Abstract – The pivotal virulence factors of foodborne zoonotic pathogen Salmonella enterica serotype Typhimurium associated with pathogenesis of systemic disease of humans and mice are the effectors of type three secretion systems. They are encoded by genes located on two different gene clusters named Salmonella pathogenicity island 1 and 2 (SPI-1 and SPI-2) and Salmonella plasmid virulence locus whose expressions are coordinated by regulatory networks in spatial and temporal manners. Secretion of the SPI-1 effectors required for bacterial internalization into specific compartments called Salmonella-containing vacuole (SCV) of infected intestinal epithelial cells, is induced by environmental conditions via Hil transcription factors network. Secretion of SPI-2 and plasmid effectors required for bacterial survival inside of the SCVs of these cells and subsequently infected phagocytic cells, systemic spread, immunosuppression and cytotoxicity, is coordinated by broader regulatory network with the two response regulators, SsrB and SlyA, as the terminal regulators that integrate multiple environmental signals.

Key words: Salmonella Typhimurium, effectors, virulence, systemic disease

Sažetak – Pivotalni faktori virulencije hranom prenosivog zoonotskog patogena Salmonella enterica serotip Typhimurium, koji su povezani s patogenezom sistemskih oboljenja ljudi i miševa, efektori su sekretornog sistema tipa tri. Oni su kodirani genima koji se nalaze u dva različita genska klastera, pod nazivom Salmonella patogenski otok 1 i 2 (SPI-1 i SPI-2), i u plazmidskom lokusu virulencije, čija je transkripcija regulirana

Ermin Schadich, MD, PhD, Assistant, Department of Microbiology, School of Biological Sciences, Christchurch, New Zealand and Centre for Chemical Biology (CCB USM), No 10, Persiaran Bukit Jambul, 11900 Bayan Lepas, Pulau Pinang, Malaysia

Dr. sc. Ermin Schadich, doktor medicine, asistent, Department of Microbiology, School of Biological Sciences, Christchurch, New Zealand i Centre for Chemical Biology (CCB USM), No 10, Persiaran Bukit Jambul, 11900 Bayan Lepas, Pulau Pinang, Malaysia
prostorno i vremenski regulatornim mrežama. Sekrecija SPI-1 efektori potrebna za
internalizaciju bakterije u posebne stanične organele zaraženih crijevnih epitelnih stanica
pod nazivom vezikule koje sadrže Salmonella (SCV) je inducirana uvjetima sredine,
putem Hil mreže transkripcijskih faktora. Sekreciju SPI-2 i plazmidskih efektori
potrebnih za preživljavanje bakterija unutar SCV ovih stanica, te posljedično inficiranih
fagocitnih stanica, sistemsko širenje, imunosupresiju i citotoksičnost koordinira šira
regulatorna mreža s dva regulatora odgovora, SsrB i SlyA, kao terminalnih regulatora
koji integriraju višestruke signale sredine.

Ključne riječi: Salmonella Typhimurium, efektori, sistemsko oboljenje, virulencija

Introduction

Salmonella enterica serotype Typhimurium is an important foodborne zoonotic
pathogen that causes an array of diseases in humans, ranging from self-limiting infective
gastroenteritis associated with strong diarrhoea to life-threatening systemic disease (27).
These diseases are classified in the group of non-typhoidal salmonellosis (NTS) (50).
They are associated with an estimated annual death rate of 155,000 worldwide. Only in
the United States of America, 1.4 million NTSs are associated with 168,000 visits to
physicians, 15,000 hospitalizations and 580 deaths annually (50, 82). Since S.
Typhimurium has low level of host specificity and infects a broad range of different
mammalian and avian species including those involved in food production, pigs, poultry
and cattle, the infections are spread rapidly by contaminated food and infected animals
(50, 73, 82). Severity of disease depends not only on pathogenicity of S. Typhimurium
but also on the status of the host-immune system, and fatality occurs frequently in
infected individuals with incompetent immune system including young children, elderly
people, HIV and cancer and immunocompromised patients (19, 50, 82).

