

At home with hostility: How do pathogenic bacteria evade mammalian immune surveillance to establish persistent infection?

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F1000 Biology Reports 2011, 3:1 (doi:10.3410/B3-1)

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Abstract

Bacterial persistence is of major concern as persistent bacterial infections involving bacteria such as *Helicobacter pylori*, *Salmonella enterica* serotype Typhi, and *Mycobacterium tuberculosis* pose significant public health problems worldwide. This report discusses the recent advances in understanding the strategies used by bacteria during persistent infection that allow them to colonize specific sites in the host and evade immune surveillance.

Long-term bacterial infections pose several fundamental biological questions: How metabolically active are bacteria during a persistent infection? Are they dividing, or in a state of quiescence? And how do these bacteria evade the immune system for so long?

Acute infections by pathogenic bacteria cause a dramatic activation of the innate and adaptive immune responses. If the pathogen survives initial contact with the host's innate immune system (and the host is not killed), the infection is usually cleared by the host's adaptive immune system. However, some bacterial pathogens maintain infections for the lifetime of their mammalian hosts, even in the presence of a robust immune response.

Most of what we've learned about persistent infections comes from the study of several well-known illnesses. For example, *Helicobacter pylori*, the cause of most stomach ulcers, inhabits the stomach lining, where its persistence can be lifelong; *Mycobacterium tuberculosis* is able to establish long-term infections that can manifest as acute or chronic versions of the lung disease, or be clinically asymptomatic yet retain the potential to reactivate; and *Salmonella enterica*, specifically the serotype Typhi, causes typhoid fever, a systemic infection that involves colonization of the reticuloendothelial system—the network of immune cells residing in some connective tissue. Some

infected individuals become lifelong carriers, periodically shedding large numbers of bacteria in their stools. These persistently infected carriers serve as a reservoir for the pathogens, and are essential for survival of the bacteria within a restricted host population. In humans, infection with another serotype, Typhimurium, is normally associated with self-limiting gastroenteritis, and systemic disease is rare in most parts of the world.

However, a highly invasive form of nontyphoidal *Salmonella* (NTS) has become a major public health problem in parts of Africa. Although NTS strains do not normally persist in immunocompetent humans, there is serious concern about the potential that these strains might acquire that ability as they become more "human-adapted" [1].

We are only now beginning to understand the bacterial and host factors involved in the host–pathogen interaction during persistent infection, and these new discoveries are likely to provide new and exciting directions for research in the fields of microbial pathogenesis and immunology.

Making a better replicative niche

H. pylori is uniquely adapted to colonize the hostile environment of the human stomach. More virulent strains of *H. pylori* inject virulence factors into gastric epithelial

cells, a step that is associated with the development of stomach cancer. These factors provide an advantage to the invading bacterium because they disrupt epithelial cell polarity. This allows bacteria to attach and grow on the apical surface of epithelial cells, where it may be easier for them to acquire the nutrients necessary for survival [2].

Salmonella has developed its own mechanisms for colonizing a host and replicating despite the presence of immune cells. Most of the information on *Salmonella* immune-evasion mechanisms has come from a mouse model of persistent *Salmonella* Typhimurium infection. *Salmonella* Typhimurium colonizes the mesenteric lymph nodes of these mice—a gathering place for immune cells—and is occasionally found in the gallbladder, liver, and spleen. One mechanism that *Salmonella* uses to subvert the immune system is to secrete the protein SseI into dendritic cells, which normally play a role in activating immunity. The bacterial protein interferes with the migration of infected cells to lymphoid tissues by specifically binding to the cell-migration regulator IQGAP. This prevents normal dendritic-cell migration, limiting presentation of *Salmonella* antigens and naive T-cell priming, and thereby inhibiting adaptive immunity [3,4].

Subverting the host

Analyzing the role of host immune factors in chronic *Salmonella* infection has shed light on the mechanisms that allow for persistent bacterial growth. For example, regulatory T cells, which control the balance between immune-cell activation and suppression, can dictate the course of persistent *Salmonella* infection by suppressing the adaptive immune response. Leukocytes can also play a role in tuberculosis, where progression from a latent, subclinical infection to active disease is controlled by foamy macrophages within a granuloma (a spherical mass of immune cells that forms around a pathogen that can't be cleared). The foamy macrophage appears to be a key participant in both sustaining bacteria and contributing to the tissue pathology that leads to the release of infectious bacilli. The normally beneficial macrophages become pathologic in this situation through pathogen-initiated dysregulation of lipid synthesis [5].

Studying mechanisms of bacterial persistence is made more complex by the presence of native (nonpathogenic) organisms, particularly in the human gut. The human gut microflora is important in regulating host inflammatory responses and preventing inappropriate (anti-self) immune responses. Interactions between gut microbiota and the immune system are under intense study because of their potential effects on persistent infections and, therefore, on the health of an individual. Recent studies have delved further into our understanding of this

relationship by identifying host-specific bacteria responsible for directly modulating the gut immune response towards *Salmonella* [6,7]. Further studies are now needed to evaluate the impact of the gut microbiota on the establishment of persistent systemic infections.

Abbreviation

NTS, nontyphoidal *Salmonella*.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

The authors would like to thank Manuel Amieva and Justin Sonnenburg for stimulating conversations.

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