Review Article

Mechanisms for the Invasion and Dissemination of *Salmonella*

Qiao Li

*Tongji Hospital, Tongji Medical College, Huazhong University of Sciences and Technology, Wuhan, Hubei, China*

Correspondence should be addressed to Qiao Li; graceliqiao@126.com

Received 26 November 2021; Revised 15 May 2022; Accepted 30 May 2022; Published 9 June 2022

Copyright © 2022 Qiao Li. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Salmonella enterica* is a gastroenteric Gram-negative bacterium that can infect both humans and animals and causes millions of illnesses per year around the world. *Salmonella* infections usually occur after the consumption of contaminated food or water. Infections with *Salmonella* species can cause diseases ranging from enterocolitis to typhoid fever. *Salmonella* has developed multiple strategies to invade and establish a systemic infection in the host. Different cell types, including epithelial cells, macrophages, dendritic cells, and M cells, are important in the infection process of *Salmonella*. Dissemination throughout the body and colonization of remote organs are hallmarks of *Salmonella* infection. There are several routes for the dissemination of *Salmonella* typhimurium. This review summarizes the current understanding of the infection mechanisms of *Salmonella*. Additionally, different routes of *Salmonella* infection will be discussed. In this review, the strategies used by *Salmonella* enterica to establish persistent infection will be discussed. Understanding both the bacterial and host factors leading to the successful colonization of *Salmonella enterica* may enable the rational design of effective therapeutic strategies.

1. Introduction

*Salmonella* is a Gram-negative, intracellular pathogen. There are more than 2,600 serovars of *Salmonella* characterized to date that are differentiated on the basis of the lipopolysaccharide (LPS) O antigen and the flagellar H antigen [1]. There are just two species of *Salmonella*: *S. enterica* and *S. bongori* [2]. *Salmonella* typhi and *Salmonella* typhimurium are well-known members of the *S. enterica* species. *S. typhimurium* and *S. enteritidis* are predominantly associated with gastroenteritis in humans [3]. Each year, there are about 155,000 deaths due to nontyphoidal *Salmonella* (NTS) infections. *Salmonella enterica* serovar typhi infections cause a staggering 20 million infections and 200,000 deaths annually [4]. Gastroenteritis induced by Salmonella infections is a major cause of morbidity and mortality in children under 5 years of age [5]. Diarrhea caused by *Salmonella* species causes a global human health burden that contributes to significant annual morbidity and mortality and requires new therapeutic strategies for effective management. Almost 60% of *Salmonella* strains have developed resistance to first-line antibiotics [6]. Most patients recover from infections after treatment. However, 3–5% of patients become chronic carriers, with chronic infection in the gall bladder [7]. Chronic carriers can intermittently shed the bacteria through their feces and urine throughout the rest of their lives [8]. The liver is also a reservoir for chronic infections with *Salmonella* Typhi; from the liver, the bacteria can be intermittently shed into the gallbladder [9]. *Salmonella* typhi infections can cause fever, hepatomegaly, splenomegaly, and bacteremia. In the disease process, the bacteria disseminate into the gall bladder, liver, and spleen [10]. Approximately 90% of chronic *Salmonella* carriers have gallstones [10–12], and are at significantly increased risk for gallbladder cancer (GC) [12, 13]. Del-Giorno et al. reported that persistent *Salmonella* infections can cause pancreatitis in a murine model of infection [14]. Some *Salmonella* carriers are asymptomatic. Roughly 2–5% of *Salmonella*-infected patients fail to clear the bacteria within one year [12]. Such chronic infections, especially asymptomatic infections, pose a huge socioeconomic burden, especially in South Asian and African countries, by unknowingly spreading infections to others, who may experience symptomatic infections and suffer economic costs as a result. Understanding the cellular routes of *Salmonella* invasion and dissemination in the host and the mechanisms
of *Salmonella* persistent infection may facilitate the exploration of novel treatment strategies for patients with chronic infections. Ultimately, this may help eliminate the asymptomatic carriage of *Salmonella* as a concern for public health.

*Salmonella* infections can result from the ingestion of contaminated foods because they can survive the low pH of the stomach [15]. Although bile in the small intestine poses a challenge for *S. typhimurium*, the PhoQ/PhoP two-component regulatory system mediates resistance to bile [16]. *Salmonella* predominantly causes inflammation of the terminal ileum and colon [17]. *S. typhimurium* can spread systemically in mice, and *S. typhimurium* infections in mice are used as an animal model for typhoid fever in humans [18]. Pretreatment of mice with streptomycin prior to *Salmonella* infection disturbs the healthy microbiota and facilitates infection of the intestinal lumen with *Salmonella* typhimurium [19]. Streptomycin-treated mice are therefore often used as animal models of *S. Typhimurium*-induced gastroenteritis [19]. Before the oral infection of *S. typhimurium* and *S. enteritidis*, approximately 20 mg of streptomycin treatment by intragastric administration in the mice will allow a high colonization level in the cecum and colon of the mice [20]. Acute microbiota depletion will reduce the colonization resistance and facilitate the infection of the bacteria. Microbiota can limit *Salmonella* colonization, and diet can affect microbiota composition. Low-fiber or high-fat diets will increase *S. typhimurium* colonization in mice [21]. Fat can promote *S. typhimurium* infection in mice by eliciting bile salts, which help fat digestion [21]. A high-fat diet will cause microbiota perturbation [21]. *E. coli* may limit *S. typhimurium* infections during diet shifts [21].

Mice with a mutation in the natural resistance-associated macrophage protein 1 gene (*Nramp*), such as *C57BL/6* or BALB/C mice, are susceptible to *Salmonella* infection [22]. *Nramp* is a macrophage-specific exporter, and the *Nramp* gene codes for an ion transporter that pumps ions out of *Salmonella*-containing vacuoles (SCV) [22]. The SCV is the intracellular vacuolar niche in which *Salmonella* can replicate and achieve dormant infection. Wild type 129×1/Sv mice, which possess the *Nramp* allele, are used as an animal model for chronic *S. typhimurium* infection [23]. Mice with a mutation in the natural resistance-associated macrophage protein 1 gene (*Nramp*), such as *C57BL/6* or BALB/C mice, are susceptible to *Salmonella* infection [22]. *Nramp* is a macrophage-specific exporter, and the *Nramp* gene codes for an ion transporter that pumps ions out of SCV [22]. The SCV is the intracellular vacuolar niche in which *Salmonella* can replicate and achieve dormant infection. Wild type 129×1/Sv mice, which possess the *Nramp* genotype, are used as an animal model for chronic *S. typhimurium* [23].

### 2. M Cells

Enteropathogenic infections start in the intestinal lumen. Dissemination through microfold or membranous (M) cells is one of the best-understood routes of *Salmonella* dissemination [24]. M cells are specialized follicle-associated epithelial (FAE) enterocytes on the surface of mucosa-associated lymphoid tissues [25, 26]. *Salmonella typhimurium* initiates infection in mice by infecting and destroying the specialized epithelial M cells and then traveling to the mesenteric lymph nodes [24]. See Figure 1.

*Salmonella* directly invades M cells but can also transform follicle-associated epithelial cells into M cells to provide additional routes for intestinal invasion [27]. Indeed, Tahoun et al. found that *S. Typhimurium* can induce an epithelial-mesenchymal transition (EMT) of FAE enterocytes and transition the FAE to M cells [27]. These processes rely on the bacterial type III effector protein SopB [27]. Through the activation of NF-κB and Wnt/b-Catenin signaling pathways, *Salmonella* induces host cell transdifferentiation through receptor activator of NF-κB ligand (RANKL) [27]. This finding was the first report that *S. typhimurium* can transform epithelial cells into M cells using a single virulence factor.

