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Virulence System of *Salmonella* with Special Reference to *Salmonella enterica*

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Abstract

Virulence system of *Salmonella* is very complex as many genes are involved in contributing the virulence of *Salmonella*. Some of the genes are involved in enhancing the invasion of organism in host defense system; some are playing their role in survival and replication of organism inside the host, while some genes are involved in the production of molecules that produce the clinical symptoms of the disease. Broadly, we can classify virulence genes into two categories: genes that are located on the virulence contributing plasmid like *spvC* gene and genes that are chromosomal in nature like *stn*. On chromosome, virulence genes are located in various clusters, which are known as *Salmonella* pathogenicity islands and till today seventeen pathogenicity islands have been identified. The genes located on these pathogenicity islands produce several effector molecules, which assist in invasion, replication and survival of *Salmonella* inside the host. The role of plasmid is still not very clear, but it is presumed that the genes located on virulence plasmids affect the intracellular growth of *Salmonella* in macrophages. Though lot of research work has been carried out to understand the virulence regulation system of *Salmonella*, still many questions are to be answered to decode the virulence regulation of *Salmonella*.

Keywords: *Salmonella*, virulence, genes, plasmid, *Salmonella* pathogenicity islands

1. Introduction

The genus *Salmonella* was discovered by Daniel Elmer Salmon with his assistant Theobald Smith in 1885. Smith isolated a new species of bacteria from ill pig and named *Salmonella Choleraesuis*. The genus *Salmonella* is Gram-negative, non-spore forming, rod-shaped bacteria

belonging to family Enterobacteriaceae. The size varies 2–5 μm in length from 0.4 to 1.5 μm in diameter. They are facultative anaerobes and show peritrichous motility. These are intracellular pathogen leading to different clinical manifestations in humans and animals [1–3]. According to Kauffmann, white scheme genus *Salmonella* consists of two species: *S. enterica* and *S. bongori*. *Salmonella enterica* is subdivided into six subspecies: (1) *S. enterica* sub sp. *salamae*; (2) *S. enterica* sub sp. *arizonae*; (3a) *S. enterica* sub sp. *diarizonae*, (3b) *S. enterica* sub sp. *houtenae*; (4) *S. enterica* sub sp. *indicia*; (5) *S. bongori* [4]. Most of the *Salmonella* isolates that cause disease in human and animals belong to *S. enterica* subspecies *enterica*. Alternatively, *S. enterica* strains can be classified on basis of their antigens (O and H) into 67 sero groups and 2557 serovars like *Salmonella typhimurium*, *S. enteritidis*, etc. *Salmonella* causes two types of diseases in human being typhoid fever and non-typhoidal salmonellosis. Typhoid fever is caused by *S. typhi* and *S. paratyphi* clinical manifestations include fever, headache, abdominal pain, and transient diarrhea, which may result in fetal respiratory, hepatic, spleen, or neurological damage. Mortality ranges from 10 to 20% in untreated cases [5, 6]. Non-typhoidal *Salmonella* (NTS) cause diarrheal disease in humans. *S. typhimurium* and *S. enteritidis* are two major serovars contributing non-typhoidal Salmonellosis. Mortality rate due to NTS is as high as 24% in developing countries where *Salmonella* infection is the major cause of childhood diarrhea morbidity and mortality [7]. After the infection host may act as the carrier for a long duration (over 10-week postinfection). These carriers are characterized by symptom-free conditions and can act as reservoirs and hence contribute to the propagation of disease. Antibiotics are used for the treatment of salmonellosis. Commonly used antibiotics are fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMZ), ampicillin or expanded-spectrum cephalosporins. Development of multiple drug resistance has become very common phenomena among the isolates which are mainly contributed by dissemination of dominant resistance clone or by dissemination of strains carrying drug-resistant plasmids [8–10]. Therefore, the rational use of antibiotics is very important to overcome the problem of development of multiple drug resistance in *Salmonella* [9, 11].

