UDC 619:615.281.9

SALMONELLA INFECTION: INTERPLAY BETWEEN THE T3SSS EFFECTORS AND NF-KB SIGNALING PATHWAY

Zhike Liu
postgraduate student
Sumy National Agrarian University, Sumy, Ukraine
ORCID: 0000-0001-5079-2390
zkeliu@163.com

Fotin Anatoliy Ivanovich
Candidate of Veterinary Sciences, Associate Professor
Sumy National Agrarian University, Sumy, Ukraine
ORCID: 0000-0001-8396-9295
fotin53@ukr.net

Petrov Roman Viktorovych
Doctor of Veterinary Sciences, Professor,
Sumy National Agrarian University, Sumy, Ukraine
ORCID: 0000-0001-6252-7965
romanpetrov1978@gmail.com

Jinyou Ma
Doctor of Veterinary Sciences, Professor,
Henan Institute of Science and Technology, Xinxiang, China
ORCID: 0000-0002-8132-0377
marsjy@163.com

Fotina Tetiana Ivanivna
Doctor of Veterinary Sciences, Professor,
Sumy National Agrarian University, Sumy, Ukraine
ORCID:0000-0001-5079-2390
tif_ua@meta.ua

Salmonella is an important foodborne pathogen that can evade host immune defense by evolving unique mechanisms. Salmonella manipulate host cell various signaling pathways by delivering specific effectors into target cells to establish infection. The nuclear factor-κB (NF-κB) is an important nuclear transcription factor that regulates the host immune system in Salmonella infection. The Salmonella pathogenicity island 1 (SPI-1) and Salmonella pathogenicity island 2 (SPI-2) encode type III secretion systems (T3SSs), effectors that are associated with the NF-κB signaling pathway through regulate host inflammation response. SPI-1 effectors SipA, SopE, SopE2, and SopB all can activate NF-κB signaling pathway to facilitate Salmonella invasion and intracellular carriage. Studies have shown that T3SS1 and/or T3SS2 effectors such as GtgA, GogA and PipA contain two histidine residues and have metalloprotease activity to control Salmonella replication. These zinc metalloproteases redundantly target the NF-κB subunits p65, RelB, and c-Rel, whereas GogA and GtgA only inhibit NF-κB-dependent gene transcription. The T3SS2 effectors SseK1, SseK2, and SseK3 are death domain-containing proteins with N-linked glycosyltransferase characteristics that can inhibit NF-κB activity by inhibiting IκBα phosphorylation in TNF-α-treated 293ET cells. Among them, SseK1 and SseK3 also suppress Salmonella-induced NF-κB activity in macrophages. SseK3-mediated inhibition of the NF-B signaling pathway is not required for protein 32 containing a tripartite E3-ubiquitin ligase motif. In addition, the SPI-2 T3SS effector SpvD inhibits NF-κB activity by preventing nuclear translocation of p65 through interaction with Exportin-2, but this does not affect IκBα degradation, which ultimately leads to systemic Salmonella growth. However, other effectors SptP, AvrA, IpaJ, SspH1, GtgA, GogA, and SPI-2 encoded SseL, SpvB, SseK1, and GogB all can effectively inhibit NF-κB signaling pathway, and contribute to Salmonella intracellular replication and virulence. In this mini-review, we summarize the special mechanism how NF-κB signaling pathway is regulated by Salmonella T3SSs effectors in the persistent infection of Salmonella, which will further elucidate the pathogenesis of Salmonella.

Key words: *Salmonella; T3SSs effectors; NF-κB signaling pathway; host immune defense; pathogenic mechanism.*

DOI https://doi.org/10.32782/bsnau.vet.2023.3.1

Introduction. *Salmonella* is an important intracellular pathogen and can cause a severe systemic disease, such as typhoid fever in humans, diarrhea in chickens, paratyphoid fever in pigs and cattle (Gal-Mor et al., 2018; Coburn et al., 2007). *Salmonella* enters the digestive tract by the oral infection of contaminated food (Ménard et al., 2022). Once

Salmonella reach the small intestine and colon, a large number of *Salmonella* attach to the intestinal mucosal epithelial cells, and invade the submucosal tissue through the M cells, then engulfed by immune cells like dendritic cells, macrophages and neutrophils, which can help the spread of *Salmonella* to systemic tissues, such as liver and spleen (Broz et al., 2012; Xie et al., 2020; Krukonis et al., 2020). In addition to *Salmonella* flagellin and lipopolysaccharide (LPS) on the surface of bacteria (Liu et al., 2019), it also has a variety of effectors that are secreted into host cells though the T3SS, and control different cellular functions (Dos Santos et al., 2020). These effectors of *Salmonella* interfere with cell signaling cascades through a variety of mechanisms, and enhanced their intracellular proliferation and survival in host cells (Walch et al., 2021). NF-κB pathway is an important signaling pathway that affects the host immune response in *Salmonella* infection (Sun et al., 2016). This article reviews the mechanism of *Salmonella* infection based on the latest research results about the interplay of *Salmonella* effectors and NF-κB signaling pathway, and will provide new ideas for the pathogenesis of *Salmonella*.

Research materials and methods. The research and review of scientific literary sources was carried out on the basis of the Department of Virology, Pathanatomy and Poultry Diseases, the Department of Veterinary Expertise, Microbiology, Zoohygiene and Safety and Quality of Livestock Products of the Faculty of Veterinary Medicine of the Sumy National Agrarian University, as well as in Henan Institute of Science and Technology, Xinxiang, China.

Results.

SPI and effectors. The genome size of *Salmonella* is similar to that of *Escherichia coli*, with only 10% difference in sequence (de Jong et al., 2012). The virulence factors of *Salmonella* pathogenicity are mainly located on its pathogenicity island (Jennings et al., 2017). The intracellular survival and proliferation of *Salmonella* rely on the T3SS effectors encoded by SPI-1 and SPI-2, which can inject some effector proteins into the cytoplasm to promote *Salmonella* invasion and dissemination (Brink et al., 2018). However, *Salmonella* T3SS effectors can stimulate the signal transduction pathways of host cells, leading to a series of cellular effects such as the rearrangement of cytoskeleton, activation of transcription factors, and stimulation of ion channels *in vivo* and *in vitro* (Dos Santos et al., 2020; Jia et al., 2022). These effectors expression of SPI-1 and SPI-2 are strictly regulated in host cells and are essential for assembled T3SS at different infection phases (Dos Santos et al., 2020).

