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Editorial overview: Host–microbe interactions: bacteria

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David Holden is Director of the MRC Centre for Molecular Bacteriology and Infection at Imperial College London. He obtained his PhD in Microbiology from University College London. He held postdoctoral fellowships in Canada, the USA and the MRC National Institute for Medical Research, London. In 1990 he was appointed Lecturer at the Royal Postgraduate Medical School, London, becoming full Professor in 1995. Holden is best known for inventing signature-tagged mutagenesis for identification of mutants with altered growth in mixed populations. Using this, his group has identified numerous bacterial virulence genes, including those encoding the *Salmonella* SPI-2 type III secretion system. The group currently studies bacterial virulence mechanisms, in particular those of *Salmonella*.

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Dana Philpott is an Associate Professor in the Department of Immunology at the University of Toronto. She obtained her PhD from the University of Toronto, where she studied host–pathogen interactions, focusing on enteropathogenic *Escherichia coli*. She then did her post-doctoral work at the Institut Pasteur under the direction of Dr. Philippe Sansonetti and later became a group leader at this institute. Dr. Philpott was recruited to Toronto in 2006 where her research focus is to understand how Nod-like receptors influence gut homeostasis and how this might impact infection and disease pathogenesis.

Bacterial infections continue to cause immense human suffering and mortality throughout the world, as well as devastating losses in agriculture. Effective vaccines are still needed for many bacterial diseases and the worldwide rise in antibiotic-resistant bacterial pathogens continues at an alarming rate. With the pharmaceutical industry struggling to produce new antibiotics, new approaches are required to diagnose, prevent and treat bacterial infection.

In contrast to this bleak picture, in the last quarter century has witnessed immense progress in our understanding of the molecular mechanisms governing bacterial virulence and host resistance. Fundamental discoveries include bacterial pathogenicity islands, virulence-associated secretion systems and surface adhesins, the astonishing array of activities of bacterial effector proteins and toxins, new and complex gene regulatory systems, novel bacterial immune mechanisms and the influence of the host microbiota on infection and immunity. On the host side, key breakthroughs in innate immunity to bacteria have included the discovery of receptors for extracellular and cytosolic bacterial molecules, inflammasomes, pyroptosis, autophagic pathways for clearance of cytosolic bacteria and neutrophil extracellular traps (NETs). Furthermore, the pace of progress shows no signs of slowing down: papers describing novel aspects of bacterial physiology, pathogenicity and host immunity are published in the leading journals on a weekly basis, suggesting that research in this field will continue to unveil surprising and fascinating new biological principals and mechanisms for many years to come.

To capture some of the recent exciting progress in the field, and to complement topics that have been covered recently in Current Opinion in Microbiology and elsewhere, we have assembled articles from experts working on a broad range of topics relevant to host–pathogen interactions, including the spread of genetic material between bacteria, how such DNA becomes integrated into host bacterial regulatory circuitry, functions of virulence proteins of animal and plant pathogens, innate immune mechanisms and the influence of the microbiota on infection and immune function.

Horizontal gene transfer (HGT) is a major influence on bacterial evolution but even if newly acquired genes confer a physiological benefit, they are likely to be selected against unless their expression is regulated appropriately. Will *et al.* describe the process of silencing of expression of horizontal-acquired genes, focusing in particular on the Gram-negative pathogen *Salmonella*. In this organism, nucleoid-associated proteins bind to and repress transcription of non-self AT-rich DNA, but this process can be relieved under appropriate physiological conditions by other DNA-binding

'counter-silencing' proteins. Interestingly, and unlike conventional transcriptional activation, counter-silencing appears to be a relatively flexible process, providing sufficient versatility to enable the integration of horizontal-acquired genes into the recipient's regulatory circuitry.

