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Helicobacter and *Salmonella* Persistent Infection Strategies

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Some host-adapted bacterial pathogens are capable of causing persistent infections in humans. For example, *Helicobacter pylori* inhabits the human gastric mucosa and persistence can be lifelong. *Salmonella enterica* serovar Typhi causes systemic infections that involve colonization of the reticuloendothelial system and some individuals become lifelong carriers. In this review, I compare and contrast the different lifestyles of *Helicobacter* and *Salmonella* within the host and the strategies they have evolved to persist in mammalian hosts. Persistently infected carriers serve as the reservoirs for these pathogens, and the carrier state is an essential feature that is required for survival of the bacteria within a restricted host population. Therefore, investigating the chronic carrier state should provide insight into bacterial survival strategies, as well as new therapeutic approaches for treatments.

On infection with a pathogenic microorganism, the host usually responds by activating the innate and adaptive immune responses. If the host survives the initial battle, the adaptive immune response usually clears the foreign invader. However, some pathogens have evolved the capacity to survive the initial robust immune response and persist. The persistent phase of infection usually involves a complex balance of protective immunity and immunopathology. The interactions between the host and pathogen are very complex and likely reflect the coevolution and fine tuning of bacterial virulence mechanisms and host immune responses.

Persistent colonization with the human-specific bacterial pathogens *Helicobacter pylori* and *Salmonella enterica* serovar Typhi (*S.* Typhi) are usually not clinically apparent. However, even in the absence of clinical symptoms, infection poses some risk to the host. For example, *H. pylori* induce gastritis with varying degrees of severity. In addition, individuals who are chronically infected with *S.* Typhi have an increased risk of developing hepatobiliary cancer. Although a deeper understanding of the mechanisms of pathology and disease caused by chronic *Helicobacter* and *Salmonella* infections is important, this work focuses on the mechanisms of persistent colonization and transmission.

PERSISTENT *H. PYLORI* INFECTIONS

H. pylori infection is an important example of a persistent bacterial pathogen that is usually acquired in early childhood and lasts for a lifetime. The majority of those infected (80%–90%) will

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carry and transmit *H. pylori* without any symptoms of disease (Hunt 1996; Amieva and El-Omar 2008). In some ways, *H. pylori* behave like commensal bacteria and not pathogens. However, this bacterium has evolved to successfully colonize the hostile environment of the human stomach in the face of a constant innate and adaptive immune response. Although most infected people do not develop disease, three main gastric phenotypes have been identified. The most common, a "benign gastritis" phenotype, is seen in asymptomatic subjects, who on the whole do not develop serious gastrointestinal disease. The second, a "duodenal ulcer" phenotype, accounts for up to 15% of infected subjects. The third, a "gastric cancer" phenotype, is more serious and affects ~1% of infected subjects as a result of a chronic inflammation induced by the infection and increases the risk of gastric cancer (Hunt 1996; Amieva and El-Omar 2008). Most basic research focuses on the diseases that are caused by *H. pylori*, the host factors for disease, and the bacterial virulence determinants. Here, we focus on the bacterial and host factors that contribute to the ability of this pathogen to persist.

Chemotaxis Is Required for Persistence

H. pylori colonize the harsh environment of the human stomach. To survive their journey through the acidic stomach, *H. pylori* generate large quantities of cytosolic and cell surface-associated urease. Urease is an enzyme that breaks down urea to generate ammonia and carbon dioxide and transiently buffers the acidic environment (Merrell et al. 2003; Pflock et al. 2006). Rather than persisting in the lumen of the stomach, *H. pylori* have evolved mechanisms to reach and colonize a very narrow anatomical niche (25–30 μm) near the surface of the epithelial cells (Schreiber et al. 2004). The ability to reach this niche is dependent on sensing pH gradients and chemotaxis away from low pH (Ottemann and Lowenthal 2002; Schreiber et al. 2004, 2005; Croxen et al. 2006). Mutant *H. pylori* that are defective for sensing low pH and chemotaxis are defective in their ability to colonize the stomachs of mice (Howitt et al. 2011; Lertsethtakarn et al. 2011). For example, CheW, CheA, CheY, and ChePep *H. pylori* mutants are defective for colonizing the mouse stomach when in competition with wild-type *H. pylori* (Terry et al. 2005; Williams et al. 2007; Howitt et al. 2011). Recent results with the ChePep-deficient *H. pylori* mutant in a mouse model suggest that chemotaxis is essential for colonizing the glands of the antrum of stomachs (Fig. 1). Both wild-type and ΔChePep strains colonize the mucus layer overlying the stomach surface. In contrast, the ΔChePep mutant is not found in the glandular region (Howitt et al. 2011). Taken together, these results indicate that chemotaxis is important in allowing the bacteria to colonize a specialized niche and in locating or persisting within the mid-glands. This tropism for the mid-glandular zone is intriguing because the gastric progenitor cells are known to reside in this region and a direct association with *H. pylori* and gastric progenitor cells could be related to the increased gastric cancer associated with *H. pylori* infection (Uemura et al. 2001; Qiao et al. 2007).

