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Salmonella Enterica Mechanisms of Overcoming Host Acquired Immune System: A Review

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Abstract

Salmonella spp. are pathogenic Gram-negative, rod-shaped, motile bacteria belonging to the family Entero bacteriaceae. Salmonella enterica serovar Typhi (S. typhi) causes typhoid fever in humans, with an annual global burden of about 16 million cases, leading to 600 000 deaths. Following infections by Salmonella, the innate immune cells like macrophages, dendritic cells (DCs) and neutrophils engulf and destroy microorganisms while adaptive immunity is mediated via the generation of antigen-specific B and T lymphocytes, through a process of gene rearrangement resulting in the production and development of specific antibodies and killer T cell, respectively. However, Salmonella has developed molecular mechanisms to prevent the presentation of bacterial antigens that prime naive T cells and therefore avoid the initiation of the acquired immunity. Such mechanisms include; modulating phagocytosis by dendritic cells, avoiding lysosomal degradation and preventing antigen presentation to T cells. The paper reviews the concept of acquired immune and some strategies used by Salmonella to deal with the different levels of acquired immunity of the host.

Keywords: *Acquired immunity, Immune system, Lymphocyte, Salmonella.*

Introduction

Salmonella spp. are pathogenic Gram-negative, rod-shaped, motile bacteria belonging to the family Enterobacteriaceae. Salmonella enterica serovar typhi (S. typhi) causes typhoid fever in humans, with an annual global burden of about 16 million cases, leading to 600 000 deaths [1]. Salmonella spp. that can be transmitted from domestic animals to humans cause gastroenteritis and represent a serious problem for the food industry [2,3]. Salmonella can cause gastroenteritis, typhoid fever, abortion, and bacteraemia, depending on the serovar and the host. For instance, S. enterica subspecies enterica serovar typhi (S. typhi) is responsible for typhoid fever in humans, whereas S. enterica subspecies enterica serovar Typhimurium (S. Typhimurium) causes gastrointestinal inflammation in humans and a systemic typhoid-like disease in mice [4]. Salmonella is a facultative intracellular pathogen that usually resides in a modified phagolysosome known as Salmonella-containing vacuole (SCV) during host infection. However, recent data indicate that this facultative intracellular pathogen has a distinct bimodal lifestyle in epithelial cells, where, there are subpopulations of vacuolar and cytosolic Salmonella [5]. During its passage through the host, Salmonella must resist or evade multiple levels of immune defence. Many virulence genes contribute to the survival of these bacteria inside the host. Some of them are clustered in horizontally acquired genomic regions known as Salmonella pathogenicity islands (SPIs) [6]. These systems are able to inject directly into the eukaryotic host cells a number of bacterial proteins known as effectors [7]. Collectively, these virulence factors contribute to invade host cells, interfere with host cellular functions subvert immunity, establish an intracellular niche, and promote pathogen proliferation.

Salmonella

Salmonella is a bacterial genus within the Family Enterobacteriaceae that consists of a large group of genetically similar organisms with the ability to infect

a large number of animal hosts [8,9]. The majority of clinical disease in animals and humans is caused by serovars within the Salmonella enterica subspecies and this can range from local gastroenteritis to a fatal disseminated disease. The exact clinical outcome of Salmonella infection depends largely on the individual serovar involved, the infected host species and the immunological status of the individual [8,9]. Some Salmonella serovars are able to infect a wide variety of mammalian hosts and are responsible for large outbreaks of gastroenteritis in the USA associated with contaminated meat, produce or processed food [10]. In contrast, Salmonella serovars Typhi and Paratyphi have a restricted host range and cause systemic disease in humans that can often be fatal [11]. Salmonella serovars that routinely cause gastroenteritis are also able to cause systemic disease in individuals with a primary or acquired immune deficiency. Indeed, Salmonella bacteremia is an emerging problem in Sub-Saharan Africa where it is associated with HIV, malaria or poor nutritional status [12]. Thus, a variety of Salmonella serovars are responsible for a wide range of disease in developed and developing nations.

