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Review

Salmonella SPI-2 type III secretion system-dependent inhibition of antigen presentation and T cell function

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ABSTRACT

Salmonella enterica serovars infect a broad range of mammalian hosts, including humans, causing both gastrointestinal and systemic diseases. Effective immune responses to *Salmonella* infections depend largely on $CD4^+$ T cell activation by dendritic cells (DCs). Bacteria are internalised by intestinal DCs and respond by translocating effectors of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (T3SS) into host cells. In this review, we discuss processes that are hijacked by SPI-2 T3SS effectors and how this affects DC biology and the activation of T cell responses.

1. Introduction

Serovars of *Salmonella enterica* cause very large numbers of serious and life-threatening diseases in humans and livestock throughout the world. In addition to its socioeconomic importance, *Salmonella* is an excellent model organism to analyse bacterial virulence, which is dependent on its ability to survive and replicate in host cells such as epithelial cells, macrophages and DCs. The broad host-range serovar *S. enterica* Typhimurium (*S.* Typhimurium) produces a systemic disease in mice that has been used extensively to model human typhoid fever, caused by *S.* Typhi and *S.* Paratyphi. *S.* Typhimurium is relatively easy to manipulate genetically and many techniques are available for analyzing bacterial phenotypes and the molecular biology of virulence proteins (effectors) and their mammalian cell targets. Although *Salmonella* is a highly adapted pathogen, it is important to bear in mind that the majority of infections (including systemic infections) are controlled effectively in immunocompetent hosts [1].

Effective immunity requires a potent innate immune response, initially involving complement-and respiratory burst-mediated killing. This is followed by detection of pathogen-associated molecular patterns (PAMPs) that stimulate NF-κB and MAP kinase signaling pathways governing production of pro-inflammatory cytokines such as TNFα and IL-1β. Interferon-γ (IFN − γ) in particular, has a critical role in the early phase of control of *Salmonella* infection [2–4]. Specific adaptive responses, especially $CD4^+$ T cell activation, then enable pathogen clearance [5]

Confronted with a multi-faceted immune response, *S. enterica* has acquired a large number of virulence functions that collectively enable evasion and subversion of the host response to pathogen detection. A major contributor to *S. enterica* virulence is the SPI-2 type III secretion system (T3SS), which delivers approximately 30 effectors across the vacuolar membrane that encloses intracellular bacteria. Several SPI-2 T3SS effectors interfere with innate immune responses. For example, the E3 ubiquitin ligase SspH1 suppresses activation of NF-κB [6]; GogB inhibits IκB degradation and NF-κB activation through interaction with SKP1 and the F-box protein FBXO22 [7]; SifA reroutes lysosomal enzymes to the extracellular space, thereby reducing lysosomal hydrolytic capacity [8]; SpvC is a phosphothreonine lyase that irreversibly dephosphorylates pERK and pJNK [9]; SpvD prevents nuclear import of NF-κB p65 [10,11]; SseK1 and SseK3 inhibit NF-κB signalling and inflammatory necroptotic cell death [12,13]; GtgA family members cleave NF-κB [14,15]. These and other studies have revealed that the innate immune response has been a major selective pressure for effectors that suppress its activation.

Since elimination of *Salmonella* in mice and humans is strictly dependent on activation of $CD4^+$ T cells [2,16–19], this branch of adaptive immunity could also represent a strong selective pressure for its avoidance or subversion by bacteria. Indeed, it is now well established that *Salmonella* dampens and delays T cell responses. In this review we discuss the direct and indirect means by which the SPI-2 T3SS

Abbreviations: IFN-γ, Interferon-γ; MLN, mesenteric lymph nodes; mMHCII, mature major histocompatibility complex class II; OVA, ovalbumin; PAMPs, pathogen-associated molecular patterns; SPI-2, *Salmonella* pathogenicity island 2; SNP, single nucleotide polymorphism; T3SS, type III secretion system; TGN, *trans*-Golgi network

