The role of dendritic cells during Salmonella infection
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One type of phagocytic antigen-presenting cell (APC) — the dendritic cell (DC) — may have specialized functions during infection with the bacterium Salmonella, including a possible role in transporting Salmonella across the intestinal barrier. In addition, changes in the number, localization and cytokine production of CD8α+CD4α−CD44+ and CD8α−CD44− DC subsets occur during infection. DCs function in stimulating bacteria-specific T cells by direct presentation of Salmonella antigens and as bystander APCs. Studying the function of DCs during Salmonella infection provides insight into the capacity of these differentiated APCs, which are a key link between innate and adaptive immunity, to initiate and modulate the immune response to a bacterial infection.

Abbreviations
APC = antigen-presenting cell
DC = dendritic cell
PP = Peyer’s patch
SED = subepithelial dome

Introduction
Secondary lymphoid organs provide the specialized microenvironment required for generating a specific immune response. Initiating immunity to a microbe that invades peripheral tissues thus requires linking the infected peripheral site with secondary lymphoid organs. One cell type in particular — the dendritic cell (DC) — is a crucial link between these two sites. DCs are widely distributed in lymphoid as well as non-lymphoid tissues but are present in low numbers. They exist in distinct stages depending on their location and signals in their immediate environment, and have the capacity to migrate. The DC is also the most efficient type of antigen-presenting cell (APC) that stimulates naïve T cells. It is these unique properties of DCs that give them a central role in initiating and modulating immune responses [1].

DCs from various tissues and organs share features in morphology, surface phenotype and function that allow their identification as DCs [2]. Although DCs from different species have distinct surface molecules that aid in their identification, surface expression of CD11c (the β2 integrin p150/95) and MHC class II are common characteristics of murine DCs.

As mentioned above, DCs exist in different stages — as so-called immature or mature cells — depending upon the signals they receive from their environment. DCs residing in peripheral tissues in the absence of inflammatory stimuli or microbial products are in an immature state. Functional features of immature DCs include a high capacity to internalize and process antigens, and a relatively poor capacity to stimulate naïve T cells. They have low surface expression of MHC-II, CD86, CD80 and CD40. Signals derived from substances associated with infection or inflammation, such as LPS, CpG-containing DNA, IL-1β or TNF-α, or triggering of CD40, initiate DC maturation. This process transforms immature DCs, which are programmed for capturing and processing antigens, into mature cells proficient at presenting antigens to, and stimulating, T cells.

The process of DC maturation includes downregulating antigen-capture capacity and upregulating MHC molecule synthesis, stability, surface expression and intracellular trafficking. It also involves increasing surface expression of costimulatory molecules, enhancing cytokine secretion and altering chemokine responsiveness [3–11]. This last property allows migration from inflamed tissues to secondary lymphoid organs. These unique features of DCs underscore their importance in initiating adaptive immunity.

The present article focuses on the role of DCs during infection with the facultative intracellular, Gram-negative bacterium Salmonella enterica serovar typhimurium (S. typhimurium). Recent data suggesting a role for DCs in transporting Salmonella across the intestinal barrier are presented. In addition, changes in the number, localization and cytokine production of CD8α+, CD8α−CD4α+ and CD8α−CD4− DC subsets during infection are summarized. The function of DCs in stimulating bacteria-specific T cells by direct presentation of Salmonella antigens and as bystander APCs is also discussed.

DC subsets
Additional characterization of murine CD11c+ DCs from secondary lymphoid organs revealed that these cells can be divided into subsets based on surface expression of molecules such as CD8α, CD4, CD11b and DEC-205 [12,13]. Approximately 25% of CD11c+ cells in mouse spleen express CD8α and DEC-205 whereas the remainder do not. Within splenic CD8α+DEC-205+ DCs, CD4+ and CD4− populations are present. Thus, murine splenic CD11c+ cells can be divided into CD8α+CD4−DEC-205+CD11b+, CD8α−CD4+DEC-205−CD11b− and CD8α−CD4−DEC-205−CD11b− subsets. Significant differences in surface expression of the costimulatory molecules CD80, CD86 or CD40 on the three splenic DC subsets are not apparent [12,14,15].

