

# *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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D.M. Monack

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.

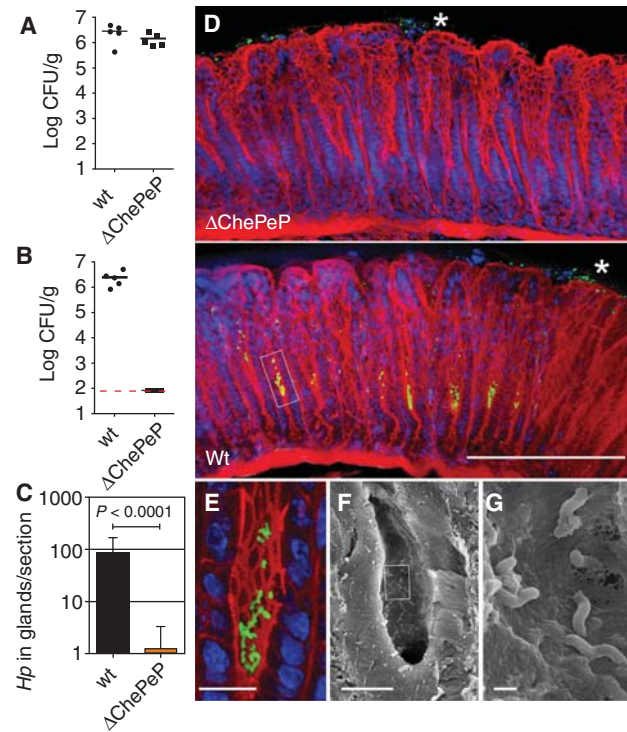
### Chemotaxis Is Required for Persistence

*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  $\mu\text{m}$ ) 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 CheP *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  $\Delta\text{ChePep}$  strains colonize the mucus layer overlying the stomach surface. In contrast, the  $\Delta\text{ChePep}$  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

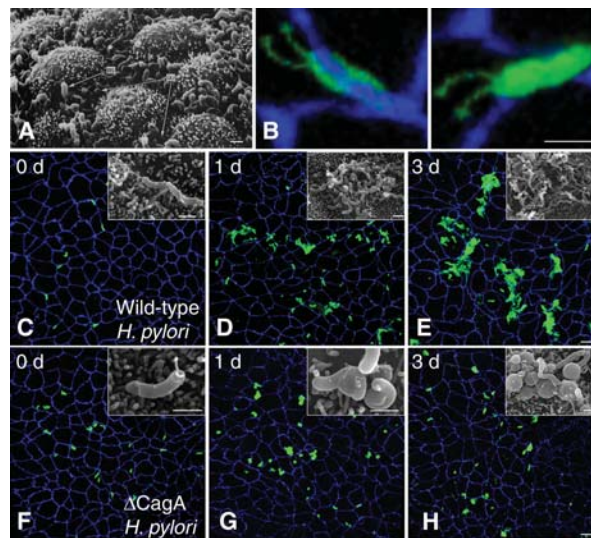


**Figure 1.** Chemotaxis is essential for *H. pylori* colonization of the antral gastric glands and colonization of the mouse stomach. (A) Colony-forming units (CFU) of *H. pylori* in the stomachs of mice colonized with either the wild-type or  $\Delta$ ChePep mutant for 2 weeks. Each marker represents an individual mouse. (B) CFU counts from the mice coinfecting with both the wild-type and  $\Delta$ ChePep 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- $\mu$ m-thick sections imaged by three-dimensional (3D) confocal microscopy from single infections of either the wild-type or  $\Delta$ ChePep mutant. (D) 3D confocal microscopy of murine stomachs infected with either wild-type or  $\Delta$ ChePep 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  $\mu$ m (D), 10  $\mu$ m (E) and (F), and 2  $\mu$ m (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 po-

larity 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*

D.M. Monack



**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  $\mu\text{m}$ . (C–E) Low-magnification 3D confocal images of wild-type *H. pylori* forming microcolonies on epithelial cells. Scale bar, 10  $\mu\text{m}$ . *Insets* show replicating wild type as visualized by SEM. Scale bar, 1  $\mu\text{m}$ . (F–H) Low-magnification 3D confocal images of  $\Delta\text{cagA}$  *H. pylori* colonizing the surface of epithelial cells. Scale bar, 10  $\mu\text{m}$ . *Insets* show CagA mutant colony morphology as visualized by SEM. Scale bar, 1  $\mu\text{m}$ .

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  $\alpha$  and  $\epsilon$  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 sys-

temic 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- $\gamma$ -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

D.M. Monack

(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 reseeded 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*<sup>wt/wt</sup> mice or their F1 hybrids (Monack et al. 2004a; Johanns et al. 2010). Oral inoculation of up to 10<sup>8</sup> 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).

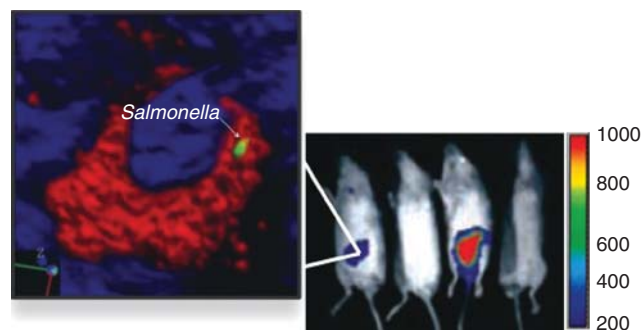
*S. Typhimurium* persist within macrophages in the reticuloendothelial system. The metabolic state of these persisting bacteria is not known. However, results of a recent study conducted in bone marrow-derived macrophages and splenocytes from susceptible mice indicate that many intracellular bacteria 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*<sup>+</sup> 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::Tn5lux* 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.