HGT frequently occurs via bacteriophage-mediated transduction. Penadés *et al.* give an overview of *Staphylococcus aureus* pathogenicity islands (SaPIs), mobile DNA segments that transmit genes encoding superantigen toxins and probably other virulence factors. Recent studies have revealed the elegant mechanisms by which some of these pathogenicity islands exploit the phage DNA-packaging machinery for their own transfer. A SaPI-encoded terminase subunit interacts with the phage terminase subunit to drive preferential packaging of SaPI DNA into small phage-like capsids, thereby effectively parasitizing the phage. Infectious SaPI particles are released by bacterial lysis, spreading the SaPI throughout the staphylococcal population and possibly beyond. Worryingly, antibiotics that damage DNA can initiate SOS-mediated prophage induction, enhancing the spread of SaPI virulence genes.

HGT, quorum sensing molecules and other metabolites enable a heady mix of interactions between pathogens and commensal bacteria. Unsurprisingly therefore, the traditional bilateral view of host–pathogen interactions is increasingly seen as inadequate; it is clear that resident commensal microbial communities can make complex and important contributions to virulence and immune mechanisms. For example, experiments with germ-free and antibiotic-treated mice have shown clearly that the gut microbiota has an important role in bacterial infections. Microbial products such as butyrate affect localized mucosal immunity while Nod-like receptor ligands derived from the bacterial cell surface stimulate immune defenses in distal tissues. Leslie and Young focus their review on the gastrointestinal microbiome, showing how metabolic interactions, immune regulators and microbial competition can all influence the outcome of an infection.

Fusobacterium nucleatum is a member of the oral microbiota, which has gained significant notoriety in the past few years due to its association not only with periodontal disease, but more recently with colon cancer and inflammatory bowel disease. Han explores the virulence mechanisms of *F. nucleatum* and discusses these factors in the context of colonization of different tissues by this bacterium and induction of inflammatory and tumorigenic responses.

Several articles review different aspects of bacterial virulence. The obligate nature of the Gram-negative pathogen *Chlamydia* has hampered progress on understanding the molecular basis of its virulence. However, in recent years methods have been developed that enable genetic transformation, the construction of targeted mutations and forward genetic screens for this pathogen. *Chlamydia* uses a type III secretion system to translocate virulence effectors across the plasma and vacuolar (inclusion) membranes. These are required for bacterial invasion and replication. Using cryo-electron tomography of infected cells, Hayward *et al.* have obtained striking images of the chlamydial type III secretion apparatus interacting with host cell plasma membranes during entry and with inclusion membranes during intracellular replication. In the latter case, a polar array of many injectisomes appears to form a pathogen 'synapse' involving bacterial, inclusion and host endoplasmic reticulum membranes. Hayward *et al.* discuss these structures and their physiological significance in relation to chlamydial biology.

Mycobacterium leprae is another obligate intracellular bacterium with a streamlined genome devoid of genes necessary for independent growth. The preferred cellular niche for *M. leprae* is Schwann cells and recent advances in understanding *M. leprae* pathogenesis have uncovered a remarkable ability of these bacteria to reprogram these lineage-committed cells to a progenitor/stem cell phenotype. Reprogramming of these cells by *M. leprae* not only provides a favorable intracellular environment for bacterial growth, but has the added advantage of providing a means of bacterial spread though the acquisition of a migratory phenotype by these cells. Hess and Rambukkana review new advances in our understanding of how *M. leprae* manipulates the plasticity of these host cells and give interesting insights into how this ability to reprogram lineage-committed cells could be used therapeutically to repair damaged and injured tissues.

Legionella pneumophila also forms an endoplasmic reticulum-interacting vacuole. However, it is distinct from the chlamydial inclusion. Once again, the unique characteristics of the vacuole are dictated by the actions of translocated bacterial effectors, in this case delivered by a type IV secretion system. Up to 275 different effectors might be delivered in this manner, making the understanding of the biogenesis of the *Legionella* vacuole a formidable challenge. Although the functions of the majority of these are obviously unknown at present, it is clear that some are involved in vacuole maturation by modulating Rab and SNARE proteins, and hence membrane fusion and trafficking events. Rab1 – a major regulator of ER-Golgi traffic – is a crucial target for *Legionella*, with no less than six effectors specifically affecting its localization and activity. Prashar and Terebiznik discuss these and other effectors that modify the *Legionella* vacuole, interfere with host cell lipid metabolism and ubiquitin and autophagy pathways.