Mouse peripheral lymph nodes contain two additional populations that appear to be emigrants from the skin. These cells lack CD4 expression, have low expression of
CD8α and intermediate to high levels of DEC-205 [13].

The picture of DC subsets is even more complex when CD11c+ cells from Peyer’s patches (PPs) are characterized. In contrast to CD11c+ cells from the spleen, PP DCs do not express CD4 and contain an abundant population of CD8α+CD11b– cells that is only a minor subset of splenic DCs [16•].

Different functions are being elucidated for the DC subsets. For example, the DC subsets from the same lymphoid organ have a differential capacity to secrete cytokines upon microbial stimulation [16•,17–19,20**,21•,22,23,24•,25]. Data show that CD8α+ DCs are more prone to produce IL-12 and influence a CD4+ T cell response towards one dominated by cells producing Th1 cytokines compared with the CD8α– subset [21•,23,26,27]. However, environmental factors can influence the capacity of both CD8α+ and CD8α– DCs to produce IL-12. For example, CD8α+ DC IL-12 production is dependent on IFN-γ, and additional signals are required for CD8α– DCs to produce IL-12 [21•,25]. In addition, the capacity of a given subset to produce cytokines may be influenced by the microenvironment of the organ. This seems to be the case for cytokine production by DCs from PPs relative to the same DC subset from the spleen [16•]. This in turn translates into a differential influence on the Th1/Th2 cytokine profile of antigen-specific T cells primed in the presence of DCs from PPs versus spleen [16•,28].

Finally, different DC subsets also localize to distinct regions in secondary lymphoid organs. Whereas CD8α+CD11b– DCs preferentially localize to T-cell-rich areas, CD8α+CD11b+ DCs are found within the splenic marginal zone [29,30]. In PPs, CD8α+CD11b+ and CD8α+CD11b– DCs are localized in the subepithelial dome (SED) whereas CD8α–CD11b– and CD8α–CD11b+ are found in the interfollicular region [16•,31]. These data suggest that the DC subsets may have different roles in an immune response.

DCs that are present in secondary lymphoid organs, which for a long time were considered to be poor at internalizing antigens, indeed have endocytic and phagocytic capacity [14,15,22,29,32–35]. Some data also suggest that the splenic DC subsets differ in their capacity to present antigen administered to mice on MHC-I and MHC-II. These studies showed that CD8α+ DCs are the most efficient stimulators of CD8+ T cells, whereas CD8α– DCs present MHC-II-restricted epitopes to CD4+ T cells more readily than CD8α+ DCs after administration of soluble or cellular antigen [32,33]. However, this dichotomy may not necessarily be true for all types of antigens. For example, it was recently shown that both CD8α+ and CD8α– splenic DCs present antigens expressed in *Mycobacterium bovis* BCG for MHC-II-restricted presentation to CD4+ T cells *in vivo* [35] (see also Update).

Thus, data are beginning to emerge to elucidate the role of DC subsets in stimulating and modulating an immune response. Despite this, relatively little is known about the contribution of DCs or DC subsets during bacterial infections. A murine infection model using *S. typhimurium* has provided some information on this and is summarized here.

### DCs as hosts for *Salmonella* during infection

Unlike the phagocytic capacity of macrophages and neutrophils, which has been known for a long time, the phagocytic capacity of immature DCs was not appreciated until relatively recently. The addition of DCs to the phagocyte family raises the question of the contribution of DCs to antibacterial immunity. This is relevant for phagocytic processing of bacteria for peptide presentation to T cells as well as their role as cytokine producers.

To begin addressing the role of DCs during *Salmonella* infection, it is worth considering the fate of this bacterium upon entry into a host by the natural route of infection, orally. The route of *Salmonella* penetration across the intestinal epithelial barrier appears to depend on the invasive phenotype of the bacteria. Whereas invasive *Salmonella* use M cells scattered in the epithelium overlying PPs to cross the intestinal barrier [36,37], non-invasive strains can penetrate the intestinal barrier in an M-cell-independent fashion [38,39**]. Within minutes of oral administration of non-invasive bacteria, CD18+ cells of the monocyte-macrophage lineage harboring *Salmonella* are found in the blood [38]. Although the study by Vasquez-Torres *et al.* [38] did not specifically identify the type of CD18+ phagocyte transporting the bacteria, the work of Rescigno *et al.* [39**] suggests that DCs could be involved in M-cell-independent transport of non-invasive *Salmonella* from the intestine. This study raises the interesting possibility that DCs breach the intestinal epithelial barrier and the cell dendrites grab non-invasive bacteria and bring them across the gut epithelium. As intestinal DCs appear to express tight-junction proteins, the integrity of the gut epithelium is preserved during this process [39**]. In support of a potential role for DCs in mediating bacterial transit from the intestinal lumen, a particular population of DCs in PPs — CD8α+CD11b– DCs — is present in the epithelial layer overlying the follicle (the follicle-associated epithelium) and can be in close contact with M cells [16•]. These DCs are thus also poised to sample intestinal bacteria.