Host immune response and NF-κB signaling pathway. In order to cope with the infection of *Salmonella*, the host has formed various defense mechanisms such as innate immunity and adaptive immunity (Noster et al., 2019). The innate immune system are initiated through a series of pattern recognition receptors, which recognize the relatively conservative and key structural components of pathogenic microorganisms, thereby control the invading pathogen (Kogut et al., 2020). Normally, pathogen-associated molecular patterns are usually composed of bacterial surface components, such as LPS, flagellin, peptidoglycan, lipoteichoic acid, and cell wall lipoproteins (Potrykus et al., 2021; Lu et al., 2022). Furthermore, the pattern recognition receptors of the innate immune responses were involved include Toll-like receptors (TLR), nucleotide oligomerizaton domain-like receptor (NLR), cytoplasmic RNA receptors, and cytoplasmic DNA-related receptors (Liao et al., 2021). NF-κB transcription factor is the regulatory center of host inflammatory response that controls DNA transcription (Stormberg et al., 2021). NF-κB is a homo- and heterodimers in mammals whose subunit consists of five members, such as c-Rel, p50 (NF-κB1), RelA (p65), p52 (NF-κB2), and RelB (Hayden et al., 2008). These members contain the Rel homologous domain with conserved DNA binding activity, and have the ability to regulate the protein dimerization and nuclear localization signals. Inactivation of NF-κB and inhibition of IκB protein phosphorylation are located within the cytoplasm (Bariana et al., 2022). When host is infected by pathogenic bacteria such as *Salmonella*, and TLRs signaling pathways are activated, resulting in initiate antigen presentation functions, thereby the NF-κB dimers rapidly dissociates from the cytoplasm to the nucleus, which triggers the pro-inflammatory-related gene expression (Liu et al., 2019; Li et al., 2022). However, *Salmonella* effectors target NF-κB signaling pathway to facilitate *Salmonella* invasion and dissemination within host cells at different stages of infection.

Activation of NF-κB signaling pathway by effectors. There are many microorganisms in the intestines of humans and animals (Markowiak et al., 2017). In order to avoid unnecessary immune reactions, the NF-κB signaling pathway is suppressed in intestinal cells (Tao et al., 2021). Pathogens induce NF-κB activity through a variety of mechanisms, which is crucial to promote intracellular replication and virulence in their host (Gómez-Chávez et al., 2021). Inflammation aggravates the accumulation of nutrients to the growth of *Salmonella* at an early stage of infection (Sharma et al., 2022). Furthermore, numerous intracellular effectors can drive the host's immune response to produce the electron acceptor tetrathionate in the respiratory chain (Bliska et al., 2012), which can enable *Salmonella* to more efficiently gain host nutrients when compared with other bacterial pathogens, leading to promote intracellular replication in the host (Lawrence et al., 2021).

TLR5 is a receptor for *Salmonella* flagella, which in turn activates MyD88-NF-κB signaling pathway, but some effectors can activate NF-κB signaling pathway by other ways (Jiang et al., 2015). SipA is a virulent effector of *Salmonella*, and is translocated into the host cells by T3SS-1, enables *Salmonella* invasion (Finn et al., 2017). Studies have found that NF-κB activity is trigged by SipA that is not dependent on the invasion of *Salmonella*, but it is requires for complete T3SS (Keestra et al., 2011). Furthermore, the heterologous expression of SipA affects NF-κB activity, but this signal does not depend on MyD88. Conceivably, the intracellular SipA and intracellular receptor NOD1 form a complex that can activate NOD1/NOD2, which lead to the invasion of epithelial cells and NF-κB activity within host cells (Keestra et al., 2011).

T3SS1-related effectors can induce activation of Rho-family GTPases such as Rac1 and Cdc42, and contribute to *Salmonella* internalization by activating Rac-1 and

inflammation by activating Cdc42, respectively (Parween et al., 2019). These two Rho GTP enzymes are components of the host signaling pathway and participate in the rearrangement of the actin cytoskeleton structure (Liu et al., 2020). Several effectors, SopE, SopE2, and SopB within the SPI1 all are associated with the stimulating MAP kinase and NF-κB signaling pathway by activate Rho-family GTPases (Bruno et al., 2009). SopE and SopE2 are guanine nucleotide exchange factors of Rac1 and Cdc42 that induces rapid membrane ruffling in host cells, which promotes *Salmonella* invasion and systemic infection (Galán, 2021). SopB is a phosphoinositide phosphatase and has the ability to activate the Rho-family GTPases, such as Rac1 and Cdc42 (Pinaud et al., 2018). These three effectors are secreted into host cells by T3SS1 that is required for *Salmonella* invasion. Therefore, the activated Rho-family GTPase significantly increases detected by NOD1, and subsequent induces inflammatory responses by activating NOD1-RIP2-NF-κB signaling pathway in host cell (Bruno et al., 2009). Studies have found that intracellular SopE forms complexes with Rac1, Cdc42, NOD1, and heat shock protein 90, indicating that SopE-dependent Rac1 and Cdc42 activation is required for the proteasome-mediated pathway, which in turn activates NF-κB signaling pathway through NOD1 (Keestra et al., 2013). Therefore, this multi-factorial and multi-channel activation mechanism strongly ensures NF-κB activity and is central to the system infection of *Salmonella* (Cuadrado et al., 2014). This phenomenon indicates that the activation of the immune response is greatly beneficial to *Salmonella* invasion at an early stage of infection. However, the underlying mechanism of these effectors between innate immune signal and innate immune receptors remains obscure.

Inhibition of NF-κB signaling pathway by effectors. Although the activation of host inflammatory response plays an important role against invading *Salmonella*, some effectors are secreted into host cells by T3SSs that have the ability to inhibit excessive immune response. However, the specific mechanism by which *Salmonella* effectors interface with NF-κB signaling pathway remains poorly understood.

AvrA. AvrA is a virulent effector of *Salmonella* within SPI-1, and its code size is 33kDa (Lin et al., 2016). AvrA has the activity of serine/threonine acetyltransferase and ubiquitin hydrolase, and play a pivotal role in suppression of host's innate immune response, thereby contribution to *Salmonella* dissemination and intracellular carriage (Zhang et al., 2015). AvrA decreases IκBα degradation and stabilizes *β*-catenin, and inhibit NF-κB activity through ubiquitin-proteasome degradation pathway *in vivo* and *in vitro* (Ye et al., 2007). AvrA is a deubiquitinase that can inhibit MAPK activity by downregulating p-MEK/p-ERK in *Salmonella*-infected HeLa cells, leading to facilitate *Salmonella* invasion (Giogha et al., 2014). AvrA as a key regulator of immune responses, which can control both the inflammatory and apoptotic signaling in infected macrophages (Jiao et al., 2020). Studies have shown that the *avrA*-deficient strain increased apoptosis in caspase-3-stimulated cells (Wu et al., 2012).