D.M. Monack



semination from the gastrointestinal tract to systemic sites [Meynell 1957; Meynell and Stocker 1957; Mecasas 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<sup>+</sup> 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<sup>+</sup> 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 (*Nramp1<sup>r</sup>*, *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<sup>r</sup>* 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

D.M. Monack

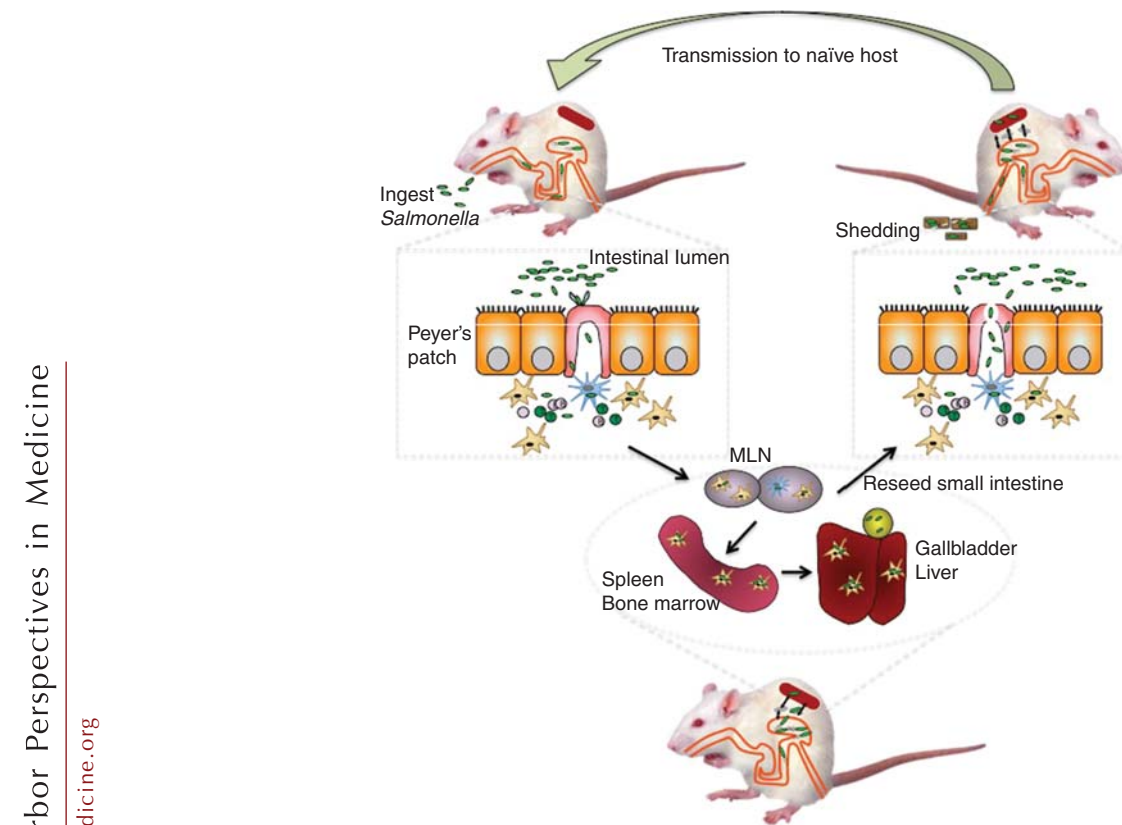
is an essential stage of a pathogen's life cycle, very little is known at a molecular level about this aspect of infection (Lipsitch and Moxon 1997; Ebert and Bull 2003). Transmission is a complex process involving components of both the pathogen and the host (Fig. 4). For example, *Salmonella* must 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*<sup>-/-</sup> mice have lower LD<sub>50</sub> after oral infection and *Pigr*<sup>-/-</sup>, 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<sup>8</sup> 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).

D.M. Monack

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, clear-

ance 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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### REFERENCES

\*Reference is also in this collection.

Alegado RA, Tan MW. 2008. Resistance to antimicrobial peptides contributes to persistence of *Salmonella typhi*-



