The cell biology of microbial infections: coming of age

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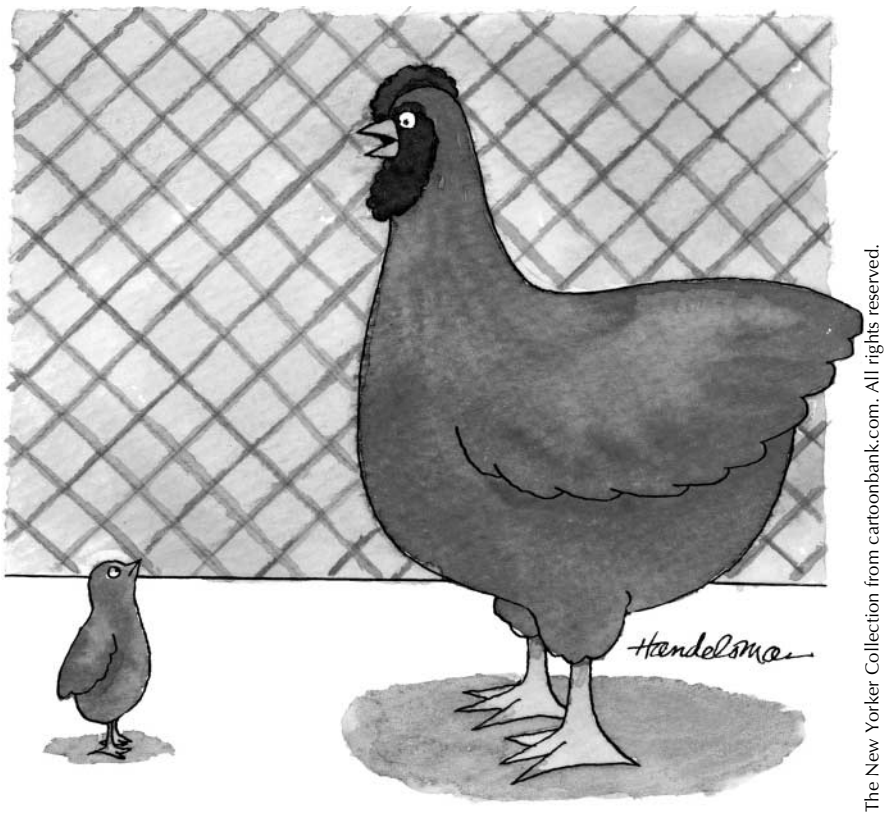
Over the last few years, there has been remarkable progress in the understanding of the interaction of microbial pathogens with their hosts (Finlay and Cossart, 1997; Boquet et al., 1999; Cameron et al., 2000; Isberg and Barnes, 2001; Stebbins and Galán, 2001). The study of the cell biology and immunobiology of microbial infections is emerging as a corner stone of microbial pathogenesis research in the postgenomic era. These studies are allowing the identification and characterization of complex pathogenic mechanisms at the molecular, and even atomic, levels. Arguably, not since the introduction of molecular biology and molecular genetics has the field seen so many advances in the understanding of the biology of pathogenic microorganisms.

Microbial pathogens, big and small, have "learned" through the process of evolution how to modulate precisely host cellular functions to ensure their replication and perpetuation. A surprising finding emerging from this level of understanding is that the interactions between pathogens and their hosts are often best characterized by their refinement and sophistication rather than by their potential for harm. This is particularly true for microbial pathogens that have sustained a long-standing association with their hosts and that, in some cases, have even lost the ability to explore other niches. Indeed, it is often overlooked that infections with these highly adapted pathogens most often do not lead to pathology. This is in contrast to infections with pathogens that are encountered "accidentally" by a host that does not play any role in the pathogen's ecology. These infections tend to have more serious consequences and can even be lethal because the functional interphases between the pathogens and their accidental hosts are unbalanced since they have not been evolutionarily refined. This latter category of pathogens perhaps better fits the more common view of host–pathogen interactions, which is often described in warfare terms.



"Even more dangerous than crossing the road is being undercooked."

However, this battle of good (us) vs. evil (the microbes) characterization of host–pathogen interactions is ill-suited to describe the more subtle and refined encounters with the large number of microbial pathogens that have co-evolved with us. Because evolution has directly shaped these interactions, their study is instructive for the understanding of basic principles of cell biology. Indeed, time and again, we have seen how the study of the strategies used by these microbial pathogens to interact with their host cells have given us remarkable insight into the inner workings of the cells themselves.

