the Inclusion Influence Chlamydia-Host Range and Tissue Tropism?

Despite the high level of genetic identity, differences in tissue tropism and disease severity are manifested by the different *Chlamydia trachomatis* biovars. Moorhead et al. (p. 781–791) describe a biovar-specific interaction between the mammalian Rab6 effector BICD1 and the *C. trachomatis* lymphogranuloma venereum serotype L2 inclusion. The elucidation of this novel biovar-specific host-pathogen interaction suggests that in addition to genetic differences in the "plasticity zones" of these organisms, some of the biovar-specific properties of *C. trachomatis* may result from the differential recruitment of host trafficking factors to each respective inclusion.

Tandem Repeat: a Novel Bioinformatic Target for Identifying *Leishmania* Antigens

Proteins containing tandem repeat domains (TR) are often targets of antibody responses during parasitic infections and thus may have significance as diagnostic or vaccine targets. However, a systematic approach for identifying proteins with TR has been lacking. Using a bioinformatic approach, Goto et al. (p. 846–851) identified a number of novel proteins containing TR from the protozoan *Leishmania donovani* and demonstrated applications of some of these proteins in serological assays. As a number of TR were found in other protozoan parasites, this approach could be beneficial for identifying antigens in various pathogens.

Mutant LT-IIa Enterotoxins Defective in Ganglioside Binding Are Potent Immunostimulatory Agents

Heat-labile enterotoxins are well-known as powerful immunostimulatory agents that have great potential as mucosal vaccine adjuvants if the problem of their inherent toxicity can be overcome. Most efforts hitherto have focused on eliminating the toxic enzyme activity of their A subunits, whereas the ganglioside-binding activities of the B subunits are considered to be crucial. Nawar et al. (p. 621–633) describe two mutant LT-IIa enterotoxins from *Escherichia coli* that exhibit altered receptor-binding patterns and dramatically diminished toxic activities yet retain their potent immunological adjuvant properties. These findings indicate that the two LT-IIa mutants have prospective utility as adjuvants for human mucosal vaccines.

TccP2-Mediated Actin Polymerization in O157 and non-O157 Enterohemorrhagic *Escherichia coli* Strains

In the attaching and effacing lesions caused by typical enterohemorrhagic *Escherichia coli* (EHEC) O157, actin polymerization is triggered once Tir is connected to N-WASP via TccP. Conversely, non-O157 EHEC strains are *tccP*-negative and contain a tyrosine-phosphorylated Tir that activates N-WASP via recruitment of Nck. Typical *E. coli* O157 strains also carry a pseudo *tccP* gene (named *tccP2*). Ogura et al. (p. 604–612) show that both *tccP* and *tccP2* are intact in atypical, sorbitol-fermenting *E. coli* O157 and that approximately 90% of the non-O157 EHEC strains carry a functional *tccP2* gene. These findings demonstrate that non-O157 EHEC can trigger actin polymerization through either the Tir-Nck or the Tir-TccP2 pathway. This ability may broaden their cell or tissue specificity in vivo.