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Mechanisms used by virulent *Salmonella* to impair dendritic cell function and evade adaptive immunity

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Summary

Innate and adaptive immunity are inter-related by dendritic cells (DCs), which directly recognize bacteria through the binding of pathogen-associated molecular patterns (PAMPs) to specialized receptors on their surface. After capturing and degrading bacteria, DCs present their antigens as small peptides bound to MHC molecules and prime naive bacteria-specific T cells. In response to PAMP recognition DCs undergo maturation, which is a phenotypic change that increases their immunogenicity and promotes the activation of naive T cells. As a result, a specific immune response that targets bacteria-derived antigens is initiated. Therefore, the characterization of DC–bacteria interactions is important to understand the mechanisms used by virulent bacteria to avoid adaptive immunity. Furthermore, any impairment of DC function might contribute to bacterial survival and dissemination inside the host. An example of a bacterial pathogen capable of interfering with DC function is *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium). Virulent strains of this bacterium are able to differentially modulate the entrance to DCs, avoid lysosomal degradation and prevent antigen presentation on MHC molecules. These features of virulent *S.* Typhimurium are controlled by virulence proteins, which are encoded by pathogenicity islands. Modulation of DC functions by these gene products is supported by several studies showing that pathogenesis might depend on this attribute of virulent *S.* Typhimurium. Here we discuss some of the recent data reported by the literature showing that several virulence proteins from *Salmonella* are required to modulate DC function and the activation of host adaptive immunity.

Keywords: antigen presentation; bacteria/bacterial immunity; Fc receptors; infection.

Introduction

The initiation of adaptive immunity against bacteria requires professional antigen-presenting cells that recognize and degrade bacterial antigens and present them as peptide–MHC complexes to naive T cells.[1–6] One of the most relevant antigen-presenting cells are dendritic cells (DCs), which are a link between innate and adaptive immunity. These cells have the capacity to directly recognize and uptake pathogens at the site of infection and migrate to the lymph nodes to activate bacteria-specific T cells.[4,5,7–9] The DCs locate in peripheral tissues, where they are usually found in an immature state.[10–13] In such a state, DCs have an elevated phagocytic capacity with reduced expression of co-stimulatory molecules, such as CD80, CD86 and CD40.[8,12,14–17] After pathogen-associated molecular pattern (PAMP) detection, peripheral/immature DCs become activated and undergo functional and phenotypic changes known as maturation.[18–20] This response is triggered on DCs by the signalling via specific receptors, such as Toll-like receptors, nucleotide oligomerization domain (NOD) proteins and NOD-like receptors (NLR). These receptors translate PAMP recognition into cellular responses,[21–23] activating the secretion of anti-bacterial molecules and pro-inflammatory cytokines that enhance the bactericidal capacity of phagocytic cells.[4,16,17,24] As the result of maturation, DCs decrease phagocytosis and increase the expression MHC-I,

MHC-II and co-stimulatory molecules, which are surface molecules required for the activation of antigen-specific naive T cells.[4,14,16,25,26] Maturing DCs also secrete cytokines that contribute to defining the nature and polarization of the effector function of T cells after recognition of peptide–MHC on the DC surface.[27–31] Mature DCs acquire the capacity to migrate from peripheral sites of infection to the lymph nodes, where naive T cells reside.[32–34] The establishment of a regulated and efficient adaptive immune response against the infecting bacteria requires DCs to prime naive T cells recognizing bacterial antigens. Consistent with this notion, the acquisition of molecular mechanisms by virulent bacteria to interfere with DC function and prevent the activation of T cells could significantly contribute to the survival and dissemination of these pathogens inside the host.[7,31,35]

An important intracellular bacterial pathogen is *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium hereafter), which is a common cause of food poisoning and gastroenteritis in humans, as well as the aetiological agent for typhoid-like disease in mice.[36,37] Infection of mice by *S.* Typhimurium has been widely used as a model for the typhoid fever caused by *S.* Typhi in humans.[36,38] It is thought that orally ingested *S.* Typhimurium accesses the Peyer's patches after invading epithelial and M cells in the small intestine.[37] Then, this pathogen spreads from the Peyer's patches to deeper organs, such as mesenteric lymph nodes, spleen and liver.[39,40] In these organs, bacteria would reside in intracellular compartments,[41] a feature that is probably required for the successful systemic dissemination of this bacterium.[41–44]

