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Review

Salmonella infection: Interplay between the bacteria and host immune system

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ABSTRACT

Salmonella infection causes morbidity and mortality throughout the world with the host immune response varying depending on whether the infection is acute and limited, or systemic and chronic. Additionally, *Salmonella* bacteria have evolved multiple mechanisms to avoid or subvert immunity to its own benefit and often the anatomical location of infection plays a role in both the immune response and bacterial fate. Here, we provide an overview of the interplay between the immune system and *Salmonella*, while discussing how different host and bacterial factors influence the outcome of infection.

1. Overview of *Salmonella* infection

Organisms belonging to the *Salmonella* genus are flagellated rod-shaped Gram-negative facultative anaerobes. Within the *Salmonella* genus, *Salmonella enterica* is further subdivided into six-subspecies with at least 2500 serotypes that are distinguished by variations in O (somatic) and H (flagellar) antigens. Approximately 99% of the *Salmonella* strains that cause infection in humans or other mammals belong to the *Salmonella enterica* species. The three major diseases caused by *Salmonella* in humans are non-invasive non-typhoidal salmonellosis, invasive non-typhoidal salmonellosis, and typhoid fever (including paratyphoid fever), all of which are described in greater detail below (Fig. 1).

1.1. Non-invasive, non-Typhoidal Salmonellosis

Nontyphoidal salmonellosis (NTS) refers to any illnesses caused to humans by all serotypes of *Salmonella,* except for the distinct typhoidal serotypes: Typhi and Paratyphi A-C. Salmonellosis is an acute, gastroenteritis, typically acquired orally through contaminated water or comestibles. Annually, there are an estimated 1.3 billion cases of *Salmonella* gastroenteritis, leading to approximately 3 million deaths worldwide [1]. It is among the most commonly isolated foodborne pathogens associated with fresh fruits and vegetables such as apples, cantaloupes, alfalfa sprouts, mangos, lettuce, cilantro, tomatoes, melons, orange juice, celery and parsley [1]. The incidence of NTS gastroenteritis is highest in the developing world, but is also of considerable importance in developed countries [2].

Salmonellosis is characterized by acute enterocolitis, which is accompanied by inflammatory diarrhea, a symptom rarely observed in individuals infected with invasive serovars (i.e. *S.* Typhi). Infection occurs after ingestion of > 50,000 bacteria in contaminated food or water, with symptoms typically occurring 6–72 h after consumption. Onset of symptoms is marked by abdominal pain and diarrhea with or without blood, while nausea and vomiting are also common. Typically, the gastroenteritis will resolve itself in 5–7 days without need for treatment although symptoms are usually more severe and longer lasting in children [3]; however, in cases were fluid loss is substantial, oral or intravenous rehydration may be necessary. In adults, antibiotics are usually contraindicated unless there is evidence of invasive disease (i.e. bacteremia), as antibiotics are unlikely to lessen the duration of illness or decrease the severity of symptoms [2,4,5] and have the potential to increase bacterial antibiotic resistance. Notably, individuals can continue to shed bacteria and infect others even after they no longer exhibit symptoms. On average, non-typhoidal serotypes persist in the intestinal tract from 6 weeks to 3 months, depending on the serotype, but approximately one person in a thousand will continue to shed *Salmonella* in their feces for periods exceeding 1 year [6]. Despite the growing morbidity of NTS infections, mortality due to *Salmonella* gastroenteritis is predominantly restricted to the developing world. This may be due in part to lack of clean water supplies and adequate sanitation [7]. In addition, reduced healthcare infrastructure may play a role, as appropriate diagnosis could be delayed and antibiotic resistant strains might go unidentified. Lastly, there are no vaccines against non-

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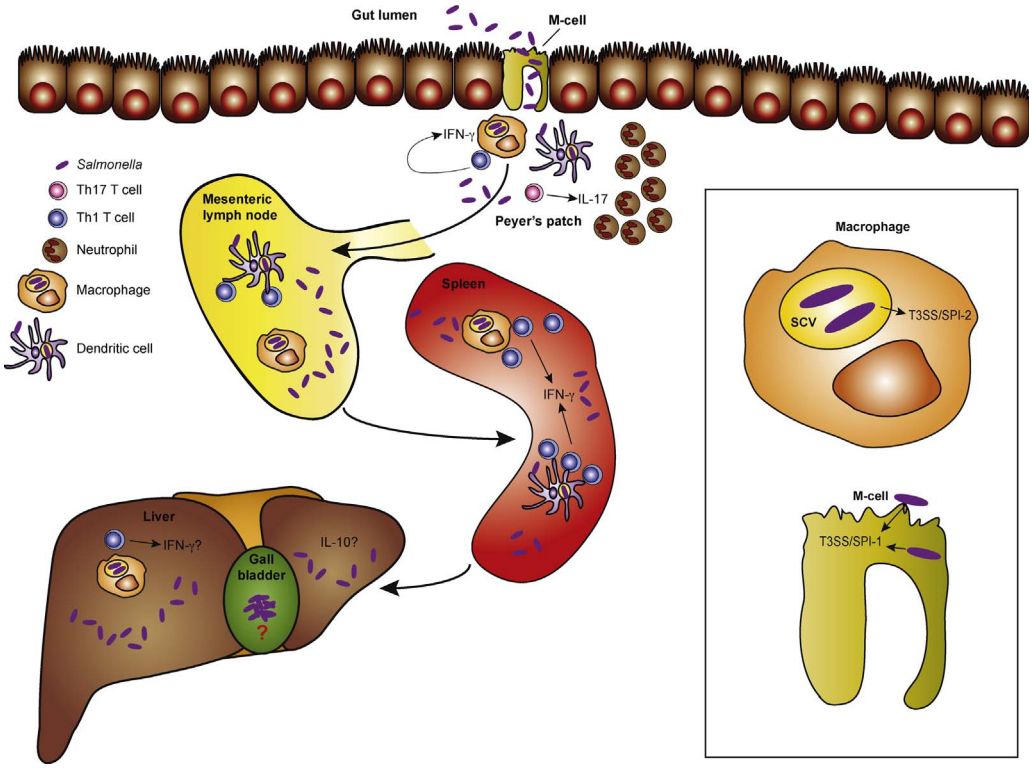

Fig. 1. Overview of the immune response to *Salmonella* infection.
Salmonella bacteria enter via the intestine and use the T3SS/SPI-1 to induce uptake by the specialized M cells of the gut. Following translocation into the Peyer's patches, *Salmonella* are engulfed by phagocytic cells such as macrophages, neutrophils monocytes, and DCs. Bacterial antigens are transported by DCs to the gut-draining MLNs where *Salmonella*-specific T cells are activated and traffic back to the intestine. These IFN-γ producing Th1 cells further activate macrophages, while IL-17 producing Th17 cells recruit large numbers of neutrophils to combat infection. *Salmonella* use the T3SS/SPI-2 to inject effector proteins from within the SCV to modulate the immune response, such as preventing DC migration to lymph nodes. Th1 cells in the MLNs and spleen continue to activate antimicrobial macrophages to combat systemic infection in these organs. The liver is also colonized with bacteria and while it is possible that Th1 cells are important here, far less is known about the liver immune response to *Salmonella* infection; however, it is known that the liver tends towards an immunosuppressive, tolerant phenotype. *Salmonella* also infects the gallbladder where bacteria are known to persist as biofilms attached to gallstones. Almost nothing is known about the anti-*Salmonella* response in the gallbladder. Abbreviations: T3SS, type three secretion system; SPI, *Salmonella* pathogenicity island; DC, dendritic cell; MLN, mesenteric lymph node; Th, T helper; IFN, interferon; IL, interleukin; SCV, *Salmonella* containing vacuole.

typhoidal *Salmonella* strains, possibly due to the fact that there is a large variance between strains and an incomplete knowledge of protective antigens. This is of particular concern for invasive non-typhoidal strains of *Salmonella*, discussed below.