Despite the suggested role of DCs in facilitating transport of *Salmonella* across the intestinal epithelium, some questions remain. For instance, are DCs the only type of intestinal phagocyte endowed with the capacity to sample intestinal bacteria? Neutrophils, for example, also have the capacity to traverse epithelial layers while maintaining the integrity of the layer [40]. These cells could thus potentially have a similar role as DCs in facilitating bacterial transport. However, in this case, being in the right place at the right time may be a critical factor. Although the SED of PPs is enriched in DCs, particularly the CD8α+CD11b+
and CD8α CD11b+ subsets [16•,31], it lacks cells staining for surface molecules that would indicate the presence of neutrophils or macrophages [31,41].

In addition to the possibility of M-cell-independent traversal of the intestinal barrier via the epithelial overlying PPs, it could occur through the epithelial layer of intestinal villi. Although physical barriers hinder bacterial penetration outside of PPs, in situ staining indicates that macrophages are present along with DCs in villus lamina propria [31,41]. Thus, if Salmonella can penetrate the intestinal epithelium outside of PPs, phagocytes other than DCs could encounter Salmonella in this process. This raises some interesting possibilities on potential presentation of Salmonella antigens by bystander APCs, which is discussed below.

Murine models have shown that both splenic [22,42] and PP [43] DCs harbor Salmonella during infection. Furthermore, Salmonella are found in DCs of the three major splenic DC subsets (CD8α+, CD8α–CD4+ and CD8α–CD4+) in vivo [22]. At low bacterial doses, CD8α+ DCs seem to internalize Salmonella somewhat more efficiently than CD8α–CD4+ or CD8α+CD4+ DCs. At higher doses, however, the percentage of DCs within each subset that take up bacteria is similar. Splenic CD11c+ cells respond to Salmonella infection by increasing surface expression of costimulatory molecules such as CD86 and CD40 beginning approximately one week after infection [42]. However, whether all subsets are equally altered in surface molecule expression in response to Salmonella infection is presently not known. The appearance of DCs exhibiting higher surface levels of costimulatory molecules corresponds to the time post-infection when Salmonella-specific T cells are beginning to appear [44].

Thus, DCs and each of the three splenic DC subsets internalize Salmonella in vivo. However, the numbers of DCs containing Salmonella are very low, particularly in orally infected mice. Whereas intravenous or intraperitoneal injection of Salmonella results in 1%–10% of splenic CD11c+ cells containing bacteria shortly after administration, depending on the dose [22,42], <1% of splenic DCs associate with Salmonella in orally infected mice (U Yridi, MJ Wick, unpublished data; see also [43]). Likewise, a similar low percentage of splenic DCs (~2%) contain Mycobacterium bovis BCG shortly after intravenous administration of the bacteria [35].

**DCs as APCs during Salmonella infection**

The observation that DCs harbor Salmonella in infected mice suggests that DCs may be the APCs that trigger the specific immune response during infection. Indeed, immature bone-marrow-derived DCs as well as freshly isolated DCs from the spleen and mesenteric lymph nodes can process Salmonella and present bacterial antigens to specific CD4+ and CD8+ T cells [22,45–47]. In addition, primary, antigen-specific CD4+ and CD8+ T cells are stimulated to proliferate upon ex vivo co-culture with splenic DCs isolated from Salmonella-infected mice [22]. As mentioned above, costimulatory molecule expression is increased on splenic DCs in Salmonella-infected mice, and DCs loaded with S. typhimurium can elicit bacteria-specific CD4+ and CD8+ T cells after transfer into naïve animals [42]. These data suggest that DCs are likely candidates for stimulating Salmonella-specific T cells during infection. However, this also raises the related question of whether direct presentation of Salmonella-specific T cells is the major means by which bacteria-specific T cells are triggered. Alternatively, what is the contribution of presentation of bacterial antigens by bystander DCs that acquire Salmonella antigens from neighboring cells?