It is striking that a low dose of virulent *S.* Typhimurium can cause systemic infection and the death of immune-competent mice.[42,45,46] It has been shown that virulent *S.* Typhimurium can efficiently avoid the activation of the adaptive immune response.[35,44] This observation is consistent with reduced antigen presentation and T-cell activation after *S.* Typhimurium infection in mice.[42,45,47]

Because DCs are fundamental for the initiation and establishment of an anti-bacterial adaptive immunity, the interference of their function can be a pathogenicity mechanism used by *S.* Typhimurium to prevent recognition by the host adaptive immunity. Several *S.* Typhimurium virulence proteins are thought to contribute to intracellular survival and systemic dissemination of this pathogen.[48–50] In agreement with this notion, recent studies have demonstrated that these virulence proteins are used by *S.* Typhimurium to interfere with DC function.[7,42,45,47,51–53] In this review we discuss recent studies supporting the notion that virulent *S.* Typhimurium has the capacity to actively interfere with the function of DCs and prevent the activation of bacteria-specific T cells.

Virulence *Salmonella* proteins required for subversion of host cells

Several genes involved in *S.* Typhimurium virulence are found in pathogenicity islands 1 and 2 (SPI-1 and SPI-2).[50,54–59] The expression of these proteins is regulated by the ability of *S.* Typhimurium to sense several molecular components of the environment.[60–63] Both pathogenicity islands encode for Type Three Secretion Systems (T3SS), which inject bacterial effector proteins into host cells.[64–66]

Genes located in SPI-1 are preferentially expressed in the extracellular environment, such as the intestinal lumen.[67,68] At this location, the virulence proteins encoded by SPI-1 are needed for bacterial entry to epithelial cells.[69–71] In contrast, SPI-2 genes are expressed in the intracellular environment and *S.* Typhimurium uses them to survive inside eukaryotic cells.[42,49,53,72] The absence of either T3SSs or effector proteins encoded by SPI-1 or SPI-2 reduces the ability of *S.* Typhimurium to cause a systemic illness in mice.[42,73,74] It has been described that proteins encoded by genes located in other pathogenicity islands or prophages are also important for invasion and survival within host cells.[56,75–79] Several reports have demonstrated that these virulence factors can also contribute to interfering with DC function during bacterial infection.[80–82]

Salmonella infection of the intestinal epithelium

After oral infection, *S.* Typhimurium reaches the small intestine and invades epithelial cells in the ileum. At this location, DCs are found residing in the lamina propria (LP) and Peyer's patches.[36,37] After adhering to epithelial cells,[83] bacteria inject effector proteins, such as SipA, SopE, SopE2 and SopB, into the host cell cytoplasm through the T3SS encoded by the SPI-1 (T3SS-1) (Fig. 1)[54,69,84–88] These proteins induce the formation and stabilization of actin filaments[54,89] in epithelial and M cells, actively promoting *S.* Typhimurium entry to non-phagocytic cells.[89,90] Together, the activity of these proteins leads to the formation of plasmatic membrane extensions, known as ruffles, which engulf extracellular bacteria (Fig. 1).[91,92]

The active invasion mechanism used by *S.* Typhimurium to invade epithelial cells is reverted by the effector protein SptP. This protein restores the normal cytoskeleton structure after bacterial entry has been completed (Fig. 1).[93] Given that SptP is also secreted by the T3SS-1 into epithelial cells,[93] it is likely that some of the *Salmonella* effector proteins require a temporal regulation. It has been suggested that this regulation is achieved by both hierarchical injection[94,95] and differential degradation of these proteins by the proteasome of the host cells.[96]

