Articles of Significant Interest in This Issue

Are Two Toxins Better Than One?

Enterotoxigenic *Escherichia coli* (ETEC) is a major diarrheal pathogen that encodes two enterotoxins, the heat-labile toxin (LT) and the heat-stable toxin (ST). Each toxin alone is sufficient to cause diarrheal disease, but many wild ETEC isolates carry both enterotoxins. Motyka et al. (e00707-20) show that ST modulates host epithelial physiology and the epithelial-immune axis. ST intoxication causes extracellular and luminal cGMP accumulation and alteration of epithelial type 1 cytokine expression, including nuclear alarmin IL-33. ETEC immunization studies also show that ST suppresses LT-based adjuvanted mucosal IgA, suggesting that two toxins act synergistically to help ETEC to evade host immune responses.

Neutrophil Oncostatin M Tunes Inflammatory Signaling in Pneumonia

Oncostatin M (OSM) is an IL-6 family cytokine previously shown to be necessary for neutrophil recruitment during pneumonia through STAT3-driven CXCL5 expression. Traber et al. (e00655-20) now demonstrate the cellular source of OSM is infiltrating neutrophils, suggesting a positive feedback loop of OSM production. Transcriptional profiling demonstrated that OSM neutralization led to early downregulation of STAT1-, STAT3-, and interferon-associated genes, yet STAT1 and STAT3 were subsequently activated in this model at later time points. From these studies, we conclude that OSM produced by recruited neutrophils may be essential for appropriate tuning of early innate immune signaling.

Isolate-Dependent Differences in Clinical, Pathological, and Transcriptional Profiles following In Vitro and In Vivo Infections with *Rickettsia rickettsii*

*Rickettsia rickettsii* is the etiological agent of Rocky Mountain spotted fever. Using in vivo and in vitro methods, Galletti et al. (e00626-20) identify phenotypical, histological, and molecular differences among six isolates from the United States, Costa Rica, and Brazil. These data suggest that a critical and previously underappreciated balance between bacterial growth and host immune response could leverage strain pathogenicity, providing insight into factors that influence the severity of disease. They also indicate that an overall assessment of strain virulence based on geographical origin should be reevaluated in the context of regional host factors that influence the immune response to *R. rickettsii* infections.

Role of Biological Sex and Bacterial Communities in Shaping Pyelonephritis

During experimental cystitis with uropathogenic *Escherichia coli*, bacterial population diversity in the bladder is sharply restricted in the female host. In pyelonephritis, male mice develop more severe infection than females, and population dynamics have not been elucidated. McLellan et al. (e00716-20) find that the kidneys in male mice maintained broad genotypic diversity throughout infection, obscuring the bottleneck normally imposed during establishment of cystitis. Moreover, kidney bacterial communities within renal tubules were shown to be clonal in nature. Thus, while ascension to the kidney does not constrain the bacterial population as a whole, pyelonephritis is initiated by individual bacteria that successfully colonize discrete nephrons.
Towards Effective, Low-Cost, Easy to Produce, Multivalent Outer Membrane Vesicle-Based Salmonella Vaccines

Typhoid, paratyphoid fever, and invasive-nontyphoidal salmonelloses (iNTS) coexist geographically in Africa and Southeast Asia with increasing levels of antimicrobial resistance. Broadly protective pan-Salmonella vaccines are highly desirable in order to achieve ease of administration, reduced costs, and compliance. Gasperini et al. (e00699-20) describe a highly immunogenic, single-vesicle, outer membrane vesicle (OMV)-based Salmonella candidate vaccine to deliver the somatic O-antigen from S. Paratyphi A and the Vi polysaccharide antigen of Salmonella Typhi. This work highlights bacterial OMV as flexible platforms for multivalent vaccines, a broad concept that can be extended to vaccines that encompass many Salmonella serovars and other pathogens.

Innovative Approaches, Novel Vaccines

The state of calamity imposed by COVID-19 reminded the world that vaccines are essential for human health. Vaccines are still necessary for many other infectious diseases, which points to the need for efficient approaches for developing vaccine candidates. Genetic engineering resulting in microbial extracellular vesicles containing multiple immunogens is an innovative and promising tool to prevent enteric fever (e00001-21). Other infectious diseases could benefit from the same approach. Although this is still an embryonic field, the perspectives are unlimited.