Infection of macrophages or DCs with Salmonella expressing the type III secretion system results in apoptotic death of the cells [48,49•,50]. A consequence of Salmonella-induced cell death is that direct presentation of Salmonella antigens to CD4+ and CD8+ T cells, which occurs when DCs or macrophages internalize Salmonella that does not kill the cells [45–47,50], is abrogated [49•]. However, Salmonella-induced apoptotic cells are nonetheless a source of bacterial antigens for T cell recognition. This was demonstrated in experiments showing that bystander DCs ingest apoptotic material from Salmonella-induced apoptotic macrophages and present bacterial antigens on MHC-I and MHC-II [49•]. In contrast, bystander macrophages internalize Salmonella-induced apoptotic cells but do not stimulate antigen-specific T cells.

Thus, DCs seem to be unique among phagocytic APCs in having the capability to directly present Salmonella antigens for T cell recognition after phagocytosis of bacteria and to act as bystander APCs to present bacterial antigens after uptake of neighboring cells that have undergone Salmonella-induced apoptotic death. Bystander DCs can also present viral antigens derived from influenza-infected apoptotic monocytes [51]. These data from bacterial and viral systems suggest that microbe-induced apoptotic cell death provides a reservoir of microbial antigens that can contribute to immunity during infections after uptake by bystander DCs.

Thus DCs, by either direct presentation of Salmonella antigens or by presenting bacterial antigens acquired from neighboring cells, may be important in triggering T cell responses during infection. The importance of direct presentation of bacterial antigens is obvious. Presentation by bystander APCs may be important in detecting microbes that kill infected APCs and destroy their capacity to directly stimulate T cells. However, the relative contribution of direct presentation of bacterial antigens by infected cells versus presentation of antigens acquired by bystander DCs is not clear. In addition, a contribution of other phagocytic APCs in stimulating T cells — either by direct presentation or indirectly by being reservoirs of bacterial antigens — and which APCs dominate presentation of bacterial antigens in primary versus secondary infection remain to be elucidated.
DC-derived cytokines during Salmonella infection

Splenic CD8α–, CD8α+ CD4+ and CD8α–CD4– DC subsets are differentially modulated with respect to number, distribution and cytokine production in response to oral Salmonella infection [18]. Although the absolute number of splenic CD8α– and CD8α+CD4+ DCs doubled five days after infection, no alteration in CD4+ DC number occurred. The quantitative increase in CD8α– and CD8α+CD4– DCs was reflected by a significant influx of these subsets in the splenic red pulp of Salmonella-infected mice. Redistribution of CD4+ DCs also occurred during infection, as CD4+ DCs surrounding B cell follicles that were present in naïve or Escherichia coli infected mice were no longer present in mice that received Salmonella, despite the presence of CD4+ DCs within the follicles.

An increase in CD8α+ DCs producing TNF-α, a cytokine critical to host survival of Salmonella infection, has been detected in the spleen of Salmonella-infected mice [18]. However, the absolute number of TNF-α+ splenic DCs in the first few days following oral Salmonella infection is low relative to the number of other cells producing this cytokine. In particular, neutrophils and macrophages are much more abundant than DCs producing TNF-α in the spleens of mice infected 5 days earlier with Salmonella (A Kirby, U Yrlid, MJ Wick, unpublished data). Thus, the function of DC-derived TNF-α may be involved in aspects of the anti-Salmonella response other than contributing to the bactericidal capacity of phagocytes and controlling initial bacterial growth. As TNF-α is capable of inducing DC maturation [4], TNF-α production by DCs may work in an autocrine or paracrine fashion during Salmonella infection to orchestrate DC maturation to link the innate and adaptive immune responses.