SseL. SseL is one of the *Salmonella* effectors secreted through T3SS2, and has the activity of the deubiquitinase (Geng et al., 2019). The function of effector SseL was performed by the two-component regulatory system SsrA/SsrB, and can induce cytotoxicity in infected macrophages (Rytkönen et al., 2007). However, SseL has no effect to the intracellular replication of *Salmonella* within *Salmonella*-containing vacuoles (SCV), but it participates in the regulation of cytotoxicity (Figueira et al., 2013). SseL inhibit NF-κB activity by deubiquitinating of IkBa in primary murine bone-marrow-derived macrophages, but the following study proposed that SseL does not affect the degradation of IκBα and inflammatory response (Mesquita et al., 2013). However, some *in vitro* experiments shown that SseL protein directly targets the K63-polyubiquitin chain in the host cell, and regulate the intracellular signal activation of host cells degraded by the ubiquitin proteasome pathway (LaRock et al., 2015). In addition, SseL also represents a member of the deubiquitinate, but the regulatory effect of this protein *in vivo* is not fully understood.

SptP. SptP is a GTPase activating protein encoded by T3SS1 (Johnson et al., 2017), and inhibit NF-κB activity by limiting the activation of Rac1, Cdc42, and Rho in host cells (Johnson et al., 2017). The SptP translocation can interfere with the actin cytoskeleton reorganization and c-Jun N-terminal kinase (JNK) activation with the ability to inhibit MAP kinases, thus causing the secretion of pro-inflammatory factors (Cain et al., 2008; Lhocine et al., 2015). SptP can increase the function of host cytoskeleton to recover homeostasis by preventing the activation of Cdc42, and contribute to the intracellular replication and dissemination of *Salmonella* (Fu et al., 1999). SptP is composed of two different effector protein regions, and the existence of the amino terminal domain of SptP protein makes it have the characteristics of activating target protein, while its carboxyl terminal domain endows the protein with potential tyrosine phosphatase activity (Pinaud et al., 2018). Some studies showed that SptP protein exerts its tyrosine phosphatase activity when *Salmonella* entry into host cells, thus causing systemic infection (Johnson et al., 2017).

SspH1. SspH1 is encoded by T3SS-1 and/or T3SS-2 encoded, and can inhibit inflammatory reactions and NF-κB signaling pathway in the mammalian nucleus (Keszei et al., 2014). SspH1 has the activity of E3 ubiquitin ligase contains a leucine-rich repeat (LRR) (Cook et al., 2019). It is well documented that serine/threonine protein kinase N1 (PKN1) is the physiological substrate of SspH1 (Haraga et al., 2006). Based on the structure of SspH1-PKN1 complex, LRR domain of SspH1 protein interacts with human PKN1 in mammalian cells (Keszei et al., 2014). It can form the catalytic domain of LRR and activate the catalytic function of SspH1 protein (Batkhishig et al., 2018). Interestingly, SspH1 does not depend on its catalytic function to the inhibition of NF-κB signaling pathway. Even if it does not interact with PKN1, SspH1 still can inhibit NF-κB activity (Cook et al., 2019). Therefore, except PKN1, SspH1 protein may also interact with other substrates with the ability to modulate host immune response. Later work suggested that SspH1-mediated degradation of PKN1 is not required for inhibiting NF-κB activation.

GogB. GogB is the first open reading frame on Gifsy-1 prophage of *Salmonella* Typhimurium (Svahn et al., 2023).

GogB is translocated into the cytoplasm of host cells by T3SS2, which are essential for cell-to-cell spread in *Salmonella* infection (Cohen et al., 2021). GogB is regulated by the transcription activating factor SsrB, which contributes to the virulence of *Salmonella* (Coombes et al., 2005). GogB is a chimeric protein with the characteristics of E3 ubiquitin linking enzyme and can inhibit degradation of IκBα (Jennings et al., 2017). GogB interacts with FBXO22 protein of F-box family in host cells, which is beneficial for synergy with other effectors (Pilar et al., 2012). More importantly, GogB can inhibit NF-κB activity by suppressing ubiquitination and degradation of IκBα in infected macrophages (Jennings et al., 2017). In addition, the *Salmonella gogB* mutant-infected mice will induce more inflammatory response, tissue damage, intestinal colonization and chronic infection than that in the wild-type *Salmonella* strain-infected group (Pilar et al., 2012). As one of the anti-inflammatory effector, GogB is required and is conducive to promote the colonization of *Salmonella* by limiting tissue damage during *Salmonella* infection.

SpvB and SpvC. Spv gene is an important pathogenic factor on the *Salmonella* virulence plasmid and secreted by T3SS2 (Wang et al., 2019). *Spv* contains three essential genes: positive transcriptional regulation gene *spvR* and two structural genes (*spvB* and *spvC*) (Passaris et al., 2018). Like SpvC protein is encoded by *spvC* that have phosphothreonine lyase activity, which can dephosphorylates Erk (pErk), p38, and JNK, all of which contribute to inhibit pyroptosis and intestinal inflammation by interfering with the MAPK pathway during systemic infection (Galán, 2021). In case of *Salmonella* infection, both SpvB and SpvC were translocated into the cytoplasm of host cells by T3SS2 to promote *Salmonella* virulence, which can induce more cell apoptosis by depolymerizing actin (Jennings et al., 2017). During the transport of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to cell membrane, NADPH oxidase was strongly associated with the function of actin cytoskeleton (Stanley et al., 2014). Therefore, SpvB-mediated depolymerization of actin may inhibit the recruitment of NADPH oxidase to phagosomes, leading to reduce the oxidative killing effect of *Salmonella*. Some studies have shown that SpvB and SpvC can prevent the synthesis of anti-apoptotic factors and induce macrophage apoptosis (Jennings et al., 2017). Surprisingly, the enzyme activity of SpvC decreases the expression of pro-inflammatory factors (IL-8 and TNF-α) and neutrophil infiltration at an early stage of infection (Haneda et al., 2012). Thereby, SpvC is required to *Salmonella* dissemination in the systemic infection. Recent evidence suggests that SpvC can also cooperate with SpvB to prevent the recruitment of NADPH oxidase to phagocytosis, promote cell apoptosis, block NF-κB activity and inhibit the differentiation of macrophages (Jennings et al., 2017).

IpaJ. IpaJ as an invasive plasmid gene of *Shigella flexneri*, was initially identified, and its code size is 27kDa (Burnaevskiy et al., 2013). IpaJ is a specific effector of *Salmonella* Pullorum encoded by T3SS1 that can present fragmentation state to Golgi body, and can attenuate NF-κB activity induced by TNF-α, LPS and IL-1 in HeLa cells (Li et al., 2020). It has been suggested that the transcription of IpaJ is regulated by ItrA with a novel DeoR family regulator to inhibit MAPK activation in *Salmonella*-infected HeLa cells (Yin et al., 2022). At the same time, IpaJ has the function to inhibit the activation of NF-κB signaling pathway by suppressing the ubiquitination degradation of IκBα during *Salmonella* infection (Li et al., 2020). In addition, the absence of SPI-1 and SPI-2 does not affect the protein expression of NF-κB p65 showed that IpaJ was not regulated by T3SS1 and T3SS2 (Yin et al., 2022).

