

# Molecular Mechanisms of *Salmonella* Effector Proteins: A Comprehensive Review

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**Abstract:** *Salmonella* can be categorized into many serotypes, which are specific to known hosts or broadhosts. It makes no difference which one of the serotypes would penetrate the gastrointestinal tract because they all face similar obstacles such as mucus and microbiome. However, following their penetration, some species remain in the gastrointestinal tract; yet, others spread to another organ like gallbladder. *Salmonella* is required to alter the immune response to sustain its intracellular life. Changing the host response requires particular effector proteins and vehicles to translocate them. To this end, a categorized gene called *Salmonella* pathogenicity island (SPI) was developed; genes like *Salmonella* pathogenicity island encode aggressive or modulating proteins. Initially, *Salmonella* needs to be attached and stabilized via adhesin factor, without which no further steps can be taken. In this review, an attempt has been made to elaborate on each factor attached to the host cell or to modulating and aggressive proteins that evade immune systems. This review includes four sections: (A) attachment factors or T3SS- independent entrance, (B) effector proteins or T3SS-dependent entrance, (c) regulation of invasive genes, and (D) regulation of immune responses.

**Keywords:** *Salmonella*, effector proteins, immune response, T3SS, pathogenesis

## Introduction

Nearly all pathogens that attack the gastrointestinal tract spring from food. Pathogenic bacteria such as *Salmonella* spp., *Campylobacter* spp., *Yersinia enterocolitica*, *Shigella* spp., and Enterotoxigenic *Escherichia coli* can invade the gastrointestinal lumen and cause diarrhea and other damage.<sup>1,2</sup> One of the most important bacteria that penetrates the lumen out of different materials, such as dairy, vegetable, egg, etc., is *Salmonella* spp.<sup>3</sup> *Salmonella* may cause death all around the world.<sup>4</sup> Some species such as <sup>5</sup> *S. Typhi* specifically show inclination towards humans and cause a higher rate of mortality; however, other species such as <sup>6</sup> *S. enteritidis* cause self-limiting diarrhea; of note, the latter can be just as deadly as the former. Further, statistics have shown a quarter of mortality rates associated with the former type. However, all species should overcome a number of barriers, such as stomach and mucus, and evade an immune cell. Pathogenic *Salmonella* has a particular factor that differs from the non-pathogenic ones such as Type-3 Secretion System (T3SS) and *Salmonella* pathogenicity island (SPI).<sup>7,8</sup> Interestingly, *Salmonella* has a two-cluster distinct T3SS, which is encoded by SPI-1 and SPI-2. Almost all effectors of SPI-1 and SPI-2 mediate cell invasion and intracellular survival, respectively.<sup>9,10</sup> Having passed through stomach via food, *Salmonella* penetrates the intestine and causes enteritis. To this end, *Salmonella* needs to be attached to the host cell and cross the intestinal membrane via M cell or dendritic

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cell (DC).<sup>11</sup> Following the attachment, (Part A) T3SS-independent entrance approach can be adopted by SiiE, Rck, PagN, and ShdA, or (Part B) T3SS-dependent entrance can be adopted by SipA, SipC, SopB, and SopE. The virulence factor is activated to modulate host cell life for the benefit of the striker. Regulation between activation of adhesion and virulence factor needs to be adjusted and activated (Part C) at a right moment. To ensure maximum coordination, this pathogenic gene is clustered into one genomic island. Finally, the immune response (Part D) is activated, and necessary actions are taken to put an end to this adventure.

## Attachment Factors (T3SS-Independent Entrance)

### Adhesin Proteins

#### SiiE

For *Salmonella* infection or invasion to occur, the first pathogen should reside in the site of infection. SiiE is a non-fimbrial adhesin of *Salmonella* that can be attached to the epithelial cell.<sup>12</sup> This effector is transferred through T1SS and encoded by SPI-4. T1SS system is formed by three subunits: SiiF as an inner membrane and ATPase, SiiD as a transmembrane unit, and SiiC as an outer membrane protein.<sup>13</sup> SPI-4 and T1SS, as well as its substrate SiiE, are required only to invade the polarized cell.<sup>14</sup> HilA regulates the transcription of SPI-4 by a master regulator, SirA.<sup>15</sup> The signal sequence of SiiE is located at terminal C and has a long linear structure to cross the LPS structure.<sup>16</sup>

#### Biofilm Association Protein (BapA)

Biofilm-associated protein (Bap) has a major role in the production of biofilm composed of cellulose and curli fimbriae. Bap secretes through T1SS and resides on the bacterial surface.<sup>17</sup> Both components are under the regulation of CsgD regulator. CsgD activates csgBAC operon to produce curli pili.<sup>18</sup> Active production of Bap is also regulated by CsgD regulator.<sup>17</sup> As a curli fimbriae operon, CsgA can be up-regulated in many ways in gallstone.<sup>19</sup>

#### Resistance to Complement Killing (Rck)

The outer membrane protein, Rck, has a major role in invading the host cell. Rck generates a zipper-like structure by stimulating Cdc42, and Rac1 may produce actin formation.<sup>20</sup> Furthermore, Rck can mediate complement resistance by inhibiting polymerization of C9 on the bacterial surface.<sup>21</sup> Rck is attached to the Epidermal Growth Factor Receptor (EGFR) directly, and the attachment site

differs from EGF, leading to the auto phosphorylation of the EGFR cytosolic tail.<sup>22</sup> This phosphorylation leads to a signaling cascade and the activation of Src, which is a signaling molecule that finally causes bacterial internalization.<sup>23</sup> Rck binds to the extracellular matrix (ECM). For more information, see Table 1.