IL-12 and IFN-γ are also important for host survival of Salmonella infection, and the capacity of DCs to produce these cytokines during Salmonella infection has been examined. However, no significant increase in either CD8α– or CD8α+ DCs producing IL-12 was apparent 1–5 days after oral Salmonella infection [18]. This was unexpected in light of the capacity of other microbial stimuli, such as LPS, killed Staphylococcus aureus or an extract of the parasite Toxoplasma gondii, to elicit IL-12 production by DCs, primarily by CD8α– DCs [16*,17,19,20**,21*,24*,25]. In vivo production of IL-12 by DCs after intravenous administration of T. gondii extract is rapid (it occurs within a few hours), transient and short-lived (its duration is <24 hours) [19,20**,24*,25]. As several days are required to detect DC responses to oral Salmonella infection [18], a slower, less pronounced IL-12 response by DCs following oral Salmonella infection may occur relative to injection of T. gondii extract. Alternatively, the inability to detect significant IL-12 production by DCs from Salmonella-infected mice may reflect the limited numbers of bacteria in the spleen and the low number of DCs containing bacteria during infection as mentioned above.

Signals necessary to enhance IL-12 production by DCs in response to Salmonella, including those mediated through CD40–CD40L or cytokines such as IFN-γ, may also be limiting early during infection [21*,24*]. The lack of DCs producing IL-12 does not seem to be due to production of IL-10 by these cells, as IL-10-producing DCs were not detected in Salmonella-infected mice [18]. However, IL-10 production by other cells could contribute to a reduced capacity of DCs to produce IL-12 during infection [21*].

Despite an inability to detect DC production of IL-12 following oral Salmonella infection — at least within the timeframe examined [18] — DCs can produce this cytokine in response to Salmonella. Both splenic and bone-marrow-derived DCs co-cultured with Salmonella produce IL-12p40 [22,45]. Consistent with data for other microbial stimuli, CD8α– DCs are the prominent producers of IL-12p40 compared with the CD8α+CD4+ and CD8α–CD4+ subsets in response to Salmonella [22]. Despite IL-12p40 production, however, only very low levels of IL-12p70 (which is a heterodimer of IL-12p40 and IL-12p35 subunits) are detected. The inability to detect significant amounts of IL-12p70 may reflect the absence of required additional signals such as CD40 engagement or cytokines such as IFN-γ, as discussed above.

Consistent with the results from Salmonella-infected mice, only low levels of IL-12p40 and no IL-12p70, were detected in culture supernatants of DCs isolated shortly after intravenous infection with M. bovis BCG and cultured ex vivo [35]. The level of IL-12p40 that accumulated in the cultures, however, was increased when the DCs were co-cultured with specific T cells. In these conditions, IL-12p40 was detected in the supernatants when either CD8α+ or CD8α– DCs purified from infected mice were co-cultured with antigen-specific T cells. As seen with T. gondii extract, IL-12p40 production by DCs from BCG-infected mice was also very transient, lasting only a few hours.

IFN-γ is a cytokine important in controlling many bacterial infections, including Salmonella. This, combined with the capacity of DCs to produce IFN-γ in an IL-12-dependent fashion [17,52,53], suggests that DCs could produce IFN-γ in response to Salmonella. This cytokine could act in an autocrine or paracrine fashion to facilitate the capacity of the DCs to control the infection. However, very few IFN-γ-producing DCs are present in the spleens of Salmonella-infected mice early after oral infection [18] or after co-culture of purified splenic DCs with Salmonella (U Yrlid, MJ Wick, unpublished data). This suggests that DCs do not contribute to IFN-γ production early during Salmonella infection.

For both TNF-α and IL-12p40 production, in vitro studies have shown that contact between Salmonella and the splenic DC subsets is required whereas bacterial internalization is not [22]. Consistent with this, a significant fraction of cytokine+ cells are not associated with bacteria, demonstrating that cytokine production by bystander DCs occurs. Although the signals mediating microbe-induced
cytokine production by DCs are not well understood, surface components of the bacteria signaling through Toll-like receptors are involved [54,55]. The role of Toll-like receptors in bacteria-mediated changes in DC function and antibacterial immunity, particularly with respect to differential function of DC subsets, is an exciting field warranting further investigation.

