The Interleukins Orchestrate Mucosal Immune Responses to Salmonella Infection in the Intestine

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Abstract: Salmonella infection remains one of the major public health problems in the world, with increasing resistance to antibiotics. The resolution is to explore the pathogenesis of the infection and search for alternative therapy other than antibiotics. Immune responses to Salmonella infection include innate and adaptive immunity. Flagellin or muramyl dipeptide from Salmonella, recognized by extracellular Toll-like receptors and intracellular nucleotide-binding oligomerization domain2, respectively, induce innate immunity involving intestinal epithelial cells, neutrophils, macrophages, dendritic cells and lymphocytes, including natural killer (NK) and natural killer T (NKT) cells. The cytokines, mostly interleukins, produced by the cells involved in innate immunity, stimulate adaptive immunity involving T and B cells. The mucosal epithelium responds to intestinal pathogens through its secretion of inflammatory cytokines, chemokines, and antimicrobial peptides. Chemokines, such as IL-8 and IL-17, recruit neutrophils into the cecal mucosa to defend against the invasion of Salmonella, but induce excessive inflammation contributing to colitis. Some of the interleukins have anti-inflammatory effects, such as IL-10, while others have pro-inflammatory effects, such as IL-1β, IL-12/IL-23, IL-15, IL-18, and IL-22. Furthermore, some interleukins, such as IL-6 and IL-27, exhibit both pro- and anti-inflammatory functions and anti-microbial defenses. The majority of interleukins secreted by macrophages and lymphocytes contributes antimicrobial defense or protective effects, but IL-8 and IL-10 may promote systemic Salmonella infection. In this article, we review the interleukins involved in Salmonella infection in the literature.

Keywords: interleukin; Salmonella; immune response; intestine; mucosa

1. Introduction

Salmonella infection remains one of the major public health problems in the world, with increasing resistance to antibiotics. Non-typhoidal Salmonella (NTS) usually causes self-limiting diarrhea in immunocompetent hosts, but may develop into sepsis or complications in immunocompromised hosts.

Immune responses to Salmonella infection include innate and adaptive immunity. The different stages of Salmonella infection are reflected in the innate and acquired immunity, orchestrated by a variety of immune cells to defend against this bacterium, having a different importance during distinct infection stages. The innate immune system can restrict the replication of Salmonella to a certain degree, but acquired immunity is essential for the effective control and eradication of bacteria.

Besides intestinal epithelial cells which form a physical barrier and produce inflammatory cytokines, chemokines, and antimicrobial peptides [1,2], a variety of immune cells accomplish the innate immunity against Salmonella infection, including dendritic cells, neutrophils, macrophages, natural killer (NK), and γδ T cells. Phagocytes, central to the control of Salmonella infection during the initial stages of Salmonella infection, are recruited and activated by the inflammation of the infected tissues and large amounts of IFN-γ produced by a variety of cells, with NK cells being an important source [3]. Interleukin (IL)-8 recruits neutrophils from the circulation system into the infected tissue to defend
against the invasion of Salmonella [4]. However, the accumulation of neutrophils gives rise to characteristic pathological changes of colitis. Macrophages appear to be crucial for protective immunity against intracellular Salmonella by phagocytosis of the bacteria and, along with dendritic cells, are major sources of many interleukins [5,6]. Moreover, dendritic cells play an important bridge between innate and acquired immunity via interleukins [7]. T cells are important for the control of S. typhimurium infection and CD4+ T cells in particular, but also CD8+ T cells and perhaps γδ T cells are involved [5]. Humoral immunity plays critical role(s) in the response to Salmonella infection, especially at the late phase [8]. Among intracellular bacteria, B cells play a notable role in resistance to Salmonella.

Infection leads to Toll-like receptors or intracellular nucleotide-binding oligomerization domain activation, the production of inflammatory interleukins such as IL-1α/β, IL-6, IL-8, IL-10, IL12/23, IL-15, IL-17A, IL-18, IL-25, IL-27, TNF-α, chemokine (C-C motif) ligand 2 (CCL2), IFN-γ, and neutrophil and macrophage recruitment. The plasma pro-inflammatory versus anti-inflammatory cytokine profile in patients with severe sepsis has been demonstrated to predict mortality [9–14]. In this article, we review the interleukins orchestrate intestinal mucosa responses to Salmonella infection in the literature (Tables 1 and 2).

Table 1. The interleukins orchestrate mucosal immune responses to defense against Salmonella infection in the intestine.

| Interleukin | Biologic Functions | Experiments | Intervention and Effects | Clinical Applications | Ref. |
|------------|-------------------|-------------|-------------------------|-----------------------|------|
| IL-1α      | Function as a plasma membrane cytokine involved in the inflammation and protection from bacterial infections though its role remains poorly defined | Mice | IL-1α-enhanced resistance of mice to S. Typhimurium infection | Salmonella | [15] |
| IL-6       | Anti-inflammation 1. | IECs | PJ-34 up-regulates IL-6 production in Salmonella-infected IECs |                       |      |
|            | 2. Mediator of epithelial barrier protection | Enterocytes | 1. Probiotic (L. paracasei) potentiates IL-6 production in IL-1beta-treated Caco-2 cells |                       |      |
|            | 3. Protection from sepsis and endotoxemia | | | | [16–19] |
| IL-8       | Recruits neutrophils to defense against the invasion of Salmonella | IECs | 1. Flagellin and MDP synergistically enhance IL-8 | |  |
|            | 2. Plasma membrane cholesterol supports the survival of Salmonella in IECs through anti-IL-8 pathways | | 1. Salmonella colitis | | [20–25] |
|            | 3. Probiotics enhance IL-8 expression | | 2. IBD | | |
| Interleukin | Biologic Functions                                                                                           | Experiments | Intervention and Effects                                                                 | Clinical Applications                  | Ref.       |
|------------|-------------------------------------------------------------------------------------------------------------|-------------|------------------------------------------------------------------------------------------|----------------------------------------|-----------|
| IL-10      | 1. Anti-inflammation Th2 cytokine<br>2. Inhibit the development of Th1-type immune responses<br>3. Reduce NK cell responses<br>4. Prevent the differentiation of naïve T cells into effector cytotoxic T cells<br>5. Dampen the secretion of pro-inflammatory cytokines, such as IL-12<br>6. Induce Treg cell proliferation<br>7. Suppression of T helper 17 (TH17)-driven colitis | Mice        | IL-10-deficient mice develop colitis<br>Salmonella sepsis                             | Recurrent, extraintestinal and invasive Salmonella diseases | [26,27]   |
| IL-12      | 1. IL-12/IL-23 component acts on NK and T cells and NKT cells to induce IFN-γ-dependent or IFN-γ-independent immunity against intracellular Salmonella infection<br>2. A Key cytokine for immunity against invasive Salmonella in humans | Humans      | IL-12 enhances internalization and early intracellular killing of Salmonella enterica Serovar Typhimurium by human macrophages | Recurrent, extraintestinal and invasive Salmonella diseases | [28–30]   |
| IL-15      | 1. Stimulating macrophages, NK cells, T cells, and B cells to proliferate, secrete cytokines, and/or produce antibody<br>2. Protection against bacterial infection | Mice        | Endogenous IL-15 functions as early protection against infection with an avirulent strain of S. choleraesuis through activation of NK cells and IFN-γ production | Salmonella infection                    | [31,32]   |
| IL-17      | A cytokine involved in neutrophil recruitment to defend against extracellular bacteria                       | Mice        | Probiotic Lactobacillus plantarum ZS2058 significantly reduced the pathogenicity of Salmonella colitis by promoting the IL23/IL-22 axis in the mouse ileum | Salmonella colitis                      | [33–36]   |
| IL-18      | 1. Promotes IFN-γ production by T cells and NK cells thereby shaping immunity towards a Th1-like phenotype<br>2. Activates the colon epithelial cells to produce antimicrobial peptides to maintain microbiome homeostasis | Human epithelial cells | Salmonella pathogenicity islands (SPI)-1 effector secretion leads to NF-κB signaling and caspase-1-mediated IL-1β/IL-18 activation |                                               | [37,38]   |
| IL-22      | 1. Inflammatory responses<br>2. Maintenance of intestine mucosal barrier<br>3. Enhanced antimicrobial activity, and mucosal healing<br>4. Resistant to intestinal colonization of opportunistic pathogens | Human epithelial cells<br>Mice | IL-22 promotes intracellular fusion of SCVs with lysosomes leading to phagolysosomal killing of S. Typhimurium in human epithelial cells<br>IL-22 is able to heal intestinal inflammation and promote epithelial repair from acute injury | 1. Salmonella colitis<br>2. IBD | [39,40]   |
Table 1. Cont.

