Functional flexibility and plasticity in immune control of systemic *Salmonella* infection

Sven Engel[1], Annabell Bachem[1], Richard A. Strugnell[1], Andreas Strasser[2, 3], Marco J. Herold[2, 3] and Sammy Bedoui[1*]

[1]Department of Microbiology and Immunology at the Peter Doherty Institute for Infection and Immunity, The University of Melbourne, Parkville, VIC, Australia

[2]The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia

[3]Department of Medical Biology, The University of Melbourne, Melbourne, VIC, Australia

* Corresponding author: Prof Sammy Bedoui, sbedoui@unimelb.edu.au

Abstract

Immunity to systemic *Salmonella* infection depends on multiple effector mechanisms. Lymphocyte-derived interferon gamma (IFN-γ) enhances cell-intrinsic bactericidal capabilities to antagonize the hijacking of phagocytes as replicative niches for *Salmonella*. Programmed cell death (PCD) provides another means through which phagocytes fight against intracellular *Salmonella*. We describe remarkable levels of flexibility with which the host coordinates and adapts these responses. This involves interchangeable cellular sources of IFN-γ regulated by innate and adaptive cues, and the rewiring of PCD pathways in previously unknown ways. We discuss that such plasticity is likely the consequence of host-pathogen coevolution and raise the possibility of further functional overlap between these seemingly distinct processes.

Introduction

Oral infection with *Salmonella enterica* causes two types of pathologies with very different consequences [1]. Gastroenteritis, a self-limiting infection, ensues when the bacteria are controlled at the epithelial level [2]. In contrast, spread of *Salmonella* into deeper tissues can result in systemic dissemination and enteric fever [3], a life-threatening disease that affects 10-20 million people worldwide and kills >100,000 individuals per annum [4]. Observations from *Salmonella* infections in inherited or infection-induced immunodeficiency indicate a major role for the immune system during both types of infections [5]. However, many aspects of precisely how immune mechanisms enable infected cells to control, purge and eliminate *Salmonella* remain unclear [6]. This opinion article focuses on systemic *Salmonella* infections in mice and discusses recent developments about the role of phagocytes, cell-intrinsic and cell-extrinsic immune effector mechanisms, and their regulation.

Salmonella replicates in cells specialized for the destruction of intracellular bacteria

Salmonella replicates primarily within phagocytes in the spleen and liver during systemic infection [7]. Key to this important virulence trait are two needle-like type III secretion systems (T3SS) encoded by *Salmonella* Pathogenicity Island (SPI)-1 and SPI-2 that enables *Salmonella* to inject dozens of effector proteins into the cytosol of phagocytes [8]. These proteins prompt the repurposing of a host cell-derived membrane compartment into *Salmonella*-containing vacuoles (SCVs), which promote bacterial replication and shield the bacteria from cytosolic effector mechanisms, such as production of reactive oxygen and nitrogen species (ROS, NO) [9]. Not all bacteria remain confined to these sanctuaries [10]. Some are shed into the cytosol from where they regain access to the extracellular space and spread further, enabling the infection of more host cells, and restarting the cycle of establishing SCVs. This transitioning in and out of the extracellular space provides the host with additional opportunities to mount

immune responses against the bacteria. Free bacteria can be engulfed by monocytes, macrophages and neutrophils. These phagocytes are equipped with Toll-like receptors (TLRs) capable of detecting vital components of *Salmonella* [11], such as flagellin or lipopolysaccharides (LPS). Stimulation of these TLRs and other pathogen recognition receptors induces the secretion of pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-6 and IL-12, which provide important cues for the orchestration of the initial immune response against this infection.

Do $CD4^+$ T cells enhance resistance of phagocytes against infection through IFN-γ?

