Archives of Microbiology (2023) 205:362
https://doi.org/10.1007/s00203-023-03702-w

MINI REVIEW

Strategies adopted by *Salmonella* to survive in host: a review

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Received: 1 September 2023 / Revised: 30 September 2023 / Accepted: 5 October 2023 / Published online: 31 October 2023

Abstract

Salmonella, a Gram-negative bacterium that infects humans and animals, causes diseases ranging from gastroenteritis to severe systemic infections. Here, we discuss various strategies used by *Salmonella* against host cell defenses. Epithelial cell invasion largely depends on a *Salmonella* pathogenicity island (SPI)-1-encoded type 3 secretion system, a molecular syringe for injecting effector proteins directly into host cells. The internalization of *Salmonella* into macrophages is primarily driven by phagocytosis. After entering the host cell cytoplasm, *Salmonella* releases many effectors to achieve intracellular survival and replication using several secretion systems, primarily an SPI-2-encoded type 3 secretion system. *Salmonella*-containing vacuoles protect *Salmonella* from contacting bactericidal substances in epithelial cells and macrophages. *Salmonella* modulates the immunity, metabolism, cell cycle, and viability of host cells to expand its survival in the host, and the intracellular environment of *Salmonella*-infected cells promotes its virulence. This review provides insights into how *Salmonella* subverts host cell defenses for survival.

Keywords *Salmonella* · Host cell · Effector · Infection · Metabolism · Cell death

Introduction

Salmonella species are among the most prevalent food-borne and facultative intracellular pathogen affecting humans and animals, including livestock and poultry. Hitherto, two species have been identified, i.e., *Salmonella bongori*, commonly found in cold-blooded animals, and *Salmonella enterica*, predominantly isolated from warm-blooded animals (Fookes et al. 2011). *Salmonella enterica* serovars are associated with four distinct clinical syndromes, i.e., typhoid fever, caused by *S. enterica* subsp. *enterica* serovar Typhi (*S.* Typhi); paratyphoid fever, caused by *S. enterica* subsp. *enterica* serovar Paratyphi (*S.* Paratyphi); gastroenteritis, caused by nontyphoidal *Salmonella* (NTS) serovars in immunocompetent individuals; and bacteremia, caused by NTS serovars in immunocompromised individuals (Gal-Mor 2019). Many virulence-related gene clusters exist in the genome of *Salmonella*, known as *Salmonella* pathogenicity islands (SPIs), such as SPI-1, 2, 4, 6, and 19. Most SPIs of *Salmonella* encode the structural proteins and secreted effectors of secretion systems (Bao et al. 2020). It should be noted that T6SS gene clusters have been identified within pathogenicity islands SPI-6, 19, 20, 21, and 22, which are differentially distributed among *Salmonella* serotypes and encode different T6SSs in terms of functions (Hernandez et al. 2020). SPI-1-encoded type 3 secretion system (T3SS1) is mainly used by *Salmonella* to invade host cell when it is outside of host cell. Following invasion into epithelial cells, *Salmonella* survives in vesicles called *Salmonella*-containing vacuoles (SCVs), and SPI-2-encoded T3SS (T3SS2) is largely used for the intracellular replication when the pathogen is inside SCVs.

The SPI-4-encoded type 1 secretion system (T1SS) and T3SS1 trigger the attachment of *Salmonella* to the intestinal epithelium. *Salmonella* can thus effectively invade intestinal epithelial cells, preferentially in the terminal ileum by injecting an array of effector proteins via T3SS1 and type 6 secretion system (T6SS) (Sana et al. 2016; Bao et al. 2020). One of the primary targets invaded by *Salmonella* are M cells (a specialized intestinal epithelial cell type), which are

Communicated by Yusuf Akhter.

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interspersed among enterocytes and cover Peyer's patches containing lymphoid follicles (Griffin and McSorley 2011). *Salmonella* utilizes various effectors secreted from the T3SS2, a T6SS, and a T4SS to evade immune responses and survive within the SCVs in host cells (Bao et al. 2020). Macrophages play a crucial role in facilitating systemic infection by *Salmonella*. Once the pathogen traverses the epithelial layer, it is phagocytosed and persists within the SCVs of macrophages. Although NTS infections typically remain localized in the intestinal mucosa and mesenteric lymph nodes, other *S. enterica* serovars can disseminate throughout the body via the bloodstream or lymphatic system, leading to the colonization of the liver, spleen, kidney, and bone marrow, eventually giving rise to typhoid fever and bacteremia when not controlled during the initial stages of infection (Ruby et al. 2012; Orf and Cunnington 2015). The processes whereby *S.* Typhi causes systemic infection in the host is shown in Fig. 1.

Extensive research has been conducted on interactions between *Salmonella* and host cells. Nonetheless, the precise pathogenic mechanisms underlying *Salmonella* infection still require further investigation. In this review, we aim to explore the survival and immune evasion strategies employed by *Salmonella* to gain a better understanding of the pathogenic processes of this intracellular pathogen.

Survival of *Salmonella* in host intestine

To infect host, *Salmonella* must survive in the host intestines and establish its growth advantage. *Salmonella* employs a strategy that involves outcompeting intestinal commensal microbes to colonize the intestines of humans and animals, which is achieved by injecting effector proteins into prokaryotic cells through T6SS to eliminate intestinal microbes (Sana et al. 2016; Sibinelli-Sousa et al. 2020; Amaya et al. 2022). Inside the gut, *Salmonella* takes advantage of the host-derived secondary metabolic products induced by inflammation, such as thiosulfate, tetrathionate, ethanolamine, and nitrate. Inflammation triggers phagocytes (such as neutrophils and macrophages) to generate superoxide anion radicals that oxidize hydrogen sulfide to thiosulfate and tetrathionate (Winter and Baumler 2011). Simultaneously, the membranes of the dead intestinal cells produce ethanolamine. *Salmonella* can grow on ethanolamine as a carbon source while using tetrathionate for anaerobic respiration. Similar to tetrathionate, host-derived superoxide anion radicals react with inflammation-induced nitric oxide to form nitrate, which promotes the intestinal growth of *Salmonella* as an electron acceptor (Behnsen et al. 2015). *Salmonella* can also grow using metabolites produced by other intestinal microorganisms, such as lactic acid and propionic acid (Gillis et al. 2018; Shelton et al. 2022).