S. Typhimurium belongs to Salmonella enterica subspecies enterica that
involves the serotypes that are pathogenic to humans and warm-blooded animals,
mammalians and birds (25, 27, 42). Salmonella enterica subspecies enterica branched
from other S. enterica subspecies, S. alamaes, S. arizonae, S. diarizonae, S. houtenae and
S. indica, after clonal divergence of S. enterica from common ancestor (12, 18, 42, 47).
Initially, this process resulted in two separate lineages of genus Salmonella, S. bongori
and S. enterica (5, 72). The close relatedness of orthologous genes of Salmonella
serotypes, which ranges between 3.8 and 4.6%, sequence divergence, and divergence in
deduced amino acids of between 0.7 and 1.3%, indicates clonal divergence, and based on
degree of divergence, it can be estimated that a common ancestor existed about 2-40
million years ago (5, 65, 72). However, despite such close relatedness, Salmonella
serotypes differ in pathogenicity and host range as only S. enterica subspecies enterica
infests warm-blooded animals while all other S. enterica subspecies and S. bongori infect
cold-blooded animals (5, 27, 50). These differences are due to differences in genes encoding virulence factors (25, 53, 61, 72).

The virulence genes of Salmonella are located on a specialized part of Salmonella chromosome called Salmonella pathogenicity islands (SPI) (5, 39, 53, 61). It is considered that the acquisition of the SPIs may have occurred via lateral gene transfer during virulence evolution (39, 41) as sequence analyses of the 22 known SPIs showed that all of them contain distinct virulence genes, (5, 25, 72), different GC content (39), presence of movable elements and association with tRNA (25, 41, 59). Three SPIs that contain genes required for intestinal phase of infection, SPI-1, 3, and 5 were identified by common lineage ancestor to all serotypes in the first phase of evolution, as they are present in all Salmonella serotypes but not E. coli and other related Enterobacteriae (25, 39, 59). Divergence of S. enterica and S. bongori as separate species is considered to be the second phase of evolution and it was associated with acquisition of SPI-2 in all S. enterica serotypes on background genetic drift (25, 39, 65). This island contains genes encoding for a unique virulence trait underlying systemic disease, bacterial survival and replication in immune cells, different phagocytes, macrophages, dendritic cells, T and B lymphocytes (5, 25, 61). Subsequently, in the third phase, S. enterica subspecies evolved with acquisition of different SPIs with genes encoding for unique virulence factors required for host restrictions, and some initially acquired genes were lost either by deletion or pseudogene formation (5, 25, 53, 61).

The differences in ability of S. enterica subspecies enterica serotypes to infect and interact with a variety of human and warm-blooded animals cells including epithelial cells, M microfold cells of Peyer’s patches, phagocytes, dendritic cells, T and B lymphocytes and macrophages, determine the differences in the host range and clinical manifestation of disease (27, 50, 69, 78, 83). The most striking difference is between S. Typhimurium and two human restricted Salmonella enterica subspecies enterica serotypes associated with Typhoid syndrome (TS) as in healthy humans, S. Typhi and S. Paratyphi cause TS while S. Typhimurium causes only gastroenteritis (27, 50). It was observed that in healthy humans, only S. Typhi and S. Paratyphi via infected CD18+ monocytes invaded extensively blood and the extra-intestinal organs including abdominal lymph nodes, liver, spleen and bone marrow (19, 27, 42). In contrast, S. Typhimurium disease is associated with infection of mainly non-phagocytic epithelial and microfold (M) cells and exudative diarrhoea (27, 50, 75, 81). This is due to strong inflammatory responses associated with massive neutrophil infiltration of the intestinal mucosa, secretion of intestinal fluids and a recruitment of dendritic cells and CD4+ lymphocytes in Peyer’s patches, solitary intestinal lymphoid tissues and mesenteric lymph nodes (27, 50, 69, 75). However, when these responses are impaired as it was observed for HIV patients, young children, elderly and immunocompromised patients, the pathogen invades extra-intestinal organs via CD18+ monocytes and cause systemic syndrome (27, 50, 69).

In its primary host mouse, S. Typhimurium infects CD18+ monocytes extensively and via them invades extra-intestinal organs and causes pathological changes as in human S. Typhi disease regardless of immune competence of infected animals (2,
22, 69, 76). These infections are very often used in experimental studies for investigation of pathogenesis of S. Typhi disease in absence of the authentic animal disease model as a disease model with the surrogate pathogen in the surrogate host.