| Interleukin | Biologic Functions | Experiments | Intervention and Effects | Clinical Applications | Ref. |
|-------------|--------------------|-------------|--------------------------|-----------------------|------|
| **IL-23**   |                    |             |                          |                       |      |
| 1.          | A member of the IL-12 family of cytokines with pro-inflammatory properties IL-23 induce IFN-γ and IL-22 production and are associated with host innate immunity against *Salmonella* | Mice | Mouse deficient for IL-23 is associated with *S. Typhimurium* colitis | IBD *Salmonella* colitis | [41,42] |
| 2.          |                    |             | IL-27-enhanced TLR4 or TLR5 expression in human monocytes and macrophages, induced greater LPS/flagellin-mediated signaling, and significantly enhanced pro-inflammatory cytokines IL-12p40, TNF-α, and IL-6 production in *S. typhimurium* infected cells | *Salmonella* infection | [43–46] |

**IL-27**

1. Has fundamental roles in innate and adaptive immune regulation
2. Has both anti- and pro-inflammatory functions
3. Enhance TLR4 or TLR5 expression in human monocytes and macrophages, to cooperate for optimal anti-bacterial responses

**Table 2.** The interleukins orchestrate mucosal immune responses to enhance *Salmonella* colitis.

| Interleukin | Biologic Functions | Experiments | Intervention and Effects | Clinical Applications | Ref. |
|-------------|--------------------|-------------|--------------------------|-----------------------|------|
| **IL-1β**   |                    |             | Active vitamin D decrease IL-1β response to *Salmonella* infection to prevent the host from detrimental inflammation | IBD | [2,47–50] |
| 1.          | Amplifying intestinal inflammation by increasing intestinal epithelial tight junction permeability Atg16L1 suppresses IL-1β expression in macrophage and IECs | IECs, Mice, Rabbit | Active vitamin D3 attenuates the severity of *Salmonella* colitis in mice by decreasing IL-1β response | IBD | [2,47–50] |
| 2.          |                    |             | Blockade of IL-1 receptors reduces the inflammatory responses in experiment colitis | *Salmonella* sepsis | [52,53] |

**IL-8**

Accumulation of neutrophils gives rise to colitis and sepsis

1. Probiotics suppress IL-8 expression

| Interleukin | Biologic Functions | Experiments | Intervention and Effects | Clinical Applications | Ref. |
|-------------|--------------------|-------------|--------------------------|-----------------------|------|
| **IL-10**   |                    |             | Active vitamin D3 suppresses IL-8 expression | IBD | [1,25,51] |
| 1.          | Promote systemic *S. Typhimurium* infection in mice | Mice | Anti-IL-10 monoclonal antibody block IL-10 to defense against systemic *Salmonella* infection | *Salmonella* sepsis | [52,53] |
| 2.          |                    |             |                          |                       |      |

Abbreviations: IECs, intestine epithelial cells; IBD, inflammatory bowel disease; MDP, muramyl dipeptide; NK, natural killer; Treg: regulatory T cells; NKT, natural killer T; IFN, interferon; TNF, tumor necrosis factor; LPS, lipopolysaccharide; Th1, type 1 helper T cells; SCVs, *Salmonella*-containing vesicles; TLR, Toll-like receptor.
Table 2. Cont.

| Interleukin | Biologic Functions | Experiments | Intervention and Effects | Clinical Applications | Ref. |
|------------|--------------------|-------------|--------------------------|-----------------------|-----|
| IL-12      | A pro-inflammatory cytokine in response to microbial pathogens | Humans | Ustekinumab, the monoclonal antibody targeting the shared p40 subunit of IL12/IL23, has been approved for treatment of IBD | IBD | [30,54] |
| IL-15      | 1. Pro-inflammatory by itself  2. Promote intestinal dysbiosis that increases susceptibility to colitis | Mice | 1. Celiac disease 2. IBD | [32,55,56] |
| IL-17      | 1. Orchestrating mucosal inflammation in IBD and *Salmonella* colitis  2. iNKT cells play a protective role against *Salmonella*-enterocolitis by downregulating IL-17-producing γδT cells | 1. Macrophages 2. iNKT cells | *Lactobacillus plantarum* Lp62 was able to suppress IL-17, IL1-β and TNF-α production in LPS-stimulated J774 macrophages | *Salmonella* colitis  IBD | [36,57,58] |
| IL-18      | 1. A member of the IL-1 family of cytokines with pro-inflammatory and tumor-suppressive properties  2. Initiates a pro-inflammatory cytokine cascade in peripheral blood mononuclear cells (PBMC) | 1. *Salmonella* pathogenicity islands (SPI)-1 effector secretion leads to NF-kB signaling and caspase-1-mediated IL-1β/IL-18 activation  2. Animal models suggest suppression of IL-18 bioactivity as a novel therapeutic concept specifically for the treatment of chronic inflammatory diseases | | |
| IL-23      | 1. Accelerate proliferation of both murine and human memory T cells producing Th17 cytokines including IL-17 and IL-22  2. Increased production of IL-23 in various mouse models of colitis and IBD patients | Human/mice | Neutralizing antibodies against IL-12/IL-23 p40 and IL-23 p19 have been successfully used in clinical trials for therapy of IBD | IBD  *Salmonella* colitis | [41,61–63] |
| IL-27      | IL-27 can directly induce expression of IL-1 and TNF-α by primary mast cells and production of IL-1, TNF-α, IL-12p35 and IL-18 by monocytes | 1. Monocytes 2. Mast cells | *Salmonella* infection | | [44] |

Abbreviations: IECs, intestine epithelial cells; IBD, inflammatory bowel disease; MDP, muramyl dipeptide; NK, natural killer; Treg: regulatory T cells; NKT, natural killer T; INF, interferon; TNF, tumor necrosis factor; LPS, lipopolysaccharide; Th1, type 1 helper T cells; SCVs, *Salmonella*-containing vesicles; TLR, Toll-like receptor.

2. IL-1

Interleukin (IL)-1α and IL-1β are equally potent inflammatory cytokines but reveal highly dissimilar functions and biogenesis. IL-1α is constitutively expressed in many cell types at a steady state, and can be induced in response to cell stress, injury, infection, or pro-inflammatory stimuli [64]. IL-1α can function as a plasma membrane-bound cytokine. The exposure of cells to bacterial infection stimulates the intracellular expression of IL-1α as well as
as resulting in membrane IL-1α expression [65–67]. Although the biogenesis of IL-1α and its distinctive role in the inflammatory process remain poorly defined, recombinant murine TNF-α and IL-1α can protect mice from lethal bacterial infections [68]. The resistance of mice to a lethal dose of *S. typhimurium* could be enhanced if the mice were pretreated with IL-1α [15]. IL-1β is a key mediator of the inflammatory response and plays a major role on the pathogenesis of inflammatory bowel disease (IBD), consistent with the finding that IL-1β is up-regulated in IBD patients [48] and IBD colonic macrophages release mature IL-1β on exposure to lipopolysaccharide (LPS) [47]. The IL-1β-induced increase in the intestinal epithelial tight junction permeability may contribute to intestinal inflammation. Autophagy protein Atg16L1 polymorphisms in Crohn disease exhibit an excessive production of IL-1β and overwhelming inflammation in the colon [69,70]. Active vitamin D might enhance autophagy and decrease the IL-1β response to defend against *Salmonella* invasiveness and prevent the host from detrimental inflammation [2]. In vivo, active vitamin D3 attenuates the severity of *Salmonella* colitis in mice by decreasing IL-1β expression [50]. Furthermore, specific blockade of IL-1 receptors reduces the inflammatory responses in rabbit immune complex colitis [49].

3. IL-6

Interleukin (IL)-6 produced by enterocytes has anti-inflammatory and cell-protective effects in intestinal mucosa and enterocytes. It may counteract some of the injurious effects of sepsis and endotoxemia [17,71]. IL-6 has been reported to be a mediator of the epithelial barrier protection [72] and endogenous IL-6 plays an essential, non-redundant role in limiting intestinal injury [16]. *Salmonella*-induced intense inflammation causes the breakdown of the intestinal epithelial barrier, translocation of bacteria, and absorption of endotoxins into the circulation [73] and, consequently, bacteremia as well as endotoxemia. The probiotic *Lactobacillus paracasei* may exert some of their beneficial effects by enhancing IL-6 production in enterocytes subjected to an inflammatory stimulus [18]. PJ-34, a potent poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor, may exert defense on intestinal epithelial cells (IECs) against invasive *Salmonella* infection by up-regulating IL-6 production through the ERK and NF-κB signal pathway [19].

4. IL-8

Current data indicate that IECs orchestrate mucosal innate immunity through their production of inflammatory cytokines, chemokines, and antimicrobial peptides [74,75]. Chemokines, such as IL-8, recruits neutrophils into cecal mucosa to defend against the invasion of *Salmonella* [20–22]. However, the accumulation of neutrophils gives rise to colitis [76] and sepsis [51]. Toll-like receptor 5 (TLR5) and intracellular nucleotide-binding oligomerization domain 2 (NOD2) are two important pattern recognition receptors involved in innate immunity to invading pathogens. Flagellin, a ligand for TLR5, is a dominant pro-inflammatory determinant in IECs infected by *Salmonella*. The cooperation of flagellin and muramyl dipeptide, a NOD2 agonist, in IECs synergistically upregulates inflammatory IL-8 response to *Salmonella* infection [23]. Intracellular *Salmonella* infection in both macrophages and IECs induces cholesterol accumulation in the *Salmonella*-containing vesicles (SCVs) [77] within which the virulent bacteria survive and replicate [78,79]. Plasma membrane cholesterol supports the survival of *Salmonella* in IECs through the PI3K-dependent anti-IL-8 pathway [24]. Contrasting to membrane cholesterol, sphingolipids act on epithelial defense against the invasive pathogen by enhancing the NOD2-mediated human beta-defensin 2 (hBD-2) response [80]. The probiotic *Lactobacillus plantarum* Lp62 inhibited IL-8 production by *Salmonella* Typhi-stimulated IECs and prevented the adhesion of pathogens to the cells [57]. The treatment of probiotics before and after infection having different effects on the *Salmonella*-induced IL-8 response in IECs suggests the critical timing of probiotic supplementation [25]. Active vitamin D modulates the pro-inflammatory IL-8 response in *Salmonella*-infected IECs to prevent the host from detrimental extreme inflammation [1].
5. IL-10

IL-10 is a powerful anti-inflammatory Th2 cytokine with a broad range of target cell types, primarily of the innate cells, such as dendritic cells (DCs), macrophages, neutrophils, B cells, and T cells. Mice deficient in IL-10 spontaneously develop colitis resembling IBD. During *Clostridium difficile* infection, IL-10 is required to avoid an excessive immune reaction and prevent the host from more severe acute colitis [81]. IL-10 can dampen the secretion of pro-inflammatory cytokines, such as IL-12 [26] and prevents tissue damage [82] by acting on antigen-presenting cells. Furthermore, IL-10 facilities the regulatory T (Treg) cell-mediated suppression of T helper 17 (Th17)-driven colitis in mice [27]. On the other hand, *S. Typhimurium* can infect and persist in B cells [83], which provide additional signals to transform T cells to Treg cells. IL-10 produced by T and B cells promotes systemic *Salmonella enterica* serovar Typhimurium infection in mice [52]. The in vivo administration of the anti-IL-10 monoclonal antibody significantly enhanced host resistance at the early stage of *Salmonella* infection by accelerating macrophage functions and, consequently, the activation of γδT cells and enhanced levels of monokine mRNA, including IL-1α, tumor necrosis factor-α (TNF-α), and IL-12 [53].

6. IL-12

IL-12, similar to IL-23, is a pro-inflammatory cytokine produced by activated DCs, macrophages in response to microbial pathogens [84,85], and stimulates natural killer (NK), T, and natural killer T (NKT) cells to produce IFN-γ, which, in turn, aid in the elimination of intramacrophage pathogens, including *S. Typhimurium* [30,86]. These two cytokines must be considered together, because both share a common p40 subunit and their biology is closely interlocked [7]. IL-12 and IL-23 can also induce TNF-α and GM-CSF production in T cells via IFN-γ-independent signal transduction and bactericidal mechanisms [28]. In a human study, a high incidence of invasive *Salmonella* diseases in patients with IL-12/IL-23-INF-γ-axis deficiency highlights the importance of IL-12/IL-23-INF-γ-axis for immunity against *Salmonella* in humans [29]. Clinicians should consider an underlying IL-12/IL-23-INF-γ-axis deficiency in patients with recurrent, extraintestinal, and invasive *Salmonella* diseases, which usually require extensive treatment. Recombinant gamma interferon enhances the internalization and early intracellular killing of *Salmonella enterica* serovar Typhimurium by human macrophages [30], which release more IL-12 and less IL-10. Ustekinumab, the monoclonal antibody targeting the shared p40 subunit, has been approved for Crohn’s disease (CD) and has demonstrated promising results in the treatment of ulcerative colitis [54].

