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REVIEW

Salmonella, the host and disease: a brief review

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***Salmonella* species cause substantial morbidity, mortality and burden of disease globally. Infections with *Salmonella* species cause multiple clinical syndromes. Central to the pathophysiology of all human salmonelloses is the induction of a strong host innate immune/inflammatory response. Whether this ultimately reflects an adaptive advantage to the host or pathogen is not clear. However, it is evident that both the host and pathogen have evolved mechanisms of triggering host responses that are detrimental to the other. In this review, we explore some of the host and pathogenic mechanisms mobilized in the two predominant clinical syndromes associated with infection with *Salmonella enterica* species: enterocolitis and typhoid.**
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Salmonella enterica (*S. enterica*) is a Gram-negative facultative intracellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of *S. enterica* have been identified belonging to six subspecies.[1,2] Subspecies are further subdivided into serovars that are differentiated by their flagellar, carbohydrate and lipopolysaccharide (LPS) structures. *S. enterica* species are typically orally acquired pathogens that cause one of four major syndromes: enteric fever (typhoid), enterocolitis/diarrhea, bacteremia and chronic asymptomatic carriage. The disease manifestation depends on both host susceptibility and the infectious *S. enterica* serovar.[2] In humans, serovars Typhi, Paratyphi and Sendai cause enteric fever, while most serovars cause enterocolitis/diarrhea. Several serovars including Choleraesuis and Dublin are more commonly associated with bacteremia in humans.[2] While serovar Typhi is largely restricted to humans, other serovars are more broadly host adapted and cause natural animal infection. Serovars Dublin, Typhimurium and Choleraesuis cause disease in both humans and animals, but cause distinct syndromes in different hosts. Serovar Dublin causes intestinal inflammatory disease, bacteremia and abortion in cows; serovar Typhimurium causes a typhoid-like systemic illness in mice; and serovar Choleraesuis causes septicemia in pigs.[3] Human typhoid fever and intestinal/diarrheal disease represent the most common syndromes associated with *S. enterica* infection and involve the pathogenic processes of both bacteria and host most thoroughly investigated in infectious models of *Salmonella* pathogenesis. Significant inflammatory disease is a common feature of typhoid and enterocolitis. The various virulence programs employed by *Salmonella* species interact with host defense mechanisms at various tissues in different stages of infection resulting in significant host immunopathology, morbidity and mortality.

TYPHOID

Human typhoid occurs following the ingestion of *S. enterica* serovar Typhi bacteria, usually from contaminated water or animal products or close contact with an infected individual or carrier.[4] Much of the understanding of typhoid pathogenesis has arisen from the study of infection of susceptible mice with *S. enterica* serovar Typhimurium. In this model, following oral inoculation, virulent serovar Typhimurium survives gastric acidity and colonizes the ileum and cecum, likely by out-competing the resident microflora.[5,6] Via invasion of the phagocytic epithelial M-cells covering Peyer's patches (PP), as well as through uptake by dendritic cells (DCs), bacteria are translocated across the intestinal epithelium and gain access to the host circulation or are carried from the gut within CD18 expressing phagocytes.[7–9] Upon extraintestinal infection, bacteria disseminate via the reticuloendothelial system (RES) and take up residence in granulomatous foci within various splenocytes, predominantly macrophages, DCs and polymorphonuclear leukocytes (PMNs), as well as hepatocytes and other non-professional phagocytes in the liver.[10–12] In the absence of intestinal infection, intracellular replication and survival may be considered the central virulence features of typhoid. Upon translocation to systemic sites, or upon inoculation of the bacteria into the peritoneal cavity, survival of phagocytic killing is an essential component of bacterial virulence. Fields *et al.*[13] demonstrated that bacterial survival within phagocytes was essential for virulence. *Salmonella* is capable of infecting a wide variety of cells including DCs, macrophages, hepatocytes, neutrophils, colonocytes and other epithelial cells. *In vitro*, within minutes of contact with cells, *Salmonella* are internalized and take up residence in a unique membrane-bound compartment distinct from a phagosome or lysosome, termed the *Salmonella* containing vacuole (SCV).[14–16] Within phagocytes, *Salmo-*

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nella SCV formation has the important function of evading endosomal fusion with the phagocyte oxidase complex.[17]

In humans, typhoid disease manifests one to 2 weeks following bacterial inoculation with generalized fever and malaise, abdominal pain with or without other symptoms including headache, myalgias, nausea, anorexia and constipation. Diarrhea occurs occasionally but is typical only of infection in the immunocompromised. Hepatosplenomegaly is common but not present in all cases and diffuse abdominal tenderness is usual. Fever is typically mild at first and worsening as disease progresses (reviewed by Parry *et al.*[18]). In the absence of complications, disease resolves following varied periods of infection although carriage of the bacteria can continue in post-symptomatic patients for months or years and relapse occurs in a minority of patients. The primary treatment for serovar Typhi infection is fluoroquinolones, although nalidixic acid and other antimicrobial agents are also used. Treatment is effective in the vast majority of cases and decreases time to bacterial clearance, carriage rates and infection-associated morbidity and mortality.[18]

ENTEROCOLITIS AND DIARRHEA

Although estimates vary greatly due to a lack of consistent diagnosis and reporting, between 200 million and 1.3 billion cases of intestinal disease including 3 million deaths due to non-typhoidal *Salmonella* are estimated to occur each year worldwide.[19] Like typhoid, the incidence of intestinal disease caused by non-typhoidal *Salmonella* species is highest in the developing world, but is also of considerable importance in developed countries. Until the development of a new murine model of *Salmonella* enteropathogenesis,[20] the study of intestinal disease was largely restricted to the study of bovine ileal loop inoculations and oral infections and cultured intestinal epithelial cells.

In animal models, upon colonization of the intestine by virulent *S. enterica*, bacteria localize to the apical epithelium, induce invasion-associated virulence machinery and elicit significant inflammatory changes including focal and diffuse PMN infiltrate, crypt abscesses, epithelial necrosis, edema and fluid secretion.[21–24] Human, bovine, murine and rabbit serovar Typhimurium enterocolitis is most severe in the caudal ileum, the cecum and the proximal colon. Neutrophil recruitment to intestinal epithelium is the histopathological hallmark of intestinal disease. *In vitro*, PMN recruitment to cultured epithelial monolayers occurs via the induction of interleukin-8 (IL-8) by *Salmonella* proximate to the apical epithelium.[25] The ability of various *S. enterica* strains to cause human intestinal disease correlated to their ability to attract PMNs across T84 cell monolayers, notably without requiring epithelial invasion.[26] While neutrophil recruitment by serovar Typhimurium occurs within the first 1–3 h of infection, massive neutrophil migration and the secretion of protein-rich exudates into the intestinal lumen do not occur until 8–10 h following infection and diarrhea begins approximately 8–72 h after bacterial colonization.[27,28] Both the temporal separation of inflammation and secretory diarrhea and other evidence indicating that *Salmonella* in different growth stages show differential induction of inflammation vs secretory responses[29] suggest that, although perhaps related, diarrhea and inflammation occur independently in enteropathogenesis.

Disease in humans typically follows the ingestion of greater than 50 000 bacteria in contaminated food or water with symptoms occurring between 6 and 72 h after consumption. Onset of symptoms is marked by acute onset, crampy, abdominal pain and diarrhea with or without blood. Nausea and vomiting are also common. Commonly a disease of the ileum, inflammation in non-typhoidal disease also occurs in the large bowel, with rare infections in the jejunum, duodenum and stomach.[21,30] Enterocolitic infection in children is marked by increased inflammatory severity, bloody diarrhea and increased duration of infection and risk of complication.

