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The complex interactions of bacterial pathogens and host defenses

Editorial overview

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Denise M Monack received her Bachelor's in Science in Genetics from the University of California at Davis. She attended graduate school in the Department of Microbiology and Immunology at Stanford University and obtained her PhD in the laboratory of Dr. Stanley Falkow in the field of bacterial pathogenesis in 2002. She is currently an associate professor in the Dept. of Microbiology and Immunology at Stanford University where she teaches and has a laboratory in which graduate students and postdoctoral students conduct research in the field of bacterial pathogenesis. The primary focus of her research is to understand the genetic and molecular mechanisms of intracellular bacterial pathogenesis. In particular, they study the complex host–pathogen interactions that occur in macrophages. Macrophages express Pattern Recognition Receptors on the surface as well as in the cytosol. Her laboratory focuses on the cytosolic recognition of bacteria that leads to Type I Interferon signaling and Inflammasome activation. They take both genetic and biochemical approaches to understand the molecular mechanisms involved in host recognition pathways leading to inflammation and pathogen evasion mechanisms. In addition, the Monack Lab studies chronic *Salmonella* infections. *Salmonella typhi*, the causative agent of the human-specific disease typhoid fever, is capable of causing long-term chronic systemic infections and sporadically is shed in the feces to transmit to new hosts. These persistently infected individuals serve as a significant reservoir for disease transmission. The Monack Lab uses genetic approaches to identify mechanisms of persistence and has

The introduction of antibiotics into clinical practice in the 1950s led to the presumption that bacterial infectious diseases would become a ‘thing of the past’. While antibiotics have resulted in major decreases in morbidity and mortality in the subsequent decades, the global burden of infectious diseases remains one of the largest challenges facing the international biomedical community. Bacterial diseases that were thought to be defeated are still major health care problems. For example, tuberculosis kills an estimated 3 million individuals per year. Diarrheal diseases, some of which are caused by bacterial infections such as cholera, still affect numerous individuals with severe effects on children in the developing world. Most worrying is the increasing prevalence of bacterial pathogens that are resistant to multiple antibiotics, including some that are resistant to all known antibiotics. Thus, there is a desperate need for novel strategies to successfully treat bacterial infections. To achieve this end, it is imperative that we increase our understanding of the molecular ‘players’ in the complex host–pathogen interactions that lead to microbial infection and disease. In this issue of Current Opinions in Microbiology we have brought together scientists involved in cutting-edge research on the molecular basis of host–pathogen interactions. These articles are not meant to be comprehensive reviews, but rather to provide updates on recent advances in the field of bacterial pathogenesis and to share their views of this rapidly evolving area of research.

Infections with bacterial pathogens, and the ability of the host to survive the infection, can be seen as an evolutionary battle between bacteria and the incredibly diverse defense mechanisms of the host. In addition, we are beginning to understand that a critical component of the host defense against invasive bacterial colonization is the indigenous/commensal microbiota that colonize mammalian mucosal surfaces, including those of the respiratory, genitourinary, and gastrointestinal tracts, as well as the skin. The study of the complex interactions between bacterial pathogens, the commensal bacteria and the host immune system is a rapidly emerging area of research. We now know that commensal bacteria play an important role in shaping the immune cell function in the steady-state. In the article by [Abt and Artis](#), they focus on the critical roles commensal bacteria have on shaping the immune response to invading bacterial, parasitic and viral pathogens in the intestinal microenvironment, at other barrier surfaces, and in peripheral tissues. However, under certain circumstances commensals can also cause disease. In the article by [Gilmore et al.](#) the acquisition of antibiotic resistance profiles by gut commensals, particularly *Enterococcus* is

recently been studying how this pathogen manipulates host cell migration in microfluidics devices that mimic host cell tissues. They also study the role of the intestinal microbiota in controlling *Salmonella* infection, disease, and transmissibility.

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Scott J Hultgren, PhD was elected to membership in the National Academy of Sciences in 2011. He is the Helen Lehbrink Stoeber Professor of Molecular Microbiology at Washington University in St. Louis, where he also serves as the inaugural Director of the Center for Women's Infectious Disease Research. He received his undergraduate education at Indiana University, his Ph.D. from Northwestern University in Chicago, and his postdoctoral training at Sweden's Umeå University under the tutelage of Staffan Normark. He joined the faculty of Washington University in 1989. His studies blend multiple scientific disciplines elucidating bacterial and host mechanisms that determine the onset, course and outcome of interactions between a host mucosal surface and bacterial pathogens. Using genetics, genomics, biochemistry, structural biology, high-resolution imaging, animal models, clinical studies and combinatorial chemistry, he has illuminated how bacterial intracellular lifestyles and community behaviors play critical roles in urinary tract infection (UTI). He uncovered principles of adhesive pili biogenesis in Gram-negative bacteria of the chaperone/usher pathway; delineating molecular details of donor strand complementation and exchange mechanisms by which subunit folding is coupled with translocation and assembly of pili across the outer membrane. He delineated how uropathogenic *E. coli* use type 1 pili to invade and establish biofilm-like intracellular bacterial communities within bladder cells subverting extracellular host defenses and how quiescent intracellular reservoirs can seed recurrent infection. He identified complex networks governing mucosal epithelial responses that determine disease outcome. Further, he elucidated a mechanism by which bacteria form a directed biofilm-associated amyloid fiber called curli. Finally, his work has also revealed fundamental insights into catheter-associated urinary tract infections caused by *Enterococcus* and *E. coli*. Together, his work is changing the way UTIs are evaluated, re-shaping models of bacterial infections in general and spawning new technologies to design novel vaccines and anti-microbial therapeutics to diagnose, treat and/or prevent UTIs and their sequelae.

discussed. Genomic analyses of hospital-adapted pathogenic isolates of these normally commensal organisms show evidence of multiple mobile genetic elements and pathogenicity islands, which allow the bacterial to opportunistically colonize other sites.