7. IL-15

Interleukin-15 (IL-15) is a cytokine that resembles IL-2 in its biological activities [31], stimulating macrophages, NK cells, T cells, and B cells to secrete cytokines, and has pro-inflammatory properties by itself [55]. It is upregulated under the conditions of tissue destruction and during infection [87,88]. IL-15 was reported to be involved in protection against bacterial infection mediated by NK and γδ T cells [31]. IL-15 overexpression promotes intestinal dysbiosis with a decrease in luminal butyrate-producing bacteria, lowers butyrate levels, and is associated with an increased susceptibility to colitis [56] and impacts on the pathogenesis of intestinal inflammatory diseases, such as celiac disease and IBD. Endogenous IL-15 had an important function in early protection against infection with an avirulent strain of *S. choleraesuis* through the activation of NK cells and IFN-γ production [32].

8. IL-17

Interleukin-17 (IL-17), a cytokine produced by Th17 cells, recruits neutrophils and plays a crucial role in host defense against extracellular bacteria [33]. Additionally, IL-17 helps to orchestrate mucosal inflammation by inducing the production of neutrophil chemoattractants (e.g., IL-8, CCL20, Lipocalin-2, and iNOS) in the intestines [41]. In IBD
patients, the increased expression of IL-17 was observed in the intestinal mucosa [89]. In the mouse colitis model of S. Typhimurium infection, IL-23 orchestrates mucosal responses to release IL-17 [41] that contribute specifically to neutrophil recruitment into the cecal mucosa to prevent Salmonella dissemination [34,35]. iNKT cells play a protective role against Salmonella enterocolitis by downregulating IL-17-producing γδT cells [58]. The probiotic Lactobacillus plantarum ZS2058 significantly reduced the pathogenicity of Salmonella colitis by promoting the colon IL23/IL-22 axis in the mouse [36]. Lactobacillus plantarum Lp62 was able to suppress IL-17, IL1-β, and TNF-α production in LPS-stimulated J774 macrophages [57].

9. IL-18

IL-18 is a cytokine that binds to a specific receptor expressed on various types of cells and has pleiotropic functions [37,59]. Its capability to promote INF-γ production by T cells and NK cells leads to pro-inflammatory activity. Colon epithelial cells constitutively produce IL-18, which increases upon NLRP6 inflammasome and in turn activates the epithelial cells to produce antimicrobial peptides to maintain microbiome homeostasis [38]. Moreover, the binding of TLR5 to its ligand flagellin not only results in a NF-κB-mediated pro-inflammatory cytokine responses, including IL-8, TNFα, and the matrix metalloprotease (MMP)-9, but induces IL-18 secretion and Th1-like cytokine responses in human peripheral blood mononuclear cells (PBMC) [37]. Salmonella pathogenicity islands (SPI)-1 effector secretion leads to NF-κB signaling and caspase-1-mediated IL-1β/IL-18 activation [60].

10. IL-22

The major functions of IL-22 in the intestine are the inflammatory response, enhanced antimicrobial activity, the maintenance of the mucosal barrier, resistance to colonization of opportunistic pathogens, enhancement of epithelial regulation, and wound healing [40,90]. IL-22 can restrict the growth of M. tuberculosis intracellularly in macrophages by enhancing phagosomal fusion. IL-22 can also orchestrate mucosal inflammation by inducing the production of neutrophil chemoattractants (e.g., IL-8, CCL20, Lipocalin-2, and iNOS) in the intestines [41]. IL-22 promotes the intracellular fusion of SCVs with lysosomes, leading to the phagolysosomal killing of S. Typhimurium in human epithelial cells [39]. Salmonella-induced IL-22 production can suppress the growth of commensal Enterobacteriaceae, the closest competitors for Salmonella, in the inflamed gut, thereby enhancing the Salmonella colonization of mucosal layers [91]. Furthermore, the ability of IL-22 to heal intestinal inflammation and promote epithelial repair from acute injury [40] highlights IL-22 as a promising target for future IBD therapy.

11. IL-23

Interleukin-23 (IL-23) is a member of the IL-12 family of cytokines with pro-inflammatory properties. Its ability to potentially enhance the expansion of Th17 cells indicates the responsibility for many of the inflammatory autoimmune responses. IL-23 is a key participant in the central regulation of the cellular mechanisms involved in inflammation [61]. IL-23 is produced by various immune cells such as dendritic cells, monocytes, as well as type 1 macrophages (MΦ1) upon Toll-like receptor signaling [92] in response to the binding of pathogens. In addition, neutrophils have been identified as a potential source of IL-23 production [93]. Recent studies have identified an increased production of IL-23 in various mouse models of colitis and IBD patients (review in [63]). IL-23 is able to accelerate the proliferation of both murine and human memory T cells producing Th17 cytokines such as IL-17A, IL-17F, and IL-22 [62]. IL-23 is known to induce IFN-γ production and is associated with host innate immunity against Salmonella. The IL-23/IL-22 axis during innate immunity against Salmonella may contribute to protection against Salmonella infection by several ways, such as IL-22-regulated expression of anti-microbial peptides and acute phase proteins and IL-17A-dependent neutrophil recruitment [42]. IL-23 deficient mice were unable to express
IL-17A during S. Typhimurium-induced colitis [41]. Infection with Salmonella can induce IL-23, IL-18, and IL-1β, but not IL-12, production in monocytes and type 1 pro-inflammatory macrophages [94].

12. IL-27

Interleukin (IL)-27, one of heterodimeric cytokines that belongs to the IL-12 family, has fundamental roles in innate and adaptive immune regulation [95]. It is produced in myeloid cells in response to bacterial infection and has both anti- and pro-inflammatory functions [95,96]. Accordingly, the role of IL-27 in human and experimental mouse colitis is controversial. IL-27 enhanced TLR4 or TLR5 expression in human monocytes and macrophages, induced greater LPS/flagellin-mediated signaling, and significantly enhanced pro-inflammatory cytokines IL-12p40, TNF-α, and IL-6 production in S. typhimurium-infected cells [43,44,46]. These findings support the role for IL-27 in anti-microbial defenses by altering the expression of innate immune sensors such as TLR4 or TLR5 [45].

13. Conclusions

Salmonella infection remains one of the major public health problems in the world, with increasing resistance to antibiotics. The resolution is to look for alternative therapy other than antibiotics based on the host immune reaction to infection. Interleukins play a crucial role in orchestrating mucosal immune responses to Salmonella infection in the intestine. How to take advantage of is knowledge and exploit effective reagents to treat Salmonella infection would be the essential next-generation issue.