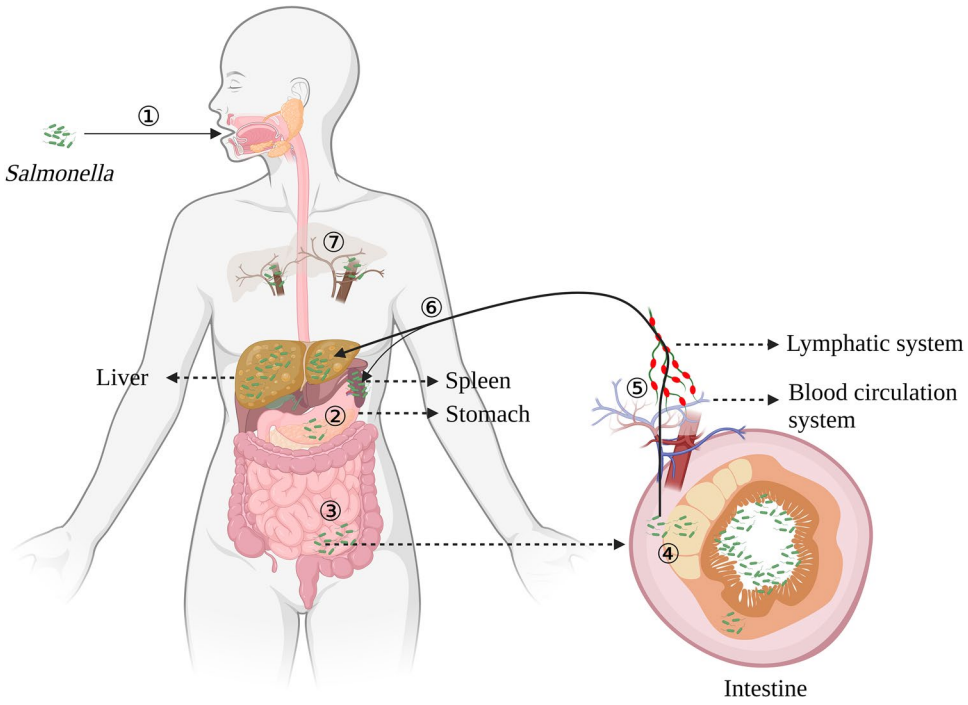

Fig. 1 Processes whereby *Salmonella enterica* subsp. *enterica* serovar Typhi causes systemic infection in its host. (1) Ingested *Salmonella* enters the host esophagus through contaminated food and water. (2) *Salmonella* survives the highly acidic environment in the stomach. (3) *Salmonella* colonizes the intestines of the host. (4) *Salmonella* invades the M cells and enterocytes of the intestines. (5) *Salmonella* released from M cells and enterocytes are engulfed by phagocytes and disseminated through the lymphatic and circulatory systems. (6) *Salmonella* colonizes internal organs such as the liver, spleen, and kidneys. (7) Increased numbers of *Salmonella* enter blood vessels from different infected organs, leading to lethal bacteremia

Entry of *Salmonella* into host cells

Adhesion of *Salmonella* on host cells

Salmonella uses a variety of fimbrial and nonfimbrial structures to adhere to host cells (Hassuna et al. 2017). Fimbrial adhesins include type 1 fimbriae (Fim), plasmid-encoded fimbriae (Pef), long polar fimbriae (Lpf), thin aggregative fimbriae (Agf). Nonfimbrial structures include autotransporter adhesins, including ShdA, MisL, and SadA, and T1SS-secreted adhesins, such as BapA, SiiE. These *Salmonella* adhesins bind to corresponding receptors on host cells to adhere to host cells (Bao et al. 2020). The four main fimbrial operons—*fim*, *pef*, *lpf*, and *agf*—are all associated with virulence; however, mutants lacking only one of these operons show little reduction in virulence. Additionally, *S.* Typhi has a 27 kDa outer membrane protein T2544/ PagN that binds to laminin with high affinity and plays a vital role in bacterial adhesion to the host (Ghosh et al. 2011).

T3SS1-independent invasion into nonphagocytic cells

Rck, PagN, and HlyE are invasins that play pivotal roles in the invasion process of *Salmonella*. *Salmonella* expresses an outer membrane protein, Rck, which interacts with the epidermal growth factor receptor on the plasma membrane of host cells, activating host cell signaling pathways that lead to actin polymerization and bacterial entry (Wiedemann et al. 2016). Additionally, Rck-mediated infection increases the number of S-phase (DNA replication phase) cells, creating an environment conducive to Rck-mediated bacterial entry (Mambu et al. 2020). Moreover, Rck provides resistance to complement killing by preventing the formation of membrane attack complexes (Heffernan et al. 1992). The outer membrane protein PagN, a hemagglutinin of *S. enterica* serovar Typhimurium (*S.* Typhimurium), contributes to invasion of epithelial cells by utilizing heparinated proteoglycan as a receptor (Lambert and Smith 2008, 2009). HlyE is a pore-forming hemolysin present in the serovars Typhi and Paratyphi A, and *hlyE* mutants are impaired in their ability to invade. Moreover, the heterologous expression of HlyE in *S.* Typhimurium improves its colonization in deep organs of mice. Therefore, HlyE can play a vital role in invasion, but the precise mechanism whereby a hemolysin enhances the invasion of intracellular pathogens remains unknown (Fuentes et al. 2008). Other invasins should be existed as there exists many unidentified genes encoding functionally unknown proteins in the genome of *Salmonella*.

T3SS1-dependent invasion

The T3SS1, encoded by SPI-1 and its secreted effectors, promotes the invasion of *Salmonella* into host cells, particularly epithelial cells (Fig. 2). For example, the effectors SopE, SopE2, SopB, SopD, SipA, and SipC secreted by T3SS1 all contribute to the invasion of host cells by *Salmonella*, mainly due to their ability to facilitate the rearrangement of the actin cytoskeleton of host cells (Clark et al. 2011). Although the primary mode of the entry of *Salmonella* into phagocytes is phagocytosis, the effector proteins required for *Salmonella* to enter monocytes and macrophages are highly similar to those required for entry into epithelial cells (Di Martino et al. 2019).

SipA and SipC work cooperatively to promote the invasion of *Salmonella* into host cells by directly binding to actin adjacent to the host cell membrane, with SipC being a component of T3SS1 (Fig. 2). The C-terminus of SipC possesses an F-actin-binding site, leading to F-actin polymerization and nucleation (LaRock et al. 2015), facilitating the formation of F-actin filament bundles. SipA enhances the action of SipC by stimulating actin polymerization, inhibiting the depolymerization of F-actin caused by actin-depolymerization factor (ADF) and/ or cofilin, and preventing the severing of F-actin caused by gelsolin (Dai et al. 2004; McGhie et al. 2004).

Unlike SipA and SipC, SopE, SopE2, and SopB promote the internalization of *Salmonella* into host cells by indirectly acting on actin (Fig. 2). The guanine nucleotide exchange factors SopE and SopE2 can transfer GTP to Rho family guanosine triphosphatases (GTPases), such as Cdc42, Rac1, and RhoG. GTP-bound GTPases can then induce actin cytoskeleton rearrangement and stimulate cell membrane ruffling, which promotes the invasion of *Salmonella* into cells. However, after *Salmonella* enters the cell, the effector SptP—a GTPase-activating protein—can normalize cell morphology as it hydrolyzes GTP on GTPases into GDP.

SopB and SopD act together to promote the scission of the host plasma membrane, driving the invasion of *Salmonella* into host cells, generating SCVs (Fig. 2). SopB, an inositol phosphate phosphatase, dephosphorylates phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), thus forming phosphatidylinositol 5-phosphate (PI(5)P), leading to plasma membrane fission (Terebiznik et al. 2002). Moreover, SopB increases the amounts of phosphatidylinositol 3-phosphate in the membranes of bacteria-containing vacuoles, thereby promoting SCV maturation and intracellular replication of *Salmonella* (Hernandez et al. 2004; Mallo et al. 2008). SopD also drives the scission of the cell plasma membrane by promoting the inactivation of Rab10 and consequent recruitment of Dynamin-2 (Boddy et al. 2021). Furthermore, the phosphatase activity of SopB activates SH3-containing guanine nucleotide exchange factor (SGEF), a

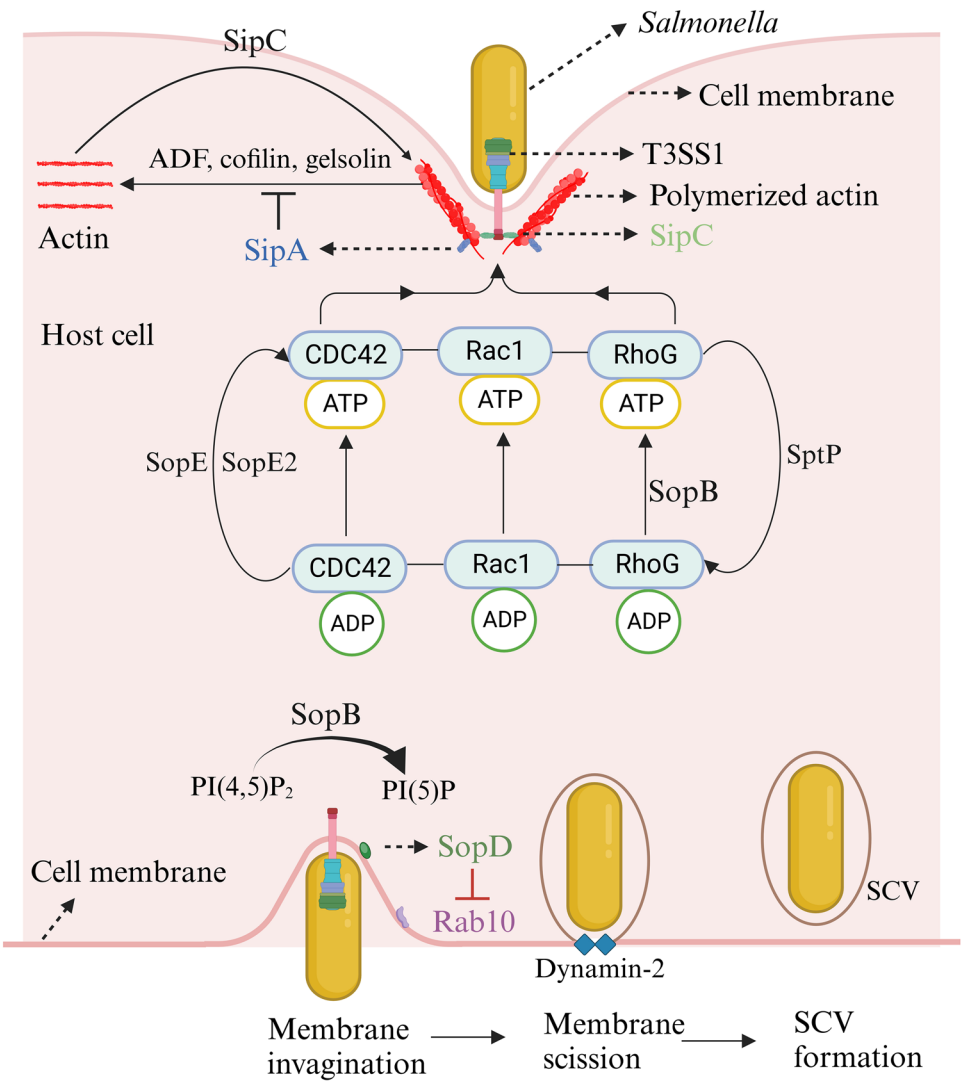

Fig. 2 *Salmonella* effectors secreted by its T3SS1 promote the invasion of host cells

guanosine nucleotide exchange factor for RhoG, resulting in actin rearrangements that facilitate bacterial internalization (Bakowski et al. 2010).

Phagocytosis of *Salmonella* by host phagocytic cells

Salmonella can be phagocytosed by typical phagocytes such as macrophages and neutrophils. However, macrophages offer a relatively more permissive environment for *Salmonella* survival and replication than provided by neutrophils (Tyrkalska et al. 2016). Phagocytosis of *Salmonella* can occur through opsonin-independent mechanisms, wherein phagocytes recognize the surface structural determinants of *Salmonella* via pattern recognition receptors (PRRs). Alternatively, opsonin-dependent phagocytosis occurs when *Salmonella* is labeled with opsonins such as antibodies or complements (Drecktrah et al. 2006), facilitating recognition by Fc receptors or complement receptors on phagocytes, leading to phagocytosis.

Several PRRs, including scavenging receptors (CD36), mannose receptors (CD206), and toll-like receptors (TLRs), have been reported to promote the phagocytosis of *Salmonella*. Overexpression of CD36 and TLR4 increases the number of bacteria phagocytosed into cells (Wan et al. 2018). The activation of PRRs not only enhances the phagocytosis of *Salmonella* but also initiates immune signaling pathways involved in antigen processing, cytokine/ chemokine production, and bacterial killing. After being phagocytosed by macrophages, *Salmonella* reduces the negative electric charge on the macrophage surface. This effect reverses the galvanotaxis direction of macrophages, keeping the macrophages containing *Salmonella* migrating to lymphatic drainage, bloodstream, or both (Sun et al. 2019).

Immune evasion by *Salmonella*

Inhibition of autophagy

Numerous pathogenic bacteria, including *S.* Typhimurium, *Shigella flexneri*, *Burkholderia pseudomallei*, *Listeria monocytogenes*, *Streptococcus pyogenes*, *Mycobacterium tuberculosis*, and *Legionella peumophila*, reportedly induce autophagy. In mice, the autophagy of intestinal epithelial cells has been shown to prevent the spread of invasive *S.* Typhimurium (Benjamin et al. 2013). In the case of *Salmonella*-infected macrophages, canonical autophagy, xenophagy (selective autophagy against bacteria), and LC3-associated phagocytosis (LAP) can be triggered. Autophagosomes and vesicles transport *Salmonella* to lysosomes, limiting its growth and replication (Wang et al. 2022). *Salmonella* growth increases in cells with lower than normal lysosomal activity and decreases in cells with higher than normal lysosomal activity (McGourty et al. 2012). During *Salmonella*-induced LAP, LC3 is recruited to the single membrane of the phagosome, unlike canonical autophagy, wherein LC3 marks double membranes of autophagosomes (Masud et al. 2019a). Notably, LAP induced by *S.* Typhimurium is mediated by the host protein Rubicon, which typically acts as a negative regulator of canonical autophagy and as an inducer of LAP (Masud et al. 2019b). It is believed that LAP is the primary autophagy pathway directed against *Salmonella* under macrophage-mediated immune defense conditions (Masud et al. 2019b).

Intracellular pathogens like *Salmonella* can employ a common strategy for entering a vacuolar environment during host cell invasion, with *Salmonella* surviving in an acidic and nutrient-deficient compartment known as SCV (Lahiri et al. 2010). One study suggested that SCVs divide along with *Salmonella* replication, resulting in an SCV containing a single *Salmonella*. Additionally, *Salmonella* infection reduces the number of lysosomes in host macrophages. Therefore, it has been inferred that the number of acidic lysosomes in cells infected with *Salmonella* is insufficient to cope with increasing SCV numbers (Eswarappa et al. 2010). Studies have shown live salmonellae to exist in SCVs, which avoid fusion with lysosomes. SopB reduces the membrane surface charge of nascent SCVs by reducing the levels of negatively charged $PI(4,5)P_2$ and phosphatidylserine, resulting in the dissociation of numerous host-cell proteins involved in endocytic trafficking from SCVs, and this effect inhibits SCV–lysosome fusion (Bakowski et al. 2010). Although SCVs exhibit lysosomal characteristics, they contain fewer hydrolytic enzymes. The effector SifA forms a stable complex with sphingosine kinase interacting protein and Rab9 in infected cells that disrupts the retrograde transport of hydrolytic enzymes to lysosomes by the mannose-6-phosphate receptor, thereby reducing the bactericidal effect of lysosomes (McGourty et al. 2012). Therefore, *Salmonella* exploits T3SS-secreted effectors to avoid the fusion of SCVs with lysosomes and reduce the levels of hydrolytic enzymes in lysosomes (Fig. 3).

Cellular stress and infection can lead to the formation of ubiquitinated aggregates in both nonimmune and immune cells. These ubiquitinated aggregates are recognized and bound by the autophagy receptor p62 (sequestosome 1), which directly interacts with LC3, facilitating the degradation of ubiquitinated protein aggregates via autophagy. Ubiquitination structures form during intracellular replication of *Salmonella*, and xenophagy pathways selectively bind ubiquitinated *Salmonella* or SCVs to autophagosomes via autophagy receptor proteins (Fig. 3). The T3SS2-delivered effector SseL has a unique role in deubiquitinating ubiquitin aggregates on the surface of SCVs, reducing the recruitment of autophagy markers (p62 and LC3), and, in turn, limiting autophagy against S*almonella* (Mesquita et al. 2012). Bacterial invasion often damages the host cell membrane, leading to acute amino acid starvation in the cytoplasm and triggering xenophagy. However, in *Salmonella*-infected cells, membrane integrity and cytoplasmic amino acid levels return to normal, favoring the reactivation of mTOR on the SCV surface and *Salmonella*'s escape from autophagy (Tattoli et al. 2012). In conclusion, *Salmonella* has specific ways to combat the xenophagy and LAP of the host.

With the vacuolar damage caused by *Salmonella*, vacuolar (H^+)-ATPase (V-ATPase) recruits ATG16L1 to SCVs and initiates autophagy; nevertheless, this process is inhibited by the T3SS effector SopF, which targets Gln124 of ATP6V0C (the main component of the C ring) in V-ATPase for ADP-ribosylation (Xu et al. 2019). In both epithelial cells and macrophages, SpvB (a protein encoded by the pSLT plasmid) also inhibits the autophagy of host cells during autophagosome formation, possibly by depolymerizing the actin cytoskeleton (Chu et al. 2016). As SpvB acts as an intracellular toxin, it covalently modifies monomeric actin, resulting in F-actin filament loss in human macrophages infected with *Salmonella* (Browne et al. 2008). Two other effectors of *Salmonella*, i.e., SseF and SseG, inhibit autophagosome formation by interfering with Rab1A signaling (Feng et al. 2018). The binding of these two effectors to Rab1A (a GTPase) disrupts the interaction of Rab1A and transport protein particle III complex, a guanine nucleotide exchange factor, and blocks the activation of Rab1A. The interruption of Rab1A signaling blocks the recruitment and activation of Unc-51-like autophagy-activating kinase-1 and reduces the production of phosphatidylinositol 3-phosphate, ultimately preventing autophagosome formation. Additionally, SpvC inhibits autophagosome formation

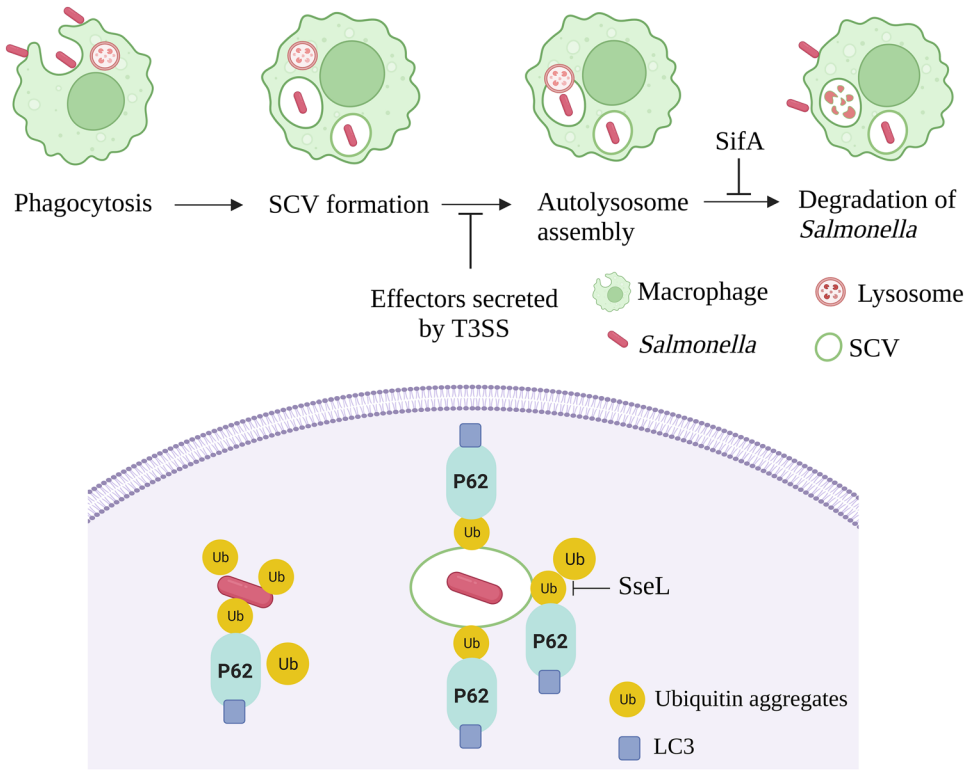

Fig. 3 *Salmonella* inhibits the autophagic clearance of host cells

via phosphothreonine lyase activity (Zhou et al. 2021). In conclusion, *Salmonella* inhibits autophagy initiation and autophagosome formation via many effector proteins.

Focal adhesion kinase (FAK) recruited to the SCV surface in *Salmonella*-infected cells amplifies signaling through the Akt-mTOR pathway and inhibits autophagy, possibly because FAK negatively regulates autophagy associated with Beclin-1 (Cheng et al. 2017). AvrA, an effector secreted by both T3SS1 and T3SS2, which can reduce Beclin-1 levels through the c-Jun N-terminal kinase (JNK) pathway, also inhibits autophagy. Increased cholesterol levels in the plasma membrane at the site of *Salmonella* entry into host cells reportedly leads to SCV formation and decreased autophagy (Huang 2014). These strategies used by *Salmonella* to inhibit autophagy wait for further exploration and explanation.

Polarization of M1 macrophages to M2 macrophages

The M1 macrophages are characterized by the expression of high levels of proinflammatory cytokines, CXCL9, CXCL10, inducible nitric oxide synthase, and reactive oxygen intermediates and exhibit strong antigen presentation abilities. Activation of M1 macrophages occurs through pathogen-associated molecular patterns, such as lipopolysaccharides (LPSs) and inflammatory cytokines, i.e., interferon-γ or tumor necrosis factor (TNF). While M1 macrophages play crucial roles in bactericidal activities, clearance of intracellular pathogens, and antitumor responses, they can also inadvertently inhibit the proliferation of neighboring cells and cause damage to adjacent tissues.

In contrast, atypical M2 macrophages highly express interleukin (IL)-4Rα and CD301 and are activated by cytokines produced by T helper-2 cells, including IL-4 or IL-13. Notably, M2 macrophages contribute to the proliferation of neighboring cells and participate in tissue repair and combating multicellular eukaryotic parasites. However, they also play a role in promoting pathological fibrosis and tumor growth (Brodsky 2020). They produce higher levels of anti-inflammatory cytokines, such as IL-10, and higher levels of ornithine and polyamine via the arginase pathway. *Salmonella* preferentially replicates in M2 rather than M1 bone marrow-derived macrophages (Lathrop et al. 2015). Notably, *S.* Typhimurium infection increases the production of proinflammatory cytokines TNF-α, IL-1β, IL-6, and CXCL8 in M1 macrophages, and the levels of these cytokines are lower in anti-inflammatory M2 macrophages than in M1 macrophages (Lathrop et al. 2015).

Salmonella can polarize macrophages to the M2 state by utilizing the effector SteE, which enhances the survival of *Salmonella* in macrophages. The serine/ threonine kinase glycogen synthase kinase-3 (GSK3) promotes SteE phosphorylation. The protein complex containing phosphorylated SteE and GSK3 binds to signal transduction and transcription activator 3 (STAT3), leading to the phosphorylation of

STAT3 at tyrosine-705 and activation of this transcription regulator. The activated STAT3 (pY705) drives macrophages towards polarization into the M2 state and promotes the production of the anti-inflammatory cytokine IL-10 (Panagi et al. 2020).

Modulation of inflammatory pathways

Nuclear factor (NF)-κB belongs to a family of crucial transcriptional regulation factors involved in immune homeostasis in intestinal cells and early pathogen detection, including *Salmonella*. It consists of homo- and heterodimeric complexes formed by various Rel/NF-κB proteins. In mammals, five known Rel/NF-κB proteins are RelA (p65), RelB, c-Rel, p50 (NF-κB1), and p52 (NF-κB2). Under normal conditions, NF-κB is bound to the inhibitory protein IκB and remains inactive in the cytoplasm. Upon stimulation by membrane-bound or cytoplasmic PRRs, IκB kinase is activated, leading to IκB phosphorylation and dissociation from NF-κB. The phosphorylated IκB is then ubiquitinated by a specific E3 ubiquitin ligase $SCF^{\beta-TrCP}$ for degradation, enabling NF-κB to enter the nucleus and activate the expression of target genes (Pilar et al. 2013). Activated NF-κB upregulates the expression of proinflammatory cytokines and enhances inflammatory response. In the early infection phase, a few *Salmonella* effectors and other components are needed for invasion and the induction of inflammation. Once bacteria are inside the host cells, *Salmonella* secretes other effectors to down-regulate inflammatory responses. *Salmonella* effectors, such as SopE, SopE2, and SopB, play a role in activating GTPases of the Rho family (Cdc42, Rac1, and RhoG), disrupting tight junctions, stimulating innate immune responses, and promoting inflammation in intestinal epithelial cells. These processes are critical for *Salmonella* to invade organs, such as the liver and spleen, during systemic infections (Huang et al. 2004).

Cdc42 and Rac1 activation ultimately triggers the NF-κB pathway, in addition to mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated protein kinases (ERKs), JNKs, and p38 MAPKs. This activation leads to significant transcriptional reprogramming in the host cell, resembling the response of innate immune receptors to stimulation (Du and Galan 2009). *Salmonella* LPS and TNF-α also activate the NF-κB pathway. The *Salmonella* effector SipA contains the central region of the SipA–SipA interaction (F2) required for T3SS1 translocation, which is critical for NF-κB activation. Additionally, NOD1, NOD2, and their downstream adapter RIP2 are required for SipA to activate the NF-κB pathway; however, its underlying mechanism remains unknown (Yang et al. 2021a).

Salmonella employs various strategies to ensure survival upon entering host cells by downregulating the immune response in the host. One such approach is the downregulation of NF-κB signaling (Table 1). *Salmonella* inhibits NF-κB and ERK signaling by hampering the phosphorylation of IκBα and ERK in macrophages, respectively. This anti-inflammatory effect of *Salmonella* is mediated by *Nlrp12*, as *Nlrp12*-deficient mice display higher tolerance

Table 1 *Salmonella* effectors that inhibit the nuclear factor (NF)-κB pathway

Effectors	Biochemical activities	Ways to inhibit the NF-κB pathway	References
AvrA	Acetyltransferase	Blocks the degradation of IκBα and β-catenin via their deubiquitination; blocks MAPKK phosphorylation activities by acetylating MAPKK	Yin et al. (2020)
SseL	Deubiquitinating enzyme	Inhibits the degradation of IκBα and RPS3	Wu et al. (2018)
SptP	GAP, tyrosine phosphatase	A GTPase-activating protein for Cdc42 and Rac1, transforming GTP-bound Cdc42/Rac1 to the GDP-bound form	Stebbins and Galan (2000)
GtgA	Zinc metalloprotease	Cleaves both RelA and RelB transcription factors	Sun et al. (2016)
GogA			Sun et al. (2016)
PipA			Sun et al. (2016)
GogB	Unknown	Inhibits IκB degradation	Pilar et al. (2012)
SpvB	Mono (ADP-ribosyl) transferase	Reduces the expression and phosphorylation of IκB kinase-β	Yang et al. (2021b)
SpvD	Cysteine hydrolase	Interacts with exportin Xpo2 to disrupt the normal recycling of importin-α from the nucleus to cytoplasm, leading to a defect in the nuclear translocation of p65	Rolhion et al. (2016)
SseK1 SseK2 SseK3	Protein-arginine N-acetylglucosaminyltra-nsferase	Modifies the TNF-α receptor 1 and its ligand, TRADD, preventing TNF-α mediated NF-κB activation	Günster et al. (2017)
SspH1	E3 ubiquitin-protein ligase	Unknown	Keszei et al. (2014)

MAPKK mitogen-activated protein kinase kinase; *GAP* GTPase-activated protein; *TNF-α* tumor necrosis factor-alpha; *TRADD* type 1-associated death domain protein

to *S.* Typhimurium infection, with significantly upregulated NF-κB and ERK signaling pathways compared with that in wild-type mice (Zaki et al. 2014). AvrA, an effector, acetylates MAPK kinase 4 (MKK4) and MAPK kinase 7 (MKK7), inhibiting NF-κB signaling. Additionally, AvrA can deubiquitinate IκBα, further preventing the activation of NF-κB. AvrA-induced acetylation of MKK4 and MKK7 effectively inhibits the JNK signaling pathway, thus suppressing JNK-mediated apoptosis and rapid bacterial spread. Inhibition of apoptosis through the JNK pathway may represent a conservative survival strategy for intracellular *Salmonella* (Wu et al. 2012). SseL, another effector, deubiquitinates IκBα and ribosomal protein S3 (RPS3), inhibiting its degradation and thereby suppressing the activation of NF-κB in macrophages (Wu et al. 2018).

The zinc metalloprotease GtgA, GogA, and PipA secreted by *Salmonella* can recognize the relatively conserved P1′ sites in both subunits RelA (p65) and RelB of the NF-κB transcription factor, leading to the cleavage of both RelA and RelB transcription factors, ultimately inhibiting the NF-κB pathway (Jennings et al. 2018). The GogB effector interacts with Skp1 and F-box only 22 proteins to inhibit the polyubiquitination of IκB, thereby preventing IκB degradation and blocking the NF-κB pathway (Pilar et al. 2013). SpvB inhibits the activation of NF-κB, which is associated with the downregulated expression and phosphorylation of IκB kinase-β, as well as the upregulation of E3 ligase Kelch-like ECH-associated protein 1 (KEAP1). The underlying mechanism may be intricate, as KEAP1 downregulates Nrf2 expression, an inhibitor of the NF-κB pathway, through several axes (Yang et al. 2021b). The effector SpvD, located on the pSLT plasmid and secreted by T3SS2, interacts with exportin Xpo2, disrupting normal importin-α circulation from nucleus to cytoplasm, leading to the accumulation of importin-α in the nucleus and the subsequent failure of p65 nuclear translocation, inhibiting the NF-κB pathway (Rolhion et al. 2016).

A group of effectors encoded by SPI-2, including SseK1, SseK2, and SseK3, inhibits the TNF-α-activated NF-κB pathway. SseK1, an effector secreted by T3SS2 with protein-arginine N-acetylglucosaminyltransferase activity, modifies TNF-α receptor 1 (TNFR1), TNFR1-associated death domain protein (TRADD), and FAS-associated death domain protein (FADD). Similarly, SseK3 modifies TNFR1 and TRADD and is a member of the TNFR superfamily 10B. Consequently, SseK1 and SseK3 jointly prevent TNF-α-induced NF-κB pathway activation and inhibit macrophage apoptosis. Although SseK2 translocates during *Salmonella* infection in macrophages, its effect on the NF-κB pathway is limited and appears confined to the arginine *N*-acetylglucosaminylation of FADD (Xue et al. 2020). The E3 ubiquitin ligase SspH1 can inhibit NF-κB signaling, but its precise mechanism of action remains unclear, as it does not affect the activity of NF-κB despite its interaction with PKN1 through the LLR domain (Keszei et al. 2014).