Dendritic cells (DCs) residing at sites of infection can also capture *Salmonella* [12]. These specialized phagocytes process proteins from engulfed bacteria and upon migration to the lymph node present peptide antigens to naïve T cells in complex with major histocompatibility complex (MHC) molecules [13]. Naïve $CD4^+$ T cells recognizing MHC class II-restricted *Salmonella*-derived antigens (pMHC) on activated, IL-12 secreting DCs differentiate into T helper type 1 (Th1) cells and migrate to sites of infection. Here, they scan cells for matching pMHC, and upon T cell receptor (TCR) stimulation synthesize and release IFN-γ. This cytokine promotes phagolysosome fusion, acidification of the lysosomal content and ROS/NO production [14]. These bactericidal activities combine to inactivate microbial proteins, oxidize lipids and destroy microbial DNA, thus leaving the bacteria irreversibly damaged and preventing their replication. Mice lacking $CD4^+$ T cells fail to clear *Salmonella* infections [15, 16] and patients with reductions in $CD4^+$ T cells caused by acquired immunodeficiency syndrome (AIDS) are particularly susceptible to severe *Salmonella* infection, especially by serovars that normally only cause self-limiting gastroenteritis [17, 18]. Together with IFN-γ-deficient mice failing to control *Salmonella* infections [16, 19] and humans with mutations in

the receptor for IFN-γ being particularly susceptible to *Salmonella* infections [20], these observations suggest that *Salmonella*-specific Th1 cells are the critical source of IFN-γ [5].

Antigen-independent provision of IFN-γ from interchangeable cellular sources

We have previously examined the relative roles of $CD4^+$ T cells and IFN-γ during murine systemic infection using a growth-attenuated *Salmonella* strain that mimics key modalities of human enteric fever. Mice lacking $CD4^+$ T cells controlled this infection over the first three weeks, but ultimately failed to clear the bacteria. Notably, this outcome differed substantially from the lethal salmonellosis that developed in IFN-γ-deficient mice, where even the initial control of bacterial replication failed [16]. Although these observations are generally consistent with important roles for $CD4^+$ T cells and IFN-γ during *Salmonella* infection, they also imply that $CD4^+$ T cells are at least partially redundant for the provision of IFN-γ. In exploring this redundancy further, we found that adoptive transfer of either $CD8^+$ T cells or NK cells could restore some control of bacterial growth in IFN-γ-deficient mice [21, 22]. We did, however, also find that *Salmonella* control was intact in mice lacking $CD8^+$ T cells or NKT cells, suggesting that as long as IFN-γ could be provided by any one type of $CD4^+$ T cells, $CD8^+$ T cells or non-conventional T cells, such as NKT cells, the infection could be controlled [16]. Intriguingly, this provision of protective IFN-γ did not depend on *Salmonella*-specific responses by lymphocytes. In fact, memory $CD8^+$ T cells specific for an unrelated viral infection conferred significant control to *Salmonella* infected *Ifng*$^{-/-}$ mice [21]. This was not due to TCR cross-reactivity but resulted from an alternative, antigen-independent cellular response, in which IL-18 stimulated protective IFN-γ secretion from $CD8^+$ T cells, $CD4^+$ T cells and NK cells [21-23]. Antigen-independent IFN-γ responses therefore compensated for the absence of *Salmonella*-specific Th1 cells as crucial providers of IFN-γ. Interestingly, we

also found that control of the infection was possible without IL-18 (unpublished data), and only broke down to levels comparable to IFN-γ-deficient mice in *Rag* × *Il2rg*$^{-/-}$ mice lacking all lymphocytes (i.e. T cells, B cells and NK cells) [21, 22]. It therefore appears that innate triggers can compensate for a lack of TCR-driven IFN-γ provision by *Salmonella*-specific Th1 cells, and conversely, that TCR-driven provision of IFN-γ is also sufficient without innate stimulation.

Control of *Salmonella* infection through inflammasomes and pyroptosis

The implication of IL-18 in the response to *Salmonella* suggested a role for the nucleotide-binding oligomerization domain-like receptors C4 (NLRC4) and its upstream adaptor proteins of the NLR apoptosis inhibitory protein (NAIP) family that together form the so-called NLRC4 inflammasomes [24]. These large protein structures serve as platforms for the activation of caspase-1, which proteolytically processes pro-IL-1β and pro-IL-18 into their bioactive forms. Active caspase-1 also cleaves N-terminal fragments from gasdermin D (GSDMD). The fragments then oligomerize and introduce pores into the host cell plasma membrane, allowing the release of IL-1β and IL-18 into the extracellular space [25]. Notably, the resulting influx of fluids and molecules initiates a form of PCD termed pyroptosis [26], which can also be triggered by the activation of caspase-11 [27]. With *Salmonella*-derived flagellin, components of its SPI-1 encoded T3SS, and LPS capable of triggering pyroptosis [28], it seemed possible that infected phagocytes would deploy this complex process to purge *Salmonella* from these cells. Indeed, NLRC4 and caspase-1 were then found to be required for the prevention of *Salmonella* replication through inflammasome-induced pyroptosis *in vitro* [29, 30]. However, subsequent *in vivo* studies painted a more complex picture, with *Casp1/11*$^{-/-}$ mice only having surprisingly minor, if any defects in controlling systemic infections with the growth-attenuated *Salmonella* strain SL1344 *ΔaroA* [31].