Pathogenesis of Salmonella Infection

Humans are typically infected with Salmonella after consuming food or drinking water contaminated with bacteria and the transmission of most serovars uses the fecal-oral route [12]. After oral ingestion of bacteria, Salmonella invade intestinal epithelial cells in the distal ileum [14]. In particular, Salmonella can target the specialized microfold cell (M cell) population overlying lymphoid structures called Peyer's patches (PPs) [15]. Although M cells are associated with PPs, they can also be found associated with smaller lymphoid aggregates known as solitary intestinal lymphoid tissues [16] and more rarely in the complete absence of defined lymphoid structures [17]. Although Salmonella normally enter the host through PPs, they can penetrate the intestinal epithelium at other locations where M cells are present[18], and also invade other (non-M cell) epithelial cells [19,20]. The ability of Salmonella to access intestinal epithelial cells is conferred by a collection of virulence genes encoded by Salmonella Pathogenicity Island 1 (SPI-1). Proteins encoded by SPI-1 form a needle-like Type III secretion system that allows the transport of several bacterial proteins into the host cell cytosol. These proteins induce changes in the host cells such as the rearrangement of cytoskeleton and cell membrane and disconnection of epithelial cell junctions [21], facilitating Salmonella invasion [22]. After penetrating PP M cells, bacteria access the underlying structure of the lymphoid tissue which is an area rich in phagocytic cells and serves as the initial site of intracellular infection [23,24].

From the initial infection site in the PP, Salmonella can travel via the afferent lymphatics to the draining mesenteric lymph nodes (MLNs), and eventually gain access to the blood and systemic tissues via transit through efferent lymphatic vessels [25]. The transport of Salmonella from PPs to MLNs likely requires CCR7-dependent migration within CD11c+ dendritic cells and one study has reported decreased bacterial loads in the MLNs of CCR7-deficient mice [26]. However, it is also possible that free bacteria can move through lymph to MLNs without help of immune cells [27]. After dissemination to systemic tissues, Salmonella replicate in phagocytes of the spleen, liver and bone marrow. The cell types involved in the transport of Salmonella to these systemic tissues are still poorly understood. Salmonella can evade degradation in host macrophages by affecting the maturation of the phagosome and reducing the deposition of NADPH oxidase. This is achieved by a second Type III Secretion System encoded by Salmonella Pathogenicity Island 2 (SPI-2) [28,29]. In some studies, Salmonella have also been described to access dendritic cells (DCs) or CD18+ intestinal phagocytes and subsequently disseminate rapidly to the blood in the absence of lymphatic access [30]. This alternative pathway could be important for rapid dissemination of bacteria but remains incompletely understood. Thus, although Salmonella initially enters the host via the intestinal mucosa, this organism can rapidly spread to systemic tissues. Any understanding of host immunity to Salmonella infection must therefore take into account the complexity of simultaneous mucosal and systemic immune responses to invading bacteria [31]

Acquired Immunity

Acquired or adaptive immunity develops following exposure to an antigen, and is mediated by B lymphocytes (B cells), or T lymphocytes (T cells), or both, having specific surface receptor for the same antigen [32]. T cells are two types: The CD4 T cells or helper T (Th) cells and CD8 T cells or cytotoxic T (Tc) cells which are activated upon recognition of an antigen presented by major

histocompatibility complex class II (MHC-II) and major histocompatibility complex class I (MHC-I), respectively by the TCR. While MHC-I is present on most cell surfaces, MHC-II is expressed on antigen presenting cells (APC) [33]. B-lymphocytes are able to make antibodies, specific antigen-recognition molecules, known as immunoglobulins, which deal with extracellular infections [34]. T-lymphocytes are involved in the control of intracellular infections. Their receptors recognize processed antigens in association with molecules of the major histocompatibility complex (MHC). Acquire immunity, unlike natural immunity doesn't have natural barriers [35]. However, what it does is generate special chemicals, also known as antibodies that neutralize the harmful toxins produced by the pathogen. Each specific type of pathogen requires a custom chemical to neutralize it [33]. The major cells of acquired immunity are B Lymphocytes and B Lymphocytes. Also, acquired immunity of our body has some really surprisingly unique features. They are:

Specificity

Our body has the ability to recognize and differentiate various pathogens. It has a specific action for each type of pathogen. So, it is actually able to differentiate between different types of bacteria, whether it is harmful or not, and able to determine the best way to eliminate it.

Diversity

It can recognize a huge variety of micro-organisms from protozoa to advanced viruses.