#### PhoP Activated Gene N (PagN)

PagN is another outer membrane protein that interacts with the eukaryotic epithelial cell via haemagglutination property. This protein plays a role in adhesion to and invasion of the host cell. Heparan sulfate on the host cell acts as a receptor for this ligand.<sup>24,25</sup> This gene is induced under cation-limited circumstances and in a PhoP-dependent manner.<sup>26</sup> This condition may occur inside a macrophage.<sup>27</sup> In the presence of cation, PhoQ inhibits the activation and expression of PhoP subset gene.<sup>27</sup>

#### Salmonella Typhi Invasion (STIV)

The next outer membrane protein involved in pathogenesis and invasion is STIV. Through the extracellular loop, STIV remains attached to the Met, the tyrosine kinase of the intestinal host cell.<sup>28</sup> After attachment, the activation of Rac1 and Src via Met phosphorylation leads to actin polymerization and bacterial engulfment. This protein is required for systemic spread and intestinal colonization in *S. Typhi*.<sup>29</sup> This protein can independently act in invasion and pathogenesis, which may encourage synergism with T3SS (Figure 1).<sup>29</sup>

#### Another Adhesin Factors

MisL is a protein of membrane insertion and secretion and is expressed in an outer membrane protein, which is encoded by SPI3, and binds to fibronectin. This attachment helps *Salmonella* invade epithelial cell and intestinal persistence.<sup>30</sup> ShdA is also translocated via an auto-transporter system to the outer membrane and binds to fibronectin.<sup>31</sup> The tip of flagella has a major role in the attachment of bacteria to the eukaryotic cell. Furthermore, flagella can actively cause bacteria to move towards a favorable attachment place.<sup>32,33</sup> OmpD can interestingly be attached to the epithelial cell, and OmpD<sup>-</sup> mutant has mitigated affinity with the host epithelial cell.<sup>34</sup>

## Virulence Factor of Salmonella Salmonella Pathogenesis Island (SPI)

SPI encoder of T3SS directly translocates effector protein inside the host cell. SPI can be found in chromosome or in plasmid and its G+C differs from that in the surrounding regions. SPI is often associated with a mobile genetic

**Table 1** Specifications of Salmonella Effector Proteins and Their Mechanisms

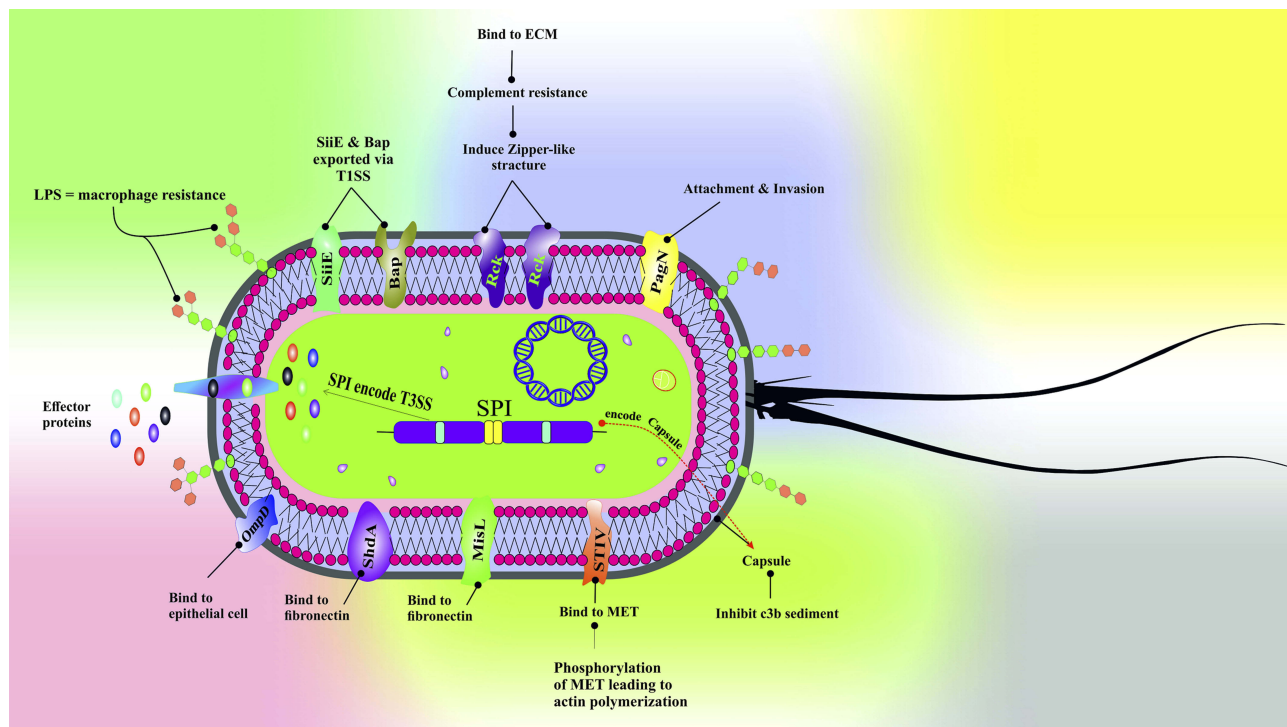
Effector Proteins	Location	Activity	Mechanisms
SipA	SPI-1	Activate caspase-1	Maturation of SCV
SopB	SPI-5	Activate Rho –GTPase, affecting ion balance	Maturation of SCV- mediate invasion
SopE	SPI-5 (Prophage)	Nucleotide exchange factor	Maturation of SCV- mediate invasion
SopA	SPI-1	Involved invasion	Maturation of SCV
SopD	Outside of SPI-1, cooperative with SopB, (translocate with SPI-1 T3SS)	Inhibit Rab-7 activity	Maturation of SCV- mediate invasion
SpvB	Plasmid (in subspecies I), chromosome in II, IIIa and VII	Induce apoptosis, Similar to <i>vibrio</i> accessory cholera entotoxin	Mediate invasion
SpiC	SPI-2	Inhibit endosomal trafficking	Mediate invasion
SseF	SPI-2	Localize the SCV to the Golgi region	Mediate invasion
SseG	SPI-2	Interact with SseF	Mediate invasion
SseJ	SPI-2	Interact with OSBP1	Mediate invasion
SseL	SPI-2	Mediate macrophage killing	Mediate invasion
SspH2	SPI-12	Immune evasion	Intracellular survival