As S. Typhimurium and other pathogenic S. enterica subspecies enterica serotypes are intracellular pathogens, a full elaboration of their pathogenicity depends on secretion of different sets of specific virulence factors that induce their internalization into the targeted cells enabling their intracellular survival and replication in both human and mouse disease (2, 27, 81, 83). These factors act as the effectors targeting different cellular processes at two different stages of infections, invasion and intracellular infection (4, 27, 45). They are trans-located across membrane and secreted by type three secretion systems (TTSS), which are the large protein complexes that have properties to secrete proteins with no signal sequences and require contact with host cells (27, 45). The genes encoding for them as well as genes encoding for protein components of TTSS apparatus are located in SPI-1 and SPI-2 with some effectors being also encoded by genes located in other SPIs (25, 53, 72).

Secretions of the SPI TTSS effectors both from intracellular and extracellular bacteria are required for pathogenesis of systemic disease. While secretion of the SPI1 effectors plays an essential role in invasion of non-phagocytic epithelial cells in intestine during intestinal phase of infection resembling similar mechanism of other enteric bacterial pathogens, secretion of SPI2 provides bacterial survival and replication inside of the infected phagocytic cells, monocytes, macrophages and dendritic cells during systemic phase of infection (10, 37, 47, 85). However, other virulence factors also have important roles in virulence including fimbriae (5), lipopolysaccharide (LPS) complexes (11), plasmid virulence factors (67), flagellar proteins (9) and regulatory two-component systems for regulation of gene expression (8, 30). A current focus of many different studies is to provide better understanding of virulence mechanisms of S. Typhimurium in pathogenesis of human systemic disease by using different in vivo and in vitro analyses of spatio-temporal patterns of expression and function of the SPI-1,2 effectors in infected tissues.

This review focused on recent advances in function of these virulence effectors. All graphical presentations were made by using Pathway Studio software (Ariadne Genomics, Rockville, MD 20850, USA).

The SPI-1 TTSS effectors - mediated epithelial cell invasion

S. Typhimurium initiates infection by self-promoted entry into intestinal M epithelial cells via trigger mechanism that includes secretion of SPI1 TTSS effectors and subsequent activation of actin nucleated related proteins (Arp2/3) and cytoskeleton rearrangement (20, 32, 36, 46). Prior to entry, S. Typhimurium adheres via adhesive fimbriae whose components are encoded by plasmid-encoded fimbriae (pef) and long polar fimbriae (lpf) operons (5) and the LPS with specified olygosaccharide chain lengths...
The SPI-1-TTSS effectors are secreted into epithelial by SPI1-TTSS secretory apparatus and initially this process includes translocase complex proteins, SipB, SipC and SipD for intimate association with the host cells (35, 83). They interact with host Rho family GTPases and Arp2/3 to produce cytoskeleton rearrangement at the site of bacterial entry causing membrane ruffles, which will engulf the bacteria and form the *Salmonella* containing vesicle (SCV), a specific vacuolar compartment required for intracellular survival (Figure 1) (20, 62, 85, 87).

The roles of the SPI-1 TTSS effectors SopB, SopE, SopE2, SipC, SipA, SipD and SptP in Arp2/3 dependent cytoskeletal arrangements have been well described (2, 20, 50, 86, 87). Two effectors, SipA and SipC, induce activity of Arp2/3 by lowering critical actin monomer concentration for polymerisation, and increasing activity of T-plastin (13, 36, 56, 87). SipA also has an additional role as it blocks actin depolymerisation by excluding ADF/cofilin (a key regulator of actin plasticity) from growing F-actin (13, 20, 87). Two effectors, SopE and SopE2, catalyse the exchange of the regulatory factor GTP and thereby directly activate three Rho-GTPase, Rac1, RhoG and Cdc42 (1, 74). Surprisingly, SopB activate RhoG and Cdc42 via host SH3 containing guanine nucleotide exchange factor endocellular (SGEF) protein (1, 62, 74). Signal from activated RhoGTPase is transmitted to Arp2/3 via complex that involves Wiscon-Aldrich syndrome protein (WAVE)) (Figure 1) (1, 74, 87) and Abelson kinase protein (Abl1) (11, 32, 74). Upon bacterial internalization, the actin cytoskeleton restores to its basal state by SptP-mediated inactivation of Rac1, RhoG and Cdc42 (Figure 1) (26, 63).

