Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

# Editorial overview: Host-microbe interactions: Bacteria

Samuel I Miller and Renée M Tsolis

**Current Opinion in Microbiology** 2017, **35**:v–viii

For a complete overview see the Issue

http://dx.doi.org/10.1016/j.mib.2017.06.002



**Samuel I Miller**

Departments of Medicine, Microbiology and Genome Sciences, University of Washington, United States

Dr. Miller holds a B.A. from Johns Hopkins University and a M.D. from Baylor College of Medicine. He is a former faculty member of the Harvard Medical School and a current Professor of Microbiology, Medicine and Genome Sciences. His laboratory is focused on defining the molecular basis of bacterial pathogenesis and interactions with eukaryotic cells. Though he is most known for his work on defining the pathogenesis of Salmonellae species, he has worked on a variety of other Gram negative bacterial pathogens, including Pseudomonas aeruginosa in cystic fibrosis and other antibiotic-resistant pathogens. His work has spanned many topics, including how bacteria sense host environments, respond by alteration of bacterial second messengers, and remodel their surfaces. He has also studied how bacteria alter host processes by studying secreted virulence proteins and mechanisms of mammalian innate immune sensing. His work has applied and developed a variety of technologies for studying bacterial host interactions, including bacterial genome analysis, analysis of proteins and lipids with mass spectrometry, and, recently, human genomic diversity in innate immunity. Dr. Miller recently turned his attention to the development of methods and analysis pipelines to translate metagenomics analysis of the intestinal microbiome to the clinic for a variety of chronic diseases, including inflammatory bowel disease and cystic fibrosis.

The study of host interactions with bacteria represents a large and diverse scientific area, the size of which reflects the importance of such interactions to the health of animals, plants, and ecosystems. The field has advanced considerably over the last two decades with the discovery of key innate immune sensing molecules, many bacterial virulence factors, and technical advances in microscopy, genomics, and protein science. The field can involve specific model systems as well as the study of organisms and hosts in nature. An understanding of the many aspects of eukaryotic biology that have been evolutionarily shaped or altered by exposure to bacterial pathogens and commensals, including diverse phenotypes of plants and animals, offers insight into the broad significance of this ongoing research.

An important pathogenic principle of bacterial host interactions is that microorganisms must sense their environments to induce pathways to achieve cell surface remodeling and bacterial metabolism that allows them to survive host innate immune killing. Only after this has been accomplished can organisms sense the proper time and place to induce the expression and delivery of molecules that directly alter host processes to promote survival and replication of the bacteria. Such molecules can result in pathogenic effects or can promote specific commensal processes that are beneficial to both host and microbe. Similar to bacterial sensing host environments higher organisms sense microbes through bacterial production of specific molecules with unique molecular patterns. Such sensing leads to activation of specific pathways leading to innate and acquired immune responses as well as important processes including damage repair or cell death. Hence the balance between bacterial host interactions through mutual sensing determines the diverse outcomes of host bacterial interactions in nature and the diversity of interactions between different individuals of the same species. Therefore, ultimately the understanding of these diverse interactions and possibilities in model systems should allow us to use this information to explain the diversity of outcomes in nature, as in why certain infectious diseases lead to death, chronic disease, or no disease in different individuals. Ultimately this information may lead to the ability to predict specific interactions among different individuals in the future. Therefore it is important for the field to continue to define specific model systems of bacterial host interactions while starting the process of defining the importance of specific molecular pathways to the diversity of outcomes in nature. Therefore this collection of articles by some of the best and most innovative members of the field of host pathogen interactions reflects the spirit and promise of this possibility.

A seminal technological advance that has broadened our view of the regulatory mechanisms linking environmental sensing and induction of pathways to increase a pathogen's fitness in the host environment has been

## Renée M Tsolis

Department of Medical Microbiology and Immunology, University of California, Davis, United States

Dr. Tsolis earned a B.S. from Tufts University, a Diploma from Eberhard Karls Universität in Tübingen and a Ph.D. from Oregon Health Sciences University. She was previously a faculty member at Texas A&M University College of Medicine and is currently Professor in the School of Medicine at the University of California, Davis and Chair of the UC Davis graduate program in Microbiology. Dr. Tsolis' laboratory studies several aspects of host–pathogen interactions during infections with intracellular bacteria, including type IV secretion systems and their effectors, bacterial mediators of chronic infection, effects of co-infections and nutrition status on the outcome of bacterial infection, and the interactions between intestinal microbial communities, pathogens and host physiology.


provided by technical advances in global measurement of bacterial and host transcription, termed RNA-seq. In this issue, Saliba, Santos and Vogel discuss these advances as well as technologies that enabled discovery of post-transcriptional networks and novel roles for noncoding RNAs. Further, single cell RNA-seq has led to an appreciation of the heterogeneity of host cell responses to infection that correlate with growth arrest of intracellular bacteria versus permissiveness for replication. The technology termed dual RNA-seq, which provides a simultaneous profiling of host and pathogen responses to infection, provides insights into global host transcriptional responses to bacteria. These technologies have the potential to provide a detailed understanding of the regulatory mechanisms that drive both manipulation of host cells to the pathogen's advantage and the regulatory cascades involved in the response of the mammalian host.

Two reviews in this issue provide updates on the interactions between toxins and host cells. Fowler, Chang, Gao, Geiger, Stack and Galán discuss the exciting discovery of the typhoid toxin as well as recent findings on its unique structure, mode of action and contribution to the clinical features of typhoid fever. Intriguingly, typhoid toxin has a unique, mosaic $A_2B_5$ structure derived from cytolethal distending toxin and pertussis toxin. Its expression is induced on uptake of *Salmonella enterica* serovar Typhi by the host cell and it is actually secreted out of the infected cell to intoxicate neighboring bystander cells. A complementary view of toxin action is provided in the review by Lubkin and Torres which focuses on an important toxin target tissue, the vascular endothelium. In the context of bloodstream infections, both Gram-positive and Gram-negative pathogens produce a variety of toxins that disrupt the function and integrity of the endothelium, and these interactions are key to eliciting the ensuing host response that can culminate in lethal sepsis.

In the past 10 years, we have seen remarkable progress in understanding how intracellular pathogens manipulate cellular processes to promote pathogen replication, and several review articles in this issue discuss recent advances in this area. Ashida and Sasakawa lead off this theme by highlighting how bacterial pathogens modulate host ubiquitination, a post-translational protein modification system that regulates nearly all host cell processes. Discovery that several effectors of pathogen Type III (T3SS) and Type IV (T4SS) secretion systems have E3 ligase function has provided key insights into how these pathogens manipulate innate immune signaling to their advantage.

One such host cell pathway regulated by ubiquitination is autophagy, the host cell's recycling process for damaged organelles and nonfunctional components, that can also be used to target intracellular bacteria for degradation, a recently recognized pathway dubbed 'xenophagy'. The review by Kohler and Roy discuss how, perhaps not surprisingly, intracellular pathogens have developed strategies to counter degradation by either avoiding or inhibiting the autophagic machinery of the host cell through injection of secreted effectors that modulate this pathway. Considering the crucial role of autophagy in inflammation as well as innate and acquired immunity, understanding how bacteria manipulate autophagic pathways is providing exciting insights into the functioning of this pathway in host cells as well.

Interestingly, a strategy utilized by *Burkholderia* and *Listeria* to escape autophagy is to 'run away' using actin-based motility. How bacteria engage the actin cytoskeleton to promote their spread within and between cells is the topic of the article by Lamason and Welch, who review the different