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Host–pathogen interactions: a diversity of themes, a variety of molecular machines

Editorial overview

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Introduction

It is becoming increasingly clear that bacterial pathogens have evolved very complex functional interfaces with their hosts. This is particularly the case for pathogens that have undergone long-standing associations with their hosts, allowing evolutionary forces to shape molecular machines and strategies that can be better characterized by their refinement than by their potential to inflict host harm. The study of the cell biology and immunobiology of these interactions is proving to be a very fruitful area of research in more ways than expected. These studies are not only yielding remarkable aspects of the host–pathogen functional interface but are also providing a unique window into basic aspects of cellular functions and in the innate immune system. This issue of *Current Opinion in Microbiology* focuses on various aspects of host–pathogen interactions. The picture that emerges from these articles is one of great diversity, not only in the themes that govern these interactions but also in the remarkable variety of pathogenic strategies and molecular machines that are involved in these encounters. Moreover, the study of the cell biology and immunobiology of host–pathogen interactions is no longer restricted to a handful of model organisms but rather it has expanded to include a diverse group of pathogens with unique and varied mechanisms to engage their hosts.

Modulation of the actin cytoskeleton by bacterial pathogens: new tricks from the ‘usual suspects’

Many pathogens have evolved a variety of mechanisms to modulate the host-cell actin cytoskeleton to enter into cells, to move inside cells and spread from cell to cell, to avoid uptake by phagocytic cells, or to promote intimate attachment. Over the years, the study of these processes has received a lot of attention and this area of research continues to attract the interest of many investigators. As a result, these events are among the best-understood processes in the host–pathogen interaction field. At the center of the temporal and spatial coordination of actin dynamics is a subset of small molecular weight GTP-binding proteins of the Rho family, in particular Cdc42, Rac1 and Rho. Not surprisingly, many pathogens have evolved the ability to modulate the activity of these proteins as a means to subvert the actin nucleating machinery to mediate their own uptake into host cells. Remarkably, however, the subverting strategies take many different forms. As discussed by Wong and Isberg, the bacterial protein invasins encoded by *Yersinia* spp binds $\alpha 5\text{-}\beta 1$ integrins very tightly,

resulting in the generation of specific signals emanating from this receptor that eventually lead to the activation of Rac1.

In contrast, *Salmonella enterica* utilizes a more direct strategy to engage the GTPase switch. As discussed by Patel and Galán, *Salmonella* delivers into cells via a type III secretion system (TTSS) a group of proteins that can activate Cdc42 and Rac1. At least two of these activators can directly catalyze exchange of GTP for GDP on these GTPases, leading to profuse actin cytoskeleton rearrangements and membrane ruffling, which results in bacterial uptake. In a remarkable Yin and Yang, once internalized in a spacious vacuole, *Salmonella* rapidly reverses the actin reorganization by injecting a GTPase activating protein (GAP) that reverses Rac1 and Cdc42 activation. *Shigella* spp. also utilizes a TTSS to activate Cdc42 and Rac to mediate its own uptake. However, as discussed by Tran Van Nhieu *et al.*, in this case the TTSS effector proteins do not engage the GTPases directly but rather, they generate signals through the activation of *src* family tyrosine kinases, which indirectly lead to Cdc42 and Rac1 activation and bacterial uptake.

The modulation of Rho-GTPase functions by bacterial pathogens has not solely evolved to mediate their internalization into non-phagocytic cells. As discussed by Navarro *et al.*, *Yersinia* spp. utilize alternative strategies to disrupt Rho-family GTPase activation to prevent their internalization into professional phagocytes. Particularly interesting is the action of YopT, which cleaves the GTPase once it is inserted in the plasma membrane due to its lipid modification. In addition, Dean *et al.* and Gouin *et al.* discuss yet other types of exploitation of the actin cytoskeleton by bacterial pathogens. Enteropathogenic *E. coli* utilizes a TTSS to deliver a number of bacterial effector proteins whose coordinated action results in the formation of well-organized actin 'pedestals' that facilitate the intimate attachment of these bacteria to mucosal surfaces. This strategy is reminiscent from that used by vaccinia virus once it is expelled out of the cell and searches for other cells to infect. Gouin *et al.* discuss this and other strategies evolved by different microbial pathogens to subvert the actin cytoskeleton to move within and between cells. Remarkably, this property is not just restricted to *Listeria*, *Shigella* and *Rickettsia* but also applies to other pathogens including mycobacterial species such as *Mycobacterium marinum* and *Burkholderia pseudomallei*. One theme emerging from recent studies in this field indicate that the Arp2/3 complex remains the central player in these processes and bacterial determinants either mimic or recruit WASP/N-WASP family proteins to activate this complex and thus generate actin tails. The study of actin-based motility is the best example of how the study of a bacterial induced process can yield insight into basic cellular processes such as actin dynamics.