Intestinal immunity is the first defense barrier that enteropathogens encounter during infection. Lymphotoxin signaling is important for maintaining intestinal immune balance. LTβR can also be activated by lymphotoxin (LTαβ) [28]. Lymphotoxin signaling promotes the differentiation of M cells from intestinal epithelial cells [29]. This signaling is involved in the regulation of intestinal inflammation, as shown by the DSS-induced colitis model [30]. Mice with knocked-out lymphotoxin signaling molecules (LTα1, LTαβ1, and LTαβ2) have abnormal lymphoid development [31]. Lymphotoxin β-receptor knockout mice lack all lymph nodes and gut-associated lymphatic tissues, including Peyer’s patches (PPs) [32]. These lymph node-defective mice are a good model for the systemic dissemination of *S. typhimurium*. Infection of *Salmonella* in LTβR−/− mice demonstrates that organized lymph tissues are dispensable for the systemic infection of the host [20]. As shown by a study from Barthel et al., without Peyer’s patches (PPs), bacteria can still reach remote organs [20]. This phenomenon indicates the importance of dendritic cell-mediated transportation in the dissemination of *S. typhimurium* [33]. *Salmonella* exploited dendritic cells as vesicles for dissemination. Cheminay et al. showed that after infection by *Salmonella*, dendritic cells could upregulate the CCR7 receptor and migrate via the CCR7 ligands CCL19 and CCL21 [13, 33–35].

A study by Wroblewska et al. showed that lymphotoxin signaling is essential for the clearance of *Salmonella* from the intestinal lumen [36]. A lack of LTβR signaling did not impact the initiation of inflammation induced by *Salmonella*. However, the resolution of *Salmonella* infection was impaired [36]. The infectious processes in *S. typhimurium* in WT and LTβR−/− mice lacking Peyer’s patches (PPs) and MLN are highly similar [20].

### 3. Epithelial Cell

*S. typhimurium* can invade polarized gallbladder epithelial cells and replicate inside the epithelial cells [37]. Gallbladder epithelial cells are a reservoir for *Salmonella* colonization [37]. Long-term colonization of *Salmonella* in the
gallbladder cells can drive the premalignant transformations of the cells. 

Salmonella can induce the extrusion of epithelial cells, which is accompanied by caspase-1 activation-related cell death. Epithelial cells can provide a shelter for the bacteria to survive and replicate in the cytosol of the epithelial cells [38, 39]. The type III secretion system is involved in the priming of the bacteria for invasion. Cytosolic bacteria can induce the extrusion of epithelial cells and be released into the intestinal lumen [38, 39].

Unlike M cells, Salmonella’s invasion of epithelial cells does not rely on phagocytosis. The type III secretion system (T3SS) is the most important virulence factor for Salmonella species, and one is encoded on Salmonella pathogenicity island 1 (SPI1) and the other is encoded on Salmonella pathogenicity island 2 (SPI2) [40]. The type III secretion system is a molecular syringe that can translocate the effector proteins directly from the bacteria into the cytosol of cells. Effector proteins are injected into the cytoplasm of the host by a T3SS gene cluster. SPI1 is involved in the invasion process of Salmonella [41]. After invading host cells, Salmonella survives in SCVs by using elements encoded on SPI2 [42–45]. Approximately 4–6 h after the cellular invasion, bacterial replication is initiated [46].

Salmonella can induce membrane ruffling in intestinal cells to cause them to engulf the bacteria [47]. Various S. Typhimurium fimbral operons contribute to bacterial attachment and invasion of epithelial cells [48]. The zipper and trigger mechanisms are two well-studied mechanisms of Salmonella entry into epithelial cells [49, 50]. The trigger mechanism is activated by the type III secretory system [49]. SipB/C in Salmonella type III secretory system assembles a pore in the epithelial cell, bacteria and epithelial cells can contact through the continuum created by the SipB/C [49].

Cytoskeletal reorganizations known as “membrane ruffles” and “internalization” are two key elements of the trigger mechanism [51]. Bacteria are internalized in SCV following a trigger mechanism [49].

In contrast, there are only minor cytoskeletal protein rearrangements involved in the zipper mechanism [50]. Instead, the zipper mechanism is mainly mediated by interactions between bacterial ligands such as Rck and host cell surface receptors [52]. There are many outer membrane proteins that participate in the invasion process of Salmonella typhimurium [53]. Rck is a 17 kDa outer membrane protein (OMP), which are membrane proteins found in the outer membranes of Gram-negative bacteria. Rck is encoded by the rck gene on the large virulence plasmid [54]. They are a family of highly conserved OMPs within the Enterobacteriaceae family. This receptor binding leads to downstream signal activation mediated by phosphorylation of tyrosine kinase. The zipper mechanism is activated by the binding of host cell receptors by the bacterial ligands. Actin polymerization and membrane extension are initiated by the activated downstream signaling.

PagN is another OMP [54] and is widely conserved in the Salmonella genus [55]. The PagN protein interacts with cell surface heparin sulfate proteoglycans to invade cells [53]. Binding between OmpV and the extracellular matrix components fibronectin and α1β1 integrin leads to the adhesion of Salmonella typhimurium to intestinal epithelial cells and ultimately activates actin modulation [56]. PAMPs of Salmonella can be recognized by the innate immune response receptors through MyD88-dependent TLR signaling [57]. Infection with SPI1 T3SS disrupted Salmonella can still induce colitis in C57BL/6 mice through a mechanism that is dependent on MyD88 signaling [58]. The effectors of type III secretion systems in the invasion and dissemination of Salmonella are summarized in Table 1.
The binding of pattern recognition receptors (PRRs) with pathogen-associated molecular patterns (PAMPs), including peptidoglycan, lipopolysaccharide, flagellin, can mediate Salmonella invasion [64, 65]. TLR4 and TLR5 play a role in the host response to Salmonella [66]. In human macrophages, Salmonella can activate NAIP/NLRC4 and canonical NLRP3 inflammasomes by its flagellin [67]. Caspase-1 will be activated after binding with NLRC4 and NLRP3 inflammasomes in response to Salmonella. Salmonella colonization was much higher in caspase 11 deficient macrophages, Salmonella role in the host response to Salmonella mediate including peptidoglycan, lipopolysaccharide, flagellin, can inhibit antigen presentation by dendritic cells that can facilitate the dissemination of Salmonella through ubiquitination [90].

By exploiting migratory dendritic cells, the Salmonella can thus traffic from the intestinal lumen to systemic organs [34]. During active infection, the dendritic cells’ expression of CCR7, a receptor for the chemokines CCL19 and CCL21, is increased [34]. This allows dendritic cells to migrate along chemotactic gradients to remote sites like the lymph nodes and spleen [34]. Salmonella survives inside the dendritic cells, subverts the function of dendritic cells, impairs the activation of adaptive immune responses, prevents fusion and lyso-endosomal degradation, and achieves systemic dissemination [45]. Cheminay et al. published the first example that Salmonella can inhibit antigen presentation by dendritic cells by altering MHC-II-dependent antigen presentation in an SPI2-dependent manner [89]. Through subversion of the antigen presentation of dendritic cells, the bacteria reduce the activation of the active immune response. Lapaque et al. demonstrated that Salmonella can inhibit the surface expression of MHC class II antigens on dendritic cells [90].