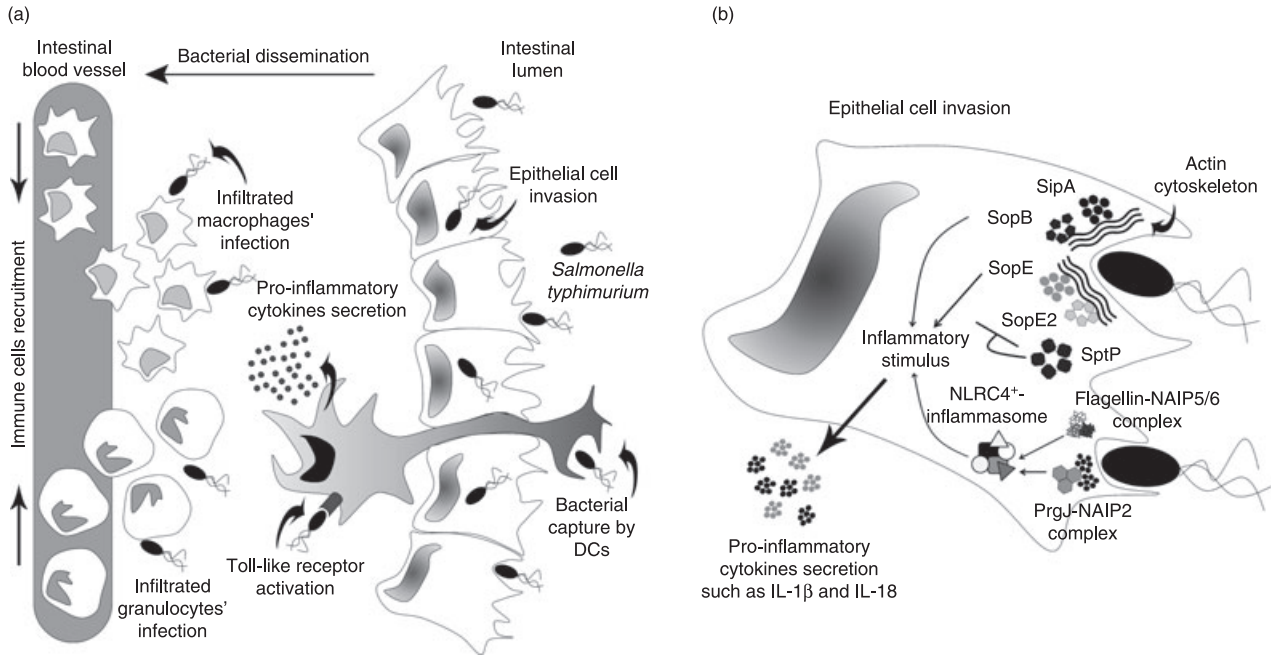

Figure 1. Lamina propria invasion and inflammatory immune response during *Salmonella enterica* serovar Typhimurium infection. (a) Once *Salmonella* arrives at the lamina propria (LP), it can traverse cell intestinal layers and cause cytokine secretion and immune cells recruitment. Intestinal dendritic cells (DCs) can sample the pathogen, enhancing the inflammatory environment by Toll-like receptor (TLR) activation after pathogen-associated molecular pattern (PAMP) recognition. Different types of cells, such as granulocytes and macrophages, can reach the site of infection increasing both the infiltrate and the acute gastroenteritis. (b) *Salmonella* pathogenicity island 1 (SPI-1)-derived proteins responsible for epithelial cell invasion during LP infection. After *Salmonella* recognize epithelial cell surface, SPI-1-encoded proteins are expressed and injected into host cells. Virulence effectors such as SipA, SopE, SopE2 and SopB are responsible for reorganizing actin cytoskeleton, promoting bacterial engulfment. Other SPI-1-secreted factors, such as SptP, decrease this process avoiding host cell death by excessive intracellular bacterial load. Proteins, such as flagellin and PrgJ can also be translocated into the host cell cytosol where they activate nucleotide oligomerization domain-like receptor (NLR)-containing inflammasomes to promote the secretion of inflammatory cytokines, including interleukin-1β (IL-1β) and IL-18.

Salmonella-induced inflammation at the intestine

Once *S.* Typhimurium invades host intestinal epithelial cells, a transcriptional re-programming occurs in these cells,[97–99] which includes expression of several pro-inflammatory molecules[99–101] and the activation of MyD88-dependent Toll-like receptor signalling processes in epithelial and local immune cells.[102–108] This inflammatory environment promotes the recruitment of neutrophils, macrophages and DCs to the LP.[109–111] Recent studies have shown that effector proteins secreted by the T3SS-1, such as SopE and SopB, can also promote an inflammatory response in epithelial cells (Fig. 1).[97,101] These proteins mediate the induction of inflammation through mitogen-activated protein kinase signalling and nuclear factor-κB activation, independently of the TLR signalling.[97] During this process, epithelial cells secrete inflammatory cytokines, such as interleukin-8 (IL-8), CCL2 and CCL20, further promoting the recruitment of more immune cells.[99,101,112,113] These inflammatory processes induced by *S.* Typhimurium help intestinal invasion, LP colonization and the spreading to other hosts by means of diarrhoea.[109,110]