1.1. Pathogenesis of *Salmonella enterica*

Ingestion of contaminated food or water is the major cause of the disease. After ingestion, once the organism reaches in the stomach to overcome the acidic pH of the stomach. *Salmonella* activates acid tolerance response, which maintains the intracellular pH of *Salmonella*. After entering in the small intestine, organism adheres to intestinal epithelial cells. The adherence of organism with intestinal cells provokes the signaling pathway which results into cytoskeletal rearrangements and disruption of epithelial brush border and leads to the formation of membrane ruffles that engulf adherence bacteria in large vesicles called *Salmonella*-containing vacuoles (SCVs) [12]. Production of several proinflammatory cytokines such as TNF and IL-8 is increased in intestinal cell and initiates recruitment and migration of phagocytes into the intestinal lumen [13]. To overcome lysosomal enzymes of host endocytic pathway, *Salmonella* direct changes in host endocytic trafficking system. *Salmonella* induces the formation of F-actin meshwork around the bacterial vacuoles, which is important for maintenance of the integrity of vacuole membrane. For replication of bacteria, SCV migrates to the peri-nuclear position in close proximity to Golgi apparatus [14]. *Salmonella* induces the formation of long filamentous membrane

structure called as *Salmonella*-induced filaments (SIFs) which may play important role in increasing availability of the nutrient in SCV. Once *Salmonella* invades intestinal epithelium, they are transported by dendritic cells (Antigen presenting cells) through the bloodstream to various organs like the liver, spleen. In these target organs, bacteria replicate more efficiently.

1.2. Virulence genes of *Salmonella*

The genes encoding the virulence factors of *Salmonella* may be divided into two major categories, that is, genes, which are located on chromosomes, (like *stn*) [15–17] mainly *Salmonella* pathogenicity islands (SPIs) [18] and genes which are located on the virulence plasmid. In *Salmonella* seventeen SPIs (SPI-1 to SPI-17) have been identified which contribute to the virulence of *Salmonella* [19] along with several genes like *Spv* operon which are located on the plasmid.

1.3. *Salmonella* pathogenicity Islands

Genes located in SPI-1 encode for several proteins, which are involved in the invasion of epithelial cells by mediating cytoskeletal rearrangement. These effector molecules are translocated into the host cells by type III secretion system (T_3SS-1), which is composed of several operons. The *prg/org* and *inv./spa* operon encode the effector protein. SPI-2 Island: mainly contribute to replication and survival of bacteria inside the host cell (epithelial cell and macrophages). SPI-2 mainly contains four groups of genes contributing to the virulence of *Salmonella*: *ssa*, the gene encoding for T_3SS-2 ; *ssr*: encoding for regulators; *ssg*: encoding the chaperones and *ssc*: encoding the effectors. SPI-3 encodes for proteins, which are involved in both initial attachment and long-term persistence and survival during systemic phase of infection. SPI-4 contains six ORF under the control of single Operon and plays their role during the initial interaction with intestinal epithelium and long-term persistence. SPI-5 is involved in accomplishing several pathogenic proven during infection [18, 20]. Apart from this, other pathogenicity islands have been identified in few serovars of *Salmonella*. These pathogenicity islands also contribute to the virulence of *Salmonella*.

1.3.1. SPI-1

The size of SPI-1 is approximately 40 Kb and the GC content of SPI-1 is significantly lower than the average G + C content of *Salmonella* genome. SPI-1 encodes for a type III secretion system (T_3SS) that mediates the contact-dependent translocation of complex sets of effector proteins into eukaryotic host cells [21]. SPI-1 produces two subsets of effector protein one subset mediates the invasion of non-phagocytic cells by *Salmonella* by modification of active cytoskeleton system of host cell while the second subset is associated with entero-pathogenesis and inflammation of intestinal epithelium cells (**Table 1**). Genes of the SPI-1 show some sequence similarity with *E. coli* and *Shigella*, and this leads to a hypothesis of that SPI-1 is a rather ancient acquisition gained at the separation of the genera *E. coli* and *Salmonella* from the common ancestor [22].

Effector protein	Major function
Sip A	Rearrangement of cytoskeletal system of non-phagocytic cells and recruitment of neutrophils
Sip B	Nucleation of actin protein and translocation of other effector proteins/molecules
Sip C	Translocation of effector molecule
SOP A	Recruitment of immune cells and secretion of fluid in intestinal lumen
SOP C	Recruitment of Neutrophils and secretion of fluid in intestinal lumen
SOP D	Recruitment of Neutrophils and secretion of fluid in intestinal lumen
SOP E and spt P	Rearrangement of cytoskeletal of host cells
Iae P	Post translational modification of effector proteins of type III secretion system
Inv B	Act as chaperone
Avr A	Inhibition of apoptosis in epithelial cell, Inhibition of macrophage pyroptosis
Sic A Sic P	Act as chaperone

Table 1. Major virulence determinants of SP-I of *Salmonella*.