CD103⁺CD11b⁺ DCs have been reported to transport Salmonella typhimurium to the mesenteric lymph nodes (MLN) after oral infection [91]. CD103⁺ dendritic cells (DCs) typically phagocytose bacteria from the small intestine and present antigens to T cells [91]. Another group of dendritic cells that can facilitate the dissemination of Salmonella is intestinal CD11c⁺ lamina propria cells (LPCs), which do so in a TLR5 dependent manner [92]; the migration of Salmonella typhimurium from the intestinal tract to MLN is impaired in TLR5⁻/⁻ mice. In TLR5⁻/⁻ mice, migration of bacteria by CD11c⁺ LPCs is impaired [92, 93].

Distinct populations of dendritic cells participate in the processing and immune sampling of Salmonella. Specialized DC subsets in Peyer’s patches (PPs), CCR6 (+) DCs, are recruited to the dome regions of Peyer’s patches (PPs) to sample the bacteria and present to CD4⁺ T cells [94, 95]. CX3CR1-positive lamina propria DCs take up S. typhimurium by transepithelial processes [96]. Indeed, CX3CR1 deficiency leads to reduced bacterial sampling in the intestinal lumen by lamina propria DCs [96]. Further, these CX3CR1-positive DCs lacking CCR6 expression, which is different from the Peyer’s patches (PPs) associated-dendritic cells [96].
S. typhimurium can be taken up by sub-epithelial DCs and can survive within murine PP dendritic cells [97]. The S. typhimurium strain PhoP\(^{+}\) has a point mutation in the phoP/Q locus [98] that attenuates its capacity to survive in macrophages but was able to persist for several weeks in vivo [97]. Salmonella can persist in the dendritic cells in the Peyer’s patch. They can also be directly sampled by dendritic cells that express tight junction proteins, such as the interepithelial dendritic cells in the intestinal villi that penetrate gut epithelial monolayers by opening tight junctions and directly sampling bacteria from the mucus [99].

Infection of CD11c\(^{+}\)CD18\(^{+}\) dendritic cells can lead to rapid entry into the systemic circulation. It has been reported by Vazquez-Torres et al. that Salmonella achieve systemic dissemination through CD18-expressing phagocytes [100]. One hour after infection, Salmonella can be detected in the blood. At sites other than M cells and Peyer’s patches, Salmonella can also disseminate from the gastrointestinal tract to the spleen. Downregulation of DC cells in the lamina propria can limit the invasion of Salmonella [100].

5. Macrophage

During the intracellular life of Salmonella in the host cells, Salmonella can interfere with the antigen-presenting process of the dendritic cells, for example, by interfering with the antigen presentation of bacteria on dendritic cells and inhibiting the adaptive immunity. Salmonella can affect the polarization of macrophages to the M2 phenotype, which will inhibit the inflammatory process and facilitate the persistent survival of Salmonella in the host. The manipulation of the macrophage is a strategy that Salmonella derived during its evolution. Uchiya et al. demonstrated that Salmonella can interfere with the function of macrophages to escape immune responses. Uchiya et al. reported that Salmonella can inhibit cytokine signaling in macrophages via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway through SPI2 [101].

In addition to dendritic cells and M cells, S. typhimurium can also disseminate via inflammatory monocytes. Monocytes are recruited to the inflammatory sites where they differentiate into macrophages. Macrophages serve as a reservoir in which Salmonella can survive and replicate [102]. Inside the macrophage, Salmonella can induce micropinocytosis [103], and spacious phagosomes (SP) are formed after Salmonella enters the macrophage and persists in the cytoplasm [103]. A T3SS encoded by SPI2 allows survival and avoids the NADPH oxidase-dependent killing of macrophages [104].

The PhoQ/PhoP regulatory system is utilized by S. typhimurium to enable survival in macrophages [105]. The PhoQ/PhoP two-component system is one of the most important regulatory mechanisms for the virulence of Salmonella. Inside the SCV, the low PH and low Mg\(^{2+}\) environment activate the two-component PhoQ/PhoP system [106]. The gene regulating the expression of O antigen, rfb, is inhibited inside the SCV [107]. Thus, the length of O antigen is decreased under the regulation of the two-component PhoQ/PhoP system. The protease PgtE in Salmonella typhimurium, a homologue for Pla in Yersinia Pestis and OmpT in E. coli, is then expressed [108]. Expression of PgtE protease dissolves the extracellular matrix and facilitates the cellular dissemination of Salmonella in vivo. S. typhimurium, when released from the macrophage, can then be phagocytosed by other cells, including other macrophages [109].

Salmonella can modify macrophage polarization during chronic infection. Macrophages can differentiate into two groups after bacterial infection; the classically activated macrophages (M1 type) or the alternatively activated macrophages (M2 type). Cytokines are the primary determinant of macrophage polarization. The M1 type is proinflammatory and activates a Th1 immune response [110]. IFNy- and LPS-induced activation of TLR4 signaling can shift the macrophage to the M1 phenotype. In contrast, the M2 type is antiinflammatory and activates the Th2 immune response [110]. The cytokine IL-4 shifts macrophages to the M2 phenotype. Usually, macrophages will exhibit M1 polarization after sensing the stimuli from bacteria or viruses. Salmonella phagocytized by the macrophage can shift the macrophage polarization state. Saliba et al. reported that macrophages harboring nongrowing Salmonella are prone to proinflammatory M1 polarization, but macrophages harboring growing bacteria shifted to an antiinflammatory M2-like state [111]. S. typhimurium preferentially lives in M2 macrophages during chronic infections [110]. Thus, Salmonella has mechanisms to shift the differentiation of macrophages into the M2 phenotype [110]. Intracellular glucose levels are higher in M2 macrophages, contributing to their permissiveness for the intracellular replication of Salmonella [112].

S. typhimurium persists within splenic granulomas enriched with CD11b\(^{+}\)CD11c\(^{+}\)Ly6C\(^{+}\) macrophages [4, 113]. Trung et al. previously reported that Salmonella can manipulate granuloma macrophage polarization towards the M2 phenotype [4]. As previously discussed, S. typhimurium preferentially persists in M2-reprogrammed macrophages. The bacterial effector SteE contributes to the establishment of persistent infection by downregulating tumor necrosis factor (TNF) signaling [4]. The bacteria have to develop strategies to overcome the immune response and persist chronically. S. typhimurium can polarize the primary macrophages to M2 polarization through the e SPI2 T3SS effector SteE. Macrophage M2 polarization can contribute to the systemic persistence of the bacteria [113].

Studies have shown that Salmonella can induce host cell death during infection [114]. Monack et al. found that caspase-1 is exploited by Salmonella to colonize the Peyer’s patches (PPs) [115]. Systemic dissemination after an oral challenge with Salmonella is impaired in Casp-1\(^{-/-}\) mice. This indicates that caspase-1 is important for the systemic dissemination of Salmonella [115]. Caspase-1 (Casp-1), an interleukin (IL)-1\(\beta\)-converting enzymes, can induce apoptosis in mammalian cells. Caspase 1 can cleave the proinflammatory cytokines IL-1\(\beta\) and IL-18. Mice lacking
Casp-1 (Casp-1−/− mice) showed a 1,000-fold higher lethal dose (LD50) of S. typhimurium in the mice than wide-type mice [115]. Casp-1−/− mice were colonized by lower intracellular bacteria and did not show systemic dissemination of the bacteria, reduced colonization of bacteria in the Peyer’s patches (PP) and spleens [115]. It suggests that Casp-1 is necessary for the establishment of systemic infection by S. typhimurium in mice [38, 67, 68, 115, 116]. Salmonella colonization was much higher in Caspase 11 deficient mice than in wild-type mice [68]. Casp1−/− and Casp1/11−/− monolayers showed significantly increased intracellular bacteria, accompanied by low intestinal epithelial cells (IECs) shedding and death [68]. Caspase activation is important for limiting the intracellular replication of Salmonella.