![Figure 1](image.png)

**Figure 1.** The SPI-1 TTSS effectors- mediated internalization of S. Typhimurium into host enteric cells. Figure was made based on information from references 13, 20 and 62.

**Slika 1.** SPI-1 TTSS efektorski posredovana internalizacija S. Typhimurium u crijevnim stanicama domaćina. Slika je kreirana na osnovu informacija iz referenci 13, 20 i 62.
Salmonella is thought to be able to determine its location in distal ileum by sensing different environmental signals via sensory systems (3), and to coordinate transcription of genes encoding for invasive phenotype including SP-1 TTSS genes by regulatory network that involves regulators responsive to a combination of environmental and intracellular signals including HilA, InvF, HilC, HilD and RtsA (3, 29). It is important that this network coordinates the assembly of SP1-TTSS apparatus and secretion of effectors of S. Typhimurium commences only when bacteria reach their target tissue in distal ileum (29, 49).

**Virulence factors involved in regulation of SCV modulation and trafficking**

Survival and replication of S. Typhimurium inside of the SCV in infected macrophages, CD18+ monocytes and dendritic cells are essential for establishment of infection and systemic bacterial dissemination in infected humans and animals (20, 22, 69, 75). These two processes depend on maturation of SCV in endocytic pathway as it creates the intracellular environmental niche required for nutrient supply and bacterial replication, and involves all of the selective interactions of the SCV with the trans-Golgy network (20, 48, 68). In its maturation, the SCV acquires all of the early endosomal markers, GTPase (Rab5) and early endosome antigen protein (EEA1), followed by late endosomal markers Rab7, lysosome associated membrane proteins (LAMP1, LAMP2 and LIMP1/LAMP3), and vacuolar proton pump (vATPase) (Figure 2) (20, 48, 68, 71). Although the SCV acquires all of the late endosomal markers required for fusion with lysosome, it does not acquire the late endosomal marker, mannose-6-phosphate receptors (M6PR) required for delivering of lysosomal hydrolases cathepsin D and L (14, 15, 20, 40) so that SCV is not targeted to phagosome-lysosomal destruction. Such interference with classical endocytic pathway S. Typhimurium achieves by secretion of SPI-2 TTSS. The SPI-1 effector SopB is an essential survival virulence factor in initial phase of intracellular infection as its phosphatase activity recruits the lysosomal markers and the sorting nexin 1 (SNX1) on the SCV membrane. Subsequently, SNX1 selectively removes M6PR-positive membrane from this compartment (15, 20). Thus S. Typhimurium does not avoid fusion of SCV with membranes of endocytic pathway during maturation, but it coordinates removal of deleterious factors from its membranes through selective process.

Positioning of the SCV around trans-Golgy network and development of Salmonella induced filaments (Sifs), the SCV tubular extensions that extend from SCV are the two main hallmarks of SCV maturation (Figure 2) (20, 40). Since Salmonella cannot replicate as free in cytosol, such SCV positioning and development facilitates bacterial access to endocytic membranes, nutrients and synthetic enzymes required for creating survival and replication (20, 40). By itself, the SCV positioning involves movement along microtubules (MT) and depends on two opposing motor kinetic systems, dynein/dynactin and kinesin-1 namely (47, 20, 21, 40). The centripetal movement of SCV
is dependent on the dynein-dynactin motor complex (21) while the centrifugal movement of SCV is dependent on kinesin-1 motor complex (20, 21, 38, 51). Coordinated balance between these two kinetic systems is essential both for SCV position and SIF development.

S. Typhimurium regulates SCV positioning and interactions with endocytotic pathway by secretion of SPI-2 TTSS effectors (2, 20, 40), and among them, the key effectors are *Salmonella* induced filaments factor A (SifA) and three system secretion effectors (Sse), SseF, SseG and SseJ (Figure 3) (1, 21, 48, 68). SifA effector is required for membrane integrity of the SCV as it regulates balance of two opposing motor kinetic systems (7, 40). It promotes interaction of a host protein named SifA and kinesin-interacting protein (SKIP) with kinesin-1 that promotes the transport of SCV derived vesicles towards periphery as well as development of Sifs (21). The SifA coordinates activity of PipB2, an SPI2 TTSS effector encoded by gene on SPI12, in recruitment of kinesin-1 to SCV (38), and oppose the interference of SopD with vesicular transport (20, 71). SifA effector might also interfere with recruitment of dynein on the SCV membrane by disengaging the Rab7-Rab interacting lysosomal protein (RILP) complex and thereby might promote centrifugal extension of the Sifs (1, 20, 40). The two effectors, SseG and SseF, act as associated complex SseF-SseG complex that regulates the activity of the dynein complexes associated with the SCV (1, 16, 38) while the effector SseJ catalyses esterification of cholesterol of lipids of the SCV membrane (48).