element such as phage, insertion sequence (IS), and transposon.<sup>35</sup> SPI-1 encodes SipA and SipB and, in a similar fashion, SPI-2 encodes SseF, Srf, and SseG; SPI-3 encodes MisL; SPI-4 encodes SiiE; SPI-5 encodes SopB; SPI-6 encodes Tae4.<sup>36</sup> One of the important proteins is called SopB (*Salmonella* outer protein B) that has a major role in the secretion system and the recurrence of neutrophil.<sup>37</sup> Further to that, SopB interacts with chloride channel, affects ion balance in the host cell, and manages *Salmonella*-containing vacuole to inhibit lysosome vacuole fusion.<sup>38</sup> After translocation, SopB activates Rho GTPase in the host cell. Furthermore, SopB has a lipid phosphatase activity and hydrolyzes phosphatidylinositol biphosphate that causes failure in Na<sup>+</sup>/H<sup>+</sup> activity exchange and diarrhea.<sup>39</sup> Phosphatase activity can reduce phosphatidylinositol biphosphate PI (3, 4) and induce Akt (Protein kinase B that regulates cell survival) to ensure the best bacterial growth inside the cell and inhibit apoptosis.<sup>40–42</sup> The reduction of the phosphatidylinositol biphosphate leads to a decrease in negative charge on the surface of *Salmonella*-containing vacuole (SCV), resulting in the prevention of lysosomal enzyme fusion.<sup>43</sup> After the invasion and lipid activity of SopB, RhoH, RhoD, RhoB, and RhoJ recurred within the location of *Salmonella*

invasion. RhoB and RhoH activate Akt, and RhoJ has a role in the invasion of *Salmonella*; finally, RhoD has a role in membrane trafficking and actin reorganization.<sup>44</sup> SopB can also subvert signaling in the host cell and cause actin rearrangement in membrane cell.<sup>44,45</sup> On the other hand, SopB increases the possibility of the return of Rab5 to the SCV and, thus, causes the aggregation of phosphatidylinositol-3- phosphate on SCV.<sup>46</sup> Tae4 encoded by SPI-6 can help *Salmonella* overcome colonization resistance. By inducing bacterial lysis, Tae4 (an antimicrobial amidase) can confer a benefit to the *Salmonella* in the gut lumen establishment.<sup>47</sup> Another effector in Sop family is SopC that mediates invasion, neutrophil recruitment, and fluid secretion. This effector is found in *S. dublin* and some strains of *S. typhimurium*.<sup>48</sup>

## Vi Antigen (Capsule)

One of the important factors present in specific *Salmonella* such as *S. Typhi* is a polysaccharide capsule, called Vi antigen. Because of polysaccharide cover, the O polysaccharide may explain the resistance of bacteria to a specific antibody against O polysaccharide. Vi inhibits the deposition of C3b in the bacterial cell.<sup>49</sup> Another noteworthy point to consider is that natural IgM secreted by B-cell cannot be attached to the



**Figure 1** Interaction between Salmonella attachment factors (T3SS-independent entrance) and host proteins.

bacterial surface, which is an important step for phagocytosis and ROS as a mediator of neutrophil killing.<sup>50</sup> Vi antigen is encoded by SPI-7, which also encodes the T3SS effector SopE and pilus type IVb.<sup>51–53</sup> Vi is encoded in *viaB* locus and TviA is a positive regulator for this locus. TviA can downregulate SPI-1 and flagellar genes to stop the invasion and motility process. TviA can repress flagellar regulator *flhDC*, the master regulator (which finally activated promoters),<sup>54</sup> and alter the expression of T3SS and Vi in response to osmolarity. In fact, HilA controls the expression of T3SS, and TivA can repress the expression of HilA.<sup>55</sup> On the other hand, SPI-1 and flagella are expressed to facilitate the *Salmonella* invasion,<sup>56</sup> because Vi mask of the cell surface can reduce inflammatory cytokine-like IL-8 by attaching it to the prohibitin molecule on the surface of the intestinal cell.<sup>57</sup> Toll-like receptors (TLR) can recognize specific molecules on the pathogens. After identifying the pathogen via TLR, chemoattractants such as IL-8 are secreted. Furthermore, Vi antigen (masking) can reduce IL-8 production in a TLR-dependent manner.<sup>58,59</sup>

## Lipopolysaccharide (LPS)

One of the important factors on the surface of *Salmonella* is LPS. This factor has an important role in intestinal colonization, macrophage resistance, and modulation of the humoral

immune response.<sup>60,61</sup> LPS consists of three parts: Lipid A as an inner part, oligosaccharide as a middle part, and O antigen as a variable-length outer part.<sup>62</sup> TLR4-MD2-CD14 can recognize the inner part of LPS, Lipid A; however, O antigen stands against humoral immune response.<sup>63</sup> Furthermore, LPS inhibits the penetration of lipophilic antibiotic such as macrolide.<sup>64</sup> However, if O antigen is too long or is modified via molecules that mimic the host cell, such a sialic acid modulates the immune system.<sup>65</sup> Factors that affect elongated O antigen production include temperature and iron. Data have shown that iron limitation in medium causes a change in the elongation of LPS. A decrease in temperature can change phosphate and amine in an LPS structure that protects *Salmonella* from bacteriophage.<sup>66,67</sup> *S. paratyphi* A expressed O2 antigen with a very long O-antigen chain that prevents both antibody binding and Neutrophil respiratory burst.<sup>68</sup> The model of LPS is presented in *Salmonella*, where O12 is the backbone in all three types, O2 in *S. Paratyphi* A, and O9 or O4 in *S. Typhi* and *S. typhimurium*. The *rfbE* gene connects cytidine diphosphate-paratose to the cytidine diphosphate-tyvelose. In the case of *S. Paratyphi* A, *rfbE* is a pseudogene and is the reason why paratose remains (very long O2 antigen) on the bacterial surface.<sup>69,70</sup> Therefore, non-opsonic paratose in a very long O2 helps *S. Paratyphi* A remain unrecognizable to human IgM.