Life on the Surface of Gastric Epithelial Cells

Once the bacteria reach the microenvironment of the epithelial lining, they survive as two major populations: one that is free-swimming in the mucus gel and a second population (~20%) found directly adhered to the epithelial surface via multiple adhesins (Hessey et al. 1990; Ilver et al. 1998; Mahdavi et al. 2002). The more virulent strains of *H. pylori* have contact-dependent mechanisms to interact with and modify epithelial cells, including a type IV secretion system that injects the virulence factor CagA into host cells (Segal et al. 1999; Asahi et al. 2000; Backert et al. 2000; Odenbreit et al. 2000; Stein et al. 2000). CagA has multiple effects on epithelial cells, including the ability to modify apical junctions and perturb cell polarity (Amieva et al. 2003; Bagnoli et al. 2005; Murata-Kamiya et al. 2007; Saadat et al. 2007; Zeaiter et al. 2008). CagA affects multiple host cell signaling pathways, which are the subject of many reviews. However, the functions of CagA that benefit the bacteria have only recently been described

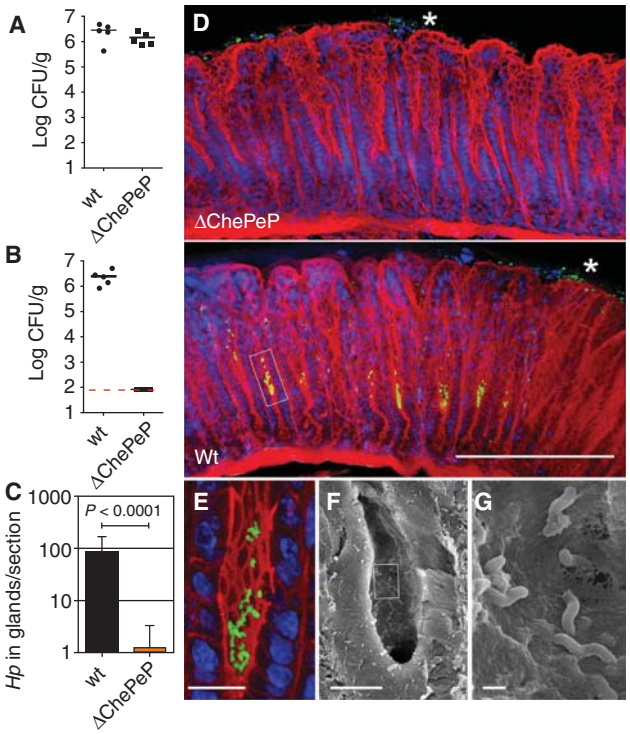

Figure 1. Chemotaxis is essential for *H. pylori* colonization of the antral gastric glands and colonization of the mouse stomach. (*A*) Colony-forming units (CFU) of *H. pylori* in the stomachs of mice colonized with either the wild-type or ΔChePep mutant for 2 weeks. Each marker represents an individual mouse. (*B*) CFU counts from the mice coinfected with both the wild-type and ΔChePep mutant in a 1:1 ratio for 2 weeks. The dashed line indicates the limit of detection. $P < 0.0001$. (*C*) Volumetric analysis of bacteria colonizing the antral glands calculated from 100-μm-thick sections imaged by three-dimensional (3D) confocal microscopy from single infections of either the wild-type or ΔChePep mutant. (*D*) 3D confocal microscopy of murine stomachs infected with either wild-type or ΔChePep mutant. F-actin is stained with phalloidin (red) and nuclei (blue), and *H. pylori* cells (green) are immunolabeled. Asterisks indicate *H. pylori* cells in the surface mucus of the stomach, whereas a box highlights bacterial colonies in mid-glands. (*E*) Magnified view of the area boxed in panel *D*. (*F*) Scanning electron microscopy (SEM) of wild-type infected gland. (*G*) Magnified view of area boxed in panel *F*. Scale bars, 100 μm (*D*), 10 μm (*E*) and (*F*), and 2 μm (*G*). *Hp*, *Helicobacter pylori*; wt, wild type.

(Hatakeyama 2004; Peek 2005; Suzuki et al. 2006; Handa et al. 2007; Hatakeyama 2008; Backert et al. 2010, 2011; Murata-Kamiya 2011). Using a polarized epithelium model system, CagA was found to play an important role in enabling *H. pylori* colonization of the epithelium (Tan et al. 2009). This occurs via a local perturbation of epithelial integrity and enables *H. pylori* to grow as microcolonies adhering to the host cell surface even in conditions that do not support growth of free-swimming bacteria (Fig. 2) (Tan et al. 2009). *H. pylori* alter the internalization, intracellular transport, and polarity of the transferrin/transferrin receptor iron uptake system by a mechanism that depends on CagA and another major virulence factor, VacA (Tan et al. 2011). CagA is important in promoting iron acquisition in vivo. This was shown in a Mongolian gerbil model by comparing wild-type and CagA-deficient strains for their ability to colonize gerbils. Although wild-type and CagA-deficient strains of *H. pylori* colonize iron-replete gerbils to the same extent, the *cagA* deletion mutants are markedly impaired in colonizing iron-deficient gerbils (Tan et al. 2011). These findings suggest that *H. pylori*