![Image](image.png)

**Figure 2.** Regulation of membrane interactions between *Salmonella* containing vacuole (SCV) and trans-Golgi network during formation and maturation of the SCV by SPI-2 TTSS effectors. Figure was made based on information from references 14, 20, 40, 68, 71 and 74

**Figure 2.** Regulacija membranske interakcije izmedju vakuole koja sadrži *Salmonellu* (SCV) i trans-Golđijeve mreže tokom formiranja i sazrijevanja SCV sa SPI-2 TTSS efektorima. Slika je kreirana na osnovu informacija iz referenci 14, 20, 40, 68, 71 i 74
Furthermore, *S.* Typhimurium could also affect host cell secretory pathway via recruitment secretory carrier associated membrane protein (Scamp3) from Golgy trans network by unidentified mechanism to coordinate the association the SKIP-kinesin complexes on the SCV membrane and maintenance of the SCV in the Golgy region of infected cells (Figure 2) (20).

**Promotion of intracellular survival of *S.* Typhimurium by plasmid virulence factors**

*S.* Typhimurium strains associated with bacteraemia and systemic dissemination both in humans and mice carry plasmids with virulence locus, and the designated name for this locus is *Salmonella* plasmid virulence (*spv*) (32, 33). The plasmid *spvABCD* genes are arranged in an operon positively regulated by SpvR, a transcriptional regulator of the LysR protein family that binds to inverted repeated recognition sequences of its own promoter and the *spvA* promoter (23, 32, 33). Genetic analyses showed that two *spvB* and *spvC* genes are indispensable for elaboration of virulence while mutations in *spvA* and *spvD* do not have reproducible virulence phenotype (43, 44, 66). The proteins encoded by *spvB* and *spvC*, *SpvB* and *SpvC*, are secreted by SPI-2 TSS and their direct role in virulence is to promote survival in infected macrophages by inhibition of antimicrobial activities in phagosome and activation of late apoptosis (34, 44, 66).

**Regulatory network controlling expression of SPI-2 genes**

Coordination of expression of SPI-2 virulence factors of *S.* Typhimurium is obtained by a synchronized operation of regulatory pathways in response to specific environmental conditions inside of SCV. These pathways include three pivotal two-component regulatory systems, PhoP/PhoQ, OmpR/EnvZ and SsrB/SsrA, required to control expression of genes required for intracellular survival and replication (8, 30, 54).

The PhoP/PhoQ system includes PhoQ sensor kinase for extracellular Mg$^{2+}$ that modifies by phosphorylation the response factor PhoP (75). PohP is a transcription factor of OmpR family that mediates adaptation to low Mg$^{2+}$ and virulence genes in different Gram negative species (27, 52, 57, 84). *S.* Typhimurium mutants lacking the PhoP/PhoQ system are unable to replicate inside of macrophages and their virulence is highly attenuated (78, 79). It is considered that by monitoring extracellular Mg$^{2+}$, the PhoP/Q system enables *Salmonella* to sense its transition from extracellular space to subcellular environment and activate the genes required for intracellular survival and replication (49, 57).

The regulatory role of the PhoP/PhoQ system in virulence of *Salmonella enterica* serotypes differ from its role in virulence of other Gram negative species as it regulates *Salmonella* unique SsrB/SsrA system encoded by genes of SPI-2. The SsrB/SsrA system is composed of histidine sensor kinase SsrA and response regulator
SsrB (79.80). SsrB activates expression of genes encoding for components of SPI-2 TTSS secretory apparatus as well as genes encoding for effectors located both in SPI-2 and elsewhere in chromosome by binding to promoters of their genes (24, 79, 80). Activated PhoP activates transcription of ssrB gene, and modulates SsrA level post-transcriptionally (8, 57). Its role in activation of stress responsive RpoS factor and regulation of other virulence genes is similar to those in other Gram negative species (77).