## Salmonella-Containing Vacuole (SCV)

SPI-2 encodes different types of secretion system (Type 3) that are important for maintaining the intracellular life of *Salmonella*.<sup>71</sup> The effector protein may mimic the structure of the main cellular proteins to interact with modulator enzyme.<sup>72</sup> To internalize the first vesicle, budding should be formed and, then, transferred to the inside of the cell; finally, its tethering and fusion take place. In brief, the membrane proximal coat binds to the specific membrane-associated GTPase; then, SNAREs and transmembrane cargo protein joined together in place of assembling coat.<sup>73</sup> Finally, following the transfer of vesicle, uncoating occurs through the inactivation of GTPase and vesicle merges with the acceptor compartment by means of Rab5.<sup>74</sup> Following the internalization of *Salmonella* into the host cell, bacteria engulf the vacuole by an early marker, which is to be later replaced by lysosomal-associated protein.<sup>75</sup> In other words, at the first hour, EEA1 (early endosomal antigen 1) and Rab5 are present on the SCV; however, after this time, they are replaced with LAMP (lysosome-associated membrane proteins).<sup>76</sup> Regulator Rab protein mediates transport and fusion of vesicle between the receptor and donor component.<sup>77</sup> Phosphatidylinositol-3-phosphate develops an interaction between EEA1 and Rab5 on the SCV.<sup>78</sup> *Salmonella*-induced filaments (SIF) are membrane tubules in the eukaryotic cell that can provide *Salmonella* with access to nutrition.<sup>79</sup> Rab5 by means of phosphatidylinositol-3-phosphate facilitates the attachment of EEA1 to SCV, which, in turn, produces fusion with endosome.<sup>80</sup> After an hour, an exchange of the marker occurs by replacing Rab5 by Rab7 and lysosomal-associated membrane protein (LAMP) on the SCV surface.<sup>81</sup> LAMP and Rab7 are centralized to SIF and, in this stage, SIFs are free of hydrolysis enzyme.<sup>82</sup> In fact, Rab7 causes the recurrence of the attachment of LAMP to the SCV and positioning in a perinuclear region.<sup>81</sup> Rab interacting lysosomal protein (RILP), the effector of Rab7, can use a microtubule motor to manage the perinuclear position of SCV.<sup>83</sup> In this stage, sorting nexin 1 (SNX1) removes the cation-independent mannose-6-phosphate receptor from SCV and prevents lysosomal hydrolases.<sup>84</sup> The most important factors absent in SCV include cathepsin D and mannose-6-phosphate receptor.<sup>85</sup> SNX1 induces tubulation in an early endosome in a dose-dependent fashion.<sup>86</sup> At the first hour of *Salmonella* invasion, SNX1 spreads out in the ruffle membrane that engulfs bacteria.<sup>84</sup> After a few hours, v-ATPase

acidifies the SCV that results in the activation of SPI-2.<sup>87</sup> SPI-2 and its effector mediate SIF. SIF is a double-membrane network, and the inner tubular space contains a portion of host cytosol; however, the outer tubular space contains an SCV material whose structure may show the elongation of vacuole-containing bacteria.<sup>88–90</sup> Nutrients can be exchanged between SIF lumen and endolysosomal system, and pathogen from SCV can reach out to nutrient through SIF.<sup>91</sup> Furthermore, *Salmonella* subverts the secretory vesicle to SCV to obtain nutrient.<sup>92</sup> In the final stage, SCV may combine with endolysosomal vesicle; yet, after a short while, endolysosomal substance separates from SCV.<sup>93</sup> Vesicle-associated membrane protein 7 (VAMP7) is a major factor in lysosomal fusion and has a role in SIF formation and recurrence of late lysosomal to SIF.<sup>94</sup> To inhibit the degradation of vesicle via the lysosomal enzyme, SopD2 as an effector protein from T3SS-2 should disrupt Rab7 activity, leading to the inhibition of nucleotide exchange and disruption of the interaction between Rab7 and dynein.<sup>95</sup> Altogether, this process facilitates the attachment of lysosome without hydrolytic enzyme to SCV and, thus, provides a safe place for *Salmonella* replication.<sup>96</sup> SopA mimics the ubiquitin ligase of host and may induce intestinal inflammation.<sup>97</sup> However, SspH2 is encoded by phage aid to downregulate proinflammatory response to the bacteria inside the SCV.<sup>98</sup> For vacuole stability, *Salmonella* translocates effector SseJ to the eukaryotic cell to interact with oxysterol binding protein 1 (OSBP1). OSBP1 is demonstrated to be involved in translocating sterols from lysosomes to the nucleus and exchanging sterol with phosphatidylinositol-4-phosphate, thus leading to the membrane stability of SCV.<sup>99</sup> SseF is an effector that secretes SPI-2 and mediates SCV position close to Golgi network. The persistence of SCV near the Golgi required the recurrence of dynein on the SCV surface.<sup>100</sup> SseG interacts with SseF to localize SCV in the Golgi region and convert the monolayer membrane to the double-membrane SIF.<sup>88,101</sup> SseL mediates macrophage killing and inhibits autophagy induced by the formation of ubiquitinated aggregates.<sup>102</sup> *Salmonella* translocates effector A (SteA) standing on the Sif and SCV and is involved in regulating SCV membrane dynamics. This attachment occurs when SteA binds to the phosphatidylinositol-4-phosphate in the eukaryotic cell.<sup>103</sup> SteD can block MHC of Class 2, deplete surface MHCII, and inhibit T-cell activation.<sup>104</sup> SteC regulates intracellular replication and interacts with MAP kinase to induce actin formation.<sup>105</sup> SpiC inhibits endosomal

trafficking and is involved in translocating effector proteins such as SseB and SseC.<sup>106</sup> *Salmonella*-induced filaments A and B (SifA and SifB) represent other effector proteins necessary for SIF formation. SifA interacts with Rab7 to block the interaction between RILP and Rab7, leading to the stability of SCV in a perinuclear position.<sup>107</sup> SifA also can block the interaction between Rab9 and SKIP (SifA and Kinesin interacting protein), which has a major role in the recurrence of Lamp1 to the SCV and membrane stability.<sup>108</sup> SifA binds to the SKIP and Rab9 and forms a stable complex that affects the return of mannose-6-phosphat receptor to the SCV surface.<sup>85</sup> *Salmonella* invasion protein A (SipA) mediates localization of SifA on SCV.<sup>109</sup>

Similar to SifA, SifB is translocated through SPI-2 T3SS and shares subcellular localization with SseJ on the SCV.<sup>110</sup> SifB is encoded outside of the SPI-2 and, similar to SifA, it mediates SIF formation, recurrent exocytic vesicle to the SCV, and prenuclear position of SCV.<sup>98</sup> For the dormant intracellular life, SPI-2 effector is needed and induced by the two-component system (OmpR-EnvZ). However, among these effectors, compared to SifB, SseG and SseJ are required for the dormant life.<sup>111</sup> The presence of two types of homologous proteins such as SifA and SifB may show their overlapping functions in the cells or synergism between these proteins.<sup>112</sup>

Another effector called PipB2 can promote SIF extension and cause the recurrence of Kinesin to the SCV membrane.<sup>98,113</sup> With the recurrence of Kinesin to the SIF, PipB2 may play a role in extending nascent filament to the outside of SCV.<sup>113</sup> PipB2 helps *Salmonella* with intramacrophage survival.<sup>114</sup> For more information, see Table 2.