Discrimination between Self and Non-Self

It is able to tell apart the cells from our own body and other foreign particles or foreign cells. So after a transplant, patients usually have to take anti-rejection pills so that the body doesn't reject the transplanted tissue. However, this does not hold true for blood transplant

Memory

Our immune system remembers each and every immunological encounter in our body. What this means is, once our body is invaded by a pathogen, it creates a specific response to that germ and eliminates it. It also remembers somehow this experience of fighting and the specific antibodies that are effective in destroying or eliminating the pathogen, so that the next time it enters, our body precisely knows the best possible way to immediately eliminate it [36].

Antigen Recognition by Acquired Immunity

B and T cells recognize and bind antigens or epitopes which are specific sites on antigen by their specific antigen-binding surface receptors. Antigen specific receptor on B cells is IgM monomer [37]. B cells recognize and bind the antigen directly with its specific receptor IgM. Antigen specific receptor on T cells is TCR (T cell receptor). TCR of T cells recognize and bind the antigen only in association with MHC (major histocompatibility complex). TCR of CD4 helper T cell (Th cell) binds peptide antigen in association with class II MHC protein which appear on the surface of antigen presenting cell (APC), e.g. macrophage. This is the essential first step in activation of most immune responses. TCR of CD8 cytotoxic T cell (Tc cell) binds peptide antigen in association with class I MHC molecule that appears on the surface of a cell like virus infected cell (altered self-cell) [38].

Immune Response

Immune response is the development of acquired immunity against an antigen. The two arms of the immune response: antibody-mediated (humoral) and cell-mediated develop concurrently [39]. Immune response occurs due to activation of B and/or T cells on recognition of specific antigen. The activation of lymphocytes leads to their proliferation and differentiation (into effector cells and memory cells) [40]. Activation of B cells develops humoral (antibody-mediated) immune response, and activation of T cells develops cell-mediated immune response. Exposure to an antigen by an individual for the first time is called primary immune response and re-exposure to the same antigen is called secondary immune response which develops due to immunologic memory [35]. After the first exposure, antigen-specific "memory cells" are formed which are responsible for immunologic memory [40].

Mechanisms to Escape Adaptive Immunity

Both Innate and adaptive immunities are linked by dendritic cells. Therefore, the activation of an effective adaptive immune response relies on efficient dendritic cells capable of priming of naive T cells. This is one of the most relevant immune evasion strategies for Salmonella. The Salmonella has developed molecular mechanisms to prevent the presentation of bacterial

antigens that prime naive T cells and therefore avoid the initiation of the adaptive immunity [41]. In general, the virulent strains of Salmonella are capable of modulating phagocytosis by dendritic cells, avoiding lysosomal degradation and preventing antigen presentation to T cells. According to Bernal-Bayard and Ramos-Morales, [41] the summary of the mechanisms developed by Salmonella to evade host acquired immune are explained below;

It is well known that Salmonella is able to induce phagocytosis on epithelial cells by active translocation of T3SS1 effectors which modulate the actin cytoskeleton. This results in internalization of Salmonella into the epithelial cell [42]. In contrast, the uptake of Salmonella by dendritic cells is tightly regulated by effector proteins of T3SS1[43], being able to control the amount of bacteria that enter into the cells, avoiding then a massive immune response that would restrict Salmonella replication and dissemination. Additionally, Riquelme et al. [44] showed that IgG-opsonized Salmonella are recognized by different receptors (FcyRIII receptors and others that have not been identified) expressed on dendritic cells surfaces. These immune complexes are internalized and degraded by the lysosomal route, restoring its capacity to present Salmonella antigens to T cells and initiate an adaptive immunity response. However, the exact molecular mechanism with which IgG interferes with the secretion of Salmonella virulent effectors or impair its capacity to evade capture in dendritic cells remains unclear [44].

After internalization, establishing a systemic infection depends on the pathogen's capacity to survive inside the host cells and to evade the immune response. In that sense, there are many studies on Salmonella virulence proteins that contribute to intracellular survival in dendritic cells and dissemination in the host [45].