- murium* in the *C. elegans* intestine. *Cell Microbiol* **10**: 1259–1273.
- Amieva MR, El-Omar EM. 2008. Host–bacterial interactions in *Helicobacter pylori* infection. *Gastroenterology* **134**: 306–323.
- Amieva MR, Vogelmann R, Covacci A, Tompkins LS, Nelson WJ, Falkow S. 2003. Disruption of the epithelial apical-junctional complex by *Helicobacter pylori* CagA. *Science* **300**: 1430–1434.
- Andersen-Nissen E, Smith KD, Strobe KL, Barrett SL, Cookson BT, Logan SM, Aderem A. 2005. Evasion of Toll-like receptor 5 by flagellated bacteria. *Proc Natl Acad Sci* **102**: 9247–9252.
- Asahi M, Azuma T, Ito S, Ito Y, Suto H, Nagai Y, Tsubokawa M, Tohyama Y, Maeda S, Omata M, et al. 2000. *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. *J Exp Med* **191**: 593–602.
- Backert S, Clyne M. 2011. Pathogenesis of *Helicobacter pylori* infection. *Helicobacter* **16**: 19–25.
- Backert S, Ziska E, Brinkmann V, Zimny-Arndt U, Faconnier A, Jungblut PR, Naumann M, Meyer TF. 2000. Translocation of the *Helicobacter pylori* CagA protein in gastric epithelial cells by a type IV secretion apparatus. *Cell Microbiol* **2**: 155–164.
- Backert S, Tegtmeyer N, Selbach M. 2010. The versatility of *Helicobacter pylori* CagA effector protein functions: The master key hypothesis. *Helicobacter* **15**: 163–176.
- Backert S, Clyne M, Tegtmeyer N. 2011. Molecular mechanisms of gastric epithelial cell adhesion and injection of CagA by *Helicobacter pylori*. *Cell Commun Signal* **9**: 28.
- Bader MW, Sanowar S, Daley ME, Schneider AR, Cho U, Xu W, Klevit RE, Le Moual H, Miller SI. 2005. Recognition of antimicrobial peptides by a bacterial sensor kinase. *Cell* **122**: 461–472.
- Bagnoli F, Buti L, Tompkins L, Covacci A, Amieva MR. 2005. *Helicobacter pylori* CagA induces a transition from polarized to invasive phenotypes in MDCK cells. *Proc Natl Acad Sci* **102**: 16339–16344.
- Baker S, Dougan G. 2007. The genome of *Salmonella enterica* serovar Typhi. *Clin Infect Dis* **45**: S29–S33.
- Bardhan PK. 1997. Epidemiological features of *Helicobacter pylori* infection in developing countries. *Clin Infect Dis* **25**: 973–978.
- Barman M, Unold D, Shifley K, Amir E, Hung K, Bos N, Salzman N. 2008. Enteric salmonellosis disrupts the microbial ecology of the murine gastrointestinal tract. *Infect Immun* **76**: 907–915.
- Bauer-Garland J, Frye JG, Gray JT, Berrang ME, Harrison MA, Fedorka-Cray PJ. 2006. Transmission of *Salmonella enterica* serotype Typhimurium in poultry with and without antimicrobial selective pressure. *J Appl Microbiol* **101**: 1301–1308.
- \* Bäumlér A, Fang FC. 2013. Host specificity of bacterial pathogens. *Cold Spring Harb Perspect Med* doi: 10.1101/cshperspect.a010041.
- Bearson BL, Wilson L, Foster JW. 1998. A low pH-inducible, PhoPQ-dependent acid tolerance response protects *Salmonella typhimurium* against inorganic acid stress. *J Bacteriol* **180**: 2409–2417.
- Bolam DN, Sonnenburg JL. 2011. Mechanistic insight into polysaccharide use within the intestinal microbiota. *Gut Microbes* **2**: 86–90.
- Brodsky IE, Ghori N, Falkow S, Monack D. 2005. Mig-14 is an inner membrane-associated protein that promotes *Salmonella typhimurium* resistance to CRAMP survival within activated macrophages and persistent infection. *Mol Microbiol* **55**: 954–972.
- Brown LM. 2000. *Helicobacter pylori*: Epidemiology and routes of transmission. *Epidemiol Rev* **22**: 283–297.
- Cash HL, Whitham CV, Behrendt CL, Hooper LV. 2006. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* **313**: 1126–1130.
- Cheminay C, Mohlenbrink A, Hensel M. 2005. Intracellular *Salmonella* inhibit antigen presentation by dendritic cells. *J Immunol* **174**: 2892–2899.
- Cirillo DM, Valdivia RH, Monack DM, Falkow S. 1998. Macrophage-dependent induction of the *Salmonella* pathogenicity island 2 type III secretion system and its role in intracellular survival. *Mol Microbiol* **30**: 175–188.
- Crawford RW, Gibson DL, Kay WW, Gunn JS. 2008. Identification of a bile-induced exopolysaccharide required for *Salmonella* biofilm formation on gallstone surfaces. *Infect Immun* **76**: 5341–5349.
- Crawford RW, Rosales-Reyes R, Ramirez-Aguilar Mde L, Chapa-Azuela O, Alpuche-Aranda C, Gunn JS. 2010. Gallstones play a significant role in *Salmonella* spp. gallbladder colonization and carriage. *Proc Natl Acad Sci* **107**: 4353–4358.
- Croxen MA, Sisson G, Melano R, Hoffman PS. 2006. The *Helicobacter pylori* chemotaxis receptor TlpB (HP0103) is required for pH taxis and for colonization of the gastric mucosa. *J Bacteriol* **188**: 2656–2665.
- Deiwick J, Nikolaus T, Shea JE, Gleeson C, Holden DW, Hensel M. 1998. Mutations in *Salmonella* pathogenicity island 2 (SPI2) genes affecting transcription of SPI1 genes and resistance to antimicrobial agents. *J Bacteriol* **180**: 4775–4780.
- Detweiler CS, Monack DM, Brodsky IE, Mathew H, Falkow S. 2003. *virK*, *somA* and *rscC* are important for systemic *Salmonella enterica* serovar Typhimurium infection and cationic peptide resistance. *Mol Microbiol* **48**: 385–400.
- Dhanoa A, Fatt QK. 2009. Non-typhoidal *Salmonella* bacteraemia: Epidemiology, clinical characteristics and its association with severe immunosuppression. *Ann Clin Microbiol Antimicrob* **8**: 15.
- Dinbar A, Altmann G, Tulcinsky DB. 1969. The treatment of chronic biliary salmonella carriers. *Am J Med* **47**: 236–242.
- Dorsey CW, Laarakker MC, Humphries AD, Weening EH, Bäumlér AJ. 2005. *Salmonella enterica* serotype Typhimurium MisL is an intestinal colonization factor that binds fibronectin. *Mol Microbiol* **57**: 196–211.
- Dougan G, John V, Palmer S, Mastroeni P. 2011. Immunity to salmonellosis. *Immunol Rev* **240**: 196–210.
- Ebert D, Bull JJ. 2003. Challenging the trade-off model for the evolution of virulence: Is virulence management feasible? *Trends Microbiol* **11**: 15–20.
- Endt K, Stecher B, Chaffron S, Slack E, Tchitchek N, Benecke A, Van Maele L, Sirard JC, Mueller AJ, Heikenwalder M, et al. 2010. The microbiota mediates pathogen clearance