1.3.2. SPI-2

The size of SPI-2 locus is approximately 40 Kb in size, and it is composed of two different regions. The larger region of approximately 25 Kb which is present only in *S. enterica* is involved in systemic pathogenesis. It encodes for second type three secretion systems of *Salmonella*. Another smaller region of approximately 15 Kb in size was detected in *S. bongori* and encodes the tetrathionate reductase (Ttr) involved in anaerobic respiration [23] (**Table 2**).

1.3.3. SPI-3

The size of SPI-3 locus is approximately 17 Kb and GC content range 47–48%. The major virulence determinants of the SPI-3 locus are Mgt CB (Magnesium transport system), Mis L and Mar T. Mgt CB are required for the adaptation of *Salmonella* in nutritional limitation conditions of the intra-phagosomal habitat. Mis L (anti-transport protein of SPI3) is very similar to the AIDA-1 auto transporter and involved in the process of adhesion to epithelial cells. Mar T (Transcriptional activator of Mis protein) has resemblance with Tax R (Toxin gene regulator) of *Vibrio cholerae* and involved in activation of Mis L auto transport protein [24]. Though there is the high degree of sequential variation in SPI-3 among the various serovars of *Salmonella* but SPI-3 was found to be conserved between *S. typhi* and *S. typhimurium*. Even among the other serovar Mgt CB region of SPI-3 was found to be conserved.

1.3.4. SPI-4

The size of SPI-4 locus is approximately 27 Kb. Though the role of SPI-4 in *Salmonella* virulence is still not very clear, SPI-4 contributes for several putative virulence factors such as putative type I secretion system and Sic E which involve in the process of adhesion to epithelial cells. SPI-4 was found to be conserved among various serovars of *Salmonella* [24, 25].

Virulence determinant	Functions
Ssa B	Disruption of Golgi apparatus and Lysosomes, Inhibition of SCV-lysosome fusion
Ssa E	Acts as chaperone
Ssc A	Acts as chaperone
Ssc F	SCV perinuclear migration, microtubule bundling and SIF formation
Sse G	SCV perinuclear migration and SIF formation
Ttr genes	Tetrathionate respiration and outgrowth in the intestine
SPi C	Disruption of vesicular transport
SIF A	<i>Salmonella</i> containing vacuole membrane integrity
SsPH ₂	Cytoskeleton rearrangements
SrFT	Apoptosis
Ssej	Cytoskeleton rearrangements
Pip B	Targeting to <i>Salmonella</i> induced filaments
SOP D ₂	Targeting to <i>Salmonella</i> induced filaments/late endosomes

Table 2. Major virulent determinants of SPI-2 and its function.

1.3.5. SPI-5

The size of SPI-5 locus is approximately 7.6 Kb. It encodes the effector proteins for both the T₃SS encoded by SPI-1 and SPI-2. It encodes for Pip A and Pip B. Pip A contributes in the development of systemic infection while Pip B is involved in the accumulation of lipid rafts and is a translocated effector of SPI-2 encoded T₃SS under the control of Ssr AB two-component systems [26].

1.3.6. SPI-6

The size of SPI-6 is approximately 59 Kb and it has been identified in *S. typhi* and *S. typhimurium*. SPI-6 contains saf gene coding for fimbriae and pag N gene encoding for invasion protein. Deletion of this region did not affect the systemic pathogenesis but reduced the invasion of bacteria in tissue-cultured cells. SPI-6 was detected in *S. enterica* subspecies I, and some of the portion of SPI-6 that was identified in subspecies III b, IV, and VII. SPI-6 has shown sequential homology with the genome of *P. aeruginosa* and *Y. pestis* [25].

1.3.7. SPI-7

The size of SPI-7 is approximately 133 Kb, and it is specific to *S. typhi*, *S. dublin* and *S. paratyphi*. This region encodes for Vi antigen (capsular exo-polysaccharides) SPI-7 contains pil gene cluster, which encodes for putative virulence factors. The genetic organization of SPI-7 is very complex and composed of several horizontally acquired elements. It contains few genes of conjugative plasmid-like *tra* and *sam*. Though sequential homology with SPI-7 has been reported in few other bacteria like *Xanthomonas axonopodis* and *Pseudomonas aeruginosa* the loss of Vi antigen from the isolates of *S. typhi* suggests the instability of SPI-7 [27].