Inflammasome activation is one important pathway during the infection of Salmonella in the intestinal epithelial cells [38]. The infection of Salmonella typhimurium can also lead to the activation of Caspase 4, and Caspase 4 can limit the replication of S. typhimurium in the cells [117]. Activation of caspase 4 can lead to the noncanonical activation of the inflammasome pathway [117].

Salmonella can activate apoptosis of Salmonella-infected macrophages using effectors encoded in pathogenicity island-1 through both intrinsic and extrinsic pathways [118]. Cell death induced by the infected cells gives the bacteria an opportunity to be released and infect further cells. Salmonella can induce cell death in macrophages through several mechanisms. Immediate cell death can be induced by the type III secretion system (T3SS) of Salmonella. Or, the macrophages harboring Salmonella can be further phagocytosed by neighboring macrophages. Bacteria are released from dead cells and phagocytized by local macrophages, enabling another cycle of intracellular replication and cell-to-cell spread [114]. Ultimately, this cycle helps ensure the intracellular survival and persistent infection of phagocyte populations with Salmonella.

### 6. Chronic and Systemic Infection of Salmonella Typhimurium

Supershedders are the hosts responsible for the host-to-host transmission and reoccurrence of S. typhimurium since supershedders shed the bacteria in their feces. Foxp3p Regulatory T cells play a role in the persistent infection of Salmonella [119]. Foxp3+ Treg ablation early after infection will accelerate bacterial eradication [119]. This indicated that immune regulatory T cells function in the early stages of infection to establish a persistent Salmonella infection [119].

Monack et al. demonstrated that Salmonella can persist in the MLNs of mice for up to one year. Macrophages in the MLNs can be the reservoirs of the bacteria. Voedisch et al. suggested that the MLN represents a restrictive site for the growth and dissemination of Salmonella [33]. In mice whose mesenteric lymph nodes have been surgically excised, the colonization of Salmonella in the liver and spleen is increased [33]. In such mice, Salmonella forms nonreplicating “persisters” in macrophages [120]. Persisters are in a state of dormant infection that is tolerant to drug treatment [121]. Indeed, they have resistance to antibiotics and can eventually reactivate and begin to replicate once more [122]. Persistor cells are one important reason for relapsed infections. Persisters facilitate the chronic infection with S. typhimurium. Persisters can undermine the host immune response [123]. These persisters can reprogram the macrophages they dominate [123]. After exposure to ciprofloxacin, a fluoroquinolone antibiotic, Salmonella enterica persisters form unstable small colony variants. These phenotypes help the bacteria survive in the face of environmental stress or antibiotic treatments.

Salmonella persisters cells are important components of biofilms [124]. Biofilm formation is an important strategy for persistent bacterial infections [125]. Forming biofilm can confer the bacteria survival advantages. Biofilm formation on gallstones is important for the chronic carriage of Salmonella. Antibiotic therapy efficiency is compromised in patients with a biofilm in the gall bladder. Salmonella infection in the gall bladder can induce the destruction of the epithelial cell integrity.

Biofilms are just one strategy for the bacteria to survive harsh environments. Even without animal reservoirs, biofilms can help Salmonella spp. to survive in the environment until uptake into a new host. However, the Salmonella Typhimurium ST313 strain which can cause blood stream infections and is typically seen in Sub Saharan Africa [126], has poor biofilm-forming ability and cannot survive long outside a host [127].

Except in antigen-presenting cells, Salmonella achieves a persistent infection in epithelial cells [128] by remaining in a dormant state. Luk et al. found that Salmonella can live in a dormant state in the vesicular compartment, different from the Salmonella-containing vacuoles (SCV). Contrary to macrophages, Salmonella in epithelial cells can express Salmonella Pathogenicity Island 2 (SPI-2) virulence factors. This report is the first to describe another persistent infection state and mechanism for S. typhimurium [128].

The Salmonella SPI2 effector SseI (also called SrfH) binds with host factor IQ motifs containing GTPase activating protein 1 (IQGAP1). SseI has been reported to mediate long-term systemic infections [60]. Pseudogenization of SseI leads to rapid systemic dissemination of Salmonella typhimurium through migratory dendritic cells [129]. In the sub-Saharan African Salmonella typhimurium strain ST313 lineage II, sseI is lost by pseudogenization. ST313 can disseminate from the gut to mesenteric lymph nodes (MLNs) via CD11b+ migratory dendritic cells (DCs) [129]. However, recovery of the gene function by expressing functional SseI in ST313 isolates reduces the dissemination of the bacteria [129].

The interplay between the host immune system and pathogens is a complex process during chronic infections. Dendritic cells and macrophages are important reservoirs for the bacteria that enable long-term survival. Helicobacter pylori, Mycobacterium tuberculosis, and Salmonella enterica all survive inside antigen-presenting cells (APCs). The gall bladder, bone marrow [130], and mesenteric lymph nodes are sites that can support persistent infection with Salmonella. Persistent infection with Salmonella can cause disease
in multiple organs, from gallbladder cancer to pancreatitis. Pancreatitis can be caused by persistent infection of mice with *Salmonella* [14]. Inflammatory, fibrotic, and epithelial responses can be detected in the pancreases of mice persistently infected with *S. typhimurium* [14]. Pancreatic acinar cells can be invaded by *S. typhimurium*.

*Salmonella* infections are associated with the development of IBD (inflammatory bowel diseases) and colon cancer [131, 132]. One study by Katrin et al. reported that mice with chronic infections with *S. typhimurium* develop severe and persistent intestinal fibrosis and have upregulation of several matrix metalloproteinases (MMPs) [133]. Transforming growth factor-β1, insulin-like growth factor-I, and type I collagen deposition levels are increased during persistent infection of *S. typhimurium* [134, 135].

As shown in mouse models, chronic infection with *S. typhimurium* increases the susceptibility to intestinal inflammation [136]. The dextran sulfate sodium (DSS)-induced colitis and interleukin (IL)-10−/− spontaneous inflammation mice models were used in this particular study [137]. Because of persistent infection of *S. typhimurium* in the liver and spleen, these mice are more susceptible to intestinal inflammation. This indicated *S. typhimurium* persistent infection might be related to the accelerated onset of IBD (inflammatory bowel diseases) of the host [137].

Various studies support the mesenteric lymph nodes as a site that harbors *Salmonella* to sustain a chronic infection [138]. *Salmonella* can persist in the hemophagocytic macrophages of MLN. Removal of MLN increases the bacterial burdens in mice, however, indicating that another reservoir of *Salmonella* exists other than MLN [138]. Bacteria can be cultured from the liver tissue of chronically infected mice [139]. Liver macrophages are shifted to the M2 phenotype during persistent infection. An immune response balance exists during chronic infection with *Salmonella*, for example, the proinflammatory IFNγ and anti-inflammatory signals IL-10. This balance allows the bacteria to survive in the persistent infection sites [139].