1.2. Invasive non-Typhoidal Salmonellosis

In sub-Saharan Africa, an emerging *Salmonella* strain is evolving and has a unique pathogenesis, in comparison to its genetic counterparts. This emerging pathogen has been termed invasive non-typhoidal *Salmonella* (iNTS). Like non-invasive NTS, the *Salmonella* serotypes most commonly associated with iNTS are *S.* Typhimurium and *S.* Enteritidis; however, other serotypes such as Choleraesuis and Dublin are also known to cause invasive disease in humans [8,9]. Whole-genome sequencing of invasive isolates have identified dominant regional genotypes uniquely found in Africa. These isolates, from strain ST313, have several genetic differences compared with other strains and suggest distinct genotypes of *Salmonella* have emerged as new pathogenic clades in sub-Saharan Africa, and might have adapted to cause invasive disease in humans [10]. Notably, other invasive *S.* Typhimurium ST313 strains have been found elsewhere in the world, reflecting a potentially increasing problem with this disease spreading globally [11]. iNTS strains were described commonly as a cause of bloodstream infections in African children predating the HIV epidemic [12]; however, shortly after the discovery of AIDS in Africa, more reports surfaced of children and adults with invasive non-typhoidal *Salmonella* bacteremia and the first epidemiological link between invasive *Salmonella* infection and AIDS was made in New Jersey. By 1990, iNTS had been confirmed as a common HIV-related pathogen in sub-Saharan African adults, implicating a role for helper (CD4) T cells in this disease as these cells are eliminated during HIV infection [10]. To this day, non-typhoidal *Salmonella* infections are the most common bacterial bloodstream infections isolated from both adults and children presenting with fever in sub-Saharan Africa [10].

iNTS typically presents as a febrile systemic illness where diarrhea is often absent (as compared to non-invasive NTS salmonellosis and acute gastroenteritis, where diarrhea is common). Diagnosis can be difficult without microbiological tests, because there is often clinical overlap with other bacterial or parasitic diseases, notably pneumonia and malaria [13]. Patients with iNTS frequently present with lower respiratory tract disease, commonly attributable to co-infections with other pathogens, such as *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* [14,15]. Even when treated with the appropriate antimicrobial, iNTS has a case fatality rate of 22–47% in both African adults and children [16]. The main risk factor to adults for iNTS is undoubtedly advanced HIV infection, however only about 20% of children presenting with iNTS are infected with HIV. Other risk factors to children are thought to include malnutrition, malaria, sickle-cell anemia and schistosomiasis [10]. Due to the increasing number of iNTS infections, the mortality associated with iNTS and the increasing difficulty in treating iNTS (due to the emergence of antibiotic-resistant strains), there is a medical need for vaccines with broad serovar coverage and high efficacy against systemic salmonellosis. Unfortunately, it is unknown what antigens are most protective against non-typhoidal *Salmonella* strains; however, work is ongoing to define potential immunodominant antigens [17].

1.3. Typhoid fever

Typhoid fever is caused by infection with *Salmonella* Typhi and is responsible for 21 million new cases each year leading to an estimated 200,000 deaths. The annual mortality from typhoid fever has increased by 39% between 1990 and 2010 [18]. Most cases occur in developing countries, or among travelers to these countries, and a recent analysis of global mortality data revealed that in endemic regions (such as sub-Saharan Africa and Asia), the relative years of life lost to enteric fever ranks similarly to those lost to breast cancer, prostate cancer, and leukemia in North America [19,20]. One particular difference between *S.* Typhi and NTS strains is the presence of the polysaccharide capsular antigen, Vi [21], which is thought to be a virulence factor of *S.* Typhi,

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