T3SS-1 also promotes inflammation by an alternative pathway that requires the activation of NLR-containing inflammasomes, specifically NLRP3 and NLRC4, which induce caspase-1 activity and the concomintant secretion of IL-1β and IL-18 (Fig. 1B).[114,115] A recent report suggests that the T3SS-1 protein PrgJ binds directly to the NAIP2 protein, promoting the activation of the NLRC4 inflammasome.[116] Although it seems possible that these inflammatory responses can facilitate the dissemination of *S.* Typhimurium towards internal organs in the host,[117] recent studies have shown that NLRC4 inflammasome activation is a protective mechanism to discriminate against commensal and pathogenic bacteria.[115,118] According to this theory, mice lacking the NLRP3 and NLRC4 inflammasome are more susceptible to *S.* Typhimurium infection than control mice, showing higher bacterial loads in the liver, spleen and mesenteric lymph nodes after oral infection.[114]

Flagellin, the main component of bacterial flagella, has also been involved in *S.* Typhimurium-induced inflammation in the LP (Fig. 1b). It has been described that this protein can also be translocated by T3SS-1 into the host

cytosol and bind directly to the intracellular receptors NAIP5 and NAIP6, which activate the NLRC4 inflammasome.[116,119–121] This promotes cell death by pyroptosis[122] and caspase-1-dependent secretion of cytokines, such as IL-1β, IL-8, IL-18 and tumour necrosis factor-α.[120,122–124] Furthermore, it has been suggested that inflammation induced by flagellin can play an important role in *S.* Typhimurium-induced enterocolitis.[125–128] However, a recent report has described that aflagellated strains of *S.* Typhimurium showed increased proliferation in Peyer's patches and mesenteric lymph nodes, as compared with wild-type strains.[129] Although these aflagellated strains failed to induce early inflammation, they promoted an enhanced secretion of IL-1β, interferon-γ and tumour necrosis factor-α later during infection.[129] Previous reports have also described that aflagellated strains can cause a more severe systemic infection in mice than do wild-type strains.[130,131] These findings also suggest that the inflammation induced by flagellin through Toll-like receptor 5 seems to reduce *S.* Typhimurium dissemination to deeper organs.[104,129]

Salmonella Typhimurium seems also able to prevent an excessive inflammatory response at the intestinal epithelium by the injection of another effector protein, known as AvrA.[132] Several reports have shown that this protein prevents IK-B degradation[133,134] and other recent studies indicate that AvrA injection through the T3SS-1 might also block the Jun N-terminal kinase pathway.[135–137] Both signalling pathways promote the transcription of genes coding for inflammatory mediators. It has been also reported that AvrA might contribute to stabilize tight junctions to prevent inflammatory damage on epithelial cells.[138] It is possible that, because of all the functions of AvrA, this protein counteracts pro-inflammatory effector proteins secreted by *S.* Typhimurium into epithelial cells. Such a molecular regulatory circuit might contribute to avoiding sustained inflammation upon *Salmonella* infection.

Role of DCs in *Salmonella* invasion of LP

Several studies have suggested that *S.* Typhimurium, even in the absence of T3SS-1, remains capable of translocating to the LP.[58,139] Furthermore, it has been shown that these strains require functional DCs to be translocated through the sub-epithelial dome.[58] Consistent with this notion, depletion of DCs from the LP can prevent the invasion of these T3SS-1 mutant strains.[58] However, the capture of virulent *S.* Typhimurium by DCs seems to be a process tightly regulated by effector proteins secreted through the T3SS-1. Our recent studies suggest that *S.* Typhimurium strains lacking functional T3SS-1 are taken up more efficiently by DCs than are wild-type strains.[140] It seems that active translocation of effector molecules through the T3SS-1 would prevent an excessive entry of bacteria to DCs, which could be required for controlling the amount of intracellular bacteria in these cells.[140] It is likely that a massive capture of *S.* Typhimurium by transepithelial DCs would promote an immune response that could contribute to restricting *Salmonella* replication and dissemination. Hence, virulent *S.* Typhimurium may optimize this process by finely regulating the entry to epithelial and DCs to translocate to the LP.