In infected macrophages, the low Ca^{2+} concentration, osmolarity and pH can also induce expression of SPI2 genes and their effects are partially sensed and mediated via OmpR/EnvZ two-component system whose response factor OmpR induces expression of ssrAB by direct binding to its promoter (30, 54, 58). This shows that both PhoP/PhoQ and OmpR/EnvZ pathways are integrated into regulatory pathways via SsrB/SsrA.

Recent studies showed the inferred core network of virulence that integrates different signals from other pathways, and coordinates activity of PhoP/PhoQ-SsrB/SsrA and OmpR/EnvZ-SsrB/SsrA regulatory pathways in regulation of virulence genes associated with intracellular infection including SPI-2 and plasmid genes (Figure 3) (52, 54, 57, 84). This was achieved by combining different in vivo and in vitro approaches including bacterial mutational analyses, animal disease models with mice, infections tissue culture studies with macrophages and transcriptome, proteomics, and computational network inference analyses (27, 52, 57, 84). It was shown that of known 300 protein regulators, four protein regulators are involved in the core network including transcriptional regulators SlyA and SpvR and two translational regulators SmpB and Hfq (54, 79, 80, 84). SlyA is transcriptional activator of ssrA gene and also directly activates expression of SPI-2 genes (Figure 3) (24, 60, 77). Binding of SlyA and SsrB to promoters of SPI-2 genes is associated with removal of two nucleoid proteins H-NS and Hha from them (60, 64). These two proteins have a predilection for binding to the A+T rich regions of the SPIs, and their removal from promoters is also necessary for expression of SPI-1 genes by activators suggesting evolutionary response of these two proteins in silencing horizontally acquired genes (64). The other transcriptional regulator is a plasmid virulence factor SpvR that regulates expression of spvABCD operon encoding for virulence factors associated with survival, and its transcription is induced by stress factor RpoS (31).

One translational regulator SmpB is a positive regulator of SsrB/SsrA while the other translational regulator Hfq is a negative regulator of SmpB as well as PhoP/PhoQ and OmpR/EnvZ (Figure 3) (58, 16). Outside of this network, SmpB is the negative regulator of proteins involved in regulation of genes involved in tissue invasiveness including SPI-1, flagellar and chemotaxis genes (54). These facts also support the regulation at post-transcriptional level as a mechanism of integration of the SPI-2 core network with other networks associated with regulation of virulence and adaptation to environment.

In infected macrophages, the expression of SPI-2 gene of *Salmonella* Typhimurium could be further down-regulated by non-specific metabolic regulators.
outside the core network (16, 84). *Salmonella* has to avoid hyper-activation of SPI-2 genes as multiple positive feedback loops promote expression of *ssrB* as well as SrB itself increases expression of SPI-2 genes to undesirable levels under activating conditions. A protein regulator EIIANtr, a component of the nitrogen-metabolic phospho-transferase system, which is encoded by *ptsN* gene could control timing and expression level of SPI-2 genes (16). It interacts directly with SrB protein and prevents its binding to its target promoters (16). Its expression is induced under stress conditions inside SCV via stress responsive factor RpoE, a transcriptional activator of *ptsN* (16, 84).

Figure 3. The core network of regulators associated with regulation of expression of the SPI-2. Construction of network was based on information from references 16, 54 and 84.

Concluding remarks

The most recent advance from experimental studies provided the evidences for the SPI1-2 TTSS effectors as pivotal mechanisms of virulence of *S. Typhimurium* both in infected humans and mice. The SPI-1 TTSS effectors in concert with fimbriae and LPS promote bacterial uptake into the epithelial cells and they modulate activity of host RhoGTPases and actin polymerisation leading to cytoskeleton rearrangements and bacterial internalization into the *Salmonella* containing vacuoles (SCV). Their activity is coordinated by a regulatory network of Hils regulators responsive to environmental conditions in infected intestine. The SPI-2 TTSS effectors including also those encoded by genes of plasmid *spv* locus mediate all of the processes associated with survival and replication in the infected macrophages and dendritic cells including maturation of SCV,
inhibition of antimicrobial mechanisms and antigen presentation and modulation of pro-inflammatory and pro-apoptotic signal transductions. Their activities are regulated by specialised network that senses and responds to the different environmental signals inside of SCV by three component systems PhoP/PhoQ, OmpR/EnvZ and SsrB/SsrA.

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