Conclusions

The advances in our understanding of how DCs and defined DC subsets respond during Salmonella infection have provided insight into the role of this sophisticated APC in orchestrating the immune response to bacteria. However, some intriguing questions regarding the role of DCs during bacterial infections — particularly to oral infections — remain. For example, if DCs transport bacteria across the intestinal lumen into deeper tissues, how is tolerance to normal gut flora maintained and what is the role of DCs in this tolerance? Indeed, there is a constant efflux of intestinal DCs to draining lymph nodes, which is enhanced by bacterial stimuli such as LPS [56].

Furthermore, despite the significant advances in defining functional differences among DC subsets, our understanding of the role of the DC subsets during infection is incomplete and we do not know if different types of microbes elicit different responses by DC subsets in vivo. This raises another issue that is not well understood: that is, what are the signaling pathways and alterations in gene expression that occur in DCs during bacterial infection? Do these differ in the DC subsets? Further studies to unravel the contribution of DCs and the DC subsets to bacterial infection will surely be an exciting area of research for some time.

Update

Recent work has demonstrated that splenic CD8α+ DCs can present cell-associated antigens to CD4+ T cells following adoptive transfer of antigen-loaded B cells into recipients [57].

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


This study is a continuation of a series of papers by this group characterizing the phenotype, localization and function of PP DCs. The authors show that PP DCs have a different capacity to produce cytokines relative to splenic DCs upon microbial stimulation or with T-cell-derived signals. In particular, PP DCs make IL-12 whereas splenic DCs have little capacity to produce this cytokine, and PP DCs induce CD4+ T cells to produce more IL-4 and IL-10 compared with T cells co-incubated with splenic DCs. This paper also defines a differential cytokine-production capacity of DC subsets from PPs and shows that CD8α+CD11b+ PP DCs have the greatest capacity to influence CD4+ T cells to produce IL-4 and IL-10.


This report demonstrates that, signaling through the chemokine receptor CCR5 is important for DC redistribution and IL-12 production by CD8αα DCs in response to T. gondii extract. In experiments using either a CCR5 antagonist or CCR5−/− mice, the authors show that signaling via CCR5 is involved in these functions of DCs. Thus, T. gondii extract, either by direct interaction with CCR5 and/or induction of CCR5 ligands, coordinates DC movement into T-cell-rich areas of the spleen and IL-12 production by CD8αα DCs.


This paper, along with reference [24*], provides additional information on the differential capacity of CD8αα and CD8αβ dendritic cell subsets to produce cytokines, particularly IL-12p70, in response to microbial stimuli. The authors show that IL-12p70 production by CD8αα DCs is IFN-γ-dependent and that IL-12p70 secretion by CD8αβ DCs as well as CD8αα DCs is influenced by IL-10. In addition, analysis of cytokine production by antigen-specific T cells from mice primed with CD8αα or CD8αβ DCs shows that CD8αβ DCs from cytokine-deficient mice DCs derived IFN-γ and IL-12p40 are required for CD8αβ DCs to prime Th1 responses whereas Th2 skewing by CD8αα DCs is IL-10-dependent.


This study shows that macrophages that undergo Salmonella-induced apoptotic death are a source of bacterial antigens that can be presented to CD4+ and/or CD8αα T cells after uptake by bystander DCs. It seems that DCs are unique in their capacity to act as bystander APCs, because bystander macrophages do not present bacterial antigens from Salmonella-induced apoptotic cells despite internalization of apoptotic material. This paper, along with reference [24*], provides additional information on the differential capacity of CD8αα and CD8αβ dendritic cell subsets to produce cytokines, particularly IL-12p70, in response to microbial stimuli. The authors show that IL-12p70 production by CD8αα DCs is IFN-γ-dependent and that IL-12p70 secretion by CD8αβ DCs as well as CD8αα DCs is influenced by IL-10. In addition, analysis of cytokine production by antigen-specific T cells from mice primed with CD8αα or CD8αβ DCs shows that CD8αβ DCs from cytokine-deficient mice DCs derived IFN-γ and IL-12p40 are required for CD8αβ DCs to prime Th1 responses whereas Th2 skewing by CD8αα DCs is IL-10-dependent.

with reference [51], shows the role of DCs as unique APCs that — in addition to their capacity to directly present antigens to T cells upon infection with a microbe — can present microbial antigens acquired from microbe-induced apoptotic cells for T cell recognition.


