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Unveiling the Human Antibody Response to Salmonella: A Comprehensive Analysis

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ABSTRACT
We present a review of the studies that have been published about how genus Salmonella, consisting of Salmonella enterica and Salmonella bongori, infects human body.We analyze the concept of various virulence factors distinctive to each serovar are expected to be associated with it. S.typhi unique variables include typhoid toxin. Research in this field has generally evolved from Salmonella enterica is a wide species with large number of serovars with important variations in antigenic structure and potential for virulence.The diversity of criteria and methodological approaches that have been used is notable and important, as is a certain lack of conceptual delimitation that has resulted in a broad spread of prevalent data. In Order to reduce its susceptibility to host immune surveillance many bacterium-directed mechanisms which include APC's activation, antigen expression and bioavailability, combine to modify Salmonella's "pathogenic signature".The genus Salmonella, consisting of Salmonella enterica and Salmonella bongori, infects a broad variety of hosts including humans and livestock.

Keywords: Salmonella enterica, servovars, APCs activation etc.

I. INTRODUCTION

The genus Salmonella, consisting of Salmonella enterica and Salmonella bongori, infects a broad variety of hosts including humans and livestock (1). The genomes of all Salmonella are relatively similar and this identity ranges from 65 to 99 percent in Salmonella enterica (2).The optional intracellular pathogen Salmonella enterica is further categorized into six subspecies based on biochemical and antigenic properties as well as genomic phylogeny (3) and is the major family of bacteria comprising both typhoidal (causing systemic fever) and non-typhoidal serovars (causing gastroenteritis). In humans and higher primates alone, Salmonella enterica serovars Typhi and Paratyphi cause enteric fever. However, in susceptible strains of mice Salmonella enterica serovar Typhimurium causes typhoid-like disease and this model has been used to study and understand human typhoid and salmonellosis (4). The molecular bases for the different clinical outcomes produced by S.typhi and S.typhimurium and for the host specificity exhibited by these two closely related Salmonella serovars are incompletely explained, but various virulence factors distinctive to each serovar are expected to be associated with it. S.typhi unique variables include typhoid toxin, which is believed to be responsible for many of the acute unique disease manifestations associated with typhoid fever and Vi capsular polysaccharide, which is believed to modulate the inflammatory reaction. However, despite the various clinical presentations, S.typhi and S.typhimurium share a major part of their genomes and consequently many pathogenic traits (5, 6,7). For example, both serovars encode two Type III Protein secretion systems (T3SSs) within their pathogenecity-islands 1 (SPI 1) and 2 (SPI 2) which mediate their close interactions with host cells (8). TheT3SSs mediate bacterial entry, intracellular and the transcriptional reprogramming of the target cells by subverting the cellular machineries that control actin cytoskeleton dynamics, vesicle trafficking, and signal transduction through the effector proteins they deliver. Central strategy in the pathogenesis of Salmonella enterica serovars is the ability to stimulate the transcriptional responses in infected cells. For example, S.typhimurium stimulates transcriptional responses in intestinal epithelial cells leading to the production of pro-inflammatory

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cytokines that initiate the inflammatory response that is central for its pathogenesis. In addition, this transcriptional re-programming renders the infected cells more permissive for bacterial replication. In infected cells and individuals, S.typhi has also been shown to enhance transcriptional responses.

Classification and nomenclature

Salmonella was first discovered and isolated from the intestines of pigs infected with classical swine fever, by Theobald Smith in 1855. The bacterial strain was named after Dr Daniel Elmer Salmon, an American pathologists who worked with Smith.

Salmonella infection

Salmonella infection usually occurs by oral ingestion of contaminated food and water. The acidic environment of the stomach, considered as the host`s first line of defense, is effectively nullified by bacteria through the induction of acid tolerance response. These bacteria possess a pH homeostatic mechanism comprised of proton pumps that maintain their intracellular PH within a narrow range of 7.6 to 7.8, irrespective of the environmental pH. Upon entry into the small intestine, Salmonella crosses the intestinal mucous layer and gains access to the underlying epithelium. Bacteria invade and infect the microfold (M) cells through micropinocytosis. M cells are specialized epithelial cells of the follicle associated epithelium covering the gut associated lymphoid tissue, that sample the antigenic content of the gut (9). After internalization, bacteria are transported to the underlying lymphoid cells in the Peyer's patches. M-cell mediated uptake also allows interaction of Salmonella with intestinal epithelial cells through their basolateral surface, essential for intestinal colonization and pathogenesis (10). Systemic infections of Salmonella occur after rupturing of the intestinal epithelium, wherein the bacteria enter macrophages or dendritic cells, either through passive macropinocytosis or active bacteria mediated internalization (11). Bacteria then disseminate to systemic sites such as liver, spleen and bone marrow.