SptP has GTPase-activated protein (GAP) activity, which can lead to the inactivation of Cdc42 and Rac1. Thus, SptP downregulates the MAPK signaling pathway. Additionally, the tyrosine phosphatase activity of SptP inhibits MAPK activation. Both GAP and tyrosine phosphatase activities of SptP inhibit Raf activation, ERK activation, and IL-8 production (Zaki et al. 2014), thereby reducing the inflammatory response of host cells and enhancing the intracellular replication of *Salmonella* (Lin et al. 2003). The *Salmonella* phosphothreonine lyase SpvC inactivates ERK1/2, p38, and JNKs by β-elimination, thereby inhibiting their downstream signaling pathways (Haneda et al. 2012).

Salmonella interferes with antigen presentation in the host

During *Salmonella* infection, both innate and adaptive immune responses of the host are initiated; however, *Salmonella* utilizes strategies to dampen these immune pathways (Schleker et al. 2012). *Salmonella* actively hinders the migration of dendritic cells and interferes with antigen presentation via MHC-I and MHC-II molecules. Several studies have identified key effectors, such as SifA, SspH2, SlrP, PipB2, and SopD, that play crucial roles in inhibiting antigen presentation, whereas SseF and SseG exhibit a milder impact on this process than that of other effectors (Halici et al. 2008). Additionally, an unidentified *Salmonella* effector disrupts MHC-I antigen presentation and impedes the transportation of antigen-carrying vesicles to MHC-II compartments. Interaction between SlrP and ERdj3, an endoplasmic reticulum DnaJ homolog, leads to the inhibition of antigen presentation (Bernal-Bayard et al. 2010). Certain T3SS2-secreted effectors are involved in curtailing dendritic cell migration along chemokine gradients. For instance, SseI reduces the migration of *Salmonella*-infected dendritic cells from the mouse gut to mesenteric lymph nodes, potentially causing delays in T-cell responses and enhancing *Salmonella* virulence. Structural and biochemical analyses have revealed the ability of SseI to deamidate heterotrimeric G proteins of the Gαi family, including Gαi2, leading to persistent G-protein activation (Cerny and Holden 2019).

Antigen presentation by dendritic cells to $CD4^+$ T cells is crucial for controlling intracellular bacterial replication during systemic *Salmonella* infection, and specific effectors secreted by T3SS2 of *Salmonella* disrupt this process. In dendritic cells, SteD interacts with mature MHC-II (mMHC-II) and host E3 ubiquitin ligase membrane-associated RING-CH (MARCH) 8 in vesicles, promoting the ubiquitination of mMHC-II β chains. This ubiquitination of mMHC-II β chains results in mMHC-II degradation, directly obstructing antigen presentation mediated by MHC-II. Additionally,

SteD reduces the surface levels of the costimulatory molecule CD86, which is necessary for full T-cell activation and is regulated by MARCH 1. Therefore, SteD inhibits T cell activation during *Salmonella* infection in mice (Alix et al. 2020). SteD also enhances CD97 ubiquitination for degradation. The removal of CD97 by SteD hinders interactions between dendritic cells and T cells, ultimately reducing T cell activation, independent of its effect on MHC-II (Cerny et al. 2021). However, *Salmonella* indirectly impairs $CD4^+$ T cell function via asparaginase, which converts exogenous L-asparagine to aspartic acid and ammonia, leading to downregulation of the T cell receptor and inhibition of T cell proliferation (Kullas et al. 2012). *Salmonella* utilizes T3SS2 to clear $CD4^+$ T cells, and this process correlates with an increase in programmed death ligand 1 (PD-L1) expression on antigen-specific $CD4^+$ T cells. The binding of PD-L1 to its programmed cell death protein 1 receptor present on dendritic cells restricts the proliferation of antigen-specific $CD4^+$ T cells (Cerny and Holden 2019).

Inhibition of antimicrobial peptides and the use of hepcidin by *Salmonella*

Hitherto, extensively studied antimicrobial peptides include lysozymes, hepcidin, defensins, and cathelicidins. Antimicrobial peptides can disrupt cell walls and outer membranes in *Salmonella*, followed by host-derived proteases hydrolyzing periplasmic proteins; however, this process is often hindered by SCVs (Slauch 2011). Bacteria that establish symbiotic relationships with hosts or cause diseases have evolved diverse strategies to evade these antimicrobial peptides. Lysozymes represent a critical element of the ancient innate immune system in animals. They are secreted extracellularly and function to hydrolyze peptidoglycan, a constituent of the bacterial cell wall. *Salmonella* has developed multiple mechanisms to counteract lysozymes, including the production of lysozyme inhibitors. *Salmonella*'s lysozyme inhibitors, MliC (membrane-bound) and PliC (periplasmic), exhibit inhibitory effects on C-type lysozymes (Callewaert et al. 2008).

Hepcidin produced by hepatocytes can decrease iron release from macrophages. Notably, *S.* Typhimurium exploits this metabolic pathway for its benefit, growth, or survival, as *S.* Typhimurium infection induces the expression of estrogen-related receptor γ, which, in turn, stimulates the expression of hepcidin. Thus, *S.* Typhimurium ensures sufficient intracellular iron concentrations while infecting macrophages (Kim et al. 2014). Additionally, *Salmonella* promotes hepcidin synthesis in a STAT3-dependent manner through the effector SpvB. The liver contains a high content of hepcidin, which may be a primary reason why the liver is a major site for the growth and replication of *Salmonella* in systemic infection. Hepcidin binds to ferroportin in an outward-open conformation to promote its degradation, thereby increasing the iron content in the cytoplasm of host cells (Deng et al. 2021). As iron is an essential element for *Salmonella* growth, increased iron levels are associated with increased hepcidin levels to facilitate *Salmonella* replication (Fig. 4) (Kim et al. 2014).

Resistance against reactive oxygen species and reactive nitrogen species

Salmonella possesses several superoxide dismutases, namely SodA, SodB, and SodC, which utilize Mn, Fe, or Cu–Zn as cofactors. These superoxide dismutases protect cells against superoxide anion radicals produced within them. Notably, a *Salmonella sodC* mutant exhibits significantly reduced intracellular survival and virulence in mice and shows heightened sensitivity to superoxide and nitric oxide (NO) (De Groote et al. 1997). While reactive nitrogen species (RNS) have traditionally been regarded as critical mediators of host defense against pathogens, *Salmonella* can exploit the RNS produced during infection to enhance its virulence (Henard and Vazquez-Torres 2011). Notably, NO, a type of RNS, can inhibit bacterial growth by modifying various intracellular targets, including protein thiols, heme-containing proteins, thiol-coordinated metals, lipid bilayers, and DNA. *Salmonella* has evolved multiple mechanisms to limit its exposure to NO during infection. For instance, the flavin protein Hmp of *Salmonella* converts NO to nitrate, attenuating its inhibitory effects on *Salmonella* growth. In addition, NO can be oxidized to dinitrogen trioxide (N_2O_3) or peroxynitrite, mediating the deamination and oxidation of DNA bases, respectively. For example, N_2O_3 deaminates cytosine to form uracil, which can mutate DNA; however, the uracil DNA glycosylase of *Salmonella* can remove uracil (dU) that is mistakenly inserted into DNA, resulting in apurinic/apyrimidinic (AP) sites, thus avoiding mutations. Peroxynitrates oxidize adenine, guanine, and xanthine nucleosides, resulting in genetic mutations. Formamidopyrimidine-DNA glycosylase (Fpg) in *Salmonella* can remove oxidized guanine (dG) and limit peroxynitrate-mediated supermutations. In addition, adenine DNA glycosylase (MutY) blocks genetic mutations in *Fpg*-deficient cells. *Salmonella* can avoid NO-induced mutations, such as endonuclease V (*Nfi*) mutations, by not producing AP sites. In summary, the base excision repair system *of Salmonella* can prevent NO damage to DNA (Richardson et al. 2009).

