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Editorial overview: Host–microbe interactions: bacteria: War and peace: the fragile equilibrium between bacteria and host

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Pathogenic (derived from the Greek words *pathos* [suffering] and *genesis* [producer]) bacteria are strictly defined as those that cause disease. In 1890, when Koch's Postulates were first published, a handful of bacterial diseases including typhoid, cholera, plague and tuberculosis were responsible for devastating death tolls in times of war and peace. Almost 100 years later, thanks to improved sanitation, chlorination of water, antibiotics and the development of vaccines most people in the developed world were unlikely to ever encounter these diseases. However, in the developing world these infectious diseases, and others, continue to exact a huge toll. In addition, the emergence of antibiotic resistance and strains with increased virulence are a constant threat. At the same time our understanding of what defines a pathogen and the complex microbial–host interactions that occur in healthy and diseased animals is rapidly increasing, thanks largely to recent technical developments in genomics and sequencing. These technologies are revealing the vast numbers and diversity of microbes that make up the healthy microbiota. These microbial communities are primarily beneficial since, broadly speaking, hosts offer a stable, nutrient-rich environment for microbes to live, while bacteria provide the host with novel metabolic capabilities. This win–win situation is a fragile equilibrium, which is maintained by a complex series of microbe–host and microbe–microbe interactions. Destabilization of the equilibrium can lead to profound modifications of the microbiota and severe pathologies in the host. Whether this is caused by the activities of a pathogen or by some other mechanism, for example, antibiotic treatment, the end effect can be disease, either acute or chronic. The goal of this issue of *Current Opinion in Microbiology* was to highlight some of the areas of rapid growth in the field of bacterial pathogenesis. The 15 reviews cover a range of topics, divided roughly into three categories: *Innate Immunity*, *Bacterial Weaponry* and *Technical Advances*, all of which provide insights into the complex host–pathogen relationship, while some of them also bring into consideration the microbe–microbe interactions that we now know can play such an important part in pathogenesis.

Innate immunity

For mammals the innate immune system, consisting of physical barriers, antimicrobial proteins, phagocytic cells and the normal flora, is the first line of defense against bacterial pathogens. One of the key components of this system is the recognition of conserved microbial motifs (PAMPs or pathogen-associated molecular patterns) by pattern recognition

receptors (PRRs). Hagar and Miao describe how, in the cytosol, inflammasomes detect PAMPs and trigger the inflammatory caspases, caspase-1 and caspase-11, leading to cytokine secretion and pyroptosis of the infected cell. Not only is this an efficient way to destroy the replicative niche of cytosolic bacteria but it also exposes the intruders to extracellular defenses and neutrophils. The definition of PRRs, as eukaryotic molecules that recognize highly conserved 'non-self' microbial signatures, has been somewhat complicated by the identification of galectins as bacterial sensors. These animal lectins, which contain characteristic carbohydrate recognition domains (CRDs) and have affinity for β -galactosides, were originally characterized based on their abilities to bind endogenous 'self' glycans and their involvement in basic developmental processes and cancer. But galectins also bind exogenous 'non-self' glycans on the surfaces of pathogens and have roles in the recognition of, and response to, both intracellular and extracellular bacteria as reviewed by Chen *et al.*

As well as directly targeting intracellular and intracellular bacteria, the innate immune system can target infected cells via a process known as efferocytosis, the phagocytic uptake of apoptotic cells. Efferocytosis aids in resolution of inflammation by removing dead cells and preventing release of phlogistic cellular contents and also promotes tissue repair and wound healing. Martin *et al.* describe how efferocytosis participates in pathogen clearance, when the engulfment of infected cells is followed by pathogen destruction, as well as how it can be usurped by pathogens as an alternative mechanism to gain entry into phagocytes.

The intestinal tract presents the largest and most densely populated mucosal surface in the human body. Serving as an interface between the internal and external environments, the intestinal barrier has to control uptake across the mucosa while also protecting against assault from microbes in the gut. Damage to the intestinal barrier or dysbiosis of the intestinal microbiota is often caused, or taken advantage of, by bacterial pathogens. Barreau and Hugot review how the intestinal barrier can be disrupted by infection, allowing the passage of bacteria and large molecules from the lumen through the mucosa. This has consequences at the site of infection, including on commensal bacteria, and can also have distal and long-term effects, through the activity of circulating activated immune cells. Pham and Lawley provide a synthetic view on the intestinal microbiota during infection and explain why the restitution of a healthy microbiota holds great promise as a therapy, at least for some infections.