D.M. Monack



- from the gut lumen after non-typhoidal *Salmonella* diarrhea. *PLoS Pathog* **6**: e1001097.
- Erickson KD, Detweiler CS. 2006. The Rcs phosphorelay system is specific to enteric pathogens/commensals and activates ydeI, a gene important for persistent *Salmonella* infection of mice. *Mol Microbiol* **62**: 883–894.
- Falush D, Wirth T, Linz B, Pritchard JK, Stephens M, Kidd M, Blaser MJ, Graham DY, Vacher S, Perez-Perez GI, et al. 2003. Traces of human migrations in *Helicobacter pylori* populations. *Science* **299**: 1582–1585.
- Foster JW. 1995. Low pH adaptation and the acid tolerance response of *Salmonella typhimurium*. *Crit Rev Microbiol* **21**: 215–237.
- Galan JE. 2001. *Salmonella* interactions with host cells: Type III secretion at work. *Annu Rev Cell Dev Biol* **17**: 53–86.
- Gal-Mor O, Gibson DL, Baluta D, Vallance BA, Finlay BB. 2008. A novel secretion pathway of *Salmonella enterica* acts as an antivirulence modulator during salmonellosis. *PLoS Pathog* **4**: e1000036.
- Gewirtz AT, Yu Y, Krishna US, Israel DA, Lyons SL, Peek RM Jr. 2004. *Helicobacter pylori* flagellin evades toll-like receptor 5-mediated innate immunity. *J Infect Dis* **189**: 1914–1920.
- Glynn MK, Reddy V, Hutwagner L, Rabatsky-Ehr T, Shiferaw B, Vugia DJ, Segler S, Bender J, Barrett TJ, Angulo FJ. 2004. Prior antimicrobial agent use increases the risk of sporadic infections with multidrug-resistant *Salmonella enterica* serotype Typhimurium: A FoodNet case-control study, 1996–1997. *Clin Infect Dis* **38**: S227–S236.
- Gonzalez-Escobedo G, Marshall JM, Gunn JS. 2011. Chronic and acute infection of the gall bladder by *Salmonella Typhi*: Understanding the carrier state. *Nat Rev Microbiol* **9**: 9–14.
- Gordon MA, Graham SM, Walsh AL, Wilson L, Phiri A, Molyneux E, Zijlstra EE, Heyderman RS, Hart CA, Molyneux ME. 2008. Epidemics of invasive *Salmonella enterica* serovar enteritidis and *S. enterica* serovar Typhimurium infection associated with multidrug resistance among adults and children in Malawi. *Clin Infect Dis* **46**: 963–969.
- Govoni G, Vidal S, Cellier M, Lepage P, Malo D, Gros P. 1995. Genomic structure, promoter sequence, and induction of expression of the mouse *Nramp1* gene in macrophages. *Genomics* **27**: 9–19.
- Groisman EA, Kayser J, Soncini FC. 1997. Regulation of polymyxin resistance and adaptation to low-Mg<sup>2+</sup> environments. *J Bacteriol* **179**: 7040–7045.
- Guina T, Yi EC, Wang H, Hackett M, Miller SI. 2000. A PhoP-regulated outer membrane protease of *Salmonella enterica* serovar Typhimurium promotes resistance to  $\alpha$ -helical antimicrobial peptides. *J Bacteriol* **182**: 4077–4086.
- Halici S, Zenk SF, Jantsch J, Hensel M. 2008. Functional analysis of the *Salmonella* pathogenicity island 2-mediated inhibition of antigen presentation in dendritic cells. *Infect Immun* **76**: 4924–4933.
- Hall-Stoodley L, Stoodley P. 2009. Evolving concepts in biofilm infections. *Cell Microbiol* **11**: 1034–1043.
- Handa O, Naito Y, Yoshikawa T. 2007. CagA protein of *Helicobacter pylori*: A hijacker of gastric epithelial cell signaling. *Biochem Pharmacol* **73**: 1697–1702.
- Haraga A, Ohlson MB, Miller SI. 2008. Salmonellae interplay with host cells. *Nat Rev Microbiol* **6**: 53–66.
- Hatakeyama M. 2004. Oncogenic mechanisms of the *Helicobacter pylori* CagA protein. *Nat Rev Cancer* **4**: 688–694.
- Hatakeyama M. 2008. Linking epithelial polarity and carcinogenesis by multitasking *Helicobacter pylori* virulence factor CagA. *Oncogene* **27**: 7047–7054.
- Helaine S, Thompson JA, Watson KG, Liu M, Boyle C, Holden DW. 2010. Dynamics of intracellular bacterial replication at the single cell level. *Proc Natl Acad Sci* **107**: 3746–3751.
- Hensel M, Shea JE, Waterman SR, Mundy R, Nikolaus T, Banks G, Vazquez-Torres A, Gleeson C, Fang FC, Holden DW. 1998. Genes encoding putative effector proteins of the type III secretion system of *Salmonella* pathogenicity island 2 are required for bacterial virulence and proliferation in macrophages. *Mol Microbiol* **30**: 163–174.
- Hesse M, Piccirillo CA, Belkaid Y, Pruffer J, Mentink-Kane M, Leusink M, Cheever AW, Shevach EM, Wynn TA. 2004. The pathogenesis of schistosomiasis is controlled by cooperating IL-10-producing innate effector and regulatory T cells. *J Immunol* **172**: 3157–3166.
- Hessey SJ, Spencer J, Wyatt JJ, Sobala G, Rathbone BJ, Axon AT, Dixon MF. 1990. Bacterial adhesion and disease activity in *Helicobacter* associated chronic gastritis. *Gut* **31**: 134–138.
- Hisaeda H, Maekawa Y, Iwakawa D, Okada H, Himeno K, Kishihara K, Tsukumo S, Yasutomo K. 2004. Escape of malaria parasites from host immunity requires CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells. *Nat Med* **10**: 29–30.
- Hormaeche CE. 1979. Natural resistance to *Salmonella typhimurium* in different inbred mouse strains. *Immunology* **37**: 311–318.
- Howitt MR, Lee JY, Lertsethtakarn P, Vogelmann R, Joubert LM, Ottemann KM, Amieva MR. 2011. ChePep controls *Helicobacter pylori* infection of the gastric glands and chemotaxis in the *Epsilonproteobacteria*. *MBio* **2**: e00098–11.
- Humphries AD, Townsend SM, Kingsley RA, Nicholson TL, Tsolis RM, Bäumlér AJ. 2001. Role of fimbriae as antigens and intestinal colonization factors of *Salmonella* serovars. *FEMS Microbiol Lett* **201**: 121–125.
- Hunt RH. 1996. The role of *Helicobacter pylori* in pathogenesis: The spectrum of clinical outcomes. *Scand J Gastroenterol Suppl* **220**: 3–9.
- Ibarra JA, Steele-Mortimer O. 2009. *Salmonella*—The ultimate insider. *Salmonella* virulence factors that modulate intracellular survival. *Cell Microbiol* **11**: 1579–1586.
- Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, Berg DE, Covacci A, Engstrand L, Boren T. 1998. *Helicobacter pylori* adhesin binding fucosylated histoblood group antigens revealed by retagging. *Science* **279**: 373–377.
- Johanns TM, Ertelt JM, Rowe JH, Way SS. 2010. Regulatory T cell suppressive potency dictates the balance between bacterial proliferation and clearance during persistent *Salmonella* infection. *PLoS Pathog* **6**: e1001043.
- Jones BD, Falkow S. 1996. Salmonellosis: Host immune responses and bacterial virulence determinants. *Annu Rev Immunol* **14**: 533–561.