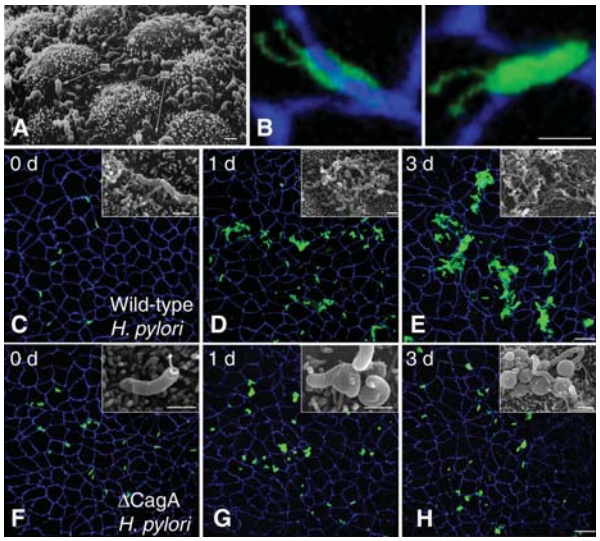

Figure 2. Formation of *H. pylori* microcolonies on the surface of epithelial cells requires CagA. (*A*) SEM of the gastric epithelial cell surface from a prepyloric biopsy from a patient with duodenal ulceration. The dome-shaped surfaces are gastric epithelial cells. Bacteria are located in the junctions or gutters between host cells (Steer 1984). (*B–D*) 3D confocal images of *H. pylori* colonizing the cell surface of polarized MDCK cells in the Transwell system described by Tan et al. (2009). View from below the junctions (*left*) and above the junctions (*right*). Bacteria are visualized with anti-*H. pylori* antibodies (green) and cell junctions are stained blue (anti-ZO-1). (*C*) Wild-type *H. pylori* is tightly adhering to junctions between epithelial cells. Scale bar, 1 μm. (*C–E*) Low-magnification 3D confocal images of wild-type *H. pylori* forming microcolonies on epithelial cells. Scale bar, 10 μm. *Insets* show replicating wild type as visualized by SEM. Scale bar, 1 μm. (*F–H*) Low-magnification 3D confocal images of *ΔcagA H. pylori* colonizing the surface of epithelial cells. Scale bar, 10 μm. *Insets* show CagA mutant colony morphology as visualized by SEM. Scale bar, 1 μm.

have evolved multiple mechanisms to manipulate the epithelium to acquire micronutrients (e.g., iron) from host cells and to grow on the cell surface.

Immune Evasion Strategies

The immunomodulatory effects of VacA and CagA and some of the *H. pylori* adhesins have been reviewed elsewhere (Monack et al. 2004b; Backert and Clyne 2011; Backert et al. 2011; Murata-Kamiya 2011; Tegtmeyer et al. 2011). In addition, a number of *H. pylori* factors have evolved to reduce recognition by the innate immune system. For example, *H. pylori* make flagellin molecules that are not recognized by TLR5 (Gewirtz et al. 2004). The mutations in *H. pylori* flagellin lead to evasion map to the TLR5 recognition domain, amino acids 89–96 of the amino-terminal D1 domain of flagellin (Andersen-Nissen et al. 2005). Mutations in these residues destroy motility in *Salmonella*. However, *H. pylori* and other α and ε Proteobacteria possess compensatory amino acid changes in other regions of the flagellin molecule that then allow them to evade TLR5 recognition and retain motility, a phenotype that is crucial for virulence (Andersen-Nissen et al. 2005).

In addition, *H. pylori* evade signaling through TLR4, which recognizes lipopolysaccharide (LPS). *H. pylori* make an LPS that is 1000 times less pyrogenic and 500-fold less toxic than other Gram-negative enteric bacteria, such as *Salmonella* (Moran 2007). This evasion is thought to be due to underphosphorylation, underacylation, and substitution of long-chain fatty acids in the lipid A moiety of *H. pylori* (Moran 2007). In addition, modifications in the *H. pylori* LPS may act as molecular mimics of human glycans to avoid immune recognition.

H. pylori possess several enzymes that may modify LPS with carbohydrate groups resembling human Lewis blood group antigens (Moran 2008).

Transmission

Although there is a very large population of humans throughout the world that is colonized with *H. pylori*, relatively little is known about how it is transmitted. Epidemiologic studies of *H. pylori* transmission show that the majority of infections tend to occur within families through close person-to-person contact (Falush et al. 2003; Linz et al. 2007). Most transmission occurs in childhood, and maternal-to-child and sibling–sibling transmission seem most likely (McCallion et al. 1996; Bardhan 1997; Kivi et al. 2005; Weyermann et al. 2006). Although viable *H. pylori* have not been isolated from many sources, such as sewage and water sources, *H. pylori* DNA is present, suggesting that they are a source of infective *H. pylori* (Brown 2000). However, it seems more likely that transmission occurs in situations in which gastric content can be transferred quickly from person to person. For example, gastric-oral transmission is suggested in association with gastroenteritis with vomiting (Brown 2000). Fecal–oral transmission may also be possible. Thus far, the contribution of specific *H. pylori* factors in transmission have not been studied or identified.

PERSISTENT *SALMONELLA* INFECTIONS

Salmonella enterica is a pathogenic bacterial species that is an important cause of disease in humans ranging from gastroenteritis to systemic infections (Monack et al. 2004b). Host-adapted *Salmonella* serovars disseminate from the gastrointestinal tract and colonize systemic sites. For example, *S. enterica* serovar Typhi (*S.* Typhi) causes human typhoid fever, whereas *S. enterica* serovar Typhimurium (*S.* Typhimurium) has a broad host range, causing disease in a variety of animals. Strains of *S.* Typhimurium cause a typhoid-like disease in mice and usually cause a self-limiting gastroenteritis in healthy human adults. However, *S.* Typhimurium can cause systemic infections in humans (Kariuki et al. 2006; Gordon et al. 2008; Dhanoa and Fatt 2009; Sigauque et al. 2009; Yen et al. 2009). Indeed, recent cases of invasive and recurrent infections in Malawi, Mozambique, Malaysia, and Taiwan were caused by nontyphoidal Salmonella (NTS), which were largely comprised of multidrug-resistant *S.* Typhimurium strains (Kariuki et al. 2006; Gordon et al. 2008; Dhanoa and Fatt 2009; Sigauque et al. 2009; Yen et al. 2009).

S. Typhi and *S. enterica* serovar Paratyphi (*S.* Paratyphi) are important human pathogens of immense concern to the public health (Parry et al. 2002). They are endemic in regions of the world where drinking water quality and sewage-treatment facilities are poor (Parry et al. 2002; Monack et al. 2004b). Chronically infected humans are the reservoirs for the spread of infection and disease.