Bacterial weaponry

Given the variety of ways that the innate immune system uses to detect and destroy invading pathogens, it is not surprising that the pathogens have developed a similarly diverse array of mechanisms to counteract these processes and even sometimes exploit them. Vromman and Subtil illustrate how both extracellular and intracellular bacteria use host lipids, for adhesion, signaling, growth, or as an energy source. Some intracellular bacteria exploit host lipids to build an intracellular vacuole in which they avoid detection by cytosolic innate immune mechanisms. As discussed by Creasey and Isberg, maintenance of vacuole integrity is dependent on multiple levels of modulation of the host cell cytoskeleton, signaling molecules and lipids.

Whether intracellular bacteria survive within a vacuole or in the cytosol, they must be able to respond rapidly to changes in the environment. Dalebroux and Miller review the mechanisms by which *Salmonella* Typhimurium modifies the lipopolysaccharide and glycerophospholipid structure of its outer membrane for intestinal colonization and systemic virulence. Many other bacteria secrete toxins or effectors that target specific host activities or can be used against bacterial competitors. Gram negative bacteria have developed a diversity of molecular machines that can transport proteins across the inner and outer membranes in a single step, namely the Type I, Type III, Type IV or Type VI secretion systems. Waksman and Orlova recapitulate our understanding, based on structural data, of the type IV secretion system (T4SS) that plays a crucial role in the pathogenicity of several bacteria. The type VI secretion system (T6SS), while originally identified by Mekalanos's group in *Vibrio cholerae* and *Pseudomonas aeruginosa*, has now been found in over a quarter of all proteobacterial genomes. It is one of several secretion systems, including T5SS and T7SS, which can be used to target other bacteria. Benz and Meinhart describe how bacteria use these antibacterial effector/immunity systems to target competitors while protecting themselves from suicide and fratricide. The general secretory pathway (Sec) is also used to secrete virulence factors, in particular by Gram positive bacteria. Secreted toxins play a predominant role in the virulence of *Staphylococcus aureus* and the review by Otto summarizes what we know of the *S. aureus* toxin repertoire and their targets. Although the activities of some of these bacterial weapons have been known for a long time, this does not exclude the possibility that additional activities may yet be discovered. As discussed by Tavernier and Lecuit the *Listeria* effector ActA provides a striking example of a bacterial protein with dual activities, acting both intracellularly to promote cell-to-cell spread and dissemination within a tissue, and extracellularly to favor transmission.

Host immunity is not the only enemy pathogens have to worry about. Bacteria are largely outnumbered by viral predators and have developed an assortment of defense mechanisms. The recently identified CRISPR-cas uses small guide RNAs to prevent the incorporation of mobile genetic elements. Hatoum-Aslan and Marrafani review novel roles for CRISPR loci as barriers to horizontal gene transfer and as modulators of gene expression, and their consequences on the emergence and virulence of human bacterial pathogens.

Technical advances

Obligate intracellular bacteria (such as *Chlamydia*, *Rickettsia*, *Anaplasma* and *Coxiella*), which only replicate within host cells, provide a special set of challenges to the scientists who study them and until recently it was virtually impossible to genetically manipulate these organisms. Wood *et al.* review recent advances in the use of genetic systems that have ushered research on these pathogens in a new era and will help in understanding the molecular basis of pathogenicity and the immunological reaction of the host. This knowledge is key to the design of potent vaccination strategies, which have to be adapted to the particular strains they aim to target. Along that line, Strugnell *et al.* explain why the development of vaccines against invasive non-typhoidal salmonellosis will require considering pathological and immunological differences between the serovars implicated and those that cause typhoid fever, for which vaccines are available. *Salmonella* Typhimurium is certainly one of the best studied bacterial pathogens, and many of the

molecular details of its interactions with the host have been deciphered. If, for many bacterial pathogens, an efficient vaccine is still an out-of-reach dream, the work being done with salmonella and the development of 'humanized' models, are providing important baselines for future development.

Biographies

Olivia Steele-Mortimer is a Senior Investigator in the Intramural Program at the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Steele-Mortimer did her PhD research at the European Molecular Biology Laboratory (EMBL) in the laboratory of Jean Gruenberg. She did postdoctoral research at the University of British Columbia with B Brett Finlay and at Washington University with Philip Stahl. Her lab at the Rocky Mountain Laboratories in Montana studies *Salmonella* Typhimurium and its interactions with mammalian host cells.

Agathe Subtil is directrice de recherche at the Centre National de la Recherche Scientifique (CNRS). After a PhD on endocytosis of membrane receptors under the supervision of Alice Dautry-Varsat at the Institut Pasteur in Paris, she joined the lab headed by Tim McGraw in the Weill Cornell Medical College in New York to study the traffic of glucose transporters. She was recruited by the CNRS in 1999 and started applying her cell biology training to the study of the interactions between an obligate intracellular bacterium, *Chlamydia*, and its eukaryotic host. The recent activities of her research group, at the Institut Pasteur, focus on the effects of infection on the host cell intracellular compartments and nucleus.