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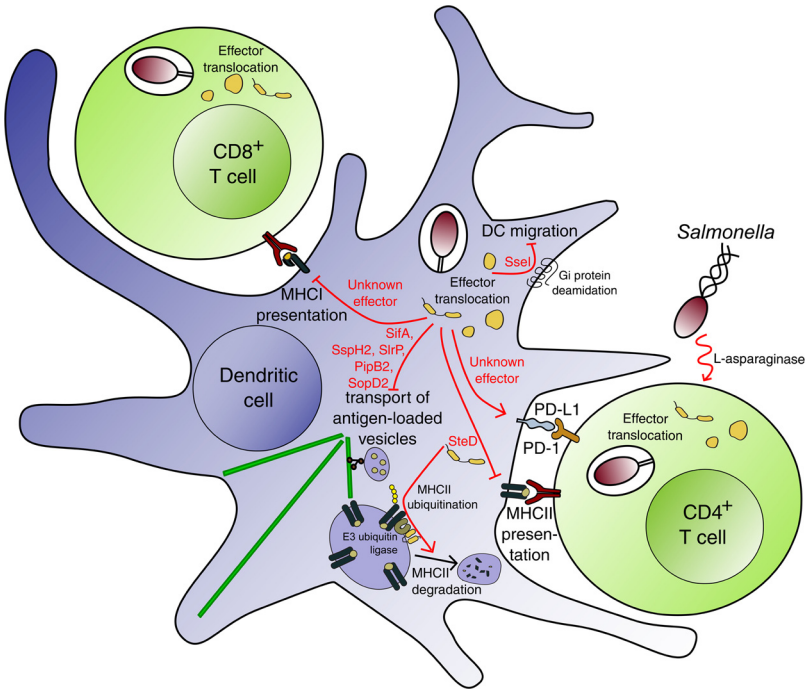

Fig. 1. Interactions between *Salmonella* and T cells. Extracellular *Salmonella* converts exogenous L-asparagine to aspartic acid and ammonia in a SPI-2 independent manner, thereby influencing T cells directly. SPI-2 T3SS effector delivery in DCs suppresses DC migration by SseI-mediated deamidation of heterotrimeric G proteins. In addition, an unknown effector blocks MHCI antigen presentation and transport of antigen-loaded vesicles to MHCII compartment is compromised by SifA, SspH2, SlrP, PipB2 and SopD. The SPI-2 T3SS effector SteD stimulates ubiquitination of mature MHCII, leading to its degradation and directly preventing MHCII antigen presentation. Lastly, unknown SPI-2 T3SS effector (s) increase PD-L1/PD-1 inhibitory signalling between antigen presenting cells and T cells.

contributes to this process. This is summarized in Fig. 1.

2. Interference with DC migration by SPI-2 effectors

DCs have a major role in the development of adaptive immunity. *Salmonella* encounters DCs in the gut lumen and as it traverses the epithelium [20]. DCs have at least three major functions in controlling *Salmonella* infections [21]: they (a) transport intracellular bacteria from Peyer's Patches to mesenteric lymph nodes (MLN); (b) secrete cytokines that stimulate recruitment and activation of T and NK cells and (c) present antigen to $CD4^+$ T cells using MHCII molecules. *Salmonella* survives within and translocates SPI-2 T3SS effectors into DCs [22].

Several SPI-2 T3SS effectors have been implicated in inhibiting DC migration along chemokine gradients [23]. One of these effectors - SseI - reduces migration of *Salmonella*-infected DCs from the mouse intestine to MLN [24], which is likely to result in slower induction of T-cell responses, thereby enhancing bacterial virulence. Structural and biochemical studies of SseI revealed that it is an enzyme that deamidates heterotrimeric Gi proteins, including $G\alpha_{i2}$, leading to its persistent activation [25]. A catalytically-dead SseI mutant no longer prevented DC migration and permanent deamidation of $G\alpha_{i2}$ inhibited DC migration [25]. Since Gi proteins have a key function in chemotaxis, their deregulation by SseI probably explains its effect on DC migration [25]. Interestingly, *sseI* is a pseudogene in some *S.* Typhi isolates [26], which might help explain their ability to disseminate rapidly from the infected intestine. SspH2 and SlrP are SPI-2 T3SS ubiquitin E3 ligases that are also implicated in the inhibition of chemotaxis [23], but the molecular mechanisms involved remain to be characterized.

3. SPI-2-dependent inhibition of CD8+ T cell response

Although the prevailing view seems to be that $CD8^+$ T cells do not contribute significantly to bacterial clearance of *Salmonella* after primary infection of mice [2,4], there is some evidence that $CD8^+$ T cells can restrict infection of attenuated *Salmonella* at late stages of bacterial clearance in mice [27]. In addition, infection of mice by wild-type *Salmonella* led to the accumulation of $CD8^+$ T cells with low cytolytic activity and decreased IL-2 production when compared to infection with a SPI-2 mutant strain [28]. Also, *Salmonella*-specific B cells that phagocytosed *Salmonella* upon B cell receptor (BCR)-ligation were able to reactivate human memory $CD8^+$ T cells via antigen cross-presentation, yielding a *Salmonella*-specific cytotoxic T cell response [29].

An approach using DCs infected with different *Salmonella* strains expressing Ovalbumin (Ova) and MHC class I and class II Ova peptide-specific T cells provided strong evidence that the SPI-2 T3SS is required for the ability of *Salmonella* to prevent presentation of Ova peptides to T cells by both MHCI and MHCII molecules [30,31]. The *in vitro* results were corroborated *in vivo* using OT-I and OT-II transgenic mice (in which the $CD8^+$ and $CD4^+$ T cells express T cell receptors specific for ovalbumin peptides presented on MHCI, or MHCII molecules, respectively). Tobar et al. showed that IFN-γ and IL-2 were produced by T cells specific for OVA- or flagellin-derived peptides in mice that were challenged with SPI-2 mutant *Salmonella* strains but not in mice infected with wild-type *Salmonella* [30]. Interestingly, the inhibitory effect of wild-type *Salmonella* on peptide-loaded MHCI was lost if the relevant Ova peptide was provided exogenously, indicating that the effect was not due to reduced surface levels of MHCI molecules. Instead, the phenomenon was attributed to the ability of wild-type but not SPI-2 mutant bacteria to avoid lysosomal degradation [30].

4. SPI-2 dependent inhibition of $CD4^+$ T cell response

Salmonella is predominantly a vacuolated intracellular pathogen and it is not surprising that strong evidence exists for the importance of $CD4^+$ T cell responses in effective immunity (e.g. [32]). Compelling evidence for the importance of MHCII-mediated $CD4^+$ T cell activation in relation to *S. enterica* infection of humans comes from a genome-wide association study which revealed an allele of *HLA-DRB1* (which encodes the β chain of the HLA-DR version of the MHCII molecule) that is strongly protective against typhoid fever, presumably through its function in antigen presentation [16], while a specific SNP in the same allele was associated with increased sensitivity to typhoid fever [33]. Work on the mouse model of systemic infection by *Salmonella* also shows unequivocally that $CD4^+$ T cell responses are crucial for effective clearance of this pathogen [2,4]. Therefore, it is not surprising to find that *Salmonella* has evolved mechanisms that interfere with MHCII-dependent T cell activation. In addition to the work described above [30] other groups have demonstrated SPI-2-dependent inhibition of

MHCII-dependent antigen presentation and $CD4^+$ T cell responses. Jantsch et al., [22], in agreement with Tobar et al [30], reported that in DCs, wild-type bacteria generally failed to co-localize with lysosomes, whereas SPI-2 mutant bacteria tended to co-localize. Cheminay et al. [34] then showed that the SPI-2 T3SS suppressed the ability of DCs to stimulate T cell proliferation. The block in T cell proliferation was further boosted by induction of iNOS in infected DCs [34]. A further study [35] implicated the SPI-2 T3SS effectors SifA, SspH2, SlrP, PipB2, and SopD2 in this phenomenon. Several of these effectors are involved in regulation of the *Salmonella*-containing vacuole membrane. Their effect on antigen presentation was proposed to be indirect, possibly via microtubule-dependent intracellular transport of antigen-loaded vesicles [36].