## Salmonella Toxins

### Cytotoxin

*Salmonella* can induce pyroptosis via T3SS effector protein (needle protein) in a flagellin manner. This protein can be detected by NLRC4 (Nod-Like Receptor) inflammasome; then, inflammasome activates caspase-1 that leads

to the secretion of IL-1 $\beta$  and programs cell death called pyroptosis.<sup>115</sup> Inflammasome is composed of multiple proteins that resist the pathogen.<sup>116</sup> To activate NLRC4, flagellin or needle protein of T3SS should be recognized by NLR family apoptosis inhibitory protein (NAIPs).<sup>117</sup> On the other hand, *Salmonella* can downregulate the flagellin expression and evade NLRC4 activation.<sup>118</sup> In the final step, *Salmonella* secretes flagellin into the cytosol and activates NLRC4 to induce pyroptosis and cell death, leading to *Salmonella* release.<sup>119</sup> *Salmonella* induces interferon type I and, therefore, leads to inducing necroptosis controlled by a receptor-interacting protein (RIP).<sup>120</sup> Interestingly, not all of the macrophage dies result from infection, and a particular phenotype that remains alive acts as a reservoir for *Salmonella*.<sup>121</sup> This phenotype is called M2 and in spleen called hemophagocytes macrophage.<sup>122</sup> Spv locus and its effector SpvB are required to induce apoptosis in macrophage. This locus has a major role in inducing systemic disease.<sup>123</sup> SpvB has an ADP-ribosylation role in the activation of caspase and inducing apoptosis and actin polymerization during the intracellular life.<sup>124</sup> SpvC is another effector that is secreted through T3SS with a phosphothreonine lyase activity and inhibits the activation of MAP kinase and de-phosphorylate ER, leading to the downregulation of proinflammatory cytokines.<sup>125,126</sup> Another effector that mediates apoptosis in epithelial cells is SrfT, which is encoded in SPI-2.<sup>127</sup> Moreover, SrfH mediates actin remodeling and is located in prophage. SrfD, SrfE, SdrI, SrfK, SrfL, and SrfM also are encoded by Phage. Among these effectors, SrfJ mediates apoptosis in host cells and, by glycoside hydrolase activity, modifies SCV membrane lipid to mediate the increase of salmonella virulence.<sup>128</sup>

### Toxins

SopE is a nucleotide exchange factor that affects Rho GTPase family such as Cdc42 and Rac1. This family is involved in activation (GTP form) and inactivation (GDP form) of Rho that is controlled by a guanine nucleotide exchange factor.<sup>129</sup>

**Table 2** Salmonella Adhesins and Their Effects

Adhesins	Species	Location	Effects
SiiE	All	SPI-4	Adhesin to the epithelial cell
MisL	All	SPI-3	Binding to the fibronectin
PagN	All	Chromosome	Bind to the heparan sulphate
STIV	<i>S.typhi</i> , <i>S.Paratyphi</i>	Chromosome	Bind to the MET in host cell
RcK	<i>S.typhimurium</i> , <i>S.entritidis</i>	Plasmid	Complement resistance