Salmonella enters the host through the gastrointestinal tract and translocates by multiple mechanisms to deeper tissues (Kohbata et al. 1986; Jones et al. 1994; Vazquez-Torres et al. 1999). In order for the infection to extend beyond the intestinal mucosa, *Salmonella* must survive and replicate in macrophages, a privileged niche that allows *Salmonella* to elude the adaptive immune response (Jones and Falkow 1996; Cirillo et al. 1998; Deiwick et al. 1998; Hensel et al. 1998; Cheminay et al. 2005; Tobar et al. 2006; Halici et al. 2008; Haraga et al. 2008). A significant percentage (1%–6%) of typhoid patients become chronic carriers of *S.* Typhi, as do many people who have never had a clinical history of typhoid fever (Levine et al. 1982; Monack et al. 2004b). These individuals serve as a reservoir of infections as the bacteria are periodically shed and transmitted to new hosts (Vogelsang and Boe 1948).

What is the immune state of human typhoid carriers? Optimal operation of IL-22- and IFN-γ-dependent immunity and T-cell function appear to be essential for the eradication of *Salmonella* from reservoirs within the reticuloendothelial system (Mastroeni and Menager 2003; Dougan et al. 2011). However, the human carrier state could be associated with an incapacity to develop an effective immune response

(Thompson et al. 2009), although further studies of typhoid patients are needed to confirm this observation. Chronic carriers likely have genetic or other more transient or stochastic differences (e.g., disruption of indigenous intestinal microbiota) that predispose them to an immune state that allows for the establishment of this "equilibrated" state. This response can be efficient enough to survive the acute peak of infection, but too weak to allow eradication of the bacteria from the host.

Mechanisms of *S.* Typhi Evasion of Innate Immunity and Persistence in the Gallbladder

There are several strategies that *S.* Typhi use to evade detection by the host innate immune system (Tsolis et al. 2008). Genome sequencing revealed a unique region in the *S.* Typhi genome-designated *Salmonella* pathogenicity island 7 (SPI-7) (Baker and Dougan 2007). SPI-7 encodes functions for the production and export of the Vi-capsular polysaccharide antigen. The Vi capsule is expressed during infections of humans with *S.* Typhi and appears to be important for pathogenesis in humans and cultured human colonic epithelial cells (Tran et al. 2010). The Vi-antigen plays a role in evading detection of *S.* Typhi by Toll-like receptor 4, perhaps by "masking" detection of lipopolysaccharide (Wilson et al. 2008). In addition, they have shown that TviA, a SPI-7-encoded regulatory protein that controls Vi expression, flagellar motility, and the invasion-associated type 3 secretion system (T3SS) on SPI-1, is essential for the appropriate timing of virulence factor expression in the gastrointestinal tract (Wilson et al. 2008; Winter et al. 2009). Indeed, their findings suggest that TviA-mediated repression of flagellin expression helps *S.* Typhi avoid detection by host TLR5 (Winter et al. 2008).

Chronic infections with *S.* Typhi are classically associated with long-term excretion of bacteria and localization in the gallbladder (Young et al. 2002). Although humans who carry *Salmonella* chronically often have biliary tract disease, this condition is not an absolute requirement for development of the carrier state (Dinbar et al. 1969; Levine et al. 1982; Monack et al. 2004b). There is a strong correlation with the presence of gallstones and conversion to the chronic carrier state in a study conducted in typhoid-endemic Mexico City (Crawford et al. 2010; Gonzalez-Escobedo et al. 2011). The bile, a lipid-rich, detergent-like digestive secretion with antimicrobial properties present in the gallbladder induces the production of an exopolysaccharide matrix O-antigen that facilitates *S.* Typhi biofilm formation on human gallstones (Crawford et al. 2008; Hall-Stoodley and Stoodley 2009). Gallstone biofilms may promote carriage of this bacterial pathogen in the gallbladder and may lead to reseeding of the intestine, fecal shedding, and transmission to a new host. Indeed, mice fed a lithogenic diet developed cholesterol gallstones that supported biofilm formation during persistent *S.* Typhimurium infection and, as a result, showed enhanced fecal shedding and enhanced colonization of the gallbladder and bile (Crawford et al. 2010).

S. TYPHIMURIUM PERSISTENCE IN MICE

To study the basic aspects of host-pathogen interactions during the carrier state, models of long-term chronic *S.* Typhimurium infection in mice have been established. The genetic background of the mouse strain plays a pivotal role in determining *Salmonella* persistence (Hormaeche 1979). Nramp1 is a genetic locus originally identified as being a critical factor in host defense against intracellular pathogens including *Leishmania*, *Mycobacteria*, and *Salmonella* (Vidal et al. 1993). The *Nramp1* gene codes for an ion transporter and is expressed primarily in macrophages and dendritic cells (DC) (Vidal et al. 1993; Govoni et al. 1995). Commonly used mouse strains such as C57BL/6 carry two-point mutations resulting in increased susceptibility to intracellular pathogens. As a result, chronic infection models in C57BL/6 mice require attenuated *Salmonella* strains. Virulent *S.* Typhimurium strains cause a persistent infection in $Nramp1^{wt/wt}$ mice or their F1 hybrids (Monack et al. 2004a; Johanns et al. 2010). Oral inoculation of up to 10^8 CFU results in a persistent infection in which bacteria can be found within macrophages in the mesenteric lymph nodes up

to 1 year postinoculation (Fig. 3) (Monack et al. 2004a).

S. Typhimurium persist within macrophages in the reticuloendothelial system. The metabolic state of these persisting bacteria is not known. However, results of a recent study conducted in bone marrow-derived macrophages and splenocytes from susceptible mice indicate that many intracellular bacteria do not replicate, but appear to enter a dormant-like state (Helaine et al. 2010). In addition, *S.* Typhimurium survival and replication in hemophagocytic macrophages may help establish persistent infection (Nix et al. 2007).