- Jones BD, Ghori N, Falkow S. 1994. *Salmonella typhimurium* initiates murine infection by penetrating and destroying the specialized epithelial M cells of the Peyer's patches. *J Exp Med* **180**: 15–23.
- Kariuki S, Revathi G, Kariuki N, Kiiru J, Mwituria J, Muyodi J, Githinji JW, Kagendo D, Munyalo A, Hart CA. 2006. Invasive multidrug-resistant non-typhoidal *Salmonella* infections in Africa: Zoonotic or anthroponotic transmission? *J Med Microbiol* **55**: 585–591.
- Kingsley RA, van Amsterdam K, Kramer N, Bäumlner AJ. 2000. The *shdA* gene is restricted to serotypes of *Salmonella enterica* subspecies I and contributes to efficient and prolonged fecal shedding. *Infect Immun* **68**: 2720–2727.
- Kingsley RA, Santos RL, Keestra AM, Adams LG, Bäumlner AJ. 2002a. *Salmonella enterica* serotype Typhimurium ShdA is an outer membrane fibronectin-binding protein that is expressed in the intestine. *Mol Microbiol* **43**: 895–905.
- Kingsley RA, Weening EH, Keestra AM, Bäumlner AJ. 2002b. Population heterogeneity of *Salmonella enterica* serotype Typhimurium resulting from phase variation of the *lpf* operon in vitro and in vivo. *J Bacteriol* **184**: 2352–2359.
- Kingsley RA, Abi Ghanem D, Puebla-Osorio N, Keestra AM, Berghman L, Bäumlner AJ. 2004. Fibronectin binding to the *Salmonella enterica* serotype Typhimurium ShdA autotransporter protein is inhibited by a monoclonal antibody recognizing the A3 repeat. *J Bacteriol* **186**: 4931–4939.
- Kivi M, Johansson AL, Reilly M, Tindberg Y. 2005. *Helicobacter pylori* status in family members as risk factors for infection in children. *Epidemiol Infect* **133**: 645–652.
- Knodler LA, Vallance BA, Celli J, Winfree S, Hansen B, Montero M, Steele-Mortimer O. 2010. Dissemination of invasive *Salmonella* via bacterial-induced extrusion of mucosal epithelia. *Proc Natl Acad Sci* **107**: 17733–17738.
- Kohbata S, Yokoyama H, Yabuuchi E. 1986. Cytopathogenic effect of *Salmonella typhi* GIFU 10007 on M cells of murine ileal Peyer's patches in ligated ileal loops: An ultrastructural study. *Microbiol Immunol* **30**: 1225–1237.
- Lawley TD, Chan K, Thompson LJ, Kim CC, Govoni GR, Monack DM. 2006. Genome-wide screen for *Salmonella* genes required for long-term systemic infection of the mouse. *PLoS Pathog* **2**: e11.
- Lawley TD, Bouley DM, Hoy YE, Gerke C, Relman DA, Monack DM. 2008. Host transmission of *Salmonella enterica* serovar Typhimurium is controlled by virulence factors and indigenous intestinal microbiota. *Infect Immun* **76**: 403–416.
- Lee IS, Lin J, Hall HK, Bearson B, Foster JW. 1995. The stationary-phase sigma factor sigma S (RpoS) is required for a sustained acid tolerance response in virulent *Salmonella typhimurium*. *Mol Microbiol* **17**: 155–167.
- Lertsethaktarn P, Ottemann KM, Hendrixson DR. 2011. Motility and chemotaxis in *Campylobacter* and *Helicobacter*. *Annu Rev Microbiol* **65**: 389–410.
- Levine MM, Black RE, Lanata C. 1982. Precise estimation of the numbers of chronic carriers of *Salmonella typhi* in Santiago, Chile, an endemic area. *J Infect Dis* **146**: 724–726.
- Lin J, Lee IS, Frey J, Slonczewski JL, Foster JW. 1995. Comparative analysis of extreme acid survival in *Salmonella typhimurium*, *Shigella flexneri*, and *Escherichia coli*. *J Bacteriol* **177**: 4097–4104.
- Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, Falush D, Stamer C, Prugnolle F, van der Merwe SW, et al. 2007. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* **445**: 915–918.
- Lipsitch M, Moxon ER. 1997. Virulence and transmissibility of pathogens: What is the relationship? *Trends Microbiol* **5**: 31–37.
- Long TT, Nakazawa S, Onizuka S, Huaman MC, Kanbara H. 2003. Influence of CD4<sup>+</sup>CD25<sup>+</sup> T cells on Plasmodium berghei NK65 infection in BALB/c mice. *Int J Parasitol* **33**: 175–183.
- Mahdavi J, Sonden B, Hurtig M, Olfat FO, Forsberg L, Roche N, Angstrom J, Larsson T, Teneberg S, Karlsson KA, et al. 2002. *Helicobacter pylori* Saba adhesin in persistent infection and chronic inflammation. *Science* **297**: 573–578.
- Mastroeni P, Grant AJ. 2011. Spread of *Salmonella enterica* in the body during systemic infection: Unravelling host and pathogen determinants. *Expert Rev Mol Med* **13**: e12.
- Mastroeni P, Menager N. 2003. Development of acquired immunity to *Salmonella*. *J Med Microbiol* **52**: 453–459.
- Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. 2005. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122**: 107–118.
- McCallion WA, Murray LJ, Bailie AG, Dalzell AM, O'Reilly DP, Bamford KB. 1996. *Helicobacter pylori* infection in children: Relation with current household living conditions. *Gut* **39**: 18–21.
- McGhie EJ, Brawn LC, Hume PJ, Humphreys D, Koronakis V. 2009. *Salmonella* takes control: Effector-driven manipulation of the host. *Curr Opin Microbiol* **12**: 117–124.
- McLaughlin LM, Govoni GR, Gerke C, Gopinath S, Peng K, Laidlaw G, Chien YH, Jeong HW, Li Z, Brown MD, et al. 2009. The *Salmonella* SPI2 effector SseI mediates long-term systemic infection by modulating host cell migration. *PLoS Pathog* **5**: e1000671.
- Mecas J, Bilis I, Falkow S. 2001. Identification of attenuated *Yersinia pseudotuberculosis* strains and characterization of an orogastric infection in BALB/c mice on day 5 post-infection by signature-tagged mutagenesis. *Infect Immun* **69**: 2779–2787.
- Mendez S, Reckling SK, Piccirillo CA, Sacks D, Belkaid Y. 2004. Role for CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells in reactivation of persistent leishmaniasis and control of concomitant immunity. *J Exp Med* **200**: 201–210.
- Merrell DS, Butler SM, Qadri F, Dolganov NA, Alam A, Cohen MB, Calderwood SB, Schoolnik GK, Camilli A. 2002. Host-induced epidemic spread of the cholera bacterium. *Nature* **417**: 642–645.
- Merrell DS, Goodrich ML, Otto G, Tompkins LS, Falkow S. 2003. pH-regulated gene expression of the gastric pathogen *Helicobacter pylori*. *Infect Immun* **71**: 3529–3539.
- Meynell GG. 1957. The applicability of the hypothesis of independent action to fatal infections in mice given *Salmonella typhimurium* by mouth. *J Gen Microbiol* **16**: 396–404.
- Meynell GG, Stocker BA. 1957. Some hypotheses on the aetiology of fatal infections in partially resistant hosts