Other effectors. Previous study reported that T3SS1 and/or T3SS2 effectors, like GtgA, GogA, and PipA all contains two histidine residues, and have metalloprotease activity to control *Salmonella* replication (Galán, 2021). These zinc metalloproteases redundantly target the NF-κB subunits p65, RelB, and c-Rel, whereas GogA and GtgA only inhibit NF-κB-dependent gene transcription (Takemura et al., 2021). T3SS2 effectors SseK1, SseK2, and SseK3 all are a death domain-containing proteins with the characteristics of N-linked glycosyl transferase, which can inhibit NF-κB activity by suppressing the phosphorylation of IκBα in 293ET cells treated with TNF-α, (Jennings et al., 2017). Among them, SseK1 and SseK3 also inhibit *Salmonella*-induced NF-κB activity in macrophages (Günster et al., 2017). Another report showed that SseK3-mediated inhibition of NF-B signaling pathway is not required for the E3-ubiquitin ligase tripartite motif-containing protein 32 (Yang et al., 2015). In addition, the SPI-2 T3SS effector SpvD inhibit NF-κB activity by preventing nuclear translocation of p65 through interactions with the Exportin-2, but it does not affect the degradation of IκBα, which finally lead to the system grow of *Salmonella* (Rolhion et al., 2016).

Salmonella interact with host cells by using T3SSs to inject some effectors into the host cells. These effectors, like SopE, SopE2, and SopB all trigger NF-κB signaling pathway by activating Rho family small G proteins, while SptP has the activity of GTPase activating protein that can inhibit activation of G proteins**(Figure 1)**.

However, activation of NF-κB signaling pathway by SipA needs the mediation of NOD1/NOD2. Some effectors, including SspH1, AvrA, IpaJ, and SseL all suppressed NF-κB activity by blocking IκBα degradation. Furthermore, the enzymatic activity of these effectors is closely associated with their function in the regulation of NF-κB signaling pathway during *Salmonella* infection. These results suggesting that both T3SS1- and T3SS2-encode these effectors are translocated into the host cell, and contribute to downregulation of the inflammatory response and the persistent infection of *Salmonella* by targeting NF-κB signaling pathway when *Salmonella* invade target cells.

Discussion. Host-*Salmonella* interactions are a very complex process. The host's immune system has the ability to identify and clear the pathogens, which manipulate cell signaling cascades through a variety of pattern recognition receptors to facilitate bacterial invasion and its intracellular replication. The activation or inhibition of NF-κB signaling pathway was involved by effectors associated with the initiation of the inflammatory response, which is beneficial to the persistent infection of

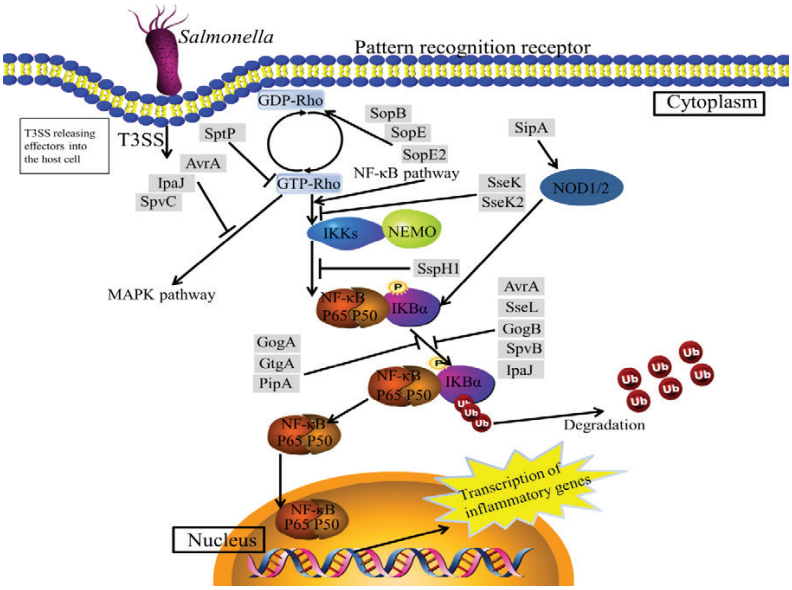

Figure 1. *Salmonella* **effectors regulate the NF-κB signaling pathway in host cells.**

Salmonella. As this review advances, the mechanism by which *Salmonella* induces host inflammatory responses by T3SSs-realted effectors are well clear now. These findings illustrated that *Salmonella* pathogenicity and host immune defense are a process of dynamic balance within the host cells. But how *Salmonella* and its host reprogram this metabolic state to establish a long-term systemic infection remains obscure. However, various hosts have significant genetic differences, and their immune defense could also have great differences in *Salmonella* infection. Future studies need to be illuminated the interplay between the different host and T3SS effectors.

Conclusions. In summary, the main objective of this review shows that *Salmonella* have evolved complex strategy to evade host immune defense. *Salmonella* utilizes T3SSs to deliver some effectors into target cells that can regulate NF-κB signaling pathway, so as to promote its survival and replication within host cells. The study of both *Salmonella* effectors and NF-κB signaling pathway will provide new ideas and countermeasures for the prevention and treatment of salmonellosis.

References:

1. Bruno, V. M., Hannemann, S., Lara-Tejero, M., Flavell, R. A., Kleinstein, S. H., Galán, J. E. (2009). *Salmonella* Typhimurium type III secretion effectors stimulate innate immune responses in cultured epithelial cells. PLoS Pathog, 5(8), e1000538. doi: 10.1371/journal.ppat.1000538

2. Bliska, J. B., van der Velden, A. W. (2012). *Salmonella* "sops" up a preferred electron receptor in the inflamed intestine. mBio, 3(4), e00226-12. doi: 10.1128/mBio.00226-12

3. Broz, P., Ohlson, M. B., Monack, D. M. (2012). Innate immune response to *Salmonella* Typhimurium, a model enteric pathogen. Gut Microbes, 3(2), 62-70. doi: 10.4161/gmic.19141

4. Burnaevskiy, N., Fox, T. G., Plymire, D. A., Ertelt, J. M., Weigele, B. A., Selyunin, A. S., Way, S. S., Patrie, S. M., Alto, N. M. (2013). Proteolytic elimination of N-myristoyl modifications by the *Shigella* virulence factor IpaJ. Nature, 496(7443), 106-9. doi: 10.1038/nature12004