The *Salmonella* factors that contribute to virulence have been extensively studied and reviewed elsewhere (Haraga et al. 2008; Ibarra and Steele-Mortimer 2009; McGhie et al. 2009; Valdez et al. 2009). However, it is unclear which of these or other bacterial factors are required specifically for persistent *Salmonella* infection. Much effort has been concentrated on the secreted effector proteins that depend on the type III secretion systems encoded by *Salmonella* pathogenicity islands 1 and 2 (SPI1 and SPI2, respectively). Yet, the extent to which these pathogenicity islands actually contribute to persistent infection remains uncertain. Clearly, a variety of *Salmonella* factors that are independent of SPI1 and SPI2 also play significant roles in persistent infection. Therefore, I will discuss both SPI1- and SPI2-dependent and -independent factors that have been reported to play a role during the persistent phase of *Salmonella* infection. Because much of the work investigating persistent *Salmonella* infection has used *S.* Typhimurium, this section of the review will concentrate on the bacterial factors from this serovar.

SPI1 and SPI2

The pathogenicity islands SPI1 and SPI2 encode two distinct type III secretion systems. Each translocates a specific group of bacterial effector proteins into host cells. SPI1-dependent translocation of bacterial invasion factors into host epithelial cells enables *S.* Typhimurium to penetrate the small intestines and Peyer's patches (Galan 2001), accomplishing an initial step of *S.* Typhimurium-dissemination from the gastrointestinal tract to host systemic sites (including the MLN, spleen, liver, and bone marrow). To search for *Salmonella* factors that contribute to later stages of infection (persistent infection), a negative-selection screen was undertaken using a transposon-mutagenized library of *S.* Typhimurium and the *Nramp1*^{r} wild-type mouse strain 129X1/SvJ (Lawley et al. 2006). Although the mice were inoculated intraperitoneally instead of orogastrically (a route that bypasses the significant bottleneck that occurs during dis-

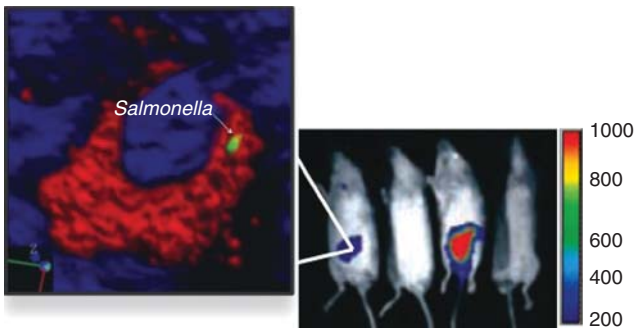

Figure 3. *S.* Typhimurium persist in macrophages within the mesenteric lymph nodes (MLN) of 129Sv mice. 129Sv mice were inoculated by oral administration of the bioluminescent labeled wild-type *S.* Typhimurium strain, SL1344*hha*::Tn5*lux* at a dose of 10^8 CFU and monitored for more than 80 days (Monack et al. 2004a). Light intensity is represented by a color scale in counts. *S.* Typhimurium (labeled with anti-*S.* Typhimurium antibodies in green) persist in the MLN and are found in macrophages (labeled with antimacrophage antibody, MOMA-2 in red). Nuclei are stained with a DNA dye, ToTo3, in blue.

semination from the gastrointestinal tract to systemic sites [Meynell 1957; Meynell and Stocker 1957; Mecsas et al. 2001]), the screen revealed that SPI1 was necessary to sustain a persistent infection for at least 1 month post-infection (Lawley et al. 2006). The SPI1 genes confirmed to be required for persistent infection in this study included the invasion and translocation effectors SipB, SipC, and SipD; however, it is possible that additional SPI1 effectors also could contribute to persistent infection. In light of the fact that *S.* Typhimurium is extruded from dying cells in the epithelia throughout an infection (Knodler et al. 2010), it is likely that the ability of *S.* Typhimurium to continuously reinvade epithelial tissues is necessary to sustain a persistent infection. In support of this notion, SPI1 is also required for a persistently infected mouse to transmit *S.* Typhimurium to naïve cage-mates (Lawley et al. 2008).

S. Typhimurium Modulates Host Cell Migration: A Trait that Mediates Persistent Infection

In addition to identifying SPI-1, this same negative-selection screen in mice identified many SPI-2 genes (Lawley et al. 2006). Although most SPI-2 genes were required for initial colonization of the spleen, the SPI-2 effector SseI did not emerge from the screen until 2 weeks post-infection, indicating that SseI plays a role in long-term carriage. SseI is a secreted effector that is expressed by intracellular *Salmonella* and translocated across the vacuolar membrane into the host cell cytosol via the SPI-2-encoded T3SS (Miao and Miller 2000). In a subsequent study, it was shown that SseI is required for maintaining a long-term systemic infection in mice by modulating normal cell migration of primary macrophages and DC (McLaughlin et al. 2009). The ability to inhibit migration requires the host factor IQ-motif-containing GTPase-activating protein 1 (IQGAP1), an important regulator of host cell migration. SseI binds directly to IQGAP1 and colocalizes with this factor at the cell periphery. Furthermore, *S.* Typhimurium inhibits DC, which are potent antigen-presenting cells that are vital to activating T-cell migration toward CCL19. Although the exact mechanism by which SseI modulates migration is still not clear, it seems to play a role in subverting the onset of adaptive immunity as spleens from mice infected with the *sseI* mutant contained more DC and $CD4^+$ T-lymphocytes compared to mice infected with wild-type *S.* Typhimurium (McLaughlin et al. 2009). It should be noted that *S.* Typhi and NTS isolates do not contain *sseI*. In addition, there are *sseI*-independent mechanisms by which *S.* Typhimurium modulates DC migration in vivo (McLaughlin et al. 2009). Future studies are needed to identify additional novel "migration modulation" factors in *Salmonella*.