Caspase-8-mediated apoptosis can compensate for the lack of pyroptosis

More recently it became clear that the initiator caspase-8 can compensate for the absence of caspases-1 and -11 by inducing GSDMD cleavage and pyroptosis instead [32]. This was intriguing, as caspase-8 was thought to play an exclusive role in the initiation of the extrinsic apoptosis pathway. In this alternative form of PCD, caspase-8 is activated by extracellular ligands of the TNF superfamily, including TNF-α and FAS ligand (FASL). Activated caspase-8 then proteolytically activates the so-called executioner caspases-3 and -7 that set-in motion cell death by cleaving hundreds of substrate proteins to orchestrate the ordered demolition of the dying cells. Caspase-8 can also activate the executioner caspases indirectly by engaging the intrinsic apoptotic pathway through proteolytic activation of the BH3-interacting-domain death agonist (BID) leading to Bcl-2-associated X and K protein (BAX/BAK) mediated mitochondrial outer membrane permeabilization (MOMP) and consequent activation of caspase-9 [33, 34]. To test if caspase-8 can compensate for the lack of caspases-1 and -11 by providing an alternative path to GSDMD-dependent pyroptosis *in vivo*, we infected *GsdmD/Bid*$^{-/-}$ mice (unpublished data) and *Casp8/Ripk3*$^{-/-}$ mice with growth-attenuated *Salmonella*. However, both mouse strains had no defect in controlling *Salmonella* infection that was greater than the defect caused by the absence of caspases-1 and -11. In striking contrast, control of bacterial replication failed when caspases-1, -11 and -8 were absent in combination [31], demonstrating that a caspase-8-dependent mechanism not only compensated for the lack of caspases-1 and -11 but also for pyroptosis itself. Intrinsic apoptosis, necroptosis and the CARD-containing caspases, caspase-12 [31] and caspase-2 [35], seemed to play only minor if any roles in the control of systemic growth-attenuated *Salmonella* infection in mice. Mechanistically, the compensation between caspase-1/caspase-11 and caspase-8 involved the rewiring of the known apoptosis and pyroptosis signaling pathways in previously unknown

ways. For example, caspase-1 could functionally replace caspase-8 by stimulating MOMP formation and triggering the executioner caspases-3 and -7. The reverse was also the case, where caspase-8 could take over the functions of caspase-1 in driving pyroptosis. In fact, we made the surprising discovery that as long as caspase-1 and caspase-8 were present, cells infected with wild-type *Salmonella* SL1344 could undergo cell death independently of all known executioner caspases and pore forming molecules [31]. Phagocytes therefore seem to have at their disposal a system of cell death-inducing pathways that they can deploy with remarkable plasticity to control *Salmonella* infections. This crosstalk between apoptosis, necroptosis and pyroptosis with caspases-1 and 8 as core mediators is reminiscent of recent reports demonstrating important overlapping roles during embryogenesis and development [36, 37].

Are IFN-γ, lymphocytes and programmed cell death linked in the control of *Salmonella* infection?

The functional interchangeability of caspase-1 and caspase-8 was reminiscent of the redundancies we have identified in the cellular sources that can provide IFN-γ to control *Salmonella* infections. Moreover, the lethal type of salmonellosis that ensued in the absence of pyroptosis and caspase-8-mediated apoptosis had comparable kinetics to that occurring in mice lacking all lymphocytes or IFN-γ. Recent studies point to a possible explanation for these similarities. IFN-γ can prime macrophages to become susceptible to TLR or TNF-α-induced cell death [38, 39] and this type of cell death was characterized by the activation of caspase-8 and the executioner caspases-3 and -7. In the case of TLR-induced cell death, this also appeared to involve NO and imbalances between inhibitors and inducers of the intrinsic apoptosis pathway. Precisely how IFN-γ priming facilitates the activation of caspase-8 was not examined, but TNF-α is a known trigger of the extrinsic apoptosis pathway and has previously been linked

to the innate control of *Salmonella* and *Mycobacterium tuberculosis* infections [40, 41]. In this context it is also interesting to consider that IFN-γ increases the expression of MHC class II molecules on phagocytes and that effector $CD4^+$ T cells do not only secrete IFN-γ but also increase the expression of FASL. It is therefore possible that a so far unexplored relationship between cytokines and PCD exists during *Salmonella* infection. IFN-γ or TNF-α could prime phagocytes for extrinsic apoptosis, and the eventual triggering of caspase-8 could be regulated in an antigen-specific manner by $CD4^+$ T cells through FASL. It will be interesting to investigate this in detail and also to compare whether the use of attenuated *Salmonella* strains in *in vivo* studies influences the levels of redundancy discussed here.

Conclusions and Perspectives

Our exploration of how particular processes of the immune system contribute to *Salmonella* control has revealed a remarkable extent of flexibility and plasticity [31, 42]. Critical cytokines, such as IFN-γ, can be released through innate immune pathways when adaptive immune responses are absent and *vice versa*. Moreover, different types of lymphocytes can act as interchangeable sources of IFN-γ. We also found a remarkable degree of flexibility in the contribution of different types of PCD and their molecular regulation to the control of *Salmonella* infections. This propensity for functional compensation is likely related to the ongoing struggle between pathogens seeking to evade protective host responses [43, 44] and the host developing strategies to offset these attempts. For example, flagellin is rapidly downregulated once *Salmonella* infects a cell [30]. This likely serves to prevent NLRC4 activation, as demonstrated by the rapid NLRC4 and caspase-1/caspase-11-dependent clearance of *Salmonella* strains engineered to continuously express flagellin [45]. Similar mechanisms occur with SPI-1 T3SS-derived agonists of NLRs [30, 46]. In this context it is also

interesting to note that the *Salmonella* SPI-2 effector protein SteD can induce the ubiquitination and subsequent depletion of MHC class II molecules from the surface of infected cells [47]. This ability has been thought of as a means to prevent the priming of *Salmonella*-specific $CD4^+$ T cells. However, it seems equally possible that the bacteria utilize this mechanism to prevent FASL-mediated induction of extrinsic apoptosis by $CD4^+$ T cells recognizing MHC class II-restricted *Salmonella* antigens on infected phagocytes.

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Legends

Fig. 1 Cell-intrinsic and cell-extrinsic immune effector mechanisms and their regulation during systemic *Salmonella* infection

(A) The detection of cytosolic *Salmonella* proteins, including flagellin and structural components of the *Salmonella* Pathogenicity Island (SPI)-1 encoded T3SS, initiates the assembly of inflammasomes. Following recruitment and activation within the NLRC4 inflammasome, caspases-1 and -8 cleave GSDMD. The N-terminal GSDMD fragment translocates to the plasma membrane and oligomerises to form pores resulting in pyroptotic cell death. In contrast, caspase-11 directly senses cytosolic *Salmonella* and is activated by LPS. Activated caspase-11 can also cleave GSDMD, thus providing an alternative path towards cell

lysis. Pyroptotic cell death results in the release of pro-inflammatory cytokines, such as IL-1β and IL-18, which are cleaved into their bioactive forms by caspase-1. IL-18 can induce the release of IFN-γ by activated NK cells, $CD8^+$ T cells and $CD4^+$ T cells. By acting on phagocytes, IFN-γ stimulates antimicrobial capacities, such as ROS production, antigen presentation and expression of death receptors. (B) *Salmonella* limits inflammasome activation and pyroptosis by downregulation of SPI-1 and flagellin, and interferes with MHC class II antigen presentation. While caspase-8-dependent apoptosis can compensate for the lack of pyroptotic cell death, it is not clear what triggers caspase-8 under these circumstances. Considering that the SPI-2 effector protein SteD depletes mature MHC class II molecules from the surface of infected cells, that effector $CD4^+$ T cells can express FASL and that IFN-γ enhances the expression of MHC class II molecules and the receptor for FASL, it is possible that the caspase-8-dependent switch from pyroptosis to apoptosis is orchestrated by *Salmonella*-specific $CD4^+$ T cells.

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