5. Batkhishig, D., Bilguun, K., Enkhbayar, P., Miyashita, H., Kretsinger, R. H., Matsushima, N. (2018). Super secondary structure consisting of a polyproline II helix and a β-turn in leucine rich repeats in bacterial type III secretion system effectors. Protein J, 37(3), 223-236. doi: 10.1007/s10930-018-9767-9

6. Brink, T., Leiss, V., Siegert, P., Jehle, D., Ebner, J. K., Schwan, C., Shymanets, A., Wiese, S., Nürnberg, B., Hensel, M., Aktories, K., Orth, J. H. C. (2018). *Salmonella* Typhimurium effector SseI inhibits chemotaxis and increases host cell survival by deamidation of heterotrimeric Gi proteins. PLoS Pathog, 14(8), e1007248. doi: 10.1371/journal.ppat.1007248

7. Bariana, M., Cassella, E., Rateshwar, J., Ouk, S., Liou, H. C., Heller, C., Colorado, I., Feinman, R., Makhdoom, A., Siegel, D. S., Heller, G., Tuckett, A., Mondello P., Zakrzewski, J. L. (2022). Inhibition of NF-κB DNA binding suppresses myeloma growth via intracellular redox and tumor microenvironment modulation. Mol Cancer Ther, 21(12), 1798-1809. doi: 10.1158/1535-7163.MCT-22-0257

8. Coombes, B. K., Wickham, M. E., Brown, N. F., Lemire, S., Bossi, L., Hsiao, W. W., Brinkman, F. S., Finlay, B. B. (2005). Genetic and molecular analysis of GogB, a phage-encoded type III-secreted substrate in *Salmonella enterica* serovar Typhimurium with autonomous expression from its associated phage. J Mol Biol, 348(4), 817-30. doi: 10.1016/j.jmb.2005.03.024

9. Coburn, B., Grassl, G. A., Finlay, B. B. (2007). *Salmonella*, the host and disease: a brief review. Immunol Cell Biol, 85(2), 112-8. doi: 10.1038/sj.icb.7100007

10. Cain, R. J., Hayward, R. D., Koronakis, V. (2008). Deciphering interplay between *Salmonella* invasion effectors. PLoS Pathog, 4(4), e1000037. doi: 10.1371/journal.ppat.1000037
11. Cuadrado, A., Martín-Moldes, Z., Ye, J., Lastres-Becker, I. (2014). Transcription factors NRF2 and NF-κB are coordinated effectors of the Rho family, GTP-binding protein RAC1 during inflammation. J Biol Chem, 289(22), 15244-58. doi: 10.1074/jbc.M113.540633
12. Cook, M., Delbecq, S. P., Schweppe, T. P., Guttman, M., Klevit, R. E., Brzovic, P. S. (2019). The ubiquitin ligase SspH1 from *Salmonella* uses a modular and dynamic E3 domain to catalyze substrate ubiquitylation. J Biol Chem, 294(3), 783-793. doi: 10.1074/jbc.RA118.004247
13. Cohen, E., Azriel, S., Auster, O., Gal, A., Zitronblat, C., Mikhlin, S., Scharte, F., Hensel, M., Rahav, G., Gal-Mor, O. (2021). Pathoadaptation of the passerine-associated *Salmonella enterica* serovar Typhimurium lineage to the avian host. PLoS Pathog, 17(3), e1009451. doi: 10.1371/journal.ppat.1009451
14. de Jong, H. K., Parry, C. M., van der Poll, T., Wiersinga, W. J. (2012). Host-pathogen interaction in invasive Salmonellosis. PLoS Pathog, 8(10), e1002933. doi: 10.1371/journal.ppat.1002933
15. Dos Santos, A. M. P., Ferrari, R. G., Conte-Junior, C. A. (2020). Type three secretion system in *Salmonella* Typhimurium: the key to infection. Genes Genomics, 42(5), 495-506. doi: 10.1007/s13258-020-00918-8
16. Fu, Y., Galán, J. E. (1999). A *Salmonella* protein antagonizes Rac-1 and Cdc42 to mediate host-cell recovery after bacterial invasion. Nature, 401(6750), 293-7. doi: 10.1038/45829
17. Figueira, R., Watson, K. G., Holden, D. W., Helaine, S. (2013). Identification of *Salmonella* pathogenicity island-2 type III secretion system effectors involved in intramacrophage replication of S. enterica serovar Typhimurium: implications for rational vaccine design. mBio, 4(2), e00065. doi: 10.1128/mBio.00065-13
18. Finn, C. E., Chong, A., Cooper, K. G., Starr, T., Steele-Mortimer, O. (2017). A second wave of *Salmonella* T3SS1 activity prolongs the lifespan of infected epithelial cells. PLoS Pathog, 13(4), e1006354. doi: 10.1371/journal.ppat.1006354
19. Giogha, C., Lung, T. W., Pearson, J. S., Hartland, E. L. (2014). Inhibition of death receptor signaling by bacterial gut pathogens. Cytokine Growth Factor Rev, 25(2), 235-43. doi: 10.1016/j.cytogfr.2013.12.012
20. Günster, R. A., Matthews, S. A., Holden, D. W., Thurston, T. L. M. (2017). SseK1 and SseK3 type III secretion system effectors inhibit NF-κB signaling and necroptotic cell death in *Salmonella*-infected macrophages. Infect Immun, 85(3), e00010-17. doi: 10.1128/IAI.00010-17
21. Gal-Mor, O. Persistent Infection and long-term carriage of typhoidal and nontyphoidal Salmonellae. (2018). Clin Microbiol Rev, 32(1), e00088-18. doi: 10.1128/CMR.00088-18
22. Geng, S., Wang, Y., Xue, Y., Wang, H., Cai, Y., Zhang, J., Barrow, P., Pan, Z., Jiao, X. (2019). The SseL protein inhibits the intracellular NF-κB pathway to enhance the virulence of *Salmonella* Pullorum in a chicken model. Microb Pathog, 129, 1-6. doi: 10.1016/j.micpath.2019.01.035
23. Galán, J. E. (2021). *Salmonella* Typhimurium and inflammation: a pathogen-centric affair. Nat Rev Microbiol, 19(11), 716-725. doi: 10.1038/s41579-021-00561-4
24. Gómez-Chávez, F., Correa, D., Navarrete-Meneses, P., Cancino-Diaz, J. C., Cancino-Diaz, M. E., Rodríguez-Martínez, S. (2021). NF-κB and its regulators during pregnancy. Front Immunol, 12, 679106. doi: 10.3389/fimmu.2021.679106
25. Haraga, A., Miller, S, I. (2006). A *Salmonella* type III secretion effector interacts with the mammalian serine/threonine protein kinase PKN1. Cell Microbiol, 8(5), 837-46. doi: 10.1111/j.1462-5822.2005.00670.x
26. Hayden, M. S., Ghosh, S. (2008). Shared principles in NF-kappaB signaling. Cell, 132(3), 344-62. doi: 10.1016/j.cell.2008.01.020
27. Haneda, T., Ishii, Y., Shimizu, H., Ohshima, K., Iida, N., Danbara, H., Okada, N. (2012). *Salmonella* type III effector SpvC, a phosphothreonine lyase, contributes to reduction in inflammatory response during intestinal phase of infection. Cell Microbiol, 14(4), 485-99. doi: 10.1111/j.1462-5822.2011.01733.x
28. Jiang, Y., He, L., Ju, C., Pei, Y., Ji, M., Li, Y., Liao, L., Jang, S., Zhu, Z., Wang, Y. (2015). Isolation and expression of grass carp toll-like receptor 5a (CiTLR5a) and 5b (CiTLR5b) gene involved in the response to flagellin stimulation and grass carp reovirus infection. Fish Shellfish Immunol, 44(1), 88-99. doi: 10.1016/j.fsi.2015.01.024
29. Jennings, E., Thurston, T. L. M., Holden, D. W. (2017). *Salmonella* SPI-2 type III secretion system effectors: molecular mechanisms and physiological consequences. Cell Host Microbe, 22(2), 217-231. doi: 10.1016/j.chom.2017.07.009
30. Johnson, R., Byrne, A., Berger, C. N., Klemm, E., Crepin, V. F., Dougan, G., Frankel, G. (2017). The type III secretion system effector SptP of *Salmonella enterica* serovar typhi. J Bacteriol, 199(4), e00647-16. doi: 10.1128/JB.00647-16
31. Jiao, Y., Zhang, Y. G., Lin, Z., Lu, R., Xia, Y., Meng, C., Pan, Z., Xu, X., Jiao, X., Sun, J. (2020). *Salmonella* Enteritidis effector AvrA suppresses autophagy by reducing beclin-1 protein. Front Immunol, 11, 686. doi: 10.3389/fimmu.2020.00686
32. Jia, H., Song, N., Ma, Y., Zhang, F., Yue, Y., Wang, W., Li, C., Li, H., Wang, Q., Gu, L., Li, B. (2022). *Salmonella* facilitates iron acquisition through UMPylation of ferric uptake regulator. mBio, 13(3), e0020722. doi: 10.1128/mbio.00207-22
33. Keestra, A. M., Winter, M. G., Auburger, J. J., Frässle, S. P., Xavier, M. N., Winter, S. E., Kim, A., Poon, V., Ravesloot, M. M., Waldenmaier, J. F., Tsolis, R. M., Eigenheer, R. A., Bäumler, A. J. (2013). Manipulation of small Rho GTPases is a pathogen-induced process detected by NOD1. Nature, 496(7444), 233-7. doi: 10.1038/nature12025
34. Keszei, A. F., Tang, X., McCormick, C., Zeqiraj, E., Rohde, J. R., Tyers, M., Sicheri, F. (2014). Structure of an SspH1-PKN1 complex reveals the basis for host substrate recognition and mechanism of activation for a bacterial E3 ubiquitin ligase. Mol Cell Biol, 34(3), 362-73. doi: 10.1128/MCB.01360-13
35. Kogut, M. H., Lee, A., Santin, E. (2020). Microbiome and pathogen interaction with the immune system. Poult Sci, 99(4), 1906-1913. doi: 10.1016/j.psj.2019.12.011
36. Krukonis, E. S., Thomson, J. J. (2020). Complement evasion mechanisms of the systemic pathogens Yersiniae and Salmonellae. FEBS Lett, 594(16), 2598-2620. doi: 10.1002/1873-3468.13771