The cytokine Interleukin-22 (IL-22) can help the colonization of *Salmonella* by suppressing other commensal bacteria [140]. IL-22 can function in tissue repair and host defense; it is induced during pathogen infection. Behnsen et al. reported that IL-22 can suppress the intestinal microbiota [140]. IL-22 suppresses commensal Enterobacteriaceae and boosts the colonization of *Salmonella*. Binding of bacteria with APCs will induce the release of cytokine IL-23; IL-23 induces IL-17 and IL-22 release [141, 142]. In IL-22−/− mice has higher *E. coli* burden and reduced *Salmonella* colonization in the intestine than wide type mice. IL-22 can induce the antimicrobial proteins lipocalin-2 and calprotectin release to inhibit the growth of commensal microbiota. This mechanism is exploited by *Salmonella* to outcompete intestinal microbiota [140].

### 7. Concluding Remarks

Achieving a better understanding of the pathogenesis of *Salmonella* will provide further insights into key host-pathogen interactions that affect persistent bacterial infections. Understanding the detailed mechanisms and the specific host cell types involved in *Salmonella* infections may help guide the future development of therapeutic interventions. Understanding the mechanisms of *Salmonella* persistent infection will enable researchers to improve upon current treatment strategies, especially for asymptotically infected patients. Treating chronically infected patients will help reduce the reservoirs for the bacteria and limit the transmission of the disease.

### Conflicts of Interest

The author declares that they have no conflicts of interest.

### Acknowledgments

This study was funded by a local grant from the Tongji Hospital of the Huazhong University of Science and Technology.

### References

[1] P. Li, Q. Liu, H. Luo et al., “O-serotype conversion in salmonella typhimurium induces protective immune responses against invasive non-typhoidal Salmonella infections,” *Frontiers in Immunology*, vol. 8, p. 1647, 2017.

[2] S. Issenhuth-Jeanjean, P. Roggentin, M. Mikoleit et al., “Supplement 2008–2010 (no. 48) to the White–Kauffmann–Le Minor scheme,” *Research in Microbiology*, vol. 165, no. 7, pp. 526–530, 2014.

[3] M. E. M. S. Ohl and S. I. Miller, “Salmonella: a model for bacterial pathogenesis,” *Annual Review of Medicine*, vol. 52, no. 1, pp. 259–274, 2001.

[4] S. E. Majowicz, J. Musto, E. Scallan et al., “The global burden of nontyphoidal Salmonella gastroenteritis,” *Clinical Infectious Diseases*, vol. 50, no. 6, pp. 882–889, 2010.

[5] M. Kosek, C. Bern, and R. L. Guerrant, “The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000,” *Bulletin of the World Health Organization*, vol. 81, no. 3, pp. 197–204, 2003.

[6] E. J. Threlfall, A. Bone, D. Murdoch, N. Banatvala, B. I. Shoismatulloev, and L. R. Ward, “Epidemic ciprofloxacin-resistant *Salmonella typhi* in Tajikistan,” *The Lancet*, vol. 351, no. 9099, p. 339, 1998.

[7] M. M. Levine, R. E. Black, and C. Lanata, “Precise estimation of the numbers of chronic carriers of *Salmonella typhi* in Santiago, Chile, an endemic area,” *The Journal of Infectious Diseases*, vol. 146, pp. 724–726, 1982.

[8] T. M. Vogelsang and J. Bee, “Temporary and chronic carriers of *Salmonella typhi* and salmonella paratyphi B,” *Journal of Hygiene*, vol. 46, no. 3, pp. 252–261, 1948.

[9] G. Nath, Y. K. Singh, P. Maurya, A. K. Gulati, R. C. Srivastava, and S. K. Tripathi, “Does Salmonella Typhi primarily reside in the liver of chronic typhoid carriers?” *Journal of Infection in Developing Countries*, vol. 4, no. 4, pp. 259–261, 2010.

[10] R. W. Crawford, R. Rosales-Reyes, L. Ramirez-Aguilar Mde, O. Chapa-Azuela, C. Alpuche-Aranda, and J. S. Gunn, “Gallstones play a significant role in Salmonella spp. gallbladder colonization and carriage,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 9, pp. 4353–4358, 2010.
Salmonella

B. Stecher, G. Paesold, M. Barthel et al., "Chronic Salmonella enterica serovar typhimurium-induced colitis and chol- angitis in streptomycin-pretreated nramp1+/+ mice," Infection and Immunity, vol. 74, no. 9, pp. 5047–5057, 2006.

B. D. Jones, N. Ghori, and S. Falkow, "Salmonella typhimurium initiates murine infection by penetrating and destroying the specialized epithelial M cells of theeyer’s patches," Journal of Experimental Medicine, vol. 180, no. 1, pp. 15–23, 1994.

J. P. Kraehenbuhl and M. R. Neutra, “Epithelial M cells: differentiation and function,” Annual Review of Cell and Developmental Biology, vol. 16, no. 1, pp. 301–332, 2000.
A. J. Baumler, K. Zhang, A. Riba et al., “Minimal SPI1-T3SS effector requirement for salmonella enterocyte invasion and intracellular proliferation in vivo,” *PLoS Pathogens*, vol. 14, no. 3, Article ID e1006925, 2018.

M. A. Bakowski, V. Braun, and J. H. Brumell, “Salmonella-containing vacuoles: directing traffic and nesting to grow,” *Traffic*, vol. 9, no. 12, pp. 2022–2031, 2008.

J. C. D. Jantsch, D. Chikkaballi, and M. Hensel, “Cellular aspects of immunity to intracellular *Salmonella enterica*,” *Immunological Reviews*, vol. 240, no. 1, pp. 185–195, 2011.

P. Malik-Kale, C. E. Jolly, S. Lathrop, S. Winfree, J. C. D. Jantsch, D. Chikkaballi, and M. Hensel, “Salmonella SPI2 effector SseI mediates long-term systemic infection by modulating host cell migration,” *PLoS Pathogens*, vol. 5, no. 11, Article ID e1006761, 2009.

M. A. Swart and M. Hensel, “Interactions of *Salmonella enterica* with dendritic cells,” *Virulence*, vol. 3, pp. 660–667, 2012.

J. Guignot, E. Caron, C. Beuzon et al., “Microtubule motors control membrane dynamics of salmonella-containing vacuoles,” *Journal of Cell Science*, vol. 117, no. 7, pp. 1033–1045, 2004.

A. Takeuchi, “Electron microscope studies of experimental salmonella infection. I. penetration into the intestinal epithelium by *Salmonella typhimurium*,” *American Journal of Pathology*, vol. 50, no. 1, pp. 109–116, 1967.

A. J. T. R. Bäumler, R. M. Tsolis, and F. Heffron, “Contribution of fimbrial operons to attachment to and invasion of epithelial cell lines by *Salmonella typhimurium*,” *Infection and Immunology*, vol. 64, pp. 1862–1865, 1996.

P. Cossart and P. J. Sansonetti, “Bacterial invasion: the paradigms of enteroinvasive pathogens,” *Science*, vol. 304, no. 5668, pp. 242–248, 2004.

J. Hanisch, T. E. Stradal, and K. Rottner, “A novel contractility pathway operating in salmonella invasion,” *Virulence*, vol. 3, no. 1, pp. 81–86, 2012.

J. C. Patel and J. E. Galan, “Manipulation of the host actin cytoskeleton by Salmonella-all in the name of entry,” *Current Opinion in Microbiology*, vol. 8, no. 1, pp. 10–15, 2005.

M. Rosselin, I. Virlogeux-Payant, C. Roy et al., “Rck of *Salmonella enterica*, subspecies enterica serovar Enteritidis, mediates Zipper-like internalization,” *Cell Research*, vol. 20, no. 6, pp. 647–664, 2010.

M. A. Lambert and S. G. J. Smith, “The PagN protein mediates invasion via interaction with proteoglycan,” *FEBS Microbiology Letters*, vol. 297, no. 2, pp. 209–216, 2009.