In the absence of treatment for gut-limited infections, symptoms usually last between 5–7 days and resolve spontaneously. Treatment of fluid and electrolyte imbalances by oral or intravenous rehydration is necessary in cases where fluid loss is substantial. In adults, specific antimicrobial therapy is indicated only in the presence of positive signs of invasive disease, and does not decrease the duration of illness or the severity of symptoms. Neonatal gut infection also requires treatment to prevent invasion.

SALMONELLA VIRULENCE DETERMINANTS IN IMMUNE ACTIVATION

Using cell culture and animal models of *Salmonella* infection, multiple virulence determinants critical for the induction of inflammatory/immune responses in infected hosts have been identified. Proinflammatory stimuli during *Salmonella* infection may be broadly considered as representative of two categories: pathogen-associated motifs that are capable of stimulating innate immunity; and virulence-associated proinflammatory behaviors that coopt or exploit host processes resulting in disease pathology. Of critical importance for *in vivo* virulence are the *Salmonella* pathogenicity islands (SPI), in particular SPI-1 and -2. Both SPIs encode a molecular apparatus called a type III secretion system (T3SS) capable of injecting bacterial proteins known as 'effectors' through bacterial and host membranes into host cells (translocation) or the extracellular milieu (secretion) to directly influence host biochemistry and cell physiology.

SPI-1 AND INFLAMMATION

In 1989, Galan and Curtiss[31] identified *Salmonella* genes essential for bacterial invasiveness in cell culture and complete oral virulence that were later shown to be part of a horizontally acquired pathogenicity island, SPI-1.[32] Although initially characterized as an invasiveness island, SPI-1 has additional functions related to the activation of innate immune pathways. SPI-1-dependent inflammation appears to reflect multiple processes: (1) the induction of PMN recruitment across intestinal epithelia by the SPI-1 secreted effector SipA; (2) the activation of NF-κB signaling by the concerted activity of SPI-1-translocated effectors, and; (3) the activation of caspase-1-mediated IL-1β/IL-18 activation and proinflammatory cell death by the SPI-1-translocated effector SipB.

SIPA AND NEUTROPHIL RECRUITMENT

The recruitment of neutrophils to and across cultured epithelial monolayers requires production of IL-8 and pathogen elicited epithelial chemoattractant (PEEC) and the SPI-1 effector SipA.[33–35] Secretion or direct addition of purified SipA within the vicinity of intestinal epithelial monolayers induces the production of PEEC and the consequent recruitment and activation of basolateral neutrophils to the apical epithelial membrane.

SIPB AND 'PYROPTOSIS'

The SPI-1 effector and translocase SipB is also critical for inflammatory disease *in vivo*,[36] and *in vitro* is required for the induction of specific inflammatory cascades.[37] Upon host cell contact, the SPI-1 T3SS translocates SipB into the host cell cytosol, where it binds caspase-1 (IL-1β-converting enzyme) resulting in the catalytic cleavage and release of the proinflammatory cytokines IL-1β and IL-18.[37] This also induces a rapid proinflammatory cell death that has features of both apoptosis and necrosis and has been termed 'pyroptosis' due to its proinflammatory nature. Studies of the importance of caspase-1 activation in model

infections have yielded conflicting results[38,39] suggesting alternately that SPI-1-mediated activation of caspase-1 was necessary for efficient translocation of bacteria from the intestinal lumen to systemic sites during murine typhoid pathogenesis,[38] and that caspase-1-deficient mice had increased susceptibility to intestinal infection with *Salmonella*.[39] The use of congenic mice, and the corroborative evidence in the latter study indicating that both caspase-1- and Ipaf-deficient mice were more susceptible to murine typhoid suggest that caspase-1 plays a protective proinflammatory role in infection.