37. Keestra, A. M., Winter, M. G., Klein-Douwel, D., Xavier, M. N., Winter, S. E., Kim, A., Tsolis, R. M., Bäumler, A. J. (2011). A *Salmonella* virulence factor activates the NOD1/NOD2 signaling pathway. mBio, 2(6), e00266-11. doi: 10.1128/mBio.00266-11

38. LaRock, D. L., Chaudhary, A., Miller, S. I. (2015). Salmonellae interactions with host processes. Nat Rev Microbiol, 13(4), 191-205. doi: 10.1038/nrmicro3420

39. Lhocine, N., Arena, E. T., Bomme, P., Ubelmann, F., Prévost, M. C., Robine, S., Sansonetti, P. J. (2015). Apical invasion of intestinal epithelial cells by *Salmonella* Typhimurium requires villin to remodel the brush border actin cytoskeleton. Cell Host Microbe, 17(2), 164-77. doi: 10.1016/j.chom.2014.12.003

40. Liu, W., Zhuang, J., Jiang, Y., Sun, J., Prinz, R. A., Sun, J., Jiao, X., Xu, X. (2019). Toll-like receptor signalling cross-activates the autophagic pathway to restrict *Salmonella* Typhimurium growth in macrophages. Cell Microbiol, 21(12), e13095. doi: 10.1111/cmi.13095

41. Lin, Z., Zhang, Y. G., Xia, Y., Xu, X., Jiao, X., Sun, J. (2016). *Salmonella enteritidis* effector AvrA stabilizes intestinal tight junctions via the JNK pathway. J Biol Chem, 291(52), 26837-26849. doi: 10.1074/jbc.M116.757393

42. Li, Q., Xu, L., Yin, C., Liu, Z., Li, Y., Yuan, Y., Hu, Y., Jiao, X. (2020). The invasion plasmid antigen J (IpaJ) from *Salmonella* inhibits NF-κB activation by suppressing IκBα ubiquitination. Infect Immun, 88(3), e00875-19. doi: 10.1128/IAI.00875-19

43. Liu, Y., Dou, Y., Yan, L., Yang, X., He, B., Kong, L., Smith, W. (2020). The role of Rho GTPases' substrates Rac and Cdc42 in osteoclastogenesis and relevant natural medicinal products study. Biosci Rep, 40(7), BSR20200407. doi: 10.1042/BSR20200407

44. Lawrence, A. E., Abuaita, B. H., Berger, R. P., Hill, D. R., Huang, S., Yadagiri, V. K., Bons, B., Fields, C., Wobus, C. E., Spence, J. R., Young, V. B., O'Riordan, M. X. (2021). *Salmonella enterica* serovar Typhimurium SPI-1 and SPI-2 shape the global transcriptional landscape in a human intestinal organoid model system. mBio, 12(3), e00399-21. doi: 10.1128/mBio.00399-21

45. Liao, Z., Su, J. (2021). Progresses on three pattern recognition receptor families (TLRs, RLRs and NLRs) in teleost. Dev Comp Immunol, 122, 104131. doi: 10.1016/j.dci.2021.104131

46. Li, R., Zhou, Y., Zhang, S., Li, J., Zheng, Y., Fan, X. (2022). The natural (poly)phenols as modulators of microglia polarization via TLR4/NF-κB pathway exert anti-inflammatory activity in ischemic stroke. Eur J Pharmacol, 914, 174660. doi: 10.1016/j.ejphar.2021.174660

47. Lu, X., Zhang, M., Yang, S., Deng, Y., Jiao, Y. (2022). Transcriptome analysis reveals the diverse response of pearl oyster pinctada fucata martensii after different PAMP stimulation. Fish Shellfish Immunol, 131, 881-890. doi: 10.1016/j.fsi.2022.10.058

48. Mesquita, F. S., Holden, D. W., Rolhion, N. (2013). Lack of effect of the *Salmonella* deubiquitinase SseL on the NF-κB pathway. PLoS One, 8(1), e53064. doi: 10.1371/journal.pone.0053064

49. Markowiak, P., Śliżewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients, 9(9), 1021. doi: 10.3390/nu9091021

50. Noster, J., Chao, T. C., Sander, N., Schulte, M., Reuter, T., Hansmeier, N., Hensel, M. (2019). Proteomics of intracellular *Salmonella enterica* reveals roles of *Salmonella* pathogenicity island 2 in metabolism and antioxidant defense. PLoS Pathog, 15(4), e1007741. doi: 10.1371/journal.ppat.1007741

51. Ménard, S., Lacroix-Lamandé, S., Ehrhardt, K., Yan, J., Grassl, G. A., Wiedemann, A. (2022). Cross-talk between the intestinal epithelium and *Salmonella* Typhimurium. Front Microbiol, 13, 906238. doi: 10.3389/fmicb.2022.906238

52. Pilar, A. V., Reid-Yu, S. A., Cooper, C. A., Mulder, D. T., Coombes, B. K. (2012). GogB is an anti-inflammatory effector that limits tissue damage during *Salmonella* infection through interaction with human FBXO22 and Skp1. PLoS Pathog, 8(6), e1002773. doi: 10.1371/journal.ppat.1002773

53. Passaris, I., Cambré, A., Govers, S. K., Aertsen, A. (2018). Bimodal expression of the *Salmonella* Typhimurium *spv* operon. Genetics, 210(2), 621-635. doi: 10.1534/genetics.118.300822

54. Pinaud, L., Sansonetti, P. J., Phalipon, A. (2018). Host cell targeting by enteropathogenic bacteria T3SS effectors. Trends Microbiol, 26(4), 266-283. doi: 10.1016/j.tim.2018.01.010

55. Parween, F., Yadav, J., Qadri, A. (2019). The virulence polysaccharide of *Salmonella* Typhi suppresses activation of Rho family GTPases to limit inflammatory responses from epithelial cells. Front Cell Infect Microbiol, 9, 141. doi: 10.3389/fcimb.2019.00141

56. Potrykus, M., Czaja-Stolc, S., Stankiewicz, M., Kaska, Ł., Małgorzewicz, S. (2021). Intestinal microbiota as a contributor to chronic inflammation and its potential modifications. Nutrients, 13(11), 3839. doi: 10.3390/nu13113839

57. Rytkönen, A., Poh, J., Garmendia, J., Boyle, C., Thompson, A., Liu, M., Freemont, P., Hinton, J. C., Holden, D. W. (2007). SseL, a *Salmonella* deubiquitinase required for macrophage killing and virulence. Proc Natl Acad Sci USA, 104(9), 3502-7. doi: 10.1073/pnas.0610095104

58. Rolhion, N., Furniss, R. C., Grabe, G., Ryan, A., Liu, M., Matthews, S. A., Holden, D. W. (2016). Inhibition of nuclear transport of NF-κB p65 by the *Salmonella* type III secretion system effector SpvD. PLoS Pathog, 12(5), e1005653. doi: 10.1371/journal.ppat.1005653

59. Stanley, A., Thompson, K., Hynes, A., Brakebusch, C., Quondamatteo, F. (2014). NADPH oxidase complex-derived reactive oxygen species, the actin cytoskeleton, and Rho GTPases in cell migration. Antioxid Redox Signal, 20(13), 2026-42. doi: 10.1089/ars.2013.5713

60. Sun, H., Kamanova, J., Lara-Tejero, M., Galán, J. E. (2016). A family of *Salmonella* type III secretion effector proteins selectively targets the NF-κB signaling pathway to preserve host homeostasis. PLoS Pathog, 12(3), e1005484. doi: 10.1371/journal.ppat.1005484