Salmonella survival inside phagocytic cells

Inside phagocytic cells *S.* Typhimurium resides in *Salmonella*-containing vacuoles (SCV).[42,45,47,141,142] Inside these compartments, intracellular *Salmonella* survives and is protected from several anti-bacterial molecules. Several studies have shown that *S.* Typhimurium can survive for up to 24 hr inside murine DCs and locate at a specific sub-cellular area inside DCs, near to the trans-Golgi network.[143] In contrast with what has been observed in macrophages, *S.* Typhimurium seem unable to replicate in a significant manner inside these cells.[42,45,47,52,53,144] Several virulent proteins encoded by SPI-2 allow *S.* Typhimurium to survive and localize inside DCs.[45,52,143] These proteins are secreted by T3SS-2, which can transverse the vacuolar membrane and inject *Salmonella* effector proteins directly into the host cell cytoplasm.[52,145,146] Accordingly, the deletion of SPI-2 or genes encoding the T3SS-2 reduces the ability of the bacterium to survive inside DCs and reduces its virulence in mice.[42]

In DCs, some *Salmonella* effectors can subvert DC function by altering the cellular trafficking and preventing fusion of SCV with lysosomes.[147] One of the effector proteins that contributes to avoiding SCV fusion with lysosomes in DCs is SpiC, which prevents vesicular trafficking in target cells.[42,148] This effector protein specifically binds a host protein known as Hook-3, which links the Golgi apparatus to the microtubules.[148] In addition, SpiC acts as a regulator for the assembly of T3SS-2 and the translocation of other virulence factors into host cell cytoplasm.[145,149] Accordingly, *Salmonella* strains lacking SpiC are unable to secrete other effector proteins to the DC cytoplasm and are targeted for lysosome degradation.[143] For this reason, SpiC-deficient strains are attenuated in mice.[42,150]

Another effector protein secreted by T3SS-2 that is required for survival inside DCs is SifA. This protein modulates the SCV integrity in macrophages and promotes the formation of *Salmonella*-induced filaments.[151–153] SifA also binds to SipA and Kinesin-interacting protein (or SKIP), which antagonizes the Rab9 protein and prevents kinesin-1 recruitment to SCV.[154–157] Strains of *S.* Typhimurium lacking SifA escape from SCV and fail to replicate inside the cytoplasm of macrophages.[153] In support of this notion, it has been shown that SifA-deficient bacteria escape from SCV to the DC

cytoplasm and fail to co-localize with lysosomal markers.[144] However, another report describes how SifA mutants still reside in an intact SCV and co-localize with the lysosomal marker Lamp-1 within DCs.[143] The reason for the discrepancies observed in these studies has not been resolved. There are additional T3SS-2-secreted effector proteins that are injected by *S.* Typhimurium into the cytoplasm of DCs, such as SseJ, SseF, SspH2 and PipB2, and that contribute to intracellular survival and subversion of DC function.[143] However, further studies are required to define whether *S.* Typhimurium strains lacking these effector proteins show reduced survival inside DCs, increased fusion with lysosomes and reduced virulence in mice.

Salmonella interference with host adaptive immunity

A hallmark of *S.* Typhimurium is its capacity to prevent the processing and presentation of bacterial antigens by DCs to T cells, both on class I and class II MHC molecules (Fig. 2).[42,47,144,158–161] Importantly, suppression of antigen presentation by *S.* Typhimurium is restricted to antigens expressed by this bacterium, because DCs infected with *Salmonella* remain capable of presenting bystander soluble antigens.[42,143] However, one study showed that the presentation of non-bacterial antigens might be also affected by *S.* Typhimurium infection.[42,51]

It has also been described that *S.* Typhimurium infection reduces the amount of MHC molecules expressed on the surface of both mouse and human DCs.[143,162] Studies in this area suggest that this evasion mechanism is the result of the negative effect of bacteria effector proteins in both endosomal trafficking and lysosomal degradation of the bacterium.[42,47,158,163] This effect results in reduced availability of bacterial antigens loaded on MHC molecules and poor activation of T cells.[47,52,142] Additionally, studies in human DCs suggest that *S.* Typhimurium infection promotes degradation of HLA-DR molecules by poly-ubiquitination.[162]