One of the most relevant strategies developed by Salmonella to survive and replicate intracellularly is the disruption of the host endocytic trafficking machinery to avoid its lysosomal degradation within the SCV. The ability to survive in dendritic cells is dependent on SPI2 effectors [45], which are injected to dendritic cells cytosol from the SCV through a T3SS2. In fact, T3SS2 mutants show a reduced capacity to survive inside dendritic cells and are attenuated in mice [46]. However, there are several examples of T3SS1 effectors that participate in avoiding lysosomal fusion. Among these SPI1 effectors, SopB and SopE were found to play a role in SCV maturation [48,49]. SopB is a phosphatase that mediates phosphatidylinositol 3-phosphate production in the SCV, through Rab5 recruitment to the SCV and its effector Vps34 [49]. Another example is SopE, which acts as a Rab5-specific exchange factor and mediates the recruitment of Rab5 in the GTP form in the SCV [48]. There are also examples of T3SS2 effectors that impair trafficking of endocytic cargo to lysosomes. The effector SopD2 directly binds and inhibits the host GTPase Rab7, a regulatory switch central to endocytic trafficking and phagosome–lysosome fusion. Consequently, this limits Rab7 interaction with its dynein- and kinesin-binding effectors RILP and FYCO1. This in turn disrupts the regulation of microtubule motors. SifA is another SPI2 effector required for bacterial survival inside dendritic cells that alters lysosomal function [50,51,52]. McGourty et al. [53] showed that SifA prevents the delivery of hydrolytic enzymes to the SCV by inhibiting Rab9- dependent retrograde trafficking of mannose-6-phosphate receptors (MPRs). This requires binding of SifA to its host cell target SKIP. Translocated SifA forms a stable complex with SKIP and Rab9 in infected cells. Sequestration of Rab9 by SifA-SKIP accounts for the effect of SifA on MPR transport and lysosome function [53]. There are other effectors of the T3SS2 that are involved in dendritic cells intracellular survival of Salmonella like SseJ, SseF, SspH2 and PipB2. Strains lacking these effectors show reduced survival inside dendritic cells but the specific role of each of these virulence proteins remains unclear [37]. One of the suggested strategies used by Salmonella to avoid antigen presentation is inhibition of lysosomal degradation [46].

There are studies that suggest that the PhoQ/PhoP regulatory system is involved in this escape mechanism. This because Salmonella strains with mutations in the PhoQ/PhoP system are not able to escape from lysosomal degradation and therefore do not interfere with antigen processing and presentation [54]. Other studies report that Salmonella regulates the expression of MHC class II antigens by polyubiquitination of HLA-DR. [55]. These mechanisms rely on virulence factors encoded in SPI2. T3SS2 effectors like SifA, SlrP,SspH2, PipB2 and SopD have been shown to participate in this evasion process since they are required for the inhibition of

MHC-II-dependent antigen presentation in dendritic cells [37]. The ability of Salmonella to prevent antigen presentation by dendritic cells seems to depend exclusively on SPI2-related proteins, since a mutant strain lacking the T3SS1 is still able to avoid antigen presentation by dendritic cells [43]. Importantly, this feature seems to be host specific and restricted to serovar Typhimurium, since other serovars like S. enteritidis and S. Typhi are not able to interfere with this function in murine dendritic cells [43]. S. Typhimurium can interfere with the host's immune response during oral infection of mice through selective killing of CD8α+ dendritic cells in a process that is dependent on MyD88 and TNFR1 [56]. It has been recently shown that the pRST98 plasmid of S. Typhi may also influence maturation, survival and cytokine production of dendritic cells, preventing activation of T-cell-mediated immunity against antigens derived from this pathogen [57].

Another strategy used by virulent Salmonella is based on down-regulation of flagellin, a target of the innate and adaptive immune responses during infection. This strategy consists in preventing T-cell activation by the active reduction of the availability of bacterial antigens for presentation to T cells [58]. Some data suggest that flagellin is differentially expressed by Salmonella populations infecting Peyer's patches [59]. Furthermore, intracellular Salmonella can make flagellin unavailable for antigen processing by dendritic cells [58]. Similar studies showed that during low-dose Salmonella infections, the microbe evades activation of flagellin-specific CD4 T cells [60].

Conclusion

Salmonella is a bacterial genus within the Family Enterobacteriaceae that consists of a large group of genetically similar organisms with the ability to infect a large number of animal hosts. During infection, Salmonella has developed molecular mechanisms to prevent the presentation of bacterial antigens that prime naive T cells and therefore avoid the initiation of the acquired immunity. Such mechanisms include; modulating phagocytosis by dendritic cells, avoiding lysosomal degradation and preventing antigen presentation to T cells. The paper reviews the concept of acquired immune and some strategies used by Salmonella to deal with the different levels of acquired immunity of the host.

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