D.M. Monack

- and their application to mice challenged with *Salmonella paratyphi-B* or *Salmonella typhimurium* by intraperitoneal injection. *J Gen Microbiol* **16**: 38–58.
- Miao EA, Miller SI. 2000. A conserved amino acid sequence directing intracellular type III secretion by *Salmonella typhimurium*. *Proc Natl Acad Sci* **97**: 7539–7544.
- Mittrucker HW, Raupach B, Kohler A, Kaufmann SH. 2000. Cutting edge: Role of B lymphocytes in protective immunity against *Salmonella typhimurium* infection. *J Immunol* **164**: 1648–1652.
- Monack DM, Bouley DM, Falkow S. 2004a. *Salmonella typhimurium* persists within macrophages in the mesenteric lymph nodes of chronically infected *Nramp1*<sup>+/+</sup> mice and can be reactivated by IFN- $\gamma$  neutralization. *J Exp Med* **199**: 231–241.
- Monack DM, Mueller A, Falkow S. 2004b. Persistent bacterial infections: The interface of the pathogen and the host immune system. *Nat Rev Microbiol* **2**: 747–765.
- Moran AP. 2007. Lipopolysaccharide in bacterial chronic infection: Insights from *Helicobacter pylori* lipopolysaccharide and lipid A. *Int J Med Microbiol* **297**: 307–319.
- Moran AP. 2008. Relevance of fucosylation and Lewis antigen expression in the bacterial gastroduodenal pathogen *Helicobacter pylori*. *Carbohydr Res* **343**: 1952–1965.
- Murata-Kamiya N. 2011. Pathophysiological functions of the CagA oncoprotein during infection by *Helicobacter pylori*. *Microbes Infect* **13**: 799–807.
- Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, Higashi H, Aburatani H, Akiyama T, Peek RM Jr, Azuma T, et al. 2007. *Helicobacter pylori* CagA interacts with E-cadherin and deregulates the  $\beta$ -catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene* **26**: 4617–4626.
- Nix RN, Altschuler SE, Henson PM, Detweiler CS. 2007. Hemophagocytic macrophages harbor *Salmonella enterica* during persistent infection. *PLoS Pathog* **3**: e193.
- Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. 2000. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. *Science* **287**: 1497–1500.
- Ottmann KM, Lowenthal AC. 2002. *Helicobacter pylori* uses motility for initial colonization and to attain robust infection. *Infect Immun* **70**: 1984–1990.
- Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. 2002. Typhoid fever. *N Engl J Med* **347**: 1770–1782.
- Peek RM Jr. 2005. Orchestration of aberrant epithelial signaling by *Helicobacter pylori* CagA. *Sci STKE* **2005**: pe14.
- Pflock M, Kennard S, Finsterer N, Beier D. 2006. Acid-responsive gene regulation in the human pathogen *Helicobacter pylori*. *J Biotechnol* **126**: 52–60.
- Qiao XT, Ziel JW, McKimpton W, Madison BB, Todisco A, Merchant JL, Samuelson LC, Gumucio DL. 2007. Prospective identification of a multilineage progenitor in murine stomach epithelium. *Gastroenterology* **133**: 1989–1998.
- Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. 2004. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* **118**: 229–241.
- Retamal P, Castillo-Ruiz M, Villagra NA, Morgado J, Mora GC. 2010. Modified intracellular-associated phenotypes in a recombinant *Salmonella* Typhi expressing *S. Typhimurium* SPI-3 sequences. *PLoS ONE* **5**: e9394.
- Riley IW, Cohen ML, Seals JE, Blaser MJ, Birkness KA, Hargrett NT, Martin SM, Feldman RA. 1984. Importance of host factors in human salmonellosis caused by multiresistant strains of *Salmonella*. *J Infect Dis* **149**: 878–883.
- Saadat I, Higashi H, Obuse C, Umeda M, Murata-Kamiya N, Saito Y, Lu H, Ohnishi N, Azuma T, Suzuki A, et al. 2007. *Helicobacter pylori* CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. *Nature* **447**: 330–333.
- Sabbagh SC, Forest CG, Lepage C, Leclerc JM, Daigle F. 2010. So similar, yet so different: Uncovering distinctive features in the genomes of *Salmonella enterica* serovars Typhimurium and Typhi. *FEMS Microbiol Lett* **305**: 1–13.
- Salzman NH. 2011. Microbiota-immune system interaction: An uneasy alliance. *Curr Opin Microbiol* **14**: 99–105.
- Scher K, Romling U, Yaron S. 2005. Effect of heat, acidification, and chlorination on *Salmonella enterica* serovar typhimurium cells in a biofilm formed at the air-liquid interface. *Appl Environ Microbiol* **71**: 1163–1168.
- Schreiber S, Konradt M, Groll C, Scheid P, Hanauer G, Werling HO, Josenhans C, Suerbaum S. 2004. The spatial orientation of *Helicobacter pylori* in the gastric mucus. *Proc Natl Acad Sci* **101**: 5024–5029.
- Schreiber S, Bucker R, Groll C, Azevedo-Vethacke M, Garten D, Scheid P, Friedrich S, Gatermann S, Josenhans C, Suerbaum S. 2005. Rapid loss of motility of *Helicobacter pylori* in the gastric lumen in vivo. *Infect Immun* **73**: 1584–1589.
- Segal ED, Cha J, Lo J, Falkow S, Tompkins LS. 1999. Altered states: Involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. *Proc Natl Acad Sci* **96**: 14559–14564.
- Sekirov I, Russell SL, Antunes LC, Finlay BB. 2010. Gut microbiota in health and disease. *Physiol Rev* **90**: 859–904.
- Sigauque B, Roca A, Mandomando I, Morais L, Quinto L, Sacarlal J, Macete E, Nhamposa T, Machevo S, Aide P, et al. 2009. Community-acquired bacteremia among children admitted to a rural hospital in Mozambique. *Pediatr Infect Dis J* **28**: 108–113.
- Song J, Gao X, Galan JE. 2013. Structure and function of the *Salmonella* Typhi chimaeric A<sub>2</sub>B<sub>5</sub> typhoid toxin. *Nature* **499**: 350–354.
- Sonnenburg JL, Chen CT, Gordon JI. 2006. Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. *PLoS Biol* **4**: e413.
- Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firbank SJ, Bolam DN, Sonnenburg JL. 2010. Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. *Cell* **141**: 1241–1252.
- Spano S, Galan JE. 2012. A Rab32-dependent pathway contributes to *Salmonella* Typhi host restriction. *Science* **338**: 960–963.
- Spector MP. 1998. The starvation-stress response (SSR) of *Salmonella*. *Adv Microb Physiol* **40**: 233–279.