SPI-1 EFFECTORS AND NF-κB SIGNALING

Salmonella SPI-1 T3S results in activation of mitogen-associated protein kinases (MAPKs) resulting in the induction of NF-κB.[40,41] This requires the activation of Cdc42 and downstream MAPK signaling by the SPI-1 effector SopE.[42] Interestingly, it is the coordinated activity of the SPI-1 effectors SipA, SopB, SopD and SopE/E2 that induce bacterial uptake by activating intracellular signaling cascades and cytoskeletal machinery. Subsequent to the activation of this important proinflammatory cascade, another SPI-1 effector, SptP antagonizes this pathway, resulting in a significant but transient SPI-1-dependent activation of NF-κB signaling.[43] *In vivo*, this combination of effectors are essential for early inflammatory pathogenesis in mice and cows, explaining in part the overlap between intestinal invasiveness and inflammatory pathogenicity in some models of infection.[44–53]

In vivo, SPI-1-mediated behaviors seem to be critical for early intestinal inflammation,[54–56] yet their absence does not influence systemic inflammation following intraperitoneal challenge,[31] and delayed intestinal inflammation occurs in their absence.[57,58] Interestingly, although incapable of inducing PEEC-mediated transmigration of neutrophils across model epithelia, comparison of the inflammatory gene expression profiles of cultured intestinal epithelial monolayers infected with wild-type serovar Typhimurium or those with a complete deletion of the SPI-1 pathogenicity island demonstrated little difference in the proinflammatory potential of these strains.[59] It is apparent therefore that additional factors operating independently of SPI-1 are sufficient to induce inflammatory disease.

SPI-2

The SPI-2 pathogenicity island is essential for intracellular parasitism and systemic virulence in murine typhoid[60–62] and is essential for evasion of the phagocyte oxidase machinery of the host.[17] Recently, roles for the SPI-2 T3SS have been identified in inflammatory disease as well, indicating that SPI-2 is critical for early and complete induction of *Salmonella* enterocolitis,[57,63,65] as well as systemic disease. Although the proinflammatory activity of SPI-2 is less well described, several interesting candidates have been identified as potential pathways of SPI-2-mediated immune agonism.

Intestinal inflammation induced in the absence of SPI-1 in mice requires the Toll-like receptor (TLR) adapter MyD88.[64] Although the specific role of SPI-2 in TLR-mediated activation has not been elucidated, it may in part depend on the delivery of other proinflammatory motifs to the appropriate compartment of the intestine, for example, the subepithelial compartment.[66] In a series of papers, Uchiya *et al*.[67–69] also demonstrate that SPI-2 is involved in the induction of cyclooxygenase as well as the modulation of host cytokine expression and signaling.

SALMONELLA PATHOGEN-ASSOCIATED MOLECULAR PATTERNS AND IMMUNE ACTIVATION

Pattern recognition receptors (PRRs) are a crucial innate immune response system that is broadly conserved across wide evolutionary lineages. Pathogen-associated molecular patterns (PAMPs) include constituents of viral, fungal and bacterial pathogens capable of stimulating PRRs to induce immune responses. Several PAMPs of pathophysiological importance are presented by *Salmonella* during infection. Principal among these are bacterial LPS and flagellin, the monomeric subunit of the bacterial flagellar apparatus.

TLR4 AND LPS

The activation of TLR4 in response to *Salmonella* LPS is essential for inducing host responses. Mice lacking a functional TLR4 show dramatically increased susceptibility to infection, regardless of the presence of other *Salmonella* resistance loci.[70–74] TLR4 is required for a complete inflammatory response to *Salmonella* LPS administered intravenously, and *Salmonella* LPS is a potent inducer of inflammatory responses in macrophages,[75,76] indicating that *Salmonella* LPS is an important inducer of sepsis during systemic infection.[77] In contrast to murine typhoid, a role for LPS in intestinal inflammatory salmonellosis has not been established. Although LPS stimulation of macrophages may be involved in intestinal disease, the absence of LPS receptor CD14 on intestinal epithelial cells makes it unlikely that the intestinal epithelium is involved in the direct response to *Salmonella* LPS.