In recent years, our group has contributed much effort to exploit the biotherapy that could prevent or treat Salmonellosis. PJ-34, a PARP-1 inhibitor, may exert its protective effect on intestinal epithelial cells against invasive Salmonella infection by up-regulating IL-6 production, which has anti-inflammatory and cell-protective effects [19], and counteracts some of the injurious effects of sepsis and endotoxia.

Salmonella-induced plasma membrane cholesterol accumulation in SCVs [24] may, subsequently, protect intestinal epithelial cells from apoptosis and produce an anti-inflammatory signal, both of which may contribute to the establishment of a Salmonella infection in cells. Contrasting to the utilization of membrane cholesterol on the maintenance of Salmonella-containing vacuoles and anti-inflammatory responses, sphingolipids act on the epithelial defense against the invasive pathogen [80]. Simvastatin or Fluvastatin, cholesterol-lowering statins, can suppress the pro-inflammatory IL-8 response in Salmonella-infected IECs to prevent the detrimental effects of overwhelming inflammation in the host [97].

Our recent in vitro and in vivo studies observed that active vitamin D prevented the host from the detrimental effects of overwhelming inflammation by downregulating pro-inflammatory responses (IL-6, TNF-α, IL-8, and IL-1β) [1,2,25] in Salmonella-infected IECs and decreased the severity of colitis in mice. The different regulation of probiotics on Salmonella-induced IL-8 responses in Caco-2 cells according to the administered timing supports a rationale for the therapeutic use of probiotics in the treatment of Salmonella colitis and inflammatory bowel disease [25]. Furthermore, we observed the synergistic effects of probiotics or postbiotics and active vitamin D on anti-inflammatory responses (IL-6, TNF-α, IL-8, and IL-1β) in Salmonella colitis mice [98,99].

It is mandatory to elucidate the pathogenesis of Salmonella infection for the design of intervention strategies that might reduce the use of antimicrobial agents and decrease the incidence of multidrug-resistant Salmonellosis. All these novel findings and thoughtful explorations of health knowledge could be applied to perform clinical trials and preventive medicine for the better lives of future generations.

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References

1. Huang, F.C. The differential effects of 1,25-dihydroxyvitamin D3 on Salmonella-induced interleukin-8 and human beta-defensin-2 in intestinal epithelial cells. Cell. Exp. Immunol. 2016, 185, 98–106. [CrossRef]

2. Huang, F.C. Vitamin D differentially regulates Salmonella-induced intestine epithelial autophagy and interleukin-1beta expression. World J. Gastroenterol. 2016, 22, 10353–10363. [CrossRef] [PubMed]

3. Ramarathinam, L.; Niesel, D.W.; Klimpel, G.R. Salmonella typhimurium induces IFN-gamma production in murine splenocytes. Role of natural killer cells and macrophages. J. Immunol. 1993, 150, 3973–3981. [PubMed]

4. Fleckenstein, J.M.; Kopecko, D.J. Breaching the mucosal barrier by stealth: An emerging pathogenic mechanism for enteroadherent bacterial pathogens. J. Clin. Investig. 2001, 107, 27–30. [CrossRef] [PubMed]

5. Mittrucker, H.W.; Kaufmann, S.H. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat. Rev. Immunol. 2003, 3, 133–146. [CrossRef] [PubMed]

6. Tam, M.A.; Rydstrom, A.; Sundquist, M.; Wick, M.J. Early cellular responses to Salmonella infection: Dendritic cells, monocytes, and more. Immunol. Rev. 2008, 225, 140–162. [CrossRef] [PubMed]

7. Trinchieri, G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat. Rev. Immunol. 2003, 3, 133–146. [CrossRef] [PubMed]

8. Takaya, A.; Yamamoto, T.; Tokoyoda, K. Humoral Immunity vs. Salmonella. Immunol. Rev. 2012, 248, 196–207. [CrossRef] [PubMed]

9. Sullivan, J.S.; Kilpatrick, L.; Costarino, A.T.; Jr.; Lee, S.C.; Harris, M.C. Correlation of plasma cytokine elevations with mortality rate in children with sepsis. J. Pediatr. 1992, 120, 510–515. [CrossRef]

10. Casey, L.C.; Balk, R.A.; Bone, R.C. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. Ann. Intern. Med. 1993, 119, 771–778. [CrossRef] [PubMed]

11. Wong, H.R.; Cvijanovich, N.; Wheeler, D.S.; Bigham, M.T.; Monaco, M.; Odoms, K.; Macias, W.L.; Williams, M.D. Interleukin-8 as a stratification tool for interventional trials involving pediatric septic shock. Am. J. Respir. Crit. Care Med. 2008, 178, 276–282. [CrossRef]

12. Carrol, E.D.; Payton, A.; Payne, D.; Miyajima, F.; Chaponda, M.; Mankhambo, L.A.; Banda, D.L.; Molyneux, E.M.; Cox, H.; Jacobson, G.; et al. The IL1RN promoter rs4251961 correlates with IL-1 receptor antagonist concentrations in human infection and is differentially regulated by GATA-1. J. Immunol. 2011, 186, 2329–2335. [CrossRef] [PubMed]

13. van Dissel, J.T.; van Langevelde, P.; Westendorp, R.G.; Kwappenberg, K.; Frolich, M. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet 1998, 351, 950–953. [CrossRef]

14. Gogos, C.A.; Drossou, E.; Bassaris, H.P.; Skoutelis, A. Pro-versus anti-inflammatory cytokine profile in patients with severe sepsis: A marker for prognosis and future therapeutic options. J. Infect. Dis. 2000, 181, 176–180. [CrossRef]

15. Morrissey, P.J.; Charrie, K. Treatment of mice with IL-1 before infection increases resistance to a lethal challenge with Salmonella typhimurium. The effect correlates with the resistance allele at the Ity locus. J. Immunol. 1994, 153, 212–219. [PubMed]

16. Jin, X.; Zimmers, T.A.; Zhang, Z.; Pierce, R.H.; Koniaris, L.G. Interleukin-6 is an important in vivo inhibitor of intestinal epithelial cell death in mice. Gut 2010, 59, 186–196. [CrossRef]

17. Xing, Z.; Gauldie, J.; Cox, G.; Baumann, H.; Jordana, M.; Lei, X.F.; Achong, M.K.; Kwappenberg, K.; Hollich, M. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet 1998, 351, 950–953. [CrossRef]

18. Reilly, N.; Poulin, V.; Menconi, M.; Onderdonk, A.; Bengmark, S.; Hasselgren, P.O. Probiotics potentiate IL-6 production in IL-1beta-treated Caco-2 cells through a heat shock-dependent mechanism. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2007, 293, R1169–R1179. [CrossRef]

19. Huang, F.C. Upregulation of Salmonella-induced IL-6 production in Caco-2 cells by muramyl dipeptide. Cell Immunol. 2016, 262, 81–86. [CrossRef]

20. McCormick, B.A.; Hofman, P.M.; Kim, J.; Carnes, D.K.; Miller, S.I.; Madara, J.L. Surface attachment of Salmonella typhimurium to epithelial cells. J. Infect. Dis. 2000, 181, 133–146. [CrossRef] [PubMed]