In agreement with the previous notion, attenuated strains of *S.* Typhimurium lacking SPI-2, T3SS-2 or T3SS-2-secreted effector proteins fail to prevent antigen presentation by DCs (Fig. 2).[42,51] These bacterial strains show a significant impairment in their intracellular survival inside DCs and become attenuated in mice.[42,51] The TTSS-2-secreted effector proteins required for avoiding antigen presentation include SlrP, SspeH2, PipB2, SopD and SifA.[143] The *S.* Typhimurium strains lacking these genes are unable to prevent the activation of T cells by *Salmonella*-infected DCs.[143] Importantly, other *Salmonella* serovars, such as *S.* Enteritidis and *S.* Typhi, are also unable to prevent antigen presentation by murine DCs.[53] These *Salmonella* serovars are less virulent in mice and similar to SPI-2 or T3SS-2 mutant strains, these bacteria are targeted for lysosomal degradation in murine DCs.[53] Therefore, the capacity of *Salmonella* to prevent antigen presentation might be a feature of host restriction.

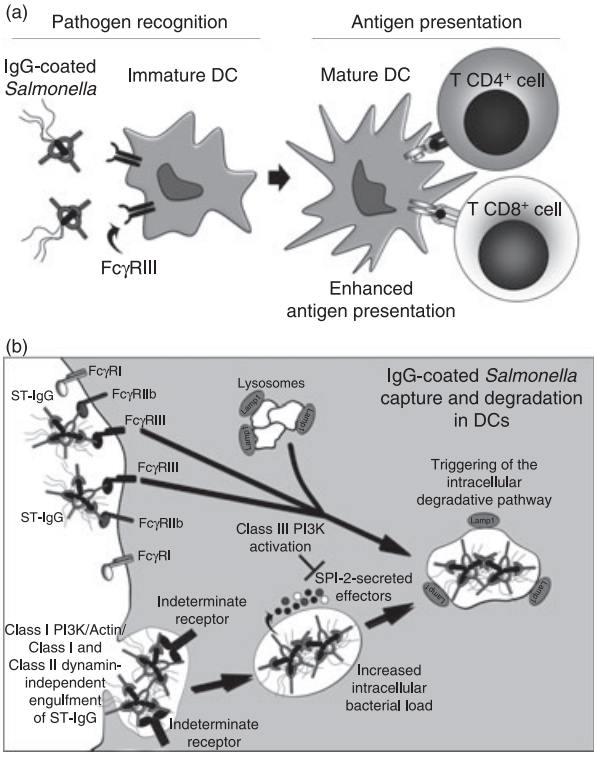

Figure 2. Fcγ receptor-mediated enhancement of T-cell priming by dendritic cells (DCs) after recognition and degradation of *Salmonella*-derived antigens. (a) After IgG opsonization, *Salmonella* can be recognized by FcγRIII expressed on the surface of DCs. Then, these cells are able to present bacterial-derived antigens MHC-I and MHC-II to $CD8^+$ and $CD4^+$ T cells, respectively. IgG opsonization can restore antigen presentation by DCs infected with *Salmonella*. (b) IgG-opsonized *Salmonella* engages FcγRIII on the surface of the DCs, triggering an intracellular class III phosphatidyl inositol 3 kniase (PI3K)-dependent degradation pathway, which enhances fusion of the *Salmonella*-containing vacuoles (SCV) with lysosomes ($Lamp1^+$). SCV-containing IgG-coated bacteria are created after internalization of elevated numbers of *Salmonella* complexes in an FcγRs/class I PI3K/Actin/Class I and Class II dynamin-independent mechanism. Internalization is driven by an unidentified receptor, which could recognize bacterial surface molecules unblocked by IgG-opsonization. Once inside the SCV, *Salmonella* still remain able to secrete *Salmonella* pathogenicity island 2 (SPI-2)-derived virulence determinants. As a result of IgG opsonization, antigen capture, degradation and presentation by DCs are significantly enhanced.

Importantly, we have described how impairment of antigen presentation would depend on effector proteins secreted largely by T3SS-2, because *S.* Typhimurium strains lacking T3SS-1 remain capable of preventing antigen presentation on MHC molecules by DCs.[140] In addition, we have observed that prevention of antigen presentation, might be fundamental for *S.* Typhimurium

to cause systemic disease in mice, as SPI-2 or T3SS-2 mutant strains fail to colonize internal organs and cause a lethal infection.[42] In contrast, either T3SS-1 or SPI-1 mutant strains show mild attenuation and remain capable of causing systemic infection.[164]

Salmonella interactions with Fcγ receptors and its role in T-cell activation by DCs