E. J. W. L. Heffernan, L. Wu, S. Okamoto, J. Fierer, D. G. Guiney, and D. G. Guiney, “Specificity of the complement resistance and cell association phenotypes encoded by the outer membrane protein genes rck from *Salmonella typhimurium* and all from *Yersinia enterocolitica*,” *Infection and Immunology*, vol. 62, no. 11, pp. 5183–5186, 1994.

M. A. Lambert and S. G. Smith, “The PagN protein of *Salmonella enterica* serovar typhimurium is an adhesin and invasin,” *BMC Microbiology*, vol. 8, no. 1, p. 142, 2008.

D. Kaur and A. Mukhopadhyaya, “Outer membrane protein OmpV mediates salmonella entericaserovar typhimurium adhesion to intestinal epithelial cells via fibronectin and αβ1 integrin,” *Cellular Microbiology*, vol. 22, no. 5, Article ID e13172, 2020.

K. Takeda, T. Kaisho, and S. Akira, “Toll-like receptors,” *Annual Review of Immunology*, vol. 21, no. 1, pp. 335–376, 2003.

S. Hafelmeier, B. Stecher, M. Barthel et al., “The Salmonella pathogenicity island (SPI)-2 and SPI-1 type III secretion systems allow Salmonella serovar typhimurium to trigger colitis via MyD88-dependent and MyD88-independent mechanisms,” *The Journal of Immunology*, vol. 174, no. 3, pp. 1675–1685, 2005.

E. Jennings, T. L. M. Thurston, and D. W. Holden, “Salmonella SPI-2 type III secretion system effectors: molecular mechanisms and physiological consequences,” *Cell Host & Microbe*, vol. 12, no. 2, pp. 217–231, 2017.

M. Hensel, L. M. McLaughlin, G. R. Govoni et al., “The Salmonella SPI2 effector SseI mediates long-term systemic infection by modulating host cell migration,” *PLoS Pathogens*, vol. 5, no. 11, Article ID e1006761, 2009.

M. A. Jepson, B. Kenny, and A. D. Leard, “Role of sipA in the early stages of *Salmonella typhimurium* entry into epithelial cells,” *Cellular Microbiology*, vol. 3, no. 6, pp. 417–426, 2001.

D. Zhou, M. S. Mooseker, and J. E. Galan, “Role of the S. typhimurium actin-binding protein SipA in bacterial internalization,” *Science*, vol. 283, pp. 5410, pp. 2092–2095, Article ID 101126, 1999.

M. Raffatellu, R. P. Wilson, D. Chessa et al., “SipA, SopB, SopD, and SopE2 contribute to *Salmonella enterica* serotype typhimurium invasion of epithelial cells,” *Infection and Immunity*, vol. 73, no. 1, pp. 146–154, 2005.

S. A. Fattinger, M. E. Sellin, and W. D. Hardt, “Epithelial inflammasomes in the defense against Salmonella gut infection,” *Current Opinion in Microbiology*, vol. 59, pp. 86–94, 2021.

J. E. Galan, “Salmonella typhimurium and inflammation: a pathogen-centric affair,” *Nature Reviews Microbiology*, vol. 19, no. 11, pp. 716–725, 2021.

V. Feuillet, S. Medjane, I. Mondor et al., “Involvement of Toll-like receptor 5 in the recognition of flagellated bacteria,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, pp. 12487–12492, 2006.

A. M. Gram, J. A. Wright, R. J. Pickering et al., “Salmonella flagellin activates NAIP/NLR4 and canonical NLRP3 inflammasomes in human macrophages,” *The Journal of Immunology*, vol. 206, no. 3, pp. 631–640, 2021.

S. M. Crowley, X. Han, J. M. Allaire et al., “Intestinal restriction of Salmonella Typhimurium requires caspase-1 and caspase-11 epithelial intrinsic inflammasomes,” *PLoS Pathogens*, vol. 16, no. 4, Article ID e1008498, 2020.

A. K. B. Iwasaki and B. L. Kelsall, “Unique functions of CD11b”, CD8α, and double-negative Peyer’s patch dendritic cells,” *The Journal of Immunology*, vol. 166, no. 8, pp. 4884–4890, 2001.

I. H. P. Marie, P. G. Holt, J. Bienenstock, and J. Bienenstock, “Class II MHC antigen (la)-bearing dendritic cells in the epithelium of the rat intestine,” *The Journal of Immunology*, vol. 156, no. 4, pp. 1408–1414, 1996.

C. H. S. Ruedl and S. Hubele, “Maturation of Peyer’s patch dendritic cells in vitro upon stimulation via cytokines or CD40 triggering,” *European Journal of Immunology*, vol. 27, no. 6, pp. 1325–1330, 1997.

B. L. S. W. Kelsall and W. Strober, “Distinct populations of dendritic cells are present in the subepithelial dome and T cell regions of the murine Peyer’s patch,” *Journal of Experimental Medicine*, vol. 183, no. 1, pp. 237–247, 1996.

A. K. B. Iwasaki and B. L. Kelsall, “Localization of distinct Peyer’s patch dendritic cell subsets and their recruitment by chemokines macrophage inflammatory protein (Mip)-3α, Mip-3β, and secondary lymphoid organ chemokine,” *Journal of Experimental Medicine*, vol. 191, no. 8, pp. 1381–1394, 2000.
P. Zhang, O. Schwartz, M. Pantelic et al., “Dc-SIGN (DC-SIGN) interacts CD209 receptors to promote host dissemination and infection,” *Infection and Immunity*, vol. 87, 2019.

T. B. Geijtenbeek, D. S. Kwon, R. Torensma et al., “DC-SIGN, a dendritic cell-specific HIV-1-Binding protein that enhances trans-infection of T cells,” *Cell*, vol. 100, no. 5, pp. 587–597, 2000.

T. B. H. Geijtenbeek and Y. van Kooyk, “Pathogens target DC-SIGN to influence their fate DC-SIGN functions as a pathogen receptor with broad specificity,” *Acta Pathologica Microbiologica et Immunologica Scandinavica*, vol. 111, no. 7-8, pp. 698–714, 2003.

D. McDonald, L. Wu, S. M. Bohks, V. N. KewalRamani, D. Unutmaz, and T. J. Hope, “Recruitment of HIV and its receptors to dendritic cell-T cell junctions,” *Science*, vol. 300, no. 5623, pp. 1295–1297, 2003.

L. Tailleux, N. Pham-Thi, A. Bergeron-Lafaurie et al., “DC-SIGN induction in alveolar macrophages defines privileged target host cells for mycobacteria in patients with tuberculosis,” *PLoS Medicine*, vol. 2, no. 12, 2005.

Y. X. He, C. L. Ye, P. Zhang et al., “Yersinia pseudotuberculosis exploits CD209 receptors for promoting host dissemination and infection,” *Infection and Immunity*, vol. 87, no. 1, Article ID e00654-18, 2019.

J. Klena, P. Zhang, O. Schwartz, S. Hull, and T. Chen, “The core lipopolysaccharide of *Escherichia coli* is a ligand for the dendritic-cell-specific intercellular adhesion molecule non-integrin CD209 receptor,” *Journal of Bacteriology*, vol. 187, pp. 1710–1715, 2005.

K. Yang, Y. He, C. G. Park et al., “Yersinia pestis interacts with SIGNR1 (CD209b) for promoting host dissemination and infection,” *Frontiers in Immunology*, vol. 10, p. 96, 2019.

K. Yang, C. G. Park, C. Cheong et al., “Host langerin (CD207) is a receptor for Yersinia pestis phagocytosis and promotes dissemination,” *Immunology & Cell Biology*, vol. 93, no. 9, pp. 815–824, 2015.

P. Zhang, O. Schwartz, M. Pantelic et al., “Dc-SIGN (DC-SIGN) recognition of Neisseria gonorrhoeae is circumvented by lipopoligosaccharide variation,” *Journal of Leukocyte Biology*, vol. 79, no. 4, pp. 731–738, 2006.

P. Zhang, M. Skurnik, S. S. Zhang et al., “Human dendritic cell-specific intercellular adhesion molecule-grabbing non-integrin (CD209) is a receptor for *Yersinia pestis* that promotes phagocytosis by dendritic cells,” *Infection and Immunity*, vol. 76, no. 5, pp. 2070–2079, 2008.

P. Zhang, S. Snyder, P. Feng et al., “Role of N-acetylgalactosamine within core lipopolysaccharide of several species of gram-negative bacteria in targeting the DC-SIGN (CD209),” *The Journal of Immunology*, vol. 177, no. 6, pp. 4002–4011, 2006.

S. S. Zhang, C. G. Park, P. Zhang et al., “Plasminogen activator Pla of *Yersinia pestis* utilizes murine DEC-205 (CD205) as a receptor to promote dissemination,” *Journal of Biological Chemistry*, vol. 283, no. 46, pp. 31511–31521, 2008.

C. Cheminay, A. Möhlenbrink, and M. Hensel, “Intracellular *Salmonella* Inhibit antigen presentation by dendritic cells,” *The Journal of Immunology*, vol. 174, no. 5, pp. 2892–2899, 2005.

N. Lapaque, J. L. Hutchinson, D. C. Jones et al., “Salmonella regulates polyubiquitination and surface expression of MHC class II antigens,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 33, pp. 14052–14057, 2009.

J. Farache, I. Koren, I. Milo et al., “Luminal bacteria recruit CD103+ dendritic cells into the intestinal epithelium to sample bacterial antigens for presentation,” *Immunity*, vol. 38, no. 3, pp. 581–595, 2013.

S. Uematsu, M. H. Jang, N. Chevrier et al., “Detection of pathogenic intestinal bacteria by Toll-like receptor 5 on intestinal CD11c+ lamina propria cells,” *Nature Immunology*, vol. 7, no. 8, pp. 868–874, 2006.

S. Uematsu and S. Akira, “Immune responses of TLR5 (+) lamina propria dendritic cells in enterobacterial infection,” *Journal of Gastroenterology*, vol. 44, no. 8, pp. 803–811, 2009.

M. Rescigno, “CCR6 (+) dendritic cells: the gut tactical-response unit,” *Immunity*, vol. 24, no. 5, pp. 508–510, 2006.

R. M. Salazar-Gonzalez, J. H. Niess, D. J. Zammit et al., “CCR6-mediated dendritic cell activation of pathogen-specific T cells in Peyer’s patches,” *Immunity*, vol. 24, no. 5, pp. 623–632, 2006.

J. H. B. S. Niess, S. Brand, L. Landsman et al., “CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance,” *Science*, vol. 307, no. 5707, pp. 254–258, 2005.

S. A. N. F. Hopkins, I. E. Courtsey-Theulaz, and J. P. Kraehenbuhl, “A recombinant *Salmonella typhimurium* vaccine strain is taken up and survives within murine Peyer’s patch dendritic cells,” *Cellular Microbiology*, vol. 2, no. 1, pp. 59–68, 2000.

J. S. Gunn, S. I. Miller, and S. Miller, “PhoP-PhoQ activates transcription of pmrAB, encoding a two-component regulatory system involved in *Salmonella typhimurium* antimicrobial peptide resistance,” *Journal of Bacteriology*, vol. 178, no. 23, pp. 6857–6864, 1996.

M. Rescigno, M. Urbano, B. Valzasina et al., “Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria,” *Nature Immunology*, vol. 2, no. 4, pp. 361–367, 2001.

A. J.-C. J. Vazquez-Torres, J. Jones-Carson, A. J. B¨aumler et al., “Extraintestinal dissemination of *Salmonella* by CD18-expressing phagocytes,” *Nature*, vol. 401, no. 6755, pp. 804–808, 1999.

K. I. Uchiya and T. Nikai, “Salmonella pathogenicity island 2-dependent expression of suppressor of cytokine signaling 3 in macrophages,” *Infection and Immunity*, vol. 73, no. 9, pp. 5587–5594, 2005.

O. L. C. Wijburg, C. P. Simmons, R. A. Strugnell, and R. A. Strugnell, “Dual role for macrophages in vivo in pathogenesis and control of murine *Salmonella enterica* var. *typhimurium* infections,” *European Journal of Immunology*, vol. 30, no. 3, pp. 944–953, 2000.

C. M. R. E. Alpuche-Aranda, E. L. Racoosin, S. I. Miller, and J. P. Kraehenbuhl, “A recombinant *Salmonella typhimurium* vaccine strain is taken up and survives within murine Peyer’s patch dendritic cells,” *Cellular Microbiology*, vol. 2, no. 1, pp. 59–68, 2000.

A. J.-C. J. Vazquez-Torres, J. Jones-Carson, A. J. B¨aumler et al., “Extraintestinal dissemination of *Salmonella* by CD18-expressing phagocytes,” *Nature*, vol. 401, no. 6755, pp. 804–808, 1999.
Canadian Journal of Infectious Diseases and Medical Microbiology 11

macrophage paradigm,” Journal of Innate Immunity, vol. 11, no. 3, pp. 289–299, 2019.

[106] C. M. S. J. Alpuce Aranda, J. A. Swanson, S. I. Miller, and S. I. Miller, “Salmonella typhimurium activates virulence gene transcription within acidified macrophage phagosomes,” Proceedings of the National Academy of Sciences of the United States of America, vol. 89, no. 21, pp. 10079–10083, 1992.

[107] S. L. S. Eriksson, S. Lucchini, M. Rhen, J. C. Hinton, and J. C. D. Hinton, “Unravelling the biology of macrophage infection by gene expression profiling of intracellular Salmonella enterica,” Molecular Microbiology, vol. 47, no. 1, pp. 103–118, 2003.

[108] K. Lähteenmäki, P. Kylloinen, L. Partanen, and T. K. Korhonen, “Antiprotease inactivation by Salmonella enterica released from infected macrophages,” Cellular Microbiology, vol. 7, no. 4, pp. 529–538, 2004.

[109] D. M. Monack, A. Mueller, and S. Falkow, “Persistent bacterial infections: the interface of the pathogen and the host immune system,” Nature Reviews Microbiology, vol. 2, no. 9, pp. 747–765, 2004.

[110] N. A. Eisele, T. Ruby, A. Jacobson et al., “Salmonella require the fatty acid regulator PPARδ for the establishment of a metabolic environment essential for long-term persistence,” Cell Host & Microbe, vol. 14, no. 2, pp. 171–182, 2013.

[111] A. E. Saliba, L. Li, A. J. Westermann et al., “Single-cell RNA-seq ties macrophage polarization to growth rate of intracellular Salmonella,” Nature Microbiology, vol. 2, Article ID 16206, 2016.

[112] R. M. Roop and C. C. Caswell, “Bacterial persistence: finding the “sweet spot”,” Cell Host & Microbe, vol. 14, no. 2, pp. 119-120, 2013.