In addition, it is important to note that *sseI* is a pseudogene in *S.* Typhi. The molecular bases for *S.* Typhi's host restriction and unique pathogenic attributes are just beginning to be understood, but they are believed to be the result of a combination of genome degradation and the acquisition of new genetic information (Retamal et al. 2010; Sabbagh et al. 2010; Trombert et al. 2011; Spano and Galan 2012; Song et al. 2013). For example, the proteolytic targeting of a host GTPase, Rab29, by an effector protein, GtgE, that is present in *S.* Typhimurium and not *S.* Typhi distinguishes the intracellular compartments of human-adapted Typhi and the broad-host *S.* Typhimurium (Spano and Galan 2012). Several functional studies indicate that *S.* Typhi pseudogenes contribute to its adaptation to humans (Retamal et al. 2010; Trombert et al. 2011). Perhaps the role of sseI is similar.

The Role of $Foxp3^+$ Regulatory T cells in *Salmonella* Persistence

The pathological damage that results from continued macrophage activation will, at some stage of the infection, outweigh the immediate risk that is posed by the residual, persisting *Salmonella*, and the immune response likely turns itself off, allowing bacterial persistence. Regulatory T cells (Tregs) have been implicated in playing a critical role in sustaining this balance in many infections. The role of Tregs during *Salmonella* persistence was recently investigated in a mouse model of persistence (Johanns et al. 2010). The

role of Tregs during chronic infection with *Leishmania major*, viruses, *Mycobacterium tuberculosis*, *Schistosoma mansoni*, and *Plasmodium berghei* has been characterized (Long et al. 2003; Suvas et al. 2003; Hesse et al. 2004; Hisaeda et al. 2004; Suvas et al. 2004). Interestingly, these studies suggest that Treg-mediated immune suppression can provide both detrimental and protective roles in host defense against these pathogens (Uzonna et al. 2001; Suvas et al. 2003; Hesse et al. 2004; Mendez et al. 2004). Johanns et al. show that early after infection with *S.* Typhimurium, when the bacterial burden is progressively increasing, the activation of protective immune components is delayed, and this coincides with increased Treg cell suppressive potency (Johanns et al. 2010). In contrast, later during infection, when reductions in bacterial burden occur, protective immune components are highly activated and Treg cell suppressive potency is reduced (Johanns et al. 2010). They also found that when Tregs were ablated early after infection, when their suppressive potency is increased, there was an accelerated bacterial eradication. This study suggests that Tregs control the early stages of setting up a persistent *Salmonella* infection.

Salmonella Factors Required for Intestinal Persistence

Sustained colonization of the gastrointestinal tract is another important aspect of persistent *Salmonella* infection because it is necessary for live bacteria to be passed in the feces and eventually transmitted to other potential hosts (Lawley et al. 2008). Using the CBA mouse strain (*Nramp*^{r}, *S.* Typhimurium-resistant), several *Salmonella* adherence factors were shown to be important for intestinal persistence of *S.* Typhimurium. The fibronectin-binding factors, ShdA and MisL, contribute significantly to persistence in the gastrointestinal tract and fecal shedding of live bacteria (Kingsley et al. 2000, 2002a,b, 2004; Dorsey et al. 2005). In addition, several fimbrial operons (encoding outer surface structures with possible adhesive functions), including *lpf*, *bcf*, *stb*, *stc*, *std*, and *sth*, are also required for long-term intestinal carriage and fecal shedding (Weening et al. 2005). In the *Salmonella* persistence screen described above, several genes from these operons were negatively selected, including *stcC*, *stcD*, *sthA*, *bcfD*, *stbD*, and *stdA*, indicating a link between intestinal persistence and systemic persistence (Lawley et al. 2006). For example, the antivirulence modulator ZirTS is expressed only by *S.* Typhimurium colonizing the gastrointestinal tract (as well as in the feces of persistently infected mice), and such expression negatively impacts systemic colonization in *Nramp1*^{r} mice (Gal-Mor et al. 2008). How ZirTS expression affects systemic persistence requires further investigation.

S. Typhimurium factors that protect against host-derived antimicrobial peptides also contribute to persistent *Salmonella* infection. For example, it was recently shown that several *Salmonella* factors are required for *S.* Typhimurium carriage in the intestines of *Caenorhabditis elegans*, including SPI-2, pSLT (virulence plasmid), PhoPQ (a sensor/kinase system that senses antimicrobial peptides (Bader et al. 2005), acidic pH (Bearson et al. 1998), and changes in metal cation concentration (Groisman et al. 1997; Alegado and Tan 2008). The PhoPQ regulon encompasses genes that protect against antimicrobial peptides such as polymixin B, C18G, and CRAMP, such as *pgtE* and *mig-14* (Guina et al. 2000; Brodsky et al. 2005; Alegado and Tan 2008). PgtE, a modifier of the bacterial outer surface membrane, was also identified in one of the *Salmonella* persistence screens performed by Lawley et al. (2006) Mig-14, along with several other *Salmonella* factors providing resistance toward antimicrobial peptides (VirK, RcsC, and YdeI) also contribute to persistent *Salmonella* infection (Detweiler et al. 2003; Erickson and Detweiler 2006). These results show that *Salmonella* resistance toward antimicrobial peptides of the host immune response is critical for *Salmonella* to maintain persistent infection in systemic sites.