- Stecher B, Hardt WD. 2011. Mechanisms controlling pathogen colonization of the gut. *Curr Opin Microbiol* **14**: 82–91.
- Stecher B, Robbiani R, Walker AW, Westendorf AM, Barthel M, Kremer M, Chaffron S, Macpherson AJ, Buer J, Parkhill J, et al. 2007. *Salmonella enterica* serovar Typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biol* **5**: 2177–2189.
- Steer HW. 1984. Surface morphology of the gastroduodenal mucosa in duodenal ulceration. *Gut* **25**: 1203–1210.
- Stein M, Rappuoli R, Covacci A. 2000. Tyrosine phosphorylation of the *Helicobacter pylori* CagA antigen after cag-driven host cell translocation. *Proc Natl Acad Sci* **97**: 1263–1268.
- Suvas S, Kumaraguru U, Pack CD, Lee S, Rouse BT. 2003. CD4<sup>+</sup>CD25<sup>+</sup> T cells regulate virus-specific primary and memory CD8<sup>+</sup> T cell responses. *J Exp Med* **198**: 889–901.
- Suvas S, Azkur AK, Kim BS, Kumaraguru U, Rouse BT. 2004. CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells control the severity of viral immunoinflammatory lesions. *J Immunol* **172**: 4123–4132.
- Suzuki T, Matsuo K, Sawaki A, Ito H, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, et al. 2006. Systematic review and meta-analysis: Importance of CagA status for successful eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* **24**: 273–280.
- Tan S, Tompkins LS, Amieva MR. 2009. *Helicobacter pylori* usurps cell polarity to turn the cell surface into a replicative niche. *PLoS Pathog* **5**: e1000407.
- Tan S, Noto JM, Romero-Gallo J, Peek RM Jr, Amieva MR. 2011. *Helicobacter pylori* perturbs iron trafficking in the epithelium to grow on the cell surface. *PLoS Pathog* **7**: e1002050.
- Tegtmeier N, Wessler S, Backert S. 2011. Role of the cag-pathogenicity island encoded type IV secretion system in *Helicobacter pylori* pathogenesis. *FEBS J* **278**: 1190–1202.
- Terry K, Williams SM, Connolly L, Ottemann KM. 2005. Chemotaxis plays multiple roles during *Helicobacter pylori* animal infection. *Infect Immun* **73**: 803–811.
- Thompson LJ, Dunstan SJ, Dolecek C, Perkins T, House D, Dougan G, Nguyen TH, Tran TP, Doan CD, Le TP, et al. 2009. Transcriptional response in the peripheral blood of patients infected with *Salmonella enterica* serovar Typhi. *Proc Natl Acad Sci* **106**: 22433–22438.
- Tobar JA, Carreno LJ, Bueno SM, Gonzalez PA, Mora JE, Quezada SA, Kalergis AM. 2006. Virulent *Salmonella enterica* serovar Typhimurium evades adaptive immunity by preventing dendritic cells from activating T cells. *Infect Immun* **74**: 6438–6448.
- Tran QT, Gomez G, Khare S, Lawhon SD, Raffatellu M, Bäumlér AJ, Ajithdoss D, Dhavala S, Adams LG. 2010. The *Salmonella enterica* serotype Typhi Vi capsular antigen is expressed after the bacterium enters the ileal mucosa. *Infect Immun* **78**: 527–535.
- Trombert AN, Rodas PI, Mora GC. 2011. Reduced invasion to human epithelial cell lines of *Salmonella enterica* serovar Typhi carrying *S. Typhimurium* sopD2. *FEMS Microbiol Lett* **322**: 150–156.
- Tsolis RM, Young GM, Solnick JV, Bäumlér AJ. 2008. From bench to bedside: Stealth of enteroinvasive pathogens. *Nat Rev Microbiol* **6**: 883–892.
- Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. 2001. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* **345**: 784–789.
- Uzonna JE, Wei G, Yurkowski D, Bretscher P. 2001. Immune elimination of *Leishmania major* in mice: Implications for immune memory, vaccination, and reactivation disease. *J Immunol* **167**: 6967–6974.