Another approach has been to use the human melanoma Mel Juso cell line (commonly used to study the MHCII trafficking pathway) to investigate the effect of *Salmonella* on MHCII antigen presentation. Mitchell et al [37] found that infection of Mel Juso cells by *Salmonella* led specifically to reduction in cell surface levels of the MHCII isotype HLA-DR and its increased intracellular accumulation. *Salmonella* infection also substantially decreased IFN-γ-induced MHCII expression on human macrophage-like THP-1 cells. Use of mutant strains implicated the SPI-2 effector SifA in this process. Since SifA is involved in regulating *Salmonella* vacuole membrane dynamics, it was suggested that involvement of SifA in altering MHCII trafficking from peptide-loading compartments to the cell surface might be an indirect effect. This would be consistent with the studies mentioned above, in that an effect of SifA on microtubule-based vesicular trafficking could interfere with antigen processing [35].

This work was followed by a detailed analysis of the effect of intracellular *Salmonella* on various molecules associated with antigen presentation - including MHCI - in human DCs derived from peripheral blood mononuclear cells. The effect of *Salmonella* was confined specifically to mature MHCII (mMHCII) and was accompanied by enhanced SPI-2-dependent ubiquitination of lysine 225 of the cytoplasmic tail of the β chain [38,39]. This is of particular interest since in DCs, ubiquitination of mMHCII is the principal mechanism regulating its recycling between the MHCII compartment and the plasma membrane [40]. This involves the E3 ubiquitin ligase MARCH1: in immature DCs, MARCH1 ubiquitinates intracellular mMHCII, leading to its lysosomal degradation [40]. In activated DCs, reduced ubiquitination enables mMHCII to avoid lysosomal degradation and recycle to the plasma membrane [41]. Although the SPI-2 T3SS was shown to be required for ubiquitination of mMHCII, a limited screen of effector gene mutants failed to identify potential candidates [39].

In the last 10 years the number of known SPI-2 T3SS effectors has risen to approximately 30 [36]. In an effort to establish if one or more of these effectors accounted for the effect on MHCII in Mel Juso cells [39], our laboratory conducted a screen using a large collection of mutants lacking individual effectors. This led to the identification of SteD as being required and sufficient to deplete surface levels of mMHCII from the surface of Mel Juso cells, and SteD accounted for the SPI-2-dependent enhancement of ubiquitination of the β chain of mMHCII [42]. In Mel JuSo cells, MARCH1 is not expressed, but the highly related protein MARCH8 is present, and our evidence suggested that SteD requires the presence of MARCH8 to mediate its effect on MHCII.

SteD comprises 111 amino acids with two transmembrane domains; both N- and C- termini are exposed to the host cell cytosol. After translocation into host cells from intracellular *Salmonella*, or after its expression following transfection, the majority of SteD localizes to the *trans*-Golgi network (TGN) and vesicles containing mMHCII [42]. We found that SteD interacts directly or indirectly with both mMHCII and MARCH8, and proposed that in DCs, SteD co-opts MARCH1 and/or MARCH8 to enforce inappropriate ubiquitination of the cytoplasmic β chain lysine residue of mMHCII. Since mMHCII does not localize at the TGN we hypothesized that SteD is delivered first to the TGN, where it interacts with MARCH1/8. Then, the SteD/MARCH complex traffics to vesicles containing mMHCII, where SteD induces its ubiquitination. SteD also reduced surface levels of the co-stimulatory molecule CD86/B7.2, which suggests that it might have more than one host target. Consistent with this, the effect of SteD on *in vitro* Ova-dependent T cell activation was very dramatic. SteD also reduced surface levels of MHCII in DCs from mesenteric lymph nodes after oral infection of mice and at 17 days post-inoculation there were significantly more activated T cells in spleens carrying the *steD* mutant compared to spleens from mice infected with wild-type *Salmonella* [42]. SteD is one of a subset of seven 'core' effectors that are present in all serovars of *S. enterica* [36] suggesting that it is very important for virulence in different hosts.