[113] T. H. M. Pham, S. M. Brewer, T. Thurston et al., “Salmonella-driven polarization of granuloma macrophages antagonizes TNF-mediated pathogen restriction during persistent infection,” Cell Host & Microbe, vol. 27, no. 1, pp. 54–67, 2020.

[114] D. G. Guiney, “The role of host cell death in Salmonella infections,” Current Topics in Microbiology and Immunology, vol. 289, 2005.

[115] D. M. H. D. Monack, D. Hersh, D. Bouley, A. Zychlinsky, S. Falkow, and S. Falkow, “Salmonella exploits caspase-1 to colonize Peyer’s patches in a murine typhoid model,” Journal of Experimental Medicine, vol. 192, no. 2, pp. 249–258, 2000.

[116] E. A. Miao and J. V. Rajan, “Salmonella and caspase-1: a complex interplay of detection and evasion,” Frontiers in Microbiology, vol. 2, p. 85, 2011.

[117] M. K. Holly, X. Han, E. J. Zhao et al., “Salmonella enterica infection of murine and human enteroid-derived monolayers elicits differential activation of epithelium-intrinsic inflammamasomes,” Infection and Immunity, vol. 88, no. 7, 2020.

[118] H. H. Lin, H. L. Chen, C. C. Weng, R. P. Janapatla, C. L. Chen, and C. H. Chiu, “Activation of apoptosis by salmonella pathogenicity island-1 effectors through both intrinsic and extrinsic pathways in Salmonella-infected macrophages,” Journal of Microbiology, Immunology, and Infection, vol. 54, no. 4, pp. 616–626, 2021.

[119] T. M. Johanns, J. M. Ertelt, J. H. Rowe, and S. S. Way, “Regulatory T cell suppressive potency dictates the balance between bacterial proliferation and clearance during persistent Salmonella infection,” PLoS Pathogens, vol. 6, no. 8, Article ID e1001043, 2010.

[120] S. Helaine, A. M. Cheverton, K. G. Watson, L. M. Faure, S. A. Matthews, and D. W. Holden, “Internalization of Salmonella by macrophages induces formation of non-replicating persisters,” Science, vol. 343, no. 6167, pp. 204–208, 2014.

[121] K. Lewis, “Persistor cells,” Annual Review of Microbiology, vol. 64, no. 1, pp. 357–372, 2010.

[122] R. A. Fisher, B. Gollan, and S. Helaine, “Persistent bacterial infections and persisters cells,” Nature Reviews Microbiology, vol. 15, no. 8, pp. 453–464, 2017.

[123] D. A. C. Stapels, P. W. S. Hill, A. J. Westermann et al., “Salmonella persisters undermine host immune defenses during antibiotic treatment,” Science, vol. 362, no. 6419, pp. 1156–1160, 2018.

[124] M. Abdallah, C. Benoliel, D. Drider, P. Dhubster, and N. E. Chihib, “Biofilm formation and persistence on abiotic surfaces in the context of food and medical environments,” Archives of Microbiology, vol. 196, no. 7, pp. 453–472, 2014.

[125] U. Romling and C. Balsalobre, “Biofilm infections, their resilience to therapy and innovative treatment strategies,” Journal of Internal Medicine, vol. 272, no. 6, pp. 541–561, 2012.

[126] N. A. Feasey, G. Dougan, R. A. Kingsley, R. S. Heyderman, and M. A. Gordon, “Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa,” The Lancet, vol. 379, no. 9835, pp. 2249–2499, 2012.

[127] G. Ramachandran, K. Aheto, M. E. Shirtliff, S. M. Tennant, and J. Kaper, “Poor biofilm-forming ability and long-term survival of invasive Salmonella Typhimurium ST313,” Pathogens and Disease, vol. 74, no. 5, Article ID fwh049, 2016.

[128] C. H. Luk, C. Valenzuela, M. Gil et al., “Salmonella enters a dormant state within human epithelial cells for persistent infection,” PLoS Pathogens, vol. 17, no. 4, Article ID e1009550, 2021.

[129] S. E. Carden, G. T. Walker, J. Honeycutt et al., “Pseudo-genization of the secreted effector gene ssef confers rapid systemic dissemination of S. Typhimurium ST313 within migratory dendritic cells,” Cell Host & Microbe, vol. 21, no. 2, pp. 182–194, 2017.

[130] F. S. J. Niedergang, J. C. Sirard, J. P. Kraehenbuhl, and J. P. Kraehenbuhl, “Entry and survival of Salmonella typhimurium in dendritic cells and presentation of recombinant antigens do not require macrophage-specific virulence factors,” Proceedings of the National Academy of Sciences of the United States of America, vol. 97, no. 26, pp. 14650–14655, 2000.

[131] L. Mughini-Gras, M. Schaapveld, J. Kramers et al., “Increased colon cancer risk after severe salmonella infection,” PLoS One, vol. 13, no. 1, Article ID e0189721, 2018.

[132] R. B. M. Lu, M. Bosland, Y. G. Zhang, I. Kato, J. Sun, and J. Sun, “Presence of Salmonella enterica in colorectal tumor and its precursor lesions in mouse intestine and human specimens,” Oncotarget, vol. 8, no. 33, pp. 55104–55115, 2017.

[133] K. Ehhardt, N. Steck, R. Kappelhoff et al., “Persistent Salmonella enterica serovar typhimurium infection induces protease expression during intestinal fibrosis,” Inflammatory Bowel Diseases, vol. 25, no. 10, pp. 1629–1643, 2019.

[134] G. A. Grasl, V. Valdez, K. S. Bergstrom, B. A. Vallance, and B. B. Finlay, “Chronic enteric salmonella infection in mice leads to severe and persistent intestinal fibrosis,” Gastroenterology, vol. 134, no. 3, pp. 768–780, 2008.

[135] L. E. M˚ ansson, M. Montero, M. Zarepour et al., “MyD88 regulates Salmonella enterica serovar typhimurium infection by activating virulence effectors and persister cells,” Current Topics in Microbiology and Immunology, vol. 343, pp. 119-120, 2013.
[136] B. M. Schultz, C. A. Paduro, G. A. Salazar et al., “A potential role of salmonella infection in the onset of inflammatory bowel diseases,” *Frontiers in Immunology*, vol. 8, p. 191, 2017.

[137] B. M. Schultz, G. A. Salazar, C. A. Paduro et al., “Persistent *Salmonella enterica* serovar typhimurium infection increases the susceptibility of mice to develop intestinal inflammation,” *Frontiers in Immunology*, vol. 9, p. 1166, 2018.

[138] A. J. Griffin, L. X. Li, S. Voedisch, O. Pabst, and S. J. McSorley, “Dissemination of persistent intestinal bacteria via the mesenteric lymph nodes causes typhoid relapse,” *Infection and Immunity*, vol. 79, no. 4, pp. 1479–1488, 2011.

[139] J. R. Kurtz, W. Nieves, D. Bauer et al., “Salmonella persistence and host immunity is dictated by the anatomical microenvironment,” *Infect Immum*, vol. 88, 2020.

[140] J. Behnse, S. Jellbauer, C. P. Wong et al., “The cytokine IL-22 promotes pathogen colonization by suppressing related commensal bacteria,” *Immunity*, vol. 40, no. 2, pp. 262–273, 2014.

[141] C. Blaschitz and M. Raffatellu, “Th17 cytokines and the gut mucosal barrier,” *Journal of Clinical Immunology*, vol. 30, no. 2, pp. 196–203, 2010.

[142] S. A. Khader and R. Gopal, “IL-17 in protective immunity to intracellular pathogens,” *Virulence*, vol. 1, no. 5, pp. 423–427, 2010.