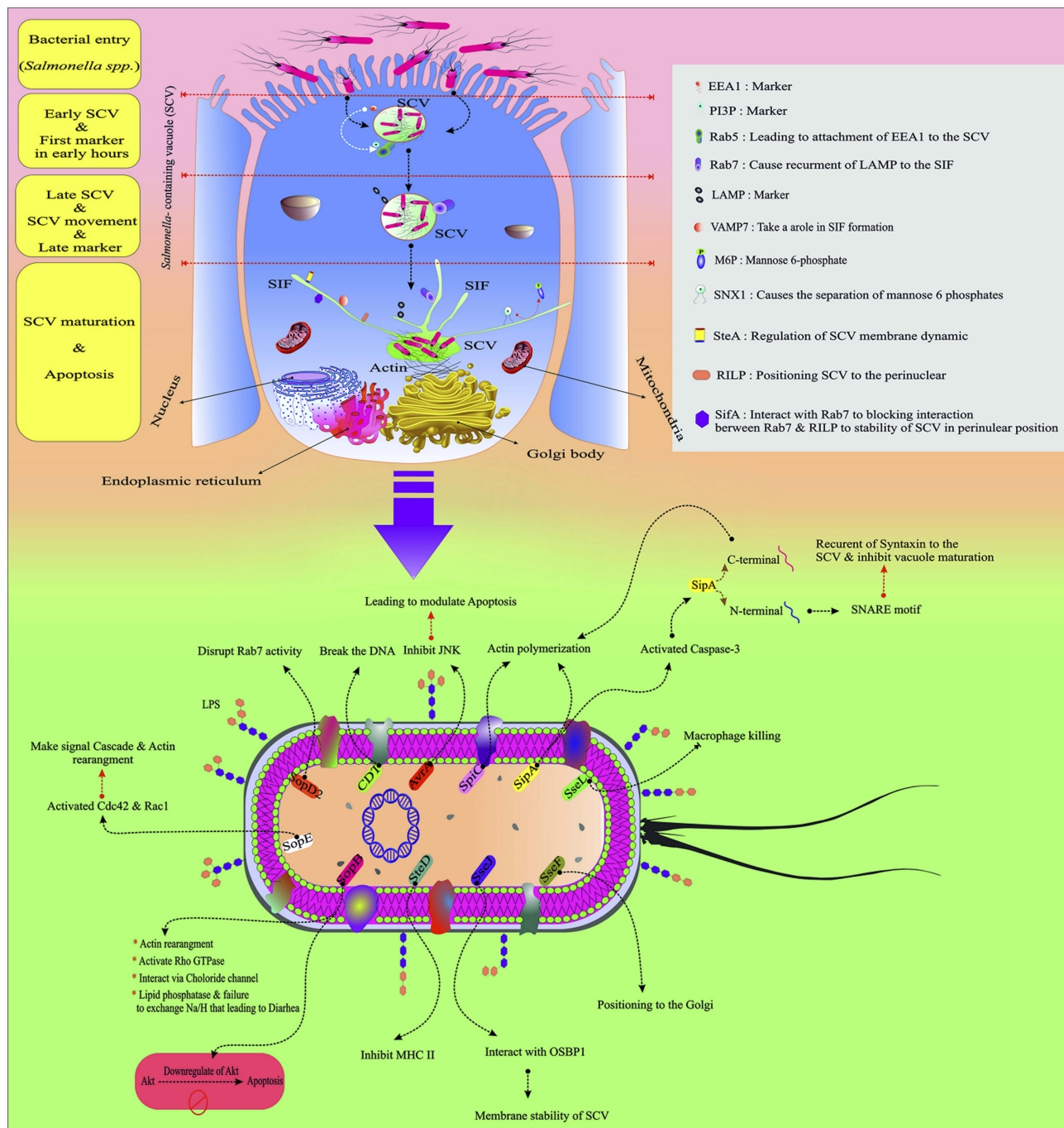
Only the activated form can affect the downstream of cascade and make a signal that causes cell responses such as gene transcription and actin rearrangement.<sup>130</sup> SopE acts as a guanine exchange factor in activating both Rac1 and Cdc42, leading to actin rearrangement and infiltration of bacteria into the host cell.<sup>131</sup> This event results from SopE and can be detected via NOD1 and proinflammatory response.<sup>132</sup> Another effector or toxin that interacts with cytoskeleton is an SptP, acting as a GTPase-activating protein, and deactivates Rac1 and Cdc42 to return cytoskeletal change to the relax form; this factor goes in contrast to the SopE factor.<sup>133</sup> Furthermore, SptP can suppress MAP kinase activation. MAP kinase is involved in the activation of cellular responses such as proinflammatory response.<sup>134</sup> In fact, the tyrosine phosphatase activity of SptP interacts with Raf-1 to inhibit the activation of the extracellular-signal-regulated kinase (ERK).<sup>135</sup> SptP toxin is not effectively presented in *Salmonella* Typhi and, because of the changes in some amino acids, chaperon cannot be attached to the effector and stabilize it.<sup>136,137</sup> SipA can activate caspase-3 and actin polymerization.<sup>138</sup> Note that SipA cannot induce caspase-3 in polymorphonuclear.<sup>138</sup> Caspase-3 can degrade SipA to C-terminal and N-terminal: the C-terminal is responsible for actin polymerization and the N-terminal contains an SNARE motif.<sup>139</sup> The latter is responsible for the attachment and recurrence of host syntaxin 8 to SCV. SNARE is involved in endocytosis and syntaxin in rapid endocytosis and vesicle mobilization.<sup>140</sup> Altogether, this effect results in the recurrence of syntaxin8 to SCV and its fusion with early endosome to inhibit vesicle maturation.<sup>139</sup> (Figure 2)

Another effector called SipC directly binds to actin and causes actin polymerization. In addition to translocated effector, SipC can interact with cell vesicle trafficking and reset the vesicle onto the cell surface.<sup>141</sup> Further, SipC interacts with p53 effector related to PMP-22 (PERP) and, thus, facilitates the formation of exocyst, which is transferred to the cell membrane. The accumulation of exocyst leads to the recurrence of vesicle to the cell surface, and this accumulation in membrane results in the rippling membrane that permits *Salmonella* entrance.<sup>142,143</sup> Spi-D is used to translocate effector proteins to the eukaryotic cell.<sup>144</sup> In the infected host cell, caspase-1 is activated to make pyroptosis; however, this effect also leads to lysophosphatidylcholine release that forces *Salmonella* to react in the form of secretion of SIPs.<sup>145</sup> In other words, *Salmonella* can detect lysophosphatidylcholine and release SIPs effector. Lysophosphatidylcholine also stimulates the invasive power of bacteria. Due to the presence of lipid in plasma, *Salmonella* can be hyperinvasive through it.<sup>146</sup>

AvrA is another effector protein that is injected into the intracellular antigen with acetyltransferase activity. Avra inhibits the activation of c-Jun kinase (JNK) and NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) in the epithelial cell to modulate apoptosis and protect pathogen strategy.<sup>147</sup> Cytolethal Distending Toxin (CDT) breaks the DNA of the host cell and, in turn, provoke DNA repair response.<sup>148</sup> Interestingly, the cell surviving the DNA repair response causes genomic instability and becomes exposed to cancer progression.<sup>149</sup> This event leads to the persistence of host and reduces the inflammatory response and the long durability of bacteria.<sup>150</sup> Typhoid toxin consists of two A subunits (enzymatic activity) and five B subunits; this toxin is transferred from SCV to the extracellular milieu and affects cell other than the infected cell.<sup>151</sup> Part A consists of PltA and CdtB; the former has an ADP-ribosylation transferase activity and the latter has a deoxyribonuclease activity, which is damaging to the cell.<sup>152</sup> Subunit A of Typhoid toxin is homologous to the CDT and pertussis toxin.<sup>153</sup>

## How to Activate Pathogenic Genes

SPI-1 mediates invasion and is controlled by HilA, InvF,<sup>154</sup> and HilD. Environmental conditions such as pH and osmolarity activate transcriptional regulatory proteins of HilC and HilD so that they can bind to the upstream of master regulatory *hilA*.<sup>155</sup> HilC and HilD counteract global repressor H-NS on the *hilA* promoter.<sup>156</sup> Following the activation of HilA, InvF is subsequently activated.<sup>157</sup> InvF activates the gene inside and outside of SPI-1. HilC and HilD also induce the expression of *hilC* and *hilD* genes that ultimately activate *hilA*.<sup>158</sup> HilD first induces *hilA* that is located in SPI-1 and, then, induces *ssrAB* located in SPI-2. Following the internalization of bacteria to the acidic vacuole, another effector from SPI-2 should be secreted to modify the circumstance. First, EnvZ/OmpR should be considered; the inner membrane protein regulatory system senses acid and activates *ssrA/ssrB* and PhoQ/P systems.<sup>159</sup> To this end, first, EnvZ interacts with OmpR and, then, OmpR activates *ssrA* transcription and produces SsrA and SsrB. Interestingly, by suppressing *cadC/BA* operon, OmpR blocks a neutralization reaction to acidity.<sup>87</sup> CadA is a lysine decarboxylase that produces cadaverine and, then, is translocated to *cadB* to export out the bacterial cell and modulate acidification.<sup>160</sup> However, OmpR blocking this event leads to the maintenance of acidification of bacterial cytoplasm, which is essential to the secretion of SPI-2 effector protein. In the presence of SsrA kinase, phosphorylated SsrB induces SPI-2; however, in neutral PH, SsrA kinase is very low and SsrB is unphosphorylated; yet, biofilm gene is

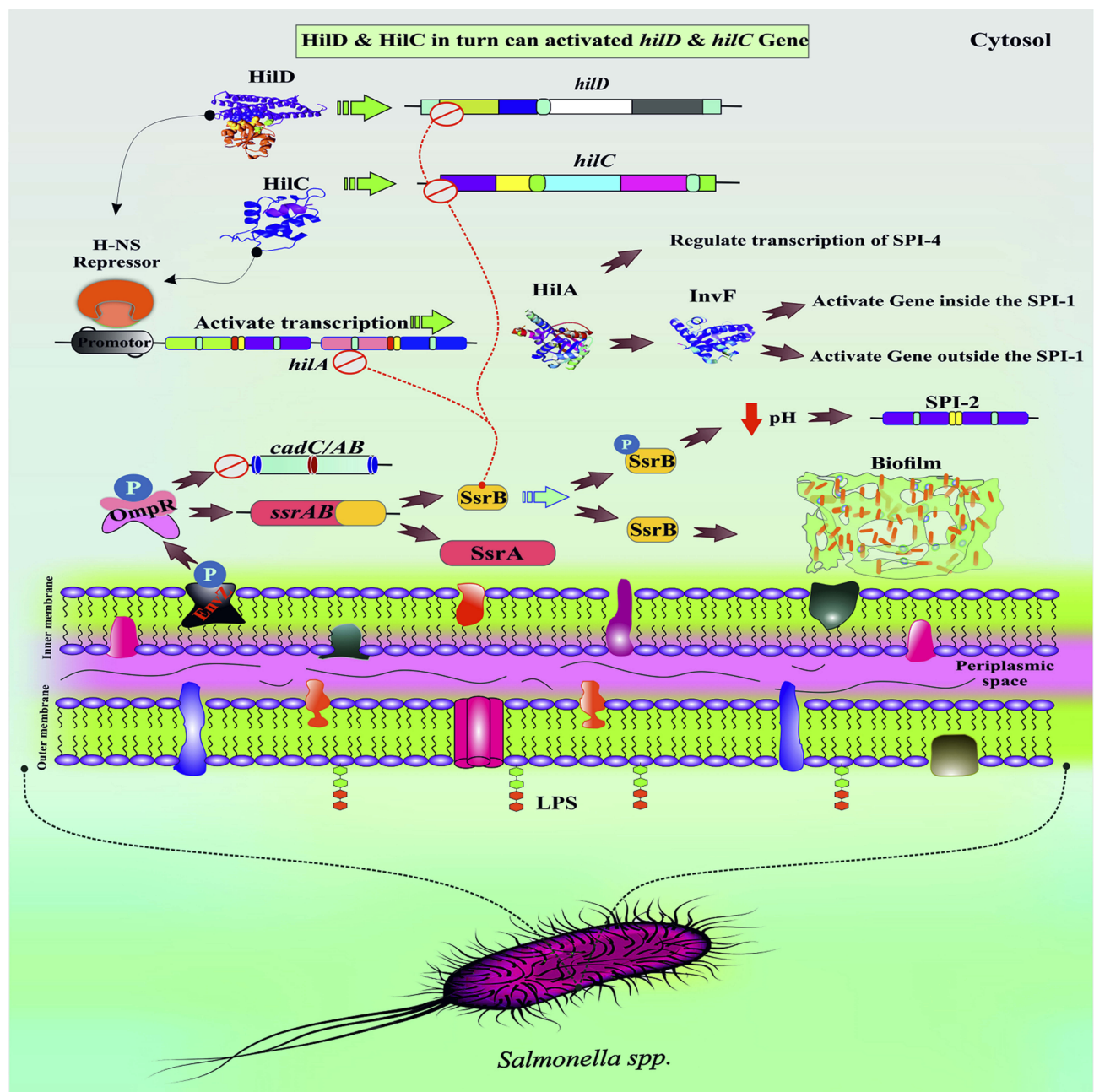


**Figure 2** An overview of the entrance, Salmonella-containing vacuole formation, Sif formation, and replication inside the host vacuole.

expressed.<sup>159</sup> In addition to the acid response, *ssrB* can induce biofilm formation and switch between intracellular and extracellular lifestyles.<sup>161</sup> When the acidification of bacterial cytoplasm increases, supercoiling of DNA may decrease and OmpR binding site is exposed.<sup>162</sup> For more information, see Figure 3. However, HilD distinctively regulates both SPI-1 and SPI-2. HilD can counteract the repressive effect of H-NS in the regulatory region of *ssrAB* operon.<sup>163</sup> In summary,

following the activation of SPI-1 and invasion against the cell and entrance, SPI-2 activates and suppresses the expression of SPI-1 through SsrB. SsrB directly binds to the regulatory region of *hilA* and *hilD* and suppress it.<sup>164</sup> Recently, it has been observed that the intestinal butyrate derived from *Clostridia* can inhibit the expression of *hilD*, encoding the T3SS-1 gene regulator.<sup>165</sup> *Salmonella* utilizes butyrate using  $\beta$ -oxidation and, in turn, provides fitness advantages during





**Figure 3** A comprehensive review of Salmonella mechanisms in the regulation of pathogenic genes.

pathogen growth. Interestingly, gene of  $\beta$ -oxidation *ydi* QRSTD is not presented in *S. Typhi*, leading to reduced invasion against the intestinal lumen.<sup>166</sup> This issue may explain why *S. Typhi* does not induce inflammation in the first phase, and this provides an opportunity to spread through another organ without inflammation.