FLAGELLIN

Salmonella flagellin is a potent inducer of host inflammation in polarized epithelial monolayers when delivered to the basolateral surface of the epithelium.[59,78] Once delivered there, *Salmonella* flagellin induces IL-8 secretion via calcium-dependent NF-κB activation by stimulating basolateral TLR5.[78–81] Recently published evidence indicates that *Salmonella* flagellin can also activate inflammatory signaling intracellularly. In primary and cultured macrophages, intracellular monomeric flagellin is capable of inducing the caspase-1 activation of IL-1β and IL-18 in a manner that requires intracellular PRR signaling.[82,83] Notably, this activation occurs in the absence of TLR5 and in LPS-tolerized macrophages, indicating that it does not require TLR activation. *Salmonella* produce and secrete monomeric flagellin *de novo* following stimulation with intestinal epithelial culture supernatants,[84] suggesting a sequence in which *Salmonella* detect host cells, produce flagellin and translocate it into host cell cytosol via the SPI-1 T3SS.

Flagellin stimulation of innate immune responses is critical for intestinal inflammation, but not for murine typhoid. In a model of murine intestinal inflammation, flagellar *Salmonella* mutants cause attenuated early intestinal disease.[85] Interestingly, the proinflammatory potential of flagellin at least partly requires its SPI-2-dependent translocation to the basolateral membrane of the intestinal epithelium.[86]

SPIS AND THE DELIVERY OF FLAGELLIN

Although capable of inducing intestinal inflammatory responses discretely in intestinal epithelial monolayers, SPI-1 and -2 and PAMP delivery seem intertwined. The proinflammatory capability of *Salmonella* flagellin monomers depends both on SPI-1 and -2. The ability of monomeric flagellin to induce caspase-1 activation requires a functional SPI-1 T3SS.[83] Furthermore, while the transcytosis of flagellin occurs within 15 min of contact with intestinal epithelium and does not require bacterial internalization,[78] it does require SPI-2 T3SS,[86] and, as noted, SPI-2-dependent SPI-1-independent inflammation requires the presence of the TLR signaling adapter MyD88.[87] These data suggest the interesting possibility that SPI-1 and SPI-2 represent PAMP-delivery systems during *in vivo* pathogenesis of

Salmonella immune activation, accounting for some component of their functions as virulence factors.

CYTOKINES IN SALMONELLA INFECTIONS

Multiple proinflammatory pathways are clearly involved in *Salmonella* immune activation. Data from murine and bovine infections with bacterial strains lacking a variety of virulence strategies substantiate this observation *in vivo*. However, bacterial virulence programs are not solely responsible for the immunopathology of typhoid or enterocolitis, as the disease manifestations represent an interaction between host and pathogen. Critical to the development of disease is the host signaling milieu induced by contact between microbe and host cells in various tissues, largely mediated by cytokine signaling.

Cytokines play a crucial role in initiating and regulating the innate and adaptive immune response against *Salmonella*. The right balance between pro- and anti-inflammatory cytokines is essential to control infections and to avoid damage to the host. Cytokines are expressed by many different cell types and they act on various cells. Experiments in tissue culture, bone marrow derived or primary cells demonstrate that *Salmonella* can trigger the synthesis of cytokines and chemokines in epithelial cells,[88] macrophages[89,90] and DCs.[91–93] The consequences of cytokine activation vary. While interferon (IFN)-γ, IL-12, tumor necrosis factor (TNF)-α, IL-18, transforming growth factor -β and CCL2 have protective functions during *Salmonella* infection, IL-4 and IL-10 interfere with host defenses (reviewed by Eckmann and Kagnoff[94]).