1.3.8. SPI-8

The size of the SPI-8 locus is 6.8 Kb and it has been identified in *Salmonella typhi*. The genes located in these islands encode for putative virulence factors, but the exact function has not reported so far.

1.3.9. SPI-9

The size of SPI-9 locus is 16,281 bp and it encodes for virulence factors of type I secretion system and RTX like protein.

1.3.10. SPI-10

The size of SPI-10 is 32.8 Kb. SPI-10 contains a cryptic bacteriophage within it. It encodes for several virulence factors which contribute to Sef fimbriae. Sef fimbriae are restricted to few serovars like *S. typhi* and *S. enteritidis*. The role of cryptic bacteriophage is still not clear.

1.3.11. SPI-11 and SPI-12

These SPIs were identified in *Salmonella choleraesuis*. The GC content of SPI-11 is 41.32%. Though the putative proteins encoded by these SPIs contribute to *Salmonella* virulence, yet the exact roles of these proteins are still not very clear.

1.3.12. SPI-13 and SPI-14

These SPIs were identified in *S. gallinarum*. SPI-13 is composed of 18 ORFs, while SPI-14 is composed of 6 ORFs. These SPIs are not present in *S. typhi* and *S. paratyphi A* but reported in *S. enteritidis* and *S. typhimurium*. The mechanism action of proteins encoded by these SPIs is not clear yet.

1.3.13. SPI-15, SPI-16 and SPI-17

These SPIs were identified in *S. typhi* and showed association with t-RNA genes. SPI-16 and SPI-17 encode for the proteins involved in LPS modification. The role of effector proteins of SPI-15 is still not clear.

Apart from pathogenicity islands of *Salmonella*, few other isolates like *Salmonella* genomic island I which plays a significant role in the multiple drug resistance of *Salmonella*. Moreover, high pathogenicity island (HPI), which has been well characterized in *Yersinia enterocolitica* and *Y. pseudo-tuberculosis*, has been identified in few serovars of *Salmonella*.

2. Plasmids and their role in virulence of *Salmonella*

Plasmids have been found only in few serovars of *Salmonella* belonging to subspecies I. The size of virulent plasmid varied from 50 to 90 Kb and have been called serovar-specific plasmids (Silva, 2017) The virulent plasmid of *Salmonella* are important for bacterial multiplication in the reticulo-endothelial system of the warm-blooded vertebrate. Spv region (7.8 Kb)

is necessary to confer the virulent phenotype of plasmid other regions are involved in other functions such as biosynthesis of fimbriae of the plasmid [28]. The exact role of the virulent plasmid in pathogenesis is unclear. Evidence exists that *spv* genes enable *S. typhimurium* to infect the liver and spleen by increasing the rate of replication within the host cells. Virulent plasmid affects the intracellular growth in macrophages but not in non-phagocytic cells.

Salmonella virulence plasmids are low copy number, stable, and nonconjugative plasmids. They contain two independent replicons rep B and rep C which function independently. Despite low copy number (1–2 copies), plasmids of *Salmonella* are very stable and Par VP region is responsible for the partition of the plasmid. Some of the plasmids of *Salmonella* contain more or less complete tra operon, whereas others have suffered the major deletions in tra operon. The presence of tra operon suggests that *Salmonella* ancestors acquired the virulence plasmid by conjugation and that divergence has occurred during the evolution of various serovars [29].