Inhibition of neutrophil function

Host neutrophils defend against pathogens in various ways, such as via phagocytosis, degranulation, cytokine production, and neutrophil extracellular traps (Delgado-Rizo et al. 2017); however, despite their potent antibacterial

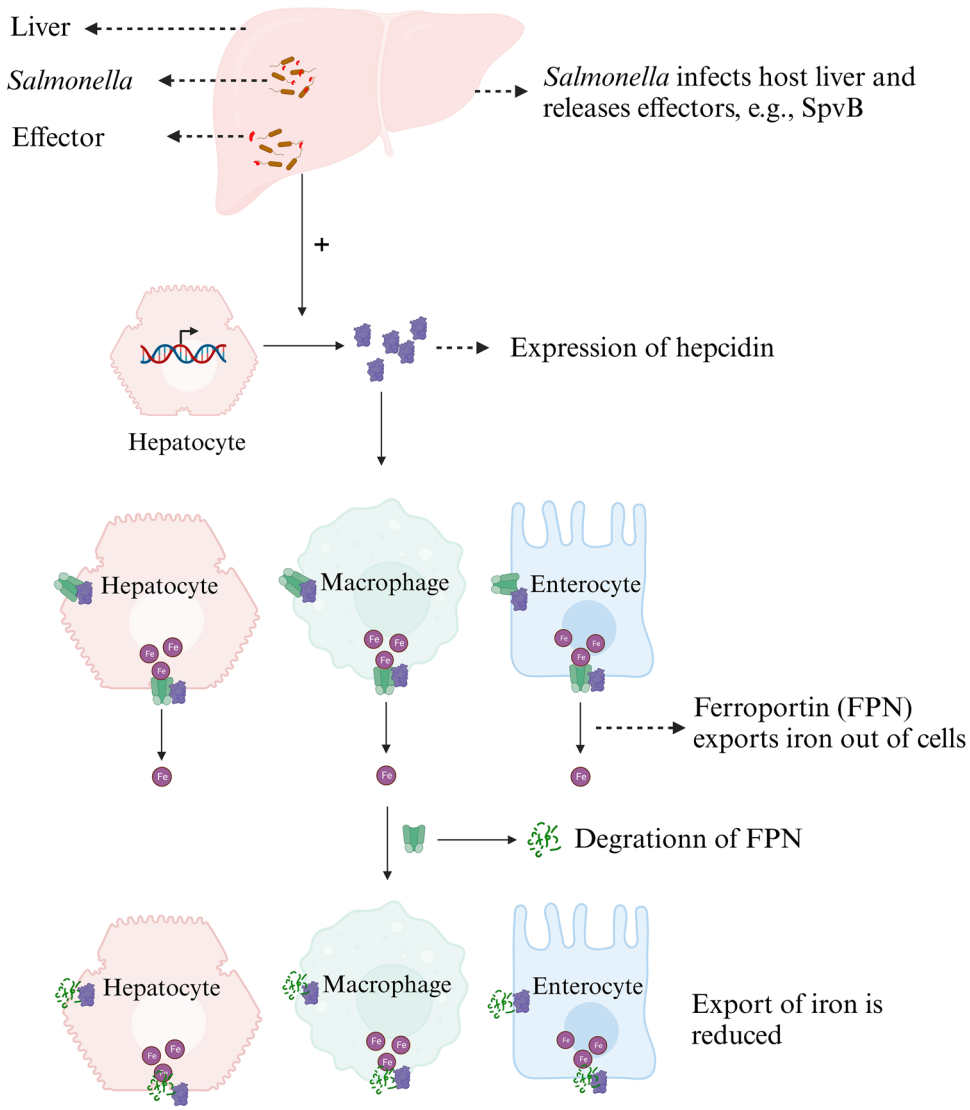

Fig. 4 *Salmonella* infection upregulates hepcidin production by host cells to inhibit iron export and promote intracellular replication

activity, their ability to clear pathogens is partly impaired by *Salmonella*. In the early stages of infection, neutrophils contain live *Salmonella* that can escape into more permissive cell types. D-alanine exists in peptidoglycan stem peptides of *Salmonella* and is a substrate of D-amino acid oxidase (DAO) produced by host cells. *Salmonella* prevents DAO-induced oxidative damage in neutrophils by expressing a D-alanine ABC importer (DalS). DalS-mediated neutrophil DAO subversion is a novel host–pathogen interaction that enhances *Salmonella* survival during systemic infections (Tuinema et al. 2014). SptP inhibits Cdc42 and Rac1 activities after *Salmonella* invasion into epithelial cells, thus inhibiting IL-8 production and reducing neutrophil recruitment (Lin et al. 2017).

Disruption of host metabolism and looting of nutrition

Carbon sources

Salmonella infection upregulates the glycolytic pathway of macrophages and downregulates the tricarboxylic acid cycle, mainly manifested by the accumulation of glycolytic intermediates and is related to a few effectors, such as SopE2 and SseK3 (Yu et al. 2020; Jiang et al. 2021). The upregulation of host glycolysis contributes to the intracellular replication of *S.* Typhimurium and systemic infection in mice, as glucose is the primary carbon source required

for intracellular replication of *S.* Typhimurium (Bowden et al. 2009). Other glycolytic products such as 2-phosphoglycerate, 3-phosphoglycerate, and phosphoenolpyruvate can also be used as carbon sources by intracellular *S.* Typhimurium (Jiang et al. 2021).

Recently, we demonstrated that *S.* Typhi—which causes systemic infection in humans—increases glucose content, glucose uptake, and glycolysis rates in human primary macrophages and reduces oxidative phosphorylation levels (Wang et al. 2021). Additionally, *Salmonella* in macrophages can directly obtain fatty acids from SCVs using FadL transporters and degrade them via β-oxidation (Taylor and Winter 2020). Different types of macrophages differ significantly regarding carbon metabolism during *Salmonella* infection. Glycolysis is significantly upregulated in M1 macrophages compared with that in M2 macrophages. In M2 macrophages, *Salmonella* activates transcription factor peroxisome proliferator-activated receptor δ, which drives fat oxidation in host cells, supplying additional available carbon sources to *Salmonella* (Eisele et al. 2013).

Nitrogen sources

Previous studies have shown that *Salmonella* uses various amino acids in host cells—such as arginine, glutamine, aspartic acid, asparagine, alanine, and proline—for survival and replication (Popp et al. 2015). *Salmonella* infection increases arginine uptake and expression of two cationic amino acid transporters, mCAT1 and mCAT2B, in macrophages and dendritic cells. To access the cytoplasmic arginine pool of macrophages, live *Salmonella* recruits mCAT1 transporter to SCVs. *Salmonella* present in SCVs acquires host-derived arginine via arginine transporter ArgT, as the knockout of *argT* attenuates the growth of *Salmonella* in mouse infection models and macrophages (Das et al. 2010). Additionally, polyamines—the degradation products of arginine—contribute to the translation of HilA, the main positive regulator of SPI-1 genes (Guerra et al. 2020). We recently reported that *Salmonella* utilizes inflammation-induced nitrate to replicate in macrophages and cause systemic infection (Li et al. 2022). How intracellular *Salmonella* obtains other amino acids and whether these amino acids promote the virulence of *Salmonella* are thus worth exploring in the future.