The innate immune response to invasive pathogens is a critical determinant of disease outcome and therefore understanding how the innate immune system recognizes and responds to molecular patterns associated with pathogens (PAMPs) or danger signals such as cellular stress (DAMPs) has been an area of intense research. Appropriate responses by the host against diverse microorganisms require rapid recruitment of inflammatory cells and release of pro-inflammatory and antimicrobial mediators. The Toll-like receptors (TLRs) and nuclear oligomerization domain (NOD)-like receptors (NLRs) are two major families of germ-line encoded receptors that recognize PAMPs and initiate immune signaling and thus are important players in the host response to bacterial infections. However, pathogens are under tremendous selective pressure to overcome innate immune responses. Two articles discuss these interactions between bacterial pathogens and TLRs/NLRs. In the first, [Arpaia and Barton](#) highlight key examples of strategies that bacterial pathogens have evolved to evade TLR-mediated defenses. In the second article, [Egil Lien's](#) group focuses on the activation of NLRs that lead to inflammasome activation upon bacterial infection. They describe new mechanisms for inflammasome activation and regulation that involve NLRs, kinases such as PKR and PKC δ , and caspases such as caspase-11 (caspase-4) and caspase-8.

Given the importance of secretion systems (SS) in bacterial virulence, we have included several articles that highlight recent advances in understanding the structure, regulation and effector functions of these systems in several host-adapted Gram-negative pathogens. We begin with two articles that highlight recent advances in host-adapted Gram-negative pathogens *Shigella* and *Salmonella*. [Nathalie Carayol and Guy Tran Van Nhieu](#) review *Shigella* type 3 SS (T3SS) effectors and the roles that they play during early invasion of epithelial cells 'discretely', which is in contrast to the devastating inflammatory response associated with the acute phase of shigellosis. In the article by [Moest and Méresse](#), they focus on the two T3SS in *Salmonella* and their shared regulatory mechanisms. They highlight recent studies that show subpopulations of *Salmonella* with respect to expression and activity of T3SSs during infection. Strikingly, this heterogeneity may give *Salmonella* a competitive advantage and help establish its niche in the host. In addition to T3SS, the [Gorvel group](#) focuses on recent findings on the regulation and role of the effector proteins of *Brucella* type 4 SS during intracellular survival. Finally, [Kapitein and Mogk](#) describe recent advances in the most widespread bacterial secretion system, the type 6 SS (T6SS). This system has components structurally related to the cell-puncturing device of tailed bacteriophages and transports effector molecules into target cells in a single, cell-contact dependent step. Activities of T6SSs range from important roles in virulence to interbacterial warfare.

[Weiser](#) presents a discussion of the role of bacterial cell size in counteracting host defense mechanisms. Bacterial cells can range from 0.15 to 700 μm in length with modulation of cell division, septation and aggregation being able to significantly impact their effective size in different host environments. Weiser discusses both pathogen and host mechanisms that influence pathogen size and infection outcomes. Another aspect of the battle between hosts and pathogens is discussed in the chapter by [Yoong and Torres](#) in which they detail the elaboration of a number of pore-forming toxins by

Staphylococcus aureus and their effect on host cells and host mechanisms to recognize sublytic levels of these leukotoxins and activate protective immune responses to neutralize toxin effects and clear the pathogens. Zhang and Orth discuss virulence determinants of *Vibrio parahaemolyticus* infections, which occur most often after the consumption of contaminated raw or undercooked seafood. Studying this pathogenic process has provided further insight into the regulation of survival mechanisms of pathogens within differing environments. David Russell intrigues us with recent findings and insights about the human-adapted pathogen *Mycobacterium tuberculosis*. *M. tuberculosis* persistence in granulomas requires dramatic tissue remodeling and unique bacterial and host tissue metabolism. This pathogen has preserved its antigenicity to elicit a robust immune response that contributes to the late-stage tissue damage that is required for transmission and completion of the pathogen's life cycle.

Two articles provide information on the role and targeting of extracellular surface fibers assembled by Gram-negative pathogens to mediate binding to host tissue and aggregation of bacteria into multi-cell communities. The article by the Remaut group presents recent progress to design small molecules to attenuate the assembly and/or function of adhesive proteinaceous appendages on Gram-negative bacteria, focusing on chaperone/usher

pathway (CUP) pili. Hundreds of operons encoding the formation of CUP pili have been found in sequenced Gram-negative bacteria. A number of avenues of therapeutic development are covered including anti-adhesives and anti-assembly molecules. The article by Schwartz and Boles describes another extracellular appendage, microbial amyloid fibers. These fibers share all the structural characteristics of disease related mammalian amyloids like those implicated in Alzheimer's disease. The production of these fibers has implications for host signaling, biofilm formation and survival of pathogens in diverse environments. Both CUP pili and amyloid fibers are made by uropathogenic *E. coli*. In the article by the Schembri group, they discuss the complex interactions between UPEC and the host that determines the course of a urinary tract infection (UTI). Treatment of UTIs has been increasingly difficult due to rising resistance to antibiotics and mechanisms UPEC has established to cause recurrent infections. Recent advances in the field are beginning to shed light on pathophysiological as well as genetic basis for resistance and recurrence.

We would like to thank all of the authors, the reviewers, and the staff of Elsevier's Editorial Office for their invaluable work in helping us to finalize this Special Issue. We hope that this collection of outstanding articles will serve as a source of inspiration to researchers in the field of host-pathogen interactions.