- Valdez Y, Ferreira RB, Finlay BB. 2009. Molecular mechanisms of *Salmonella* virulence and host resistance. *Curr Top Microbiol Immunol* **337**: 93–127.
- Vazquez-Torres A, Jones-Carson J, Bäumlér AJ, Falkow S, Valdivia R, Brown W, Le M, Berggren R, Parks WT, Fang FC. 1999. Extraintestinal dissemination of *Salmonella* by CD18-expressing phagocytes. *Nature* **401**: 804–808.
- Vidal SM, Malo D, Vogan K, Skamene E, Gros P. 1993. Natural resistance to infection with intracellular parasites: Isolation of a candidate for Bcg. *Cell* **73**: 469–485.
- Vogelsang TM, Boe J. 1948. Temporary and chronic carriers of *Salmonella* Typhi and *Salmonella* Paratyphi B. *J Hyg (Lond)* **46**: 252–261.
- Wagner C, Hensel M. 2011. Adhesive mechanisms of *Salmonella enterica*. *Adv Exp Med Biol* **715**: 17–34.
- Weening EH, Barker JD, Laarakker MC, Humphries AD, Tsolis RM, Bäumlér AJ. 2005. The *Salmonella enterica* serotype Typhimurium *lpf*, *bcf*, *stb*, *stc*, *std*, and *sth* fimbrial operons are required for intestinal persistence in mice. *Infect Immun* **73**: 3358–3366.
- Weyermann M, Adler G, Brenner H, Rothenbacher D. 2006. The mother as source of *Helicobacter pylori* infection. *Epidemiology* **17**: 332–334.
- White AP, Gibson DL, Kim W, Kay WW, Surette MG. 2006. Thin aggregative fimbriae and cellulose enhance long-term survival and persistence of *Salmonella*. *J Bacteriol* **188**: 3219–3227.
- White AP, Gibson DL, Grassl GA, Kay WW, Finlay BB, Valance BA, Surette MG. 2008. Aggregation via the red, dry, and rough morphotype is not a virulence adaptation in *Salmonella enterica* serovar Typhimurium. *Infect Immun* **76**: 1048–1058.
- Wijburg OL, Uren TK, Simpfendorfer K, Johansen FE, Brandtzaeg P, Strugnell RA. 2006. Innate secretory antibodies protect against natural *Salmonella* Typhimurium infection. *J Exp Med* **203**: 21–26.
- Williams SM, Chen YT, Andermann TM, Carter JE, McGee DJ, Ottemann KM. 2007. *Helicobacter pylori* chemotaxis modulates inflammation and bacterium-gastric epithelium interactions in infected mice. *Infect Immun* **75**: 3747–3757.
- Wilson RP, Raffatellu M, Chessa D, Winter SE, Tükel C, Bäumlér AJ. 2008. The Vi-capsule prevents Toll-like receptor 4 recognition of *Salmonella*. *Cell Microbiol* **10**: 876–890.
- Winter SE, Raffatellu M, Wilson RP, Rüssmann H, Bäumlér AJ. 2008. The *Salmonella enterica* serotype Typhi regulator TviA reduces interleukin-8 production in intestinal epithelial cells by repressing flagellin secretion. *Cell Microbiol* **10**: 247–261.
- Winter SE, Winter MG, Thiennimitr P, Gerriets VA, Nuccio SP, Rüssmann H, Bäumlér AJ. 2009. The TviA auxiliary

D.M. Monack

- protein renders the *Salmonella enterica* serotype Typhi RcsB regulon responsive to changes in osmolarity. *Mol Microbiol* **74**: 175–193.
- Winter SE, Thiennimitr P, Winter MG, Butler BP, Huseby DL, Crawford RW, Russell JM, Bevins CL, Adams LG, Tsolis RM, et al. 2010. Gut inflammation provides a respiratory electron acceptor for *Salmonella*. *Nature* **467**: 426–429.
- Yen YF, Wang FD, Chiou CS, Chen YY, Lin ML, Chen TL, Liu CY. 2009. Prognostic factors and clinical features of non-typhoid *Salmonella* bacteremia in adults. *J Chin Med Assoc* **72**: 408–413.
- Young D, Hussell T, Dougan G. 2002. Chronic bacterial infections: Living with unwanted guests. *Nat Immunol* **3**: 1026–1032.
- Zeaiter Z, Huynh HQ, Kanyo R, Stein M. 2008. CagA of *Helicobacter pylori* alters the expression and cellular distribution of host proteins involved in cell signaling. *FEMS Microbiol Lett* **288**: 227–234.



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