21. Eckmann, L.; Kagnoff, M.F.; Fierer, J. Epithelial cells secrete the chemokine interleukin-8 in response to bacterial entry. Infect. Immun. 1993, 61, 4569–4574. [CrossRef]

22. Kucharz, T.; Williams, I.R. Neutrophil migration across the intestinal epithelial barrier—summary of in vitro data and description of a new transgenic mouse model with doxycycline-inducible interleukin-8 expression in intestinal epithelial cells. Pathobiology 2002, 70, 143–149. [CrossRef]

23. Huang, F.C. Regulation of Salmonella flagellin-induced interleukin-8 in intestinal epithelial cells by muramyl dipeptide. Cell Immunol. 2012, 278, 1–9. [CrossRef]

24. Huang, F.C. Plasma membrane cholesterol plays a critical role in the Salmonella-induced anti-inflammatory response in intestinal epithelial cells. Cell Immunol. 2011, 271, 480–487. [CrossRef]
25. Huang, F.C.; Huang, S.C. The different effects of probiotics treatment on Salmonella-induced interleukin-8 response in intestinal epithelia cells via PI3K/Akt and NOD2 expression. *Benef. Microbes* **2016**, *7*, 739–748. [CrossRef]

26. Ma, X.; Yan, W.; Zheng, H.; Du, Q.; Zhang, L.; Ban, Y.; Li, N.; Wei, F. Regulation of IL-10 and IL-12 production and function in macrophages and dendritic cells. *F1000Research* **2015**, *4*. [CrossRef]

27. Chaudhry, A.; Samstein, R.M.; Treuting, P.; Liang, Y.; Pils, M.C.; Heinrich, J.M.; Jack, R.S.; Wunderlich, F.T.; Bruning, J.C.; Muller, W.; et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. *Immunity* **2011**, *34*, 566–578. [CrossRef]

28. van de Vosse, E.; Ottenhoff, T.H. Human host genetic factors in mycobacterial and Salmonella infection: Lessons from single gene disorders in IL-12/IL-23-dependent signaling that affect innate and adaptive immunity. *Microbes Infect.* **2006**, *8*, 1167–1173. [CrossRef] [PubMed]

29. MacLennan, C.; Fieschi, C.; Lammas, D.A.; Picard, C.; Dormann, S.E.; Sanal, O.; MacLennan, J.M.; Holland, S.M.; Ottenhoff, T.H.; Casanova, J.L.; et al. Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. *J. Infect. Dis.* **2004**, *190*, 1755–1757. [CrossRef]

30. Gordon, M.A.; Jack, D.L.; Dockrell, D.H.; Lee, M.E.; Read, R.C. Gamma interferon enhances internalization and early nonoxidative killing of Salmonella enterica serovar Typhimurium by human macrophages and modifies cytokine responses. *Infect. Immun.* **2005**, *73*, 3445–3452. [CrossRef]

31. Carson, W.E.; Giri, J.G.; Lindemann, M.J.; Linett, M.L.; Ahdieh, M.; Paxton, R.; Anderson, D.; Eisenmann, J.; Grabstein, K.; Caligiuri, M.A. Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. *J. Exp. Med.* **1994**, *180*, 1393–1403. [CrossRef]

32. Hirose, K.; Nishimura, H.; Matsuguchi, T.; Yoshikai, Y. Endogenous IL-15 might be responsible for early protection by natural killer cells against an avirulent strain of Salmonella choleraesuis in mice. *J. Leukoc. Biol.* **1999**, *66*, 382–390. [CrossRef]

33. Santos, R.L.; Raffatellu, M.; Bevins, C.L.; Adams, L.G.; Tukel, C.; Tsolis, R.M.; Baumler, A.J. Life in the inflamed intestine, *F1000Research* **2016**, *5*, 10. [CrossRef] [PubMed]

34. Raffatellu, M.; Santos, R.L.; Verhoeven, D.E.; George, M.D.; Winter, R.P.; Winter, S.E.; Tsolis, R.M.; Paixao, T.A.; Gordon, M.A.; et al. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. *Nat. Med.* **2008**, *14*, 421–428. [CrossRef]

35. Keestra, A.M.; Godinez, I.; Xavier, M.N.; Winter, M.G.; Winter, S.E.; Tsolis, R.M.; Baumler, A.J. Early MyD88-dependent induction of interleukin-17A expression during Salmonella colitis. *Infect. Immun.* **2011**, *79*, 3131–3140. [CrossRef]

36. Liu, J.; Gu, Z.; Song, F.; Zhang, H.; Zhao, J.; Chen, W. Lactobacillus plantarum ZS2058 and Lactobacillus rhamnosus GG Use Different Mechanisms to Prevent Salmonella Infection in vivo. *Front. Microbiol.* **2019**, *10*, 299. [CrossRef]

37. Bachmann, M.; Horn, K.; Poleganov, M.A.; Paulukat, J.; Nold, M.; Pleisachtsifer, J.; Muhl, H. Interleukin-18 secretion and Th1-like cytokine responses in human peripheral blood mononuclear cells under the influence of the toll-like receptor-5 ligand flagellin. *Cell Microbiol.* **2006**, *8*, 289–300. [CrossRef]

38. Levy, M.; Shapiro, H.; Thaiss, C.A.; Elinav, E. NLRP6: A Multifaceted Innate Immune Sensor. *Trends Immunol.* **2017**, *38*, 248–260. [CrossRef]

39. Forbester, J.L.; Lees, E.A.; Goulding, D.; Forrest, S.; Yeung, A.; Speak, A.; Clare, S.; Coomber, E.L.; Mukhopadhyay, S.; Kraicz, J.; et al. Interleukin-22 promotes phagolysosomal fusion to induce protection against Salmonella enterica Typhimurium in human epithelial cells. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 10118–10123. [CrossRef]

40. Mizoguchi, A. Healing of intestinal inflammation by IL-22. *Nat. Med.* **1999**, *5*, 5445–5452. [CrossRef] [PubMed]

41. McAlindon, M.E.; Hawkey, C.J.; Mahida, Y.R. Expression of interleukin 1 beta and interleukin 1 beta converting enzyme by intestinal macrophages in health and inflammatory bowel disease. *Gut* **1998**, *42*, 214–219. [CrossRef] [PubMed]
48. Ludwiczek, O.; Vannier, E.; Borggraefe, I.; Kaser, A.; Siegmund, B.; Dinarello, C.A.; Tilg, H. Imbalance between interleukin-1 agonists and antagonists: Relationship to severity of inflammatory bowel disease. Clin. Exp. Immunol. 2004, 138, 323–329. [CrossRef] [PubMed]

49. Cominelli, F.; Nast, C.C.; Clark, B.D.; Schindler, R.; Lierena, R.; Eysselein, V.E.; Thompson, R.C.; Dinarello, C.A. Interleukin 1 (IL-1) gene expression, synthesis, and effect of specific IL-1 receptor blockade in rabbit immune complex colitis. J. Clin. Investig. 1990, 86, 972–980. [CrossRef]

50. Huang, F.C.; Huang, S.C. Active vitamin D3 attenuates the severity of Salmonella colitis in mice by orchestrating innate immunity. Immun. Inflamm. Dis. 2021, 9, 481–491. [CrossRef] [PubMed]