Interfacing with the innate immune system: from the stimulation of cytokine production to the modulation of vesicular trafficking

The identification of surface or intracellular receptors (e.g. Toll-like, Nod, etc.) equipped to respond to a variety of bacterial products has sparked a renewed interest in the study of the interaction of microbial pathogens with the innate immune system. It is becoming increasingly clear that these interactions are crucial not only for the initiation of non-specific defense responses against the pathogen but also for the priming of the acquired immune response by professional antigen-presenting cells. This issue of *Current Opinion in Microbiology* presents a sampling of the variety of aspects of the interaction of bacterial pathogens with the innate immune system that are currently under investigation. For example, Boneca examines the role of peptidoglycan in bacterial pathogenesis. The adjuvant properties of bacterial peptidoglycan have been known for a long time. However, more recent work has begun to provide a molecular explanation for its immunostimulatory properties, which appear largely due to the ability of peptidoglycan to stimulate the Nod family of intracellular innate immunity receptors. Another theme emerging from recent studies is the interplay or synergy between specific bacterial molecular machines such as fimbriae, type III or type IV secretion systems and conserved innate immunity agonists such as lipopolysaccharide (LPS) and peptidoglycan. For example, Kau *et al.* describe how uropathogenic *Escherichia coli* utilizes specific adaptations such as pili to mediate the colonization of the urinary track. In turn, the stimulation of Toll-like receptors (TLRs) by bacterial agonists results in host inflammatory responses necessary to control infection.

Innate immunity outputs are not just restricted to the mounting of an inflammatory response to an invading pathogen. Lapaque *et al.* discuss that *Brucella* has an unconventional LPS that confers resistance to antimicrobial attacks and modulates the host immune response. Rieder *et al.* show that the VacA secreted protein of *Helicobacter pylori*, which targets epithelial cells, can also target cells of the immune system and induce immunosuppression. Finally, MacMicking describes a recently identified family of GTPases that seem to control the replication of vacuolar pathogens by regulating the trafficking of bacterial-containing phagosomes. This is indeed an emerging field and it is expected that more elements of innate immune control of bacterial pathogens will be uncovered in the coming years.

Modulating vital processes: from cell cycle progression to vesicular trafficking and beyond

It is not surprising that pathogens that have evolved an intimate functional interface with their hosts have evolved mechanisms to modulate a variety of vital

processes. For example, *Oswald et al.* describe a diversity of mechanisms evolved by bacterial pathogens to modulate cell cycle progression. Since the cell cycle has a profound impact in responses that are central to the ability of pathogens to colonize a host, it is perhaps expected that bacteria have evolved multiple strategies to modulate this event. Nevertheless, the diversity of mechanisms that have been uncovered in studies of a variety of pathogens is a testimony of the importance of these events for pathogen survival.

Residence within host cells may provide unique advantages to pathogens as they may place them out of reach for a number of innate immune defense mechanisms. However, such residence is only suitable for pathogens that have evolved unique adaptations to modulate vesicular trafficking to avoid delivery into lysosomes. *Salcedo and Holden* describe the myriad of strategies utilized by microbial pathogens to modulate the eukaryotic secretory pathway to secure a safe intracellular niche. While *Salmonella* intracellular life style is well-documented, the situation is less clear for other bacterial species, e.g. *Burkholderia* species, as discussed by *Valvano et al.*

Central to many cellular processes are the mitogen activated protein (MAP) kinases, which modulate a variety of vital processes ranging from cell cycle progression to programmed cell death. Many bacterial determinants have specifically evolved to interfere with or activate these kinases. An example of these determinants is Anthrax toxin, which has recently received a lot of attention. This toxin is composed of two enzymatically active

subunits, lethal and edema factors, and a subunit essential for their delivery into cells, the protective antigen. Edema factor is an adenylate cyclase and lethal factor is a protease that specifically inactivates Mek, the activating kinase of Erk, one of the members of the MAP kinase family of proteins. *Scobie and Young* review the latest advances in the understanding of the interaction of protective antigen with its cellular receptors.

Future perspectives

The past few years have seen an explosion of information in the field of host–pathogen interactions. The study of bacterial factors other than proteins has regained center stage, an overdue recognition of the importance of these factors in host–pathogen interactions. This line of inquiry will continue to yield important insights into mechanisms of pathogenesis. The interface between pathogens and the innate immune system has attracted and will continue to attract a lot of attention from researchers, not only to understand non-specific mechanisms to control bacterial infections but also to unravel principles that govern the mounting of specific immune responses. A welcome trend in the field has been that advances have occurred not just in systems that were already under close scrutiny but also in a variety of new systems poorly understood until recently. It is expected that this trend will continue and the great diversity of pathogenic strategies utilized by different bacterial pathogens will continue to surprise us. Without an end in sight for the battle against infectious diseases and the increasing occurrence of multiple antibiotic resistances, the understanding of how pathogens interact with their host is more important than ever.