2.1. Gene organization on SPV region of plasmid

SPV must be written in uppercase when referring to regions and in lowercase when referring to genes (*spv*). This rule has to be followed through the whole text. Please check). In *Salmonella* subspecies I, SPV region is present on the virulent plasmid but in some other subspecies like II, IIIa, and VII the homologous region is present on the chromosome. The SPV region is composed of five genes *spv* R, A, B, C, D. *spv* R acts as regulator protein and binds to the promoter of *spv* A. Though the expression of SPV R protein is self-regulated, some factors like σ^s (product of *rpos* gene) and H-Ns protein also play important role in the regulation of *spv* operon. Expression of *rpos* is induced after entry of *Salmonella* into macrophages or epithelial cell. Therefore, the expression of *spv* genes in response to intracellular signal supports the view that the virulent plasmid may play a role in the multiplication of *Salmonella* as an intracellular parasite (Silva, 2017). Gene *spvA* encodes for 28 kDa protein, which is found on the outer membrane. The function of SPVA is still not clear as the mutation in SPVA does not reduce the virulence of *Salmonella*. SPVB (66Kda) is found in two fractions. The small amount of SPV B is found in the inner membrane while the larger fraction in cytoplasmic. SPV B sequence shows a certain degree of similarity to all toxin of *Vibrio cholerae* (Accessory cholera enterotoxin) which acts as ion transporter across the cell membrane and contribute to diarrhea. SPV B is absolutely essential for virulence of *Salmonella* and mutation in *spv* B gene resulted in the loss of virulence. SPV C is a cytoplasmic protein of 28 KDa while SPV D (25 kDa) is exported outside the cell. Mutations in *spv* C and *spv* D genes caused the various defect in *Salmonella* virulence [30, 31].

2.2. Plasmid-encoded genes involved in serum resistance and fimbriae

The *pef* (plasmid-encoded fimbriae locus contains four genes (*pef* B C D1). In *Salmonella* Typhimurium *pef* genes carried on multicopy plasmid determine the formation of surface filamentous structures. *Pef* mediates adhesion to the small intestine. Adhesion mediated by PEF is different from induced by chromosomally encoded by long polar fimbriae (*lpf*), which promote the adhesion of *Salmonella* to Peyer's patches. Three virulence plasmid genes have been reported to be involved in serum resistance. These are *tra* T, *rck* and *rsk*. *Tra* T, 27 kDa protein which is encoded by transfer region of plasmid confers weak serum resistance. The exact mechanism of serum resistance contributed by *Tra* T protein is not clear, but it has been

observed that after continuous passage for 20 generations tra T mediated resistance was lost. In some serovars like *S. enteritidis*, *S. dublin* and *S. choleraesuis*, tra T gene was found to be absent. The rck gene has been detected in *S. typhimurium* and *S. enteritidis*, and it is located near pef genes on the plasmid. The rck gene encodes for 19 kDa protein that is inserted in the outer membrane after the cleavage of the leader sequence and inhibit the polymerization of the C9 protein of complement and contribute to serum resistance. Rck has also been found to be involved in the invasion of epithelial cells. Another gene rsk is a regulatory element able to bind the replication protein, Rep A. It is found to be involved in regulation of integration of plasmid on the chromosome, which not only increases the susceptibility to serum, but also the log time of culture grown in minimal medium (Silva, 2017) .

2.3. Regulation of virulence in *Salmonella*

Virulence system of *Salmonella* is very complex and more than 300 genes have been reported to play their role in contributing the virulence of *Salmonella*. There are 14 regulators including PhoP/PhoQ, Spv R, RpoS, Omp R/Env z, and Hfq are involved in regulation of virulence system of *Salmonella*. *Salmonella* is a facultative, intracellular pathogen, and PhoP/PhoQ is an important sensor for extracellular and intracellular life [32, 33]. Two major events of *Salmonella* virulence host invasion and intracellular proliferation are regulated by genes located in SPI-1 and SPI-2 respectively. Type III secretion system plays a major role in the invasion of the host cell by *Salmonella*. The biological function of T₃SS is the translocation of proteins from bacterial cytoplasm into the host cell, thus, functioning as the molecular syringe. On interaction with the host epithelial cell, T₃SS of SPI-1 triggers and facilitate the invasion of the host cell. The two major structural components of T₃SS are base structure and needle structure in the inner rod that forms the connection between cytoplasm and host cell membrane. Major structural genes of T₃SS of SPI-1 includes prg HIJK, spa MOPORS and inv. ABCDEFGH along with regulatory protein of T₃SS. The assembly of SPI-1, T3SS starts from the base and inner ring structure is assembled by Prg H and Prg K proteins followed by cytoplasmic export machinery, which is composed of Inv A, Inv C, SPo P, SPoQ, SpaR, and SPaS proteins. The outer ring structure is composed of Inv G and Inv H protein, remains connected with inner ring structure, and is stabilized with the aid of regulatory protein Inv J. The needle and inner structure are made up of Prg J and Prg I subunits [34].