51. Gilchrist, J.J.; Heath, J.N.; Msefula, C.L.; Gondwe, E.N.; Naranbhai, V.; Mandala, W.; MacLennan, J.M.; Moloney, E.M.; Graham, S.M.; Drayson, M.T.; et al. Cytokine Profiles during Invasive Nontyphoidal Salmonella Disease Predict Outcome in African Children. Clin. Vaccine Immunol. 2016, 23, 601–609. [CrossRef] [PubMed]

52. Salazar, G.A.; Penaloza, H.F.; Parde-Roa, C.; Schultz, B.M.; Munoz-Durango, N.; Gomez, R.S.; Salazar, F.J.; Pizarro, D.P.; Riedel, C.A.; Gonzalez, P.A.; et al. Interleukin-10 Production by T and B Cells Is a Key Factor to Promote Systemic Salmonella enterica Serovar Typhimurium Infection in Mice. Front. Immunol. 2017, 8, 889. [CrossRef]

53. Arai, T.; Hiromatsu, K.; Nishimura, H.; Kimura, Y.; Kobayashi, N.; Ishida, H.; Nimura, Y.; Yoshikai, Y. Effects of in vivo administration of anti-IL-10 monoclonal antibody on the host defence mechanism against murine Salmonella infection. Immunology 1995, 85, 381–388.

54. Hong, W.; Cross, R.K. Expert opinion on interleukin-12/23 and interleukin-23 antagonists as potential therapeutic options for the treatment of inflammatory bowel disease. Expert Opin. Investig. Drugs 2019, 28, 473–479. [CrossRef] [PubMed]

55. Waldmann, T.A. The biology of interleukin-2 and interleukin-15: Implications for cancer therapy and vaccine design. Nat. Rev. Immunol. 2006, 6, 595–601. [CrossRef]

56. Meisel, M.; Mayassi, T.; Fehlner-Peach, H.; Koval, J.C.; O’Brien, S.L.; Hinterleitner, R.; Lesko, K.; Kim, S.; Bouziat, R.; Chen, L.; et al. interleukin-15 promotes intestinal dildoisys with butyrate deficiency associated with increased susceptibility to colitis. ISME J. 2017, 11, 15–30. [CrossRef]

57. Ferreira Dos Santos, T.; Alves Melo, T.; Almeida, M.E.; Passos Rezende, R.; Romano, C.C. Immunomodulatory Effects of Lactobacillus plantarum Lp62 on Intestinal Epithelial and Mononuclear Cells. Biomed. Res. Int. 2016, 2016, 840416. [CrossRef] [PubMed]

58. Noto Llana, M.; Sarnacki, S.H.; Morales, A.L.; Aya Castaneda, M.D.R.; Giacomodonato, M.N.; Blanco, G.; Cerquetti, M.C. Activation of iNKT Cells Prevents Salmonella-Enterocolitis and Salmonella-Induced Reactive Arthritis by Downregulating (IL-1) gene expression, synthesis, and effect of specific IL-1 receptor blockade in rabbit immune complex colitis. [CrossRef] [PubMed]

59. Muhl, H.; Pfeilschifter, J. Interleukin-18 bioactivity: A novel target for immunopharmacological anti-inflammatory intervention. Eur. J. Pharm. 2004, 500, 63–71. [CrossRef]

60. Raupach, B.; Peuschel, S.K.; Monack, D.M.; Zychlinsky, A. Caspase-1-mediated activation of interleukin-1beta (IL-1beta) and IL-18 contributes to innate immune defenses against Salmonella enterica serovar Typhimurium infection. Infect. Immun. 2006, 74, 4922–4926. [CrossRef]

61. Tang, C.; Chen, S.; Qian, H.; Huang, W. Interleukin-23: As a drug target for autoimmune inflammatory diseases. Immunology 2012, 135, 112–124. [CrossRef] [PubMed]

62. Buonocore, S.; Ahern, P.P.; Uhlig, H.H.; Ivanov, I.I.; Littman, D.R.; Maloy, K.J.; Pober, E. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. Nature 2010, 464, 1371–1375. [CrossRef] [PubMed]

63. Neurath, M.F. IL-23 in inflammatory bowel diseases and colon cancer. Cytokine Growth Factor Rev. 2004, 15, 193–207. [CrossRef] [PubMed]

64. Dinarello, C.A.; Gonzalez, P.A.; et al. Interleukin-1alpha/cachectin and murine interleukin 1alpha protects mice from lethal bacterial infection. J. Immunol. 1985, 135, 1548–1550.

65. Di Paolo, N.C.; Shaﬁani, S.; Day, T.; Papayannopoulou, T.; Russell, D.W.; Iwakura, Y.; Sherman, D.; Urdahl, K.; Shayakhmetov, D.M. Interdependence between Interleukin-1 and Tumor Necrosis Factor Regulates TNF-Dependent Control of Mycobacterium tuberculosis Infection. Immunity 2015, 43, 1125–1136. [CrossRef]

66. Cross, A.S.; Sadoff, J.C.; Kelly, N.; Berntson, E.; Gemski, P. Pretreatment with recombinant murine tumor necrosis factor alpha/cachectin and murine interleukin 1 alpha protects mice from lethal bacterial infection. J. Exp. Med. 1989, 169, 2021–2027. [CrossRef]

67. Kurt-Jones, E.A.; Kiely, J.M.; Unanue, E.R. Conditions required for expression of membrane IL 1 on human endothelial cells and dermal fibroblasts. J. Immunol. 1987, 139, 2317–2324. [PubMed]

68. Di Paolo, N.C.; Shaﬁani, S.; Day, T.; Papayannopoulou, T.; Russell, D.W.; Iwakura, Y.; Sherman, D.; Urdahl, K.; Shayakhmetov, D.M. Interdependence between Interleukin-1 and Tumor Necrosis Factor Regulates TNF-Dependent Control of Mycobacterium tuberculosis Infection. Immunity 2015, 43, 1125–1136. [CrossRef]

69. Kurt-Jones, E.A.; Fiers, W.; Pober, J.S. Membrane interleukin 1 induction on human endothelial cells and dermal fibroblasts. J. Immunol. 1987, 139, 2317–2324. [PubMed]