61. Stormberg, T., Filliaux, S., Baughman, H. E. R., Komives, E. A., Lyubchenko, Y. L. (2021). Transcription factor NF-κB unravels nucleosomes. Biochim Biophys Acta Gen Subj, 1865(9), 129934. doi: 10.1016/j.bbagen.2021.129934
62. Sharma, A., Raman, V., Lee, J., Forbes, N. S. (2022). Microbial imbalance induces inflammation by promoting *Salmonella* penetration through the mucosal barrier. ACS Infect Dis, 8(5), 969-981. doi: 10.1021/acsinfecdis.1c00530
63. Svahn, A. J., Suster, C. J. E., Chang, S. L., Rockett, R. J., Sim, E. M., Cliff, O. M., Wang, Q., Arnott, A., Ramsperger, M., Sorrell, T. C., Sintchenko, V., Prokopenko, M. (2023). Pangenome analysis of a *Salmonella* Enteritidis population links a major outbreak to a Gifsy-1-like prophage containing anti-Inflammatory gene *gogB*. Microbiol Spectr, e0279122. doi: 10.1128/spectrum.02791-22
64. Takemura, M., Haneda, T., Idei, H., Miki, T., Okada, N. (2021). A *Salmonella* type III effector, PipA, works in a different manner than the PipA family effectors GogA and GtgA. PLoS One, 16(3), e0248975. doi: 10.1371/journal.pone.0248975
65. Tao, H., Li, W., Zhang, W., Yang, C., Zhang, C., Liang, X., Yin, J., Bai, J., Ge, G., Zhang, H., Yang, X., Li, H., Xu, Y., Hao, Y., Liu, Y., Geng, D. (2021). Urolithin A suppresses RANKL-induced osteoclastogenesis and postmenopausal osteoporosis by, suppresses inflammation and downstream NF-κB activated pyroptosis pathways. Pharmacol Res, 174, 105967. doi: 10.1016/j.phrs.2021.105967
66. Wu, H., Jones, R. M., Neish, A, S. (2012). The *Salmonella* effector AvrA mediates bacterial intracellular survival during infection *in vivo*. Cell Microbiol, 14(1), 28-39. doi: 10.1111/j.1462-5822.2011.01694.x
67. Wang, L., Li, Y., Liu, Y., Zuo, L., Li, Y., Wu, S., Huang, R. (2019). *Salmonella* spv locus affects type I interferon response and the chemotaxis of neutrophils via suppressing autophagy. Fish Shellfish Immunol, 87, 721-729. doi: 10.1016/j.fsi.2019.02.009
68. Walch, P., Selkrig, J., Knodler, L. A., Rettel, M., Stein, F., Fernandez, K., Viéitez, C., Potel, C. M., Scholzen, K., Geyer, M., Rottner, K., Steele-Mortimer, O., Savitski, M. M., Holden, D. W., Typas, A. (2021). Global mapping of *Salmonella* enterica-host protein-protein interactions during infection. Cell Host Microbe, 29(8), 1316-1332.e12. doi: 10.1016/j.chom.2021.06.004
69. Xie, Z., Zhang, Y., Huang, X. (2020). Evidence and speculation: the response of *Salmonella* confronted by autophagy in macrophages. Future Microbiol, 15, 1277-1286. doi: 10.2217/fmb-2020-0125
70. Ye, Z., Petrof, E. O., Boone, D., Claud, E. C., Sun, J. (2007). *Salmonella* effector AvrA regulation of colonic epithelial cell inflammation by deubiquitination. Am J Pathol, 171(3), 882-92. doi: 10.2353/ajpath.2007.070220
71. Yang, Z., Soderholm, A., Lung, T. W., Giogha, C., Hill, M. M., Brown, N. F., Hartland, E., Teasdale, R. D. (2015). SseK3 is a *Salmonella* effector that binds TRIM32 and modulates the host's NF-κB signalling activity. PLoS One, 10(9), e0138529. doi: 10.1371/journal.pone.0138529
72. Yin, C., Gu, J., Gu, D., Wang, Z., Ji, R., Jiao, X., Li, Q. (2022). The *Salmonella* T3SS1 effector IpaJ is regulated by ItrA and inhibits the MAPK signaling pathway. PLoS Pathog, 18(12), e1011005. doi: 10.1371/journal.ppat.1011005
73. Zhang, Y., Wu, S., Ma, J., Xia, Y., Ai, X., Sun, J. (2015). Bacterial protein AvrA stabilizes intestinal epithelial tight junctions via blockage of the C-Jun N-terminal kinase pathway. Tissue Barriers, 3(1-2), e972849. doi: 10.4161/21688362.2014.972849
74. Zhang, K., Riba, A., Nietschke, M., Torow, N., Repnik, U., Pütz, A., Fulde, M., Dupont, A., Hensel, M., Hornef, M. (2018). Minimal SPI1-T3SS effector requirement for *Salmonella* enterocyte invasion and intracellular proliferation *in vivo*. PLoS Pathog, 14(3), e1006925. doi: 10.1371/journal.ppat.1006925

Жук Ли, *аспірант, Сумский національній аграрній університет, м. Суми, Україна*
Фотін А. І., *кандидат ветеринарних наук, доцент, Сумский національній аграрній університет, м. Суми, Україна*
Петров Р. В., *доктор ветеринарних наук, професор, Сумский національній аграрній університет, м. Суми, Україна*
Дженью Ма, *доктор ветеринарних наук, професор, Хенанський інститут науки і технологій, м. Хенань, Китай*
Фотіна Т. І., *доктор ветеринарних наук, професор, Сумский національній аграрній університет, м. Суми, Україна*

Сальмонельозна інфекція: взаємодія між ефекторами T3SSs та сигнальним шляхом NF-κB

Сальмонела є важливим харчовим патогеном, який може уникати імунного захисту хазяїна за допомогою унікальних механізмів. Сальмонели маніпулюють різними сигнальними шляхами клітини-господаря, доставляючи специфічні ефектори в клітини-мішені для встановлення інфекції. Ядерний фактор-κВ (NF-κB) є важливим ядерним фактором транскрипції, який регулює імунну систему хазяїна при зарженні Salmonella. Острівець патогенності сальмонели 1 (SPI-1) і острівець патогенності сальмонели 2 (SPI-2) кодують системи секреції III типу (T3SSs), ефектори, які пов'язані з сигнальним шляхом NF-κB через регуляцію запальної реакції господаря. Дослідження показали, що ефектори T3SS1 та/або T3SS2, такі як GtgA, GogA та PipA, містять два залишки гістидину та мають металопротеазну активність для контролю реплікації Salmonella. Ці металопротеази цинку надмірно націлені на NF-κB субодиниці p65, RelB і c-Rel, тоді як GogA і GtgA лише інгібують NF-κB-залежну транскрипцію гена. Ефектори T3SS2 SseK1, SseK2 і SseK3 є білками, що містять домен смерті з характеристиками N-пов'язаної глікозилтрансферази, які можуть пригнічувати активність NF-κB шляхом інгібування фосфорилювання IκBα в клітинах 293ET, оброблених TNF-α. Серед них SseK1 і SseK3 також пригнічують індуковану Salmonella NF-κB активність у макрофагах. SseK3-опосередковане інгібування сигнального шляху NF-B не вимагається для білка 32, що містить тристоронній E3-убіквітинлігазний мотив. Крім того, ефектор SPI-2 T3SS SpvD інгібує активність NF-κB, запобігаючи ядерній транслокації p65 через взаємодію з Exportin-2, але це не впливає на деградацію IκBα, що в кінцевому підсумку призводить до системного росту сальмонели. Ефектори SPI-1 SipA, SopE, SopE2

і SopB можуть активувати сигнальний шлях NF-κB, щоб сприяти інвазії Salmonella та внутрішньоклітинному переноснику. Однак інші ефектори SptP, AvrA, IpaJ, SspH1, GtgA, GogA та SPI-2, кодовані SseL, SpvB, SseK1 та GogB, можуть ефективно інгібувати шлях передачі сигналів NF-κB та сприяти внутрішньоклітинній реплікації та вірулентності Salmonella. У цьому міні-огляді ми підсумовуємо спеціальний механізм того, як сигнальний шлях NF-κB регулюється ефекторами T3SSs Salmonella при персистуючій інфекції Salmonella, що дозволить додатково з'ясувати патогенез Salmonella.

Ключові слова: *сальмонели; T3SSs ефектори; сигнальний шлях NF-κB; імунний захист господаря; патогенний механізм.*