However sophisticated and balanced some of the interactions of the host with these "tamer" pathogens may be, the fact remains that, on occasions, these pathogens do cause

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harm. What is the difference then between this type of balanced pathogen and harmless, commensal, microorganisms? Why does pathology sometimes occur in one case but not in the other? Although the answer to this question is not simple, the difference may lie in the degree of proximity of the microorganisms to the host. Commensal microorganisms have established a niche at a safe distance from the host and therefore do not tend to engage it in close interactions. In contrast, microbial pathogens have evolved to replicate in extreme proximity to the host, sometimes even within it, resulting in a more delicate balance. Therefore, even minor alterations in the host defenses or in the pathogen's virulence can occasionally disrupt this delicate balance, resulting in disease.

In this issue, a number of articles describe eloquent examples of sophisticated strategies evolved by microbial pathogens to modulate host cell functions. Cornelis et al. describe a fascinating organelle, the type III secretion system, evolved by a number of microbial pathogens for the sole purpose of injecting bacterial proteins into the host cell (Cornelis, 2002). It is now known that many bacterial pathogens of both plants and animals deliver into the host cell bacterial proteins that can mimic precisely host cell products. Through these mimics, bacteria can regulate a number of diverse cellular functions, ranging from actin cytoskeletal dynamics to cell cycle arrest and programmed cell death.

Roy and Tilney describe the remarkable ability of the bacterial pathogen *Legionella pneumophila* to alter host vesicular trafficking to establish a unique niche permissive for its replication, which is in intimate association with the ER (Roy and Tilney, 2002). These bacteria are not usually considered to have sustained a long-standing association with humans. Rather, it appears that their encounters with the human host are recent and are an undesirable byproduct of human progress. Indeed, the first recognized incident of disease associated with *L. pneumophila* was the result of their colonization of the air conditioning system in a hotel in Philadelphia, where a Legionnaires convention was being held. It turns out that air conditioning towers provide an unexpected fertile ground for the growth of these bacteria, which otherwise spend their life in close association with freshwater amoeba. However, intimate association with the amoeba has provided *L. pneumophila* with a training ground to evolve its remarkable ability to modulate cellular functions.

Portnoy et al. (2002) describe the interface between *Listeria monocytogenes* and its host. The study of this pathogen has been one of the most instructive in providing clues about basic aspects of cell biology and immunobiology. The contribution of *Listeria*'s actin-based motility within host cells to the understanding of actin dynamics is well known and these bacteria or some of its virulence factors are now a common feature in many laboratories interested in the study of the actin cytoskeleton.

The study of the protozoan parasite *Trypanosome cruzi* is another eloquent example of how the rigorous examination of microbial pathogens can lead to unexpected findings that help illuminate poorly understood areas of basic cell biology. As discussed by Andrews (2002), the study of the mechanisms by which *T. cruzi* enters into cells has led to major insights into the mechanisms by which cells repair wounds in the plasma membrane.

Mycobacterium tuberculosis, perhaps the most ancient human pathogen, remains one of the most serious worldwide health problems today. The resilience of this pathogen is due to its remarkable ability to avoid host defenses and cause persistent infections that are most often asymptomatic. Russell et al. (2002) discuss how *M. tuberculosis* modulates vesicular trafficking and how, through the release of bacterial lipids, this bacterium can modulate the host innate immune response to ensure persistent infection.

Viruses, forced by the limited size of their genome to a minimalistic existence, have evolved to utilize even the most basic host cellular functions to secure their replication. Bushell and Sarnow described how a family of viruses has evolved remarkable strategies to usurp host cell translation factors to initiate their replication (Bushell and Sarnow, 2002).

The systems described in these articles, which are just a few examples of the many remarkable interactions between pathogens and their host cells, highlight not only the complexity of microbial pathogens but also their potential as tools to learn basic cell biology. Advances made over the last few years have made cell biologists aware that microorganisms can be more than just a nuisance for tissue culture. Undoubtedly, during the next few years we can expect to see many instances of cell biologists taking advantage of these remarkable biological probes. The knowledge gained in the process will help the development of novel therapeutic strategies to combat infectious diseases.

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