HUMAN CYTOKINE ABNORMALITIES AND SUSCEPTIBILITY TO SALMONELLA

A variety of cytokine abnormalities contribute to susceptibility to *Salmonella* infections in humans. Genetic deficiencies in the type I cytokine pathway (IFN-γ/IL-12/IL-23) result in increased susceptibility to infection with intracellular pathogens such as *Salmonella* and *Mycobacteria*.[95,96] Non-typhoidal *Salmonella* serovars can cause severe extraintestinal disease in patients with these abnormalities. IL-12, produced by antigen presenting cells (APC) such as macrophages and DCs, induces the production of IFN-γ by natural killer (NK) cells and T cells which in turn further upregulates IL-12 production in APC. IFN-γ then enhances antimicrobial activity in macrophages, NK cells and neutrophils, although this role in *Salmonella* infection may not be critical for control of infection. Deficiencies in IL-12b, the common p40 subunit of IL-12 and IL-23, and IL-12Rβ1 which is the common receptor subunit for IL-12 and IL-23, result in susceptibility to *Salmonella*. In contrast patients with deficiencies in IFN-γR1 or IFN-γR2 are frequently infected with *Mycobacteria* but less frequently with *Salmonella*.[97–101] Thus, it seems that IL-12/IL-23 exert protective effects against infection with *Salmonella* independently of induction of IFN-γ. A possible IFN-γ-independent mechanism could be the upregulation of TNF-α, granulocyte–macrophage colony-stimulating factor and IL-17 by IL-23 leading to enhanced bacterial killing and enhanced nitric oxide (NO) production in macrophages, respectively.

MURINE CYTOKINES IN CONTROL OF SALMONELLA INFECTION

In mice, the first cells encountered by *Salmonella* are intestinal epithelial cells, DCs and macrophages. Interaction with these cells leads to the synthesis of proinflammatory cytokines and chemokines leading to a massive influx of neutrophils, macrophages and immature DCs. IFN-γ, TNF-α and IL-12 have been well demonstrated to be crucial for resistance to *Salmonella*. IFN-γ is important for control of bacterial replication in the early phase of infection,[102] but is not sufficient for eradication of bacteria.[103] TNF-α enhances microbicidal activity synergistically with IFN-γ and triggers the production of NO.[104] Neutralization of IFN-γ results in decreased killing of *Salmonella* whereas neutralization of TNF-α results in a increased bacterial replication.[105]

IFN-γ production is rapidly upregulated in gut-associated lymphoid tissue (GALT) and spleen by infection with serovar Typhimurium.[106,107] The main producers of IFN-γ and TNF-α in naïve *Salmonella*-infected mice appear to be macrophages and neutrophils,[108] although CD1d-restricted NKT cells also contribute to early IFN-γ production in *Salmonella* infected mice in a manner dependent on IL-12 produced by APCs.[109] T cells and NK cells only produce trace amounts of IFN-γ in a primary infection. In contrast, infection of immunized animals leads to IFN-γ production primarily by T cells and NK1.1+ cells but not by APCs.[108] Furthermore, IFN-γ has been demonstrated to control chronic infections with serovar Typhimurium. Anti-IFN-γ antibody treatment of mice carrying a chronic infection with *Salmonella* reactivates the infection and the bacterial burden in systemic sites increases.[110]

In addition, preweaned mice exhibit increased susceptibility to *Salmonella* compared to adult mice. This is due to the low expression of IFN-γ in these mice. IFN-γ is upregulated in 6-week-old mice compared to young animals during enterocolitic infection, and intestinal inflammatory disease in preweaned animals results in higher bacterial load in the spleen and lower TNF-α, similar to an infection of IFN-$\gamma^{-/-}$ mice.[111] Thus, IFN-γ is important in animal models of both typhoid and enterocolitis. As is clear from the data of human patients IL-12 is important to control *Salmonella* infections.[112] This may relate to IFN-γ function, as IL-12 is a potent activator of IFN-γ production. However, it may also be in part due to IFN-γ independent IL-23-mediated effects as discussed above. IL-12p35−/− mice are more resistant than IL-12p40−/− mice to infection with serovar Typhimurium or serovar Enteritidis as IL-12p40−/− have higher bacterial burdens and decreased serum cytokine levels of IFN-γ and TNF-α.[113] IL-18 contributes to IL-12 induced IFN-γ in *Salmonella* infected mice and anti IL-18 treatment diminishes IFN-γ levels in PP late in infection and survival time.[114,115]