70. Saitoh, T.; Fujita, N.; Jang, M.H.; Uematsu, S.; Yang, B.G.; Satoh, T.; Omori, H.; Noda, T.; Yamamoto, N.; Komatsu, M.; et al. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature 2008, 456, 264–268. [CrossRef] [PubMed]
70. Plantinga, T.S.; Crisan, T.O.; Oosting, M.; van de Veerdonk, F.L.; de Jong, D.J.; Philpott, D.J.; van der Meer, J.W.; Girardin, S.E.; Joosten, L.A.; Netea, M.G. Crohn’s disease-associated ATG16L1 polymorphism modulates pro-inflammatory cytokine responses selectively upon activation of NOD2. Gut 2011, 60, 1229–1235. [CrossRef]
71. Barton, B.E.; Jackson, J.V. Protective role of interleukin 6 in the lipopolysaccharide-galactosamine septic shock model. Infect. Immun. 1993, 61, 1496–1499. [CrossRef] [PubMed]
72. Wang, L.; Srinivasan, S.; Theiss, A.L.; Merlin, D.; Sitaraman, S.V. Interleukin-6 induces keratin expression in intestinal epithelial cells: Potential role of keratin-8 in barrier function alterations. J. Biol. Chem. 2007, 282, 8219–8227. [CrossRef] [PubMed]
73. Ding, J.W.; Andersson, R.; Soltesz, V.; Willen, R.; Bengmark, S. Obstructive jaundice impairs reticuloendothelial function and promotes bacterial translocation in the rat. J. Surg. Res. 1994, 57, 238–245. [CrossRef]
74. Catron, D.M.; Sylvester, M.D.; Lange, Y.; Kadekoppala, M.; Jones, B.D.; Monack, D.M.; Falkow, S.; Haldar, K. The Salmonella-containing vacuole: Moving with the times. J. Biol. Chem. 2001, 2, 1004–1009. [CrossRef]
75. Santos, R.L.; Tsolis, R.M.; Baumler, A.J.; Adams, L.G. Pathogenesis of Salmonella-induced enteritis. Braz. J. Med. Biol. Res. 2003, 36, 3–12. [CrossRef] [PubMed]
76. Catron, D.M.; Sylvester, M.D.; Lange, Y.; Kadekoppala, M.; Jones, B.D.; Monack, D.M.; Falkow, S.; Haldar, K. The Salmonella-containing vacuole is a major site of intracellular cholesterol accumulation and recruits the GPI-anchored protein CD55. Cell Microbiol. 2002, 4, 315–328. [CrossRef]
77. Garcia-del Portillo, F.; Nunez-Hernandez, C.; Eisman, B.; Ramos-Vivas, J. Growth control in the Salmonella-containing vacuole. Curr. Opin. Microbiol. 2008, 11, 46–52. [CrossRef] [PubMed]
78. Steele-Mortimer, O. The Salmonella-containing vacuole: Moving with the times. Curr. Opin. Microbiol. 2008, 11, 38–45. [CrossRef]
79. Huang, F.C. De Novo sphingolipid synthesis is essential for Salmonella-induced autophagy and human beta-defensin 2 expression in intestinal epithelial cells. Gut Pathog. 2016, 8, 5. [CrossRef]
80. Kim, M.N.; Koh, S.J.; Kim, J.M.; Im, J.P.; Jung, H.C.; Kim, J.S. Clostridium difficile infection aggravates colitis in interleukin 10-deficient mice. World J. Gastroenterol. 2014, 20, 17084–17091. [CrossRef]
81. Iyer, S.S.; Cheng, G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit. Rev. Immunol. 2012, 32, 23–63. [CrossRef] [PubMed]
82. Castro-Eguiluz, D.; Pelayo, R.; Rosales-Garcia, V.; Rosales-Reyes, R.; Alpuce-Aranda, C.; Ortiz-Navarrete, V. B cell precursors are targets for Salmonella infection. Microb. Pathog. 2009, 47, 52–56. [CrossRef] [PubMed]
83. Brigl, M.; Bry, L.; Kent, S.C.; Gumperz, J.E.; Brenner, M.B. Mechanism of CD1d-restricted natural killer T cell activation during microbial infection. Nat. Immunol. 2003, 4, 1230–1237. [CrossRef] [PubMed]
84. O’Shea, J.J.; Paul, W.E. Regulation of T(H)1 differentiation—controlling the controllers. Nat. Immunol. 2002, 3, 506–508. [CrossRef]
85. Ramirez-Alejo, N.; Santos-Argumedo, L. Innate defects of the IL-12/IFN-gamma axis in susceptibility to infections by mycobacteria and salmonella. J. Interferon. Cytokine Res. 2014, 34, 307–317. [CrossRef]
86. Jabri, B.; Abadie, V. IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction. Nat. Rev. Immunol. 2015, 15, 771–783. [CrossRef] [PubMed]
87. Fehniger, T.A.; Caligiuri, M.A. Interleukin 15: Biology and relevance to human disease. Blood 2001, 97, 14–32. [CrossRef]
88. Iacomino, G.; Rotondi Aufiero, V.; Iannaccone, N.; Melina, R.; Giardullo, N.; De Chiara, G.; Venezia, A.; Taccone, F.S.; Iaquinto, G.; Mazzarella, G. IBD: Role of intestinal compartments in the mucosal immune response. Immunobiology 2019, 225, 151849. [CrossRef]
89. Pham, T.A.; Clare, S.; Goulding, D.; Arasteh, J.M.; Stares, M.D.; Browne, H.P.; Keane, J.A.; Page, A.J.; Kumasaka, N.; Kane, L.; et al. Epithelial IL-22RA1-mediated fucosylation promotes intestinal colonization resistance to an opportunistic pathogen. Cell Host Microbe 2014, 16, 504–516. [CrossRef]
90. Behnsen, J.; Jellbauer, S.; Wong, C.P.; Edwards, R.A.; George, M.D.; Ouyang, W.; Raffatellu, M. The cytokine IL-22 promotes pathogen colonization by suppressing related commensal bacteria. Immunity 2014, 40, 262–273. [CrossRef]
91. Dennehy, K.M.; Willment, J.A.; Williams, D.L.; Brown, G.D. Reciprocal regulation of IL-23 and IL-12 following co-activation of Dectin-1 and TLR signaling pathways. Eur. J. Immunol. 2009, 39, 1379–1386. [CrossRef] [PubMed]
92. Stark, M.A.; Huo, Y.; Burcin, T.L.; Morris, M.A.; Olson, T.S.; Ley, K. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity 2005, 22, 285–294. [CrossRef] [PubMed]
93. van de Wetering, D.; de Paus, R.A.; van Dissel, J.T.; van de Vosse, E. Salmonella induced IL-23 and IL-1beta allow for IL-12 production by monocytes and Mphi1 through induction of IFN-gamma in CD56 NK/NK-like T cells. PLoS ONE 2009, 4, e8396. [CrossRef] [PubMed]
94. Villarino, A.V.; Hunter, C.A. Biology of recently discovered cytokines: Discerning the pro- and anti-inflammatory properties of interleukin-27. Arthritis Res. 2004, 6, 225–233. [CrossRef]
97. Huang, F.C.; Huang, S.C. Differential Effects of Statins on Inflammatory Interleukin-8 and Antimicrobial Peptide Human Beta-Defensin 2 Responses in Salmonella-Infected Intestinal Epithelial Cells. *Int. J. Mol. Sci.* 2018, 19, 1650. [CrossRef] [PubMed]

98. Huang, F.C.; Huang, S.C. The Combined Beneficial Effects of Postbiotic Butyrate on Active Vitamin D3-Orchestrated Innate Immunity to Salmonella Colitis. *Biomedicines* 2021, 9, 1296. [CrossRef] [PubMed]

99. Huang, F.C.; Huang, S.C. The Cooperation of Bifidobacterium longum and Active Vitamin D3 on Innate Immunity in Salmonella Colitis Mice via Vitamin D Receptor. *Microorganisms* 2021, 9, 1804. [CrossRef] [PubMed]