The effect of SteD on T cell activation was evident in DCs that had been infected for 16 h with *Salmonella*, then incubated with Ova peptide for 1 h prior to exposure to T cells [42]. This is consistent with the proposed model for enhanced ubiquitination and suppression of recycling of mMHCII molecules to the cell surface, and points to a mechanism that is distinct from that observed by the groups of Hensel and Kalergis [31,35], who were able to rescue the effect of *Salmonella* by exogenous addition of Ova peptide recognized by antigen-specific T cells. This suggests that there are at least two distinct mechanisms by which *Salmonella* interferes with antigen presentation in DCs: an indirect mechanism(s) involving avoidance of lysosomal degradation and reorganization of endosomal membrane trafficking, and a direct mechanism mediated by SteD.

SteD would appear to be the first example of a bacterial protein that targets mMHCII directly. Many fascinating aspects of SteD function remain to be elucidated. These include (a) the mechanism by which SteD reaches the TGN and the MHC compartment; (b) the mechanism by which SteD co-opts host E2 and E3 ligases that induce ubiquitination of mMHCII and (c) defining any additional targets of SteD, beyond MHCII and CD86.

Salmonella also appears to inhibit T cell function in ways that are independent of interference of antigen presentation. Part of the inhibitory effect can be explained by a direct interaction between bacteria and T cells. Although *Salmonella* is usually found within macrophages and DCs, SPI-2 T3SS-expressing *Salmonella* have also been detected inside T cells following intraperitoneal inoculation of mice [43]. A direct inhibitory effect on T cell proliferation was shown when *Salmonella* was co-cultured with mouse T cells in the absence of DCs. This effect was partially dependent on both SPI-1- and SPI-2- encoded T3SSs [44]. Furthermore, although not directly connected with the SPI-2 T3SS, it is noteworthy that $CD4^+$ T cell function is also suppressed through the action of a bacterial asparaginase, which converts exogenous L-asparagine to aspartic acid and ammonia. This leads to down-regulation of the T cell receptor β chain and inhibition of T cell proliferation [45].

In another study, a mouse model system was used to show that $CD4^+$ T cells with specificity to a peptide from the subunit of the *Salmonella* flagellum, expanded in response to virulent *Salmonella* infection. However, high avidity $CD4^+$ T cells were effectively eliminated at later stages of infection in a SPI-2-dependent manner [46]. A prior study also reported SPI-2 dependent clearance (or 'culling') of $CD4^+$ T cells through the action of SPI-2 and found this to be correlated with increased expression of Programmed death-ligand 1 (PD-L1) on antigen-specific $CD4^+$ T cells [47]. Upon binding its ligand PD1 on DCs, PD-L1 reduces antigen-specific T-cell proliferation. *Salmonella* also increased signalling via PD-1/PD-L1 axis between $CD8^+$ T cells and B cells [48] and between $CD8^+$ T cells and antigen-presenting cells (DCs and macrophages) [49]. Furthermore, an increase in PD-L1 expression in *Salmonella*-infected epithelial cells was shown to require the SPI-2 T3SS [50]. The effector(s) involved in this activity and their underlying mechanism(s) remain to be characterized.

Altogether, these studies have provided compelling evidence that the adaptive immune system and in particular the activation of $CD4^+$ T cell responses has represented strong selective pressure for the emergence of bacterial effectors that counteract, both directly and indirectly,

the development of protective immunity. Much work now needs to be done to understand the molecular mechanisms by which *Salmonella* interferes with these processes and the degree to which they operate in human disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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