Transmission

Host-to-host transmission of a pathogen ensures its successful propagation and maintenance within a host population. Although this

is an essential stage of a pathogen's life cycle, very little is known at a molecular level about this aspect of infection (Lipsitch and Moxon 1997; Ebert and Bull 2003). Transmission is a complex process involving components of both the pathogen and the host (Fig. 4). For example, *Salmonella* must contend with the indigenous microbiota, the host innate immune system, and the establishment of a replicative niche. *Salmonella* must also facilitate exit and spread to other hosts and finally, successfully colonize and multiply within a new host, thus repeating the cycle.

Understanding the host factors that affect *S.* Typhimurium colonization of the gut is very important for controlling persistence and transmission. Some host factors have been identified (Mastroeni and Grant 2011). For example, B cells and innate secretory antibodies contribute to control the spread of *Salmonella* beyond the gut (Mittrucker et al. 2000). $IgM^{-/-}$ mice have lower LD_{50} after oral infection and $Pigr^{-/-}$, which are unable to bind and actively transport dimeric IgA and pentameric IgM to mucosae, are more susceptible (Wijburg et al. 2006). In addition, the indigenous microbiota plays an important role in protecting the gut from colonization by pathogens by multiple mechanisms (Stecher and Hardt 2011). On the other hand, *Salmonella* has evolved multiple ways to survive in the gut. For example, *S.* Typhimurium requires intestinal inflammation to grow in the gut by using its virulence factors to invade the intestinal epithelium and survive in mucosal macrophages (Stecher et al. 2007; Barman et al. 2008; Lawley et al. 2008). In addition, Winter et al. has shown recently that reactive oxygen species generated during inflammation react with endogenous, luminal sulphur compounds (thiosulphate) to form a new respiratory electron acceptor, tetrathionate (Winter et al. 2010). The genes encoded by the *ttrSR ttrBCA* gene cluster confer the ability to use tetrathionate as an electron acceptor, thus providing a growth advantage for *S.* Typhimurium over the competing microbiota in the lumen of the inflamed gut (Bäumler and Fang 2013). In addition, fimbrial and autotransporter adhesins mediate persistence in the gut (Kingsley et al. 2000, 2002a,b, 2004; Humphries et al. 2001; Wagner and Hensel 2011) and possibly other tissues (Lawley et al. 2006).

Once *Salmonella* has colonized the gut, what are the factors that govern transmission? Using a natural model of persistently infected mice, it was found that a subset of the infected mice (~30%), termed supershedders, shed high levels ($>10^8$ CFU/g) of *S.* Typhimurium in their feces and, as a result, rapidly transmit infection (Lawley et al. 2008). Although most of the infected mice show signs of intestinal inflammation, only supershedder mice develop colitis. It was shown that development of the supershedder phenotype depends on the virulence determinants SPI-1 and -2, and it is characterized by mucosal invasion and, importantly, high luminal abundance of *S.* Typhimurium in the colon. In addition, the treatment of mice with antibiotics that alter the indigenous intestinal microbiota rapidly induces the supershedder phenotype and leads to rapid transmission to naïve hosts. Importantly, a single dose of an antibiotic given to chronically infected mice (125 days postinfection) reactivated the supershedder phenotype in mice that were not shedding detectable levels of *S.* Typhimurium, demonstrating that the intestinal microbiota has a role in controlling persistent disease (Lawley et al. 2008). Although, this model has established laboratory conditions that ensure that animals exposed to *S.* Typhimurium become supershedders, it is still not understood what circumstances dictate whether animals with identical genes and exposed to the identical inoculum become persistently infected and shed at low or moderate levels or become supershedders with significant pathology. Future studies are required to determine whether specific conditions lead to supershedders or whether it is a stochastic event. What determines the creation of a murine version of "Typhoid Mary?"

As mentioned previously, a theory to explain typhoid carriage proposes that bacteria originating from the systemic sites seed the intestinal tract through the gallbladder. Perhaps the bacteria that seed the intestinal tract from the gallbladder are "primed" to express crucial metabolic pathways and transmission factors that help the pathogen outcompete the indigenous