Cytokine and chemokine production may not only have beneficial but also pathological consequences for the host. Chemokines such as MCP-1, CCL2, CCL20 and CCL3 have protective roles in *Salmonella* infections (119, 120) but may also lead to tissue destruction by triggering a massive influx of inflammatory cells into infected organs.

Inflammation in any host is a heterogeneous process and is the culmination of the activation of numerous complex and interacting proinflammatory cascades that are collectively influenced by host and pathogenic behaviors. A double-edged sword, inflammation is the strategy by which the host controls infection, the Trojan horse by which some pathogens gain influence over host physiology and ultimately the cause of death for either the pathogen or host in all acute infections. Clearly, during infection with *Salmonella enterica* species, both host and bacteria provide powerful stimuli to host innate immune/inflammatory responses.

Salmonella contains multiple virulence mechanisms that, when activated, result in the induction of an inflammatory response within the host. Newly discovered roles for SPIs 1 and 2 in activation of innate immunity and inflammation in human cells and animal models demonstrate that these bacteria have evolved specific mechanisms to elicit a dramatic host response. While the role of some SPI-1 behaviors in innate immune activation has been well established, newly discovered pathways – such as the SPI-1 dependent delivery of PAMPs to intracellular pattern-recognition receptors – also clearly represent

critical steps in the etiopathogenesis of *Salmonella*-induced disease. Recently described roles for SPI-2 in intestinal inflammatory disease suggest that *Salmonella* employs multiple, parallel systems of innate immune activation in order to effect a specific series of inflammatory changes. These behaviors have evolved despite the obvious potential antibacterial effects of the host response induced, suggesting that they confer some adaptive advantage upon the bacteria, perhaps creating a new host environment more susceptible to invasion, or cause the recruitment of cells critical for dissemination of bacteria to systemic organs, and consequent retransmission into the environment.

Similarly, hosts susceptible to *Salmonella* infection mobilize responses that are necessary for effective control of infection. The activation of cytokine responses, or the presence of critical host resistance factors such as TLR4, Nramp1 or phagocyte oxidase, are essential for a cogent and effective immune response to *Salmonella*. In their absence, experimental infections with bacteria are almost always fatal. Yet, it is because of the induction of many of these responses that the clinical sequelae of *Salmonella* infection, such as sepsis, septic shock and inflammation, occur.

As new pathways are investigated in which *Salmonella* and hosts interact to produce innate and adaptive immune dysfunction, the pathophysiology of this important disease will come to be better understood. While judicious use of antimicrobials may represent the backbone of treatment for *Salmonella* infections, the use of immunomodulatory agents have the potential to selectively enhance the host's ability to control infection, without the risk of developing antibiotic resistance. Furthermore, identifying bacterial factors that are critical for inducing disease vs bacterial colonization suggests bacterial targets for the generation of more effective vaccines.

Whether inflammation favors the host or the bacteria may depend not only on the severity but also the nature of the inflammatory response. Using multiple interacting virulence strategies, infection with various *Salmonella* species and serovars results in significant immune activation and consequent morbidity and mortality. Host responses, while clearly critical for control of infection, can also contribute to the nature and severity of the immunopathology. While the ultimate outcome of this competition may favor the host or bacteria in ways we do not yet understand, it is clear that an understanding of these competing forces represents an important step in developing novel approaches to prophylaxis and therapy for *Salmonella* infection.

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