Although virulent strains of *S.* Typhimurium are able to prevent antigen presentation by host DCs, we have described how the presence of anti-*Salmonella* antibodies in the infected host is an efficient way to counteract these evasion mechanisms that prevent the activation of adaptive immunity. This phenomenon takes place because IgG-opsonized virulent *Salmonella* can be both taken up and processed by Fcγ receptors expressed by DCs. It is widely accepted that Fcγ receptor engagement can significantly increases the capacity of DCs to degrade and present bacterial antigens on MHC molecules and activate T cells.[47,141] It has been suggested that enhancement of processing and presentation of *Salmonella* antigens is mainly mediated by FcγRIII, a low-affinity activating Fcγ receptor expressed by DCs (Fig. 2).[141] We have shown that binding of *Salmonella*-IgG to FcγRIII results in the fusion of the SCV with DC lysosomes and subsequently in the degradation of bacteria for antigen presentation, perhaps because of the activation of specific signalling pathways.[47,141] Although opsonization with IgG does not prevent secretion of effector proteins by T3SS-1 and T3SS-2,[165] FcγRIII signalling seems to overcome the effect of the T3SS-2 secreted proteins that are responsible for evading the degradation of captured *Salmonella*. Furthermore, enhancement of *Salmonella* degradation and antigen presentation induced by FcγRIII requires class III phosphatidyl inositol 3-kinase (PI3K) activity on DCs, as it can be reverted by the PI3K inhibitor Wortmannin (Fig. 2).[141] This molecule not only reduces presentation of bacterial antigens to T cells, but also increases the intracellular survival of either virulent or attenuated *Salmonella* in DCs.[141]

In addition, we have shown that *Salmonella*-specific IgGs increase bacterial engulfment by DCs, so abrogating the uptake evasion displayed by SPI-1.[165] However, neither FcγRI, FcγRIIb nor FcγRIII are employed by DCs to capture these large immune complexes (Fig. 2).[165] Our data suggest that antigen presentation enhancement displayed by IgG-coated *Salmonella*-infected DCs is orchestrated by an FcγRIII-dependent degradation and an FcγRs-independent internalization.[165] Hence, IgG on the surface of *Salmonella* could be engaging FcγRIII, promoting intracellular degradation and, at the same time, another still undefined receptor could be recognizing different bacterial components promoting internalization. This new receptor (or cluster of receptors) does not require class I PI3K, an actin cytoskeleton or class I/class II dynamin because specific inhibitors for these molecules failed to prevent bacterial internalization by DCs (Fig. 2).[165] Hence, despite the finding that anti capture SPI-1-derived effectors could still be translocated by IgG-coated *Salmonella* into the DC cytoplasm, an alternative internalization mechanism could effectively enhance *Salmonella* uptake.[140,165] Enhanced bacterial uptake increases the amount of intracellular antigen available to be further processed. This could explain why DCs present on their surfaces elevated the numbers of bacterial-derived antigens on both class I and class II MHC molecules that can prime naive T cells, enhancing host adaptive immunity (Fig 2).[141]

In conclusion, our observations suggest that a previously acquired antibody response against *S.* Typhimurium might contribute to counteract the virulence mechanisms displayed by this pathogen, due to the targeting of bacteria to activating Fcγ receptors and to the enhancement of the DCs capacity to capture, degrade and present bacterial antigens to T cells.

Concluding remarks

Salmonella Typhimurium has successfully evolved molecular mechanisms to alter DC function and exploit the immune response to cause a successful infection in the host. Studies performed in the past decade allowed us to conclude that effector molecules encoded by SPI-1 and SPI-2 contribute to exploiting the inflammation induced by DCs and other immune cells at the intestinal mucosa to replicate and spread to new hosts. Further, *Salmonella* has evolved molecular mechanisms to prevent activation of T cells by DCs and cause an uncontrolled systemic disease. The characterization of the strategies used by *S.* Typhimurium to evade host immunity could contribute to generate new prophylactic tools aimed at improving DC function and to promote immune responses to counteract this pathogen virulence. Studies describing Fcγ receptor-independent uptake separate from Fcγ receptor-mediated intracellular degradation of *Salmonella* by DCs could provide new insights for improved immunotherapies and vaccines against salmonellosis, using DCs and antibodies as a new therapeutic approaches.

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Disclosures

The authors declare no conflict of interest.

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