T₃SS system secretes many effector proteins through the needle of secretion systems such as SIP ABC and SOP ABCDEP. SoPE and SoP E₂ act as guanine nucleotide exchange factor (GEFs) for small GTPase Cdc 42 and Rae. Additional SPI-1 translocated effectors of *Salmonella* affect actin dynamics during the invasion process. SIP A and C bind and stabilize actin dynamics and cause actin rearrangement via their distinct actin binding and actin nucleating domains that result in membrane ruffling. SIP C along with SoP E direct fusion of the exocytic vesicle with plasma membrane for the expanding ruffle or phagocytic cup. SIP D/SoP B of SIP-I also alter the actin cytoskeleton through manipulation of phosphoinositides. This increases the elasticity to facilitate remodeling of plasma membrane associated with *Salmonella* entry. SIP D is also involved in sealing plasma membrane invaginations to form bona fide vacuoles. After invasion, SIP P act as GTPase-activating protein for Cdc42 and Rae1, thereby inactivating these G proteins and returning the cell morphology into normal. SIP P is also involved in

triggering of membrane ruffling. Membrane ruffling is characterized by rearrangement of the cell membrane and cytosol such that the bacteria are surrounded by the host cell and internalized followed by formation of *Salmonella*-containing vacuole (SCV). As the SCV matures, it migrates to basal membrane and *Salmonella* interacts with macrophages associated with Peyer's patches. SoP B manipulates the surface of SCV and assists in inhibition of fusion of SCV with late endosomes [35]. This inhibition helps *Salmonella* to avoid being killed by normal phago-lysosomal processing pathways. The SCVs play an important role in survival and transportation of *Salmonella* within the phagocytic cells during the enteric phase of infection. Once *Salmonella* has formed SCV, the genes of SPI-2 T₃SS system expressed. A number of environmental factors have been associated with induction of these genes through OmpR/Env Z regulatory system. These factors include low osmolarity, low pH and low level of certain nutrients [36]. The major function of effector proteins of SPI-T₃SS are disruption of vesicular transport and formation of *Salmonella*-induced filaments (SCF) is still not clear, but they may play their role in intracellular replication of *Salmonella*. To facilitate systemic phase of infection *Salmonella* present in immune cells (macrophages) of the intestine is carried to other organs of the body like liver, spleen, etc. [37]. Dendritic cells are mainly involved in transportation and spread of *Salmonella* in various parts of the body. In dendritic cells, *Salmonella* does not replicate but remain viable. Genes encoded by SPI-2 T₃SS appear to suppress antigen presentation by dendritic cells which limit the immune response by host cells [38]. The metabolic activity of dendritic cell possessing *Salmonella* is significantly reduced and a combination of reduced metabolic activity and immune-suppression contribute the persistence of *Salmonella* in the host cell. Dendritic cells express the antigens of *Salmonella* which further activate T and B cell immune response. Macrophages containing *Salmonella* are transported to Liver and Spleen by reticulo-endothelial where *Salmonella* replicate and multiply more efficiently. In the liver, Kupffer cells are activated by the presence of *Salmonella* and try to neutralize the bacteria with oxidative free radicals, nitric oxides as well as enzymes active in acidic pH. The survived bacteria invade hepatocyte and cause cellular death by apoptosis. The bacteremic phase of the disease is characterized by dissemination of organism in the spleen, bone marrow, and gall bladder where it can replicate and survive for the longer duration.

3. Conclusion

Salmonella is an enteric pathogen who has versatile abilities to invade and survive in host system. It contains more than 300 genes which contribute in various aspects of virulence such as adhesion, invasion, and replication. *Salmonella* has evolved a complex which not only hosts immune system but also coordinates the various genes for providing a suitable environment for invasion and proliferation of *Salmonella*. *Salmonella* pathogenicity islands (SPIs) along with the virulence plasmids play an important role in survival and proliferation of bacteria in host system. SPI-1 along with SPI-4 is involved in primary stage of disease that is adhesion and invasion of intestinal mucosa. SPI-2 is referred for growth and survival of bacteria inside the host cell during systemic phase of disease. SPI-3 and SPI-5 play a dual role in pathogenesis as their protein are involved in invasion and intracellular survival. An extremely complex gene regulation and expression system are involved in various aspects

of virulence like invasion, replication, Quorum sensing, and 14 regulators are involved in regulation of virulence. In spite of large number of regulators reported to influence the virulence gene expression, the role of many regulators and genes is still not very clear. Therefore, further studies are needed to decode and understand the complex and interesting virulence gene system of *Salmonella*.

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