## Regulation of Immune Response

One of the important immune cells that controls *Salmonella* is DC and is responsible for cytokine secretion, presenting

antigen to a T cell, and activating natural killer cells (NK cells).<sup>167</sup> Following the phagocyte of bacteria, the DC process presents bacterial antigen to the T cell. However, if bacterial cell survives, it can migrate through DC to another organ.<sup>168</sup> *Salmonella* can prevent DC migration through Ssel protein that secretes via T3SS.<sup>169</sup> This effector inhibits chemotaxis of DC toward the T cell zone by following chemokine (C-C motif) ligand 19 (CCL19).<sup>170</sup> *Salmonella* Ssel interacts with the downstream of CC-chemokine receptor 7 (CCR7) that responds to CCL19.<sup>168</sup> Chemotaxis towards

CCR7 is controlled by MAP kinase.<sup>171</sup> SseI can interact with filamins<sup>172</sup> and cytoskeletal regulatory protein, IQ motif-containing GTPase-activating protein (IQGAP1). The migration of DC and macrophage requires the IQGAP1 factor, and SseI exactly interacts with it to suppress the migration and prevent T CD4<sup>+</sup> response.<sup>173</sup> Deletion or pseudogenization of SseI causes systemic infection.<sup>169</sup> Macrophage via TLR2 and 4 is able to recognize *Salmonella*; however, this signaling also induces *Salmonella* replication. This event can be explained by acidification in *Salmonella*-containing phagosome that activates SPI-2.<sup>174</sup> TLR controls DC maturation and, thus, activates the adaptive immune response.<sup>175</sup> Although other TLRs such as TLR2, TLR5, and TLR9 are involved in detecting *salmonella*, TLR4 has a major role in apoptosis.<sup>176</sup> It should be noted that, in normal macrophage, TLR4 also activates NF- $\kappa$ B and MAP kinase with an anti-apoptosis effect.<sup>177</sup> Mucus property influenced by the gel-forming composition is called musin. Musin is composed of glycosylated and non-glycosylated domains with a peptide backbone.<sup>178</sup> At the end of the oligosaccharide branch of musin, sialic acid or sulfate can be found. *Salmonella* can be attached to the mannose and sialic acid, and it goes through the mucus via sialidase.<sup>179</sup> This enzyme can cleave the  $\alpha$ -ketosidic bond in the terminal of sialic acid residue.<sup>180</sup> Interestingly, IFN $\gamma$  has a dual role in mucosal defense; first, signaling of IFN $\gamma$ R in Goblet cell (mucosal secretion cell) leads to the loss of mucus; on the other hand, IFN $\gamma$ R restricts the growth of pathogen in macrophage.<sup>181</sup> After passing the mucus layer and entering the lamina propria, TLR is activated via flagelin and mediates phagocyte by DC and macrophage.<sup>182</sup> Another host sensor, NLRC4, can recognize an intracellular antigen such as flagellin.<sup>118</sup> This recognition leads to the secretion of proinflammatory cytokines such as IL-1 $\beta$  and IL-18. NLRP3 is activated through reactive oxygen species (ROS), or membrane damage leading to activated caspase-1 and pyroptosis.<sup>183</sup> The activation of pyroptosis secures the release of *Salmonella* from macrophage and swallowing by Neutrophil and degradation by ROS.<sup>119</sup> However, *Salmonella* can degrade superoxide and limit peroxynitrite formation by superoxide dismutase.<sup>184</sup> *Salmonella* forces macrophage and epithelial cell to release IL-18 and IL-23 secretion from the dendritic cell.<sup>185</sup> Then, IL-18 stimulates Th1 to release IFN $\gamma$  and IL-23, thus stimulating Neutrophil, TH 17, and T $\gamma$  $\delta$  to produce IL-22 and IL-17.<sup>186,187</sup> The activation of TH 17 expresses CXC chemokine such as CXCL and CXCL2 and results in the recurrence of Neutrophil to the infection site.<sup>188</sup> IL-22 can cause Neutrophil and epithelial cell to secrete Lipocalin-2 and

calprotectin; these molecules inhibit *Salmonella* access to iron and manganese.<sup>189</sup> However, oxidative stress can stimulate *Salmonella* to upregulate the sitABCD manganese transport system (high-affinity transporter) that effectively helps the bacteria overcome growth inhibition, which started with calprotectin.<sup>190</sup> Manganese acts as a cofactor in the superoxide dismutase enzyme. Furthermore, in the periplasmic space, Dsb proteins can act as an oxidase reductase, and this protein with four components of DsbA, DsbB, DsbD, and DsbC also works as follows: DsbA is tasked with creating a disulfide bond; DsbB, DsbD are electron donors; DsbC proofreads the disulfide bond formation.<sup>191</sup>

## Conclusion

Following the attachment of *Salmonella* to the epithelial cell, two routes can be selected: (a) one entrance to the cell in a T3SS-dependent fashion, thus mediating effector protein and forming SCV; (b) entrance in a T3SS-independent fashion. The formation of SCV management with T3SS-1 secretes invasive protein; however, afterwards, there are two ways ahead: either maintaining in SCV or exiting it. For the first one, *Salmonella* requires to be transferred from SPI-1 (invasive) to SPI-2 (maintaining). After maintenance in the SCV, the next step is replication that requires a nutrient; for this reason, a long appendage is extended into the cytoplasm called SIFs. *Salmonella* can exit SCV, replicates in the cytoplasm, and targets autophagy system; however, it can stop autophagy or kill the macrophage and is released afterwards. Following its release, *Salmonella* is engulfed by Neutrophil and degraded with ROS; like other bacteria, it can resist ROS (ref. staph). After the activation of macrophage and DC that migrated to the lymph node, the antigen, which was modified earlier inside the macrophage and DC, was presented to the T-cell existing in the paracortex. *Salmonella* that induces enteritis utilizes the butyrate via  $\beta$ -oxidation and provides energy for the duplication, and this in turn made the inflammation as derived from the duplication. On the contrary, *S. Typhi* did not activate inflammation and, thus, is the reason for the lack of immune attention, giving *S. Typhi* time to spread.

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## Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or interpretation of data. They played an active role in drafting the article or revising it critically to achieve important intellectual content. They gave the final approval of the version to be published and agreed to be accountable for all aspects of the work.

## Disclosure

All of the authors declare that there are no commercial, personal, political, and any other potentially conflicting interests related to the submitted manuscript.

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