Metal ions

Salmonella requires metal ions (such as iron, magnesium, and zinc) from host cells for normal metabolism, growth, and virulence. Iron promotes the growth and adhesion of *Salmonella*, as well as its invasion and translocation across the epithelial monolayer (Kortman et al. 2012). *Salmonella* can directly acquire free ferrous iron using a ferrous transporter, Feo. *Salmonella* secretes two catecholate-type siderophores to obtain iron, including enterobactin and its glycosylated derivative, salmochelin (Crouch et al. 2008). Intracellular *Salmonella* maintain intracellular magnesium balance through regulatory systems, such as PhoQ/PhoP and magnesium ion transport systems, thus contributing to virulence gene expression and intracellular survival (Choi and Groisman 2016). The sequestration of zinc by macrophages is considered a vital host defense strategy against intracellular *Salmonella* infection; however, *Salmonella* has evolved several strategies to obtain zinc, such as using a high-affinity zinc transport system. *Salmonella* infection increases zinc levels in macrophages, helping to inhibit the transcriptional activation of p65 and thus inhibiting the production of ROS and RNS mediated by NF-κB (Wu et al. 2017). Further research is needed to elucidate how intracellular *Salmonella* acquire other essential nutrients for ensuring their survival and growth.

Host intracellular environment promotes the virulence of *Salmonella*

During infection, macrophages shift their metabolism to aerobic glycolysis, resulting in the intracellular accumulation of glycolytic products like succinate. The increased succinate can be sensed by intracellular *S.* Typhimurium, promoting expression of the T3SS, its secreted effectors, and the factors involved in resistance to antimicrobial peptides (Rosenberg et al. 2021). Additionally, the accumulation of pyruvate and lactate in macrophages increases the expression of a *Salmonella* two-component system called CreBC. CreB, in turn, enhances VrpB expression by binding to the *vrpB* promoter. VrpB further binds to the promoter of *ssrA/B*, directly activating the expression of T3SS2-related genes (Jiang et al. 2021). The acidic pH (< 5–5.5) of SCVs is crucial for the expression of genes encoding T3SS2 and its secreted effectors, which are required for the replication of *Salmonella* in host cells (Yu et al. 2010). In *S.* Typhimurium, a weakly acidic cytoplasmic pH contributes to the activation of at least three two-component systems, i.e., PhoQ/PhoP, EnvZ/OmpR, and SsrA/B, thereby promoting the expression of T3SS2-related genes (Kenney 2019). In addition, intracellular signals inside host cells contribute to increased kinase activity of PhoQ, enhancing PhoP phosphorylation and the expression of T3SS2-related genes. The periplasmic domain of PhoQ senses low levels of Mg^{2+} ions, certain antimicrobial peptides (e.g., antimicrobial peptide C18G), and polymyxin B, whereas its cytoplasmic domain senses a mildly acidic pH, collectively activating the expression of T3SS2-related genes (Choi and Groisman 2016). The transcriptional regulatory protein AsiR positively regulates flagellar gene expression by directly binding to the *flhDC* promoter. However, the acidic pH in macrophages downregulates the

expression of AsiR, leading to the downregulation of flagellar gene expression, ultimately promoting the intracellular survival and systemic infection of *Salmonella* (Ma et al. 2021). Additionally, the acidic pH in SCVs promotes *yaeB* expression (encoding an N6 methyltransferase) through inhibiting global regulator histone-like nucleoid structuring protein (H-NS), directly promoting the expression of genes associated with phosphate acquisition and the virulence of *S.* Typhimurium (Zhang et al. 2019).

Effects of *Salmonella* infection on host cell survival

A few serovars of *S. enterica* cause chronic inflammation and mucosal damage and produce toxins such as cytolethal distending toxins (CDTs) that cause DNA damage and cell cycle inhibition. In a few salmonellae, such as *S. enterica* serovars Javiana and Typhi, CDTs are hetero-trimer toxins composed of PltA, CdtB, and PltB subunits. The CdtB subunit exhibits DNAse I activity, leading to cell cycle arrest in the G2/M phase, whereas PltA and PltB facilitate CdtB entry into host cells (Zha et al. 2019). The *Salmonella* effector PheA can be translocated into the nucleus of RAW 264.7 macrophages to mimic the E2F7 transcription factor of host cells, promoting cell cycle arrest in the G1/S phase, thereby reducing the proportion of cells in the G2/M phase (Na et al. 2015). The effector AvrA acetylates P53, retarding the cycle of intestinal epithelial cells, resulting in an increase in the number of cells in the G0/G1 phase and a decrease in the number of cells in the G2/M phase (Wu et al. 2010).

Salmonella infection can lead to cell death through apoptosis, necroptosis, and pyroptosis. Apoptosis is related to caspases 3/7/8/9, pyroptosis to caspases 1/4/5/11, and necroptosis to mixed lineage kinase domain-like protein and other unknown factors (Wemyss and Pearson 2019). Moreover, *Salmonella*-derived LPS and effectors (SlrP, SpvB, and SpvC) promote host cell apoptosis in *Salmonella* infection (Man et al. 2013). Pyroptosis is a vital host defense mechanism against *Salmonella*, and many virulence factors participate in its activation, including flagellin proteins (FliC and FljB), LPS, rod-shaped proteins (PrgJ), and effectors (SopE and SipB). Moreover, *Salmonella*-induced ROS and dsDNA can accelerate pyroptosis (Wemyss and Pearson 2019). Certain *Salmonella* effectors, such as SseK1 and SseK3, inhibit apoptosis and necroptosis in macrophages through arginine glycosylation of FADD and TRADD. S*almonella* effector protein SopB delays the apoptosis of epithelial cells by sustaining activation of Akt, allowing sufficient time for its intracellular replication (Knodler et al. 2005; Chu et al. 2021). *Salmonella* can survive in B cells but the mechanisms are not very clear. Two studies found SopB activates PI3K/Akt pathway to downregulate of NLRC4 transcription and IL-1β secretion of B cells, which delaying pyroptosis of infected B cells and therefore providing a stable niche for *Salmonella* survival (García-Gil et al. 2018; Luis et al. 2022). Additionally, the effector AvrA inhibits apoptosis, whereas SpvC inhibits pyroptosis (Haneda et al. 2012). Hence, *Salmonella* exploits various effectors to regulate the host cell death response, which might be a conservative strategy employed by *Salmonella* to increase its populations and prepare for its next invasion, finally spreading to other cells and organs.

Conclusions and future perspectives

Salmonella establishes infection in hosts by overwhelming host cell defenses. Following invasion into epithelial or M cells in the intestine, the pathogen is taken up by phagocytes that transport the bacteria to organs, such as the liver, spleen, kidney, and bone marrow, through the blood or lymph circulation. If hosts fail to quickly eliminate *Salmonella* in the early infection/invasion processes because of the slowness of immune signaling activation and shortage of immune cells/substances/molecules, the rapid replication of *Salmonella* inside host cells destroys the host cells and damages host organs, further promoting the spread of *Salmonella* and weakening the host immunity.

Salmonella exploits various strategies to combat epithelial and immune cells, including macrophages, dendritic cells, and neutrophils. It uses many secreted effectors/ proteins to survive in the host, and resists immune responses of the host through the production of inhibitors, blockage of immune signaling pathways, disruption of host metabolism, cell cycle arrest, or modulation of host cell death. The exact functions of many proteins and effectors of *Salmonella* and their interactions with host cells remain unknown. Therefore, there is much room to explore the mechanisms underlying *Salmonella* pathogenicity regarding its survival strategies in host cells, tissues, and organs.

Acknowledgements The authors are thankful for the suggestions provided by Dr. Lingyan Jiang from Nankai University for the revision of the manuscript.

Author contributions W.L. wrote and revised the manuscript. Q.R. drew the figures and made revisions for the manuscript. T.N., Y.Z., Z.S., and R.L. collected the references and verified the points presented in the manuscript. Z.L. and S.L. conceived and revised the manuscript. All authors reviewed the manuscript.

Funding This work was supported by the National Natural Science Foundation of China [grant number 82170606] and the Basic Research Project of Key Scientific Research Projects of Universities in Henan Province [grant number 23ZX006].

Data availability Data sharing does not apply to this article as no new data were created or analyzed in this review.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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