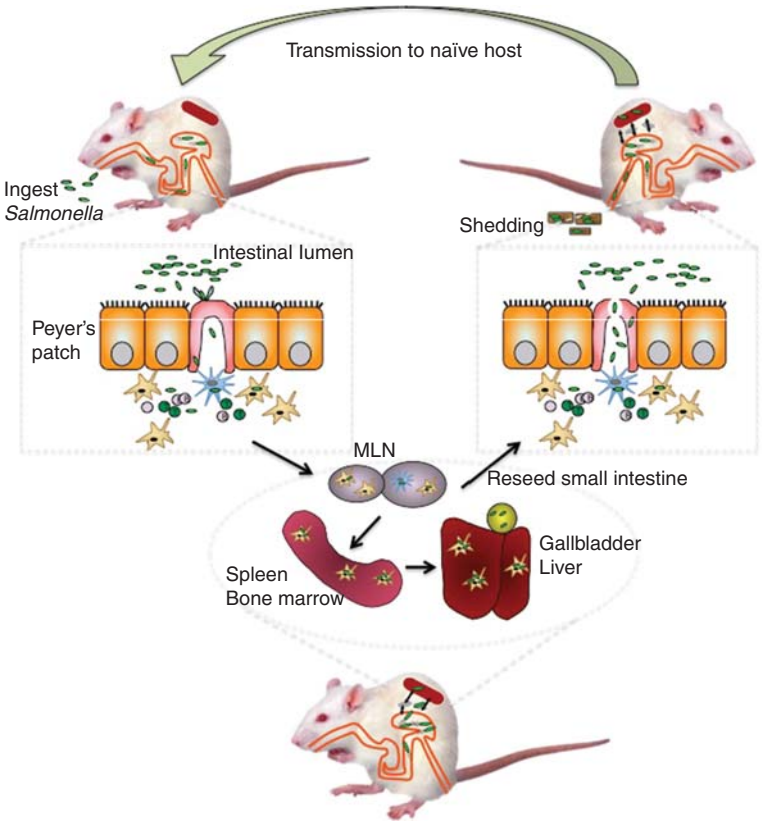

Figure 4. Life cycle of *Salmonella* in mammalian hosts. Bacteria are ingested in contaminated food or water and enter the gastrointestinal tract. *Salmonella* enters the Peyer's patches of the intestinal tract mucosal surface by invading M cells—specialized epithelial cells that take up and transcytose luminal antigens for uptake by phagocytic immune cells. This is followed by inflammation and phagocytosis of bacteria by neutrophils, macrophages, and DC. In systemic salmonellosis, such as typhoid fever, *Salmonella* may target specific types of host cells, such as DC and macrophages that favor dissemination through the lymphatics and bloodstream to the MLNs and deeper tissues. This then leads to transport to the spleen, bone marrow, liver, and gallbladder. Bacteria can persist in the MLNs, bone marrow, and gallbladder for life, and periodic reseeding of the mucosal surface via the bile ducts and/or the lymphatics occur, and shedding can take place from the mucosal surface. Some mice that are infected orally with *S.* Typhimurium develop a supershedder phenotype (~30%). Supershedders shed high levels ($>10^8$ CFU/g) of *S.* Typhimurium in their feces, and as a result, rapidly transmit infection. Some of the factors that influence the supershedder phenotype include: *Salmonella* virulence factors, gut inflammation, indigenous intestinal microbiota, and antibiotic treatment. Factors that influence efficient transmission could include survival in the environment (Foster 1995; Lee et al. 1995; Lin et al. 1995; Spector 1998; Scher et al. 2005; White et al. 2006, 2008). For example, the *Salmonella* rdar (red, dry, and rough) morphotype, a multicellular phenotype characterized by fimbria- and cellulose-mediated colony pattern formation, has been linked to survival in nutrient-limited environments and may enhance *Salmonella* survival outside the host, thereby aiding in transmission between hosts (White et al. 2006, 2008). In addition, there could be additional transmission-specific factors or conditions that aid in efficient transmission, similar to what has been described for *Vibrio cholera* (Merrell et al. 2002). Finally, factors within the naïve host that influence efficient transmission include survival in the acidic conditions of the stomach (Foster 1995), alterations in the indigenous intestinal microbiota that could be induced by alterations in diet (Sonnenburg et al. 2010), immune state (Dhanoa and Fatt 2009), or recent antibiotic treatment (Riley et al. 1984).

intestinal microbiota even in the absence of antibiotic treatment. Certainly, the finding that antibiotic treatment induces the supershedder phenotype has relevance to understanding how antibiotic therapy is a risk factor for the development of salmonellosis (Riley et al. 1984), gastroenteritis associated with antibiotic-resistant *S.* Typhimurium (Glynn et al. 2004), and increased transmission of antibiotic-resistant *S. enterica* in poultry (Bauer-Garland et al. 2006). These findings indicate that alterations in the intestinal microbiota caused by antibiotic use may induce fecal shedding and transmission of enteric pathogens.

MECHANISMS OF INTESTINAL MICROBIOTA CONTROLLING *SALMONELLA* COLONIZATION

The indigenous intestinal microbiota plays an important role in maintaining health (Sekirov et al. 2010). It provides digestive functions, modulates host metabolism, and stimulates development of lymphatic tissue and the mucosal immune system (Rakoff-Nahoum et al. 2004; Mazmanian et al. 2005; Cash et al. 2006). Importantly, it can efficiently limit infection of the gut by pathogenic microbes (Sonnenburg et al. 2010; Salzman 2011). Some of the microbiota-mediated mechanisms of protection include (1) blocking growth of invading pathogen by a mechanism referred to as colonization resistance, (2) priming the host's innate and adaptive immune defenses, and (3) helping eliminate the pathogen from the gut lumen at the end of infection. The role of colonization resistance during *Salmonella* infection has recently been reviewed and could include direct inhibition, nutrient depletion, and stimulation of immune defenses (Stecher and Hardt 2011). In addition to colonization resistance, it has been shown in a model of *Salmonella* diarrhea that the microbiota mediates *S.* Typhimurium clearance from the gut lumen (Endt et al. 2010). It was very nicely shown that the *Salmonella*-elicited secretory IgA (sIgA) prevents disease when the animal is infected with *S.* Typhimurium for a second time. However, sIgA was dispensable for pathogen clearance from the gut. Instead, clearance was mediated by the microbiota, which was necessary and sufficient for terminating long-term fecal shedding. These results have implications for developing diet- or microbiota-based therapies for curing *Salmonella* infections in humans (Sonnenburg et al. 2006, 2010; Bolam and Sonnenburg 2011).

CONCLUDING REMARKS

Bacterial persistence and host-to-host transmission are key phases of a pathogen's life cycle and represent a window when there can be intervention to reduce and control disease. Although we describe some possible mechanisms of *Helicobacter* and *Salmonella* persistence, we actually know very little about how these pathogens survive for long periods of time in the mammalian host in the presence of immunosurveillance. In addition, our current understanding of disease transmission comes largely from retrospective epidemiological analysis and mathematical modeling of infectious disease transmission within natural populations. Future applications of genome-based techniques, including high throughput sequencing analysis of libraries of bacterial mutants, bacterial and host gene expression profiling, and system-wide microbiome analyses, as well as metabolomics, will allow further investigation of the fundamental genetics and immune responses of bacterial persistence and transmission. We believe that an increased understanding of the molecular mechanisms that control host–pathogen interactions could provide new targets to disable persistence and transmission of pathogens with preventative and/or therapeutic interventions.

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