Table 1: **Examples of Salmonella enterica serovars; their hosts and diseases**

Salmonella enterica serovar	**Host specificity**	**Disease and symptoms**
Typhoid		
S.typhi: S.paratyphi	Human-restricted	Enteric fever; fever; abdominal pain; transient diarrhoea or constipation; and a salmon-coloured maculopapular rash on the trunk
Non-typhoid		
S. typhimurium S. enteritidis	Broad-range	Gastroenteritis: abdominal pain; vomiting; and inflammatory diarrhoea

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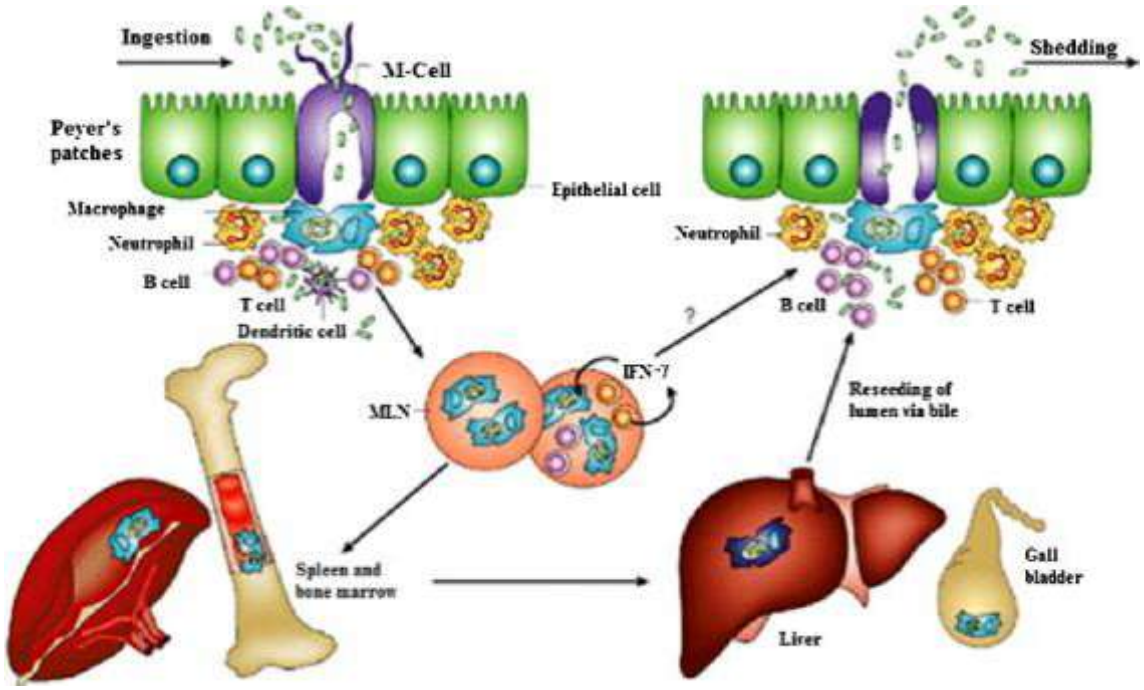

Figure 1: Schematic representation of persistent infection with Salmonella enterica serovar typhi in humans.

Salmonella pathogenecity Islands and Type III Secretion System

The mechanism of invasion, replication and survival within cells are mediated by a number of virulence associated genes that are located on the bacterial chromosome. These gene clusters are defined as ''pathogenecity islands''. Salmonella enterica possesses a greater majority of these islands as compared to Salmonella bongori or other Salmonella species, giving them a unique genetic identity. T3SS are encoded by genes present in SPI-1 or SPI-2. SPI-1 effector proteins are essential for the invasion of non-phagocytic cells. SPI-1 effectors SopB and SopE are required for actin cytoskeleton reorganisation and membrane ruffling leading to internalization of bacteria (10). SipA initiates actin polymerization and SipC nucleates and bundles the actin filament (12). SPI-2 T3SS is expressed within the phagosome and translocates effectors across the vacuolar membrane. Effector secretion through the SPI-2 T3SS is important for bacterial survival in macrophages and establishment of systemic disease (10). SPI-2 effectors SpiC and SifA have been implicated in modifying endosomal trafficking inside host cell (8).

Innate Immune Receptors

The innate immune receptors identifies microorganisms by a limited number of germ line encoded PRRs (pattern recognition receptors). These PRRs detect conserved components of microbes called PAMPs (pathogen associated molecular patterns) and activate downstream signals that promote inflammation and immunity. There are three reasons by which PAMPs are suited for the recognition of innate immunity.

1. Their invariance in microorganism in a given class.
2. PAMPs are product of pathways, unique to microorganism which enables self and non-self-discrimination.
3. They are important components of microbial physiology and hence limit the ability of microbes to avoid responses by adaptive evolution (13).

There are two different classes of PRRs based on their location – Transmembrane and cytosolic (14). Transmembrane PRRs, present on the surface of cell and in compartments of endosomes, include the Toll-like receptor (TLR) family .Cytosolic receptors are intracellular and function in the pattern recognition in bacterial and viral pathogens pattern recognition. They include NOD- like receptor (NLR) family. In terms of innate immunity against Salmonella, TLRs and NLRs are most important and have been extensively studied.

Toll-like receptors (TLRs)

TLRs are conserved receptors present on eukaryotic organisms ranging from Caenorhabditis

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elagans to mammals (15). They are type 1 integral membrane glycoprotein characterised by leucine rich repeat (LRR) motifs in the extracellular domains and a cytoplasmic signalling domain homologous to that of the interleukin-1 receptor (IL-1R), termed the Toll/ IL-IR homology (TIR) domain (16). These receptors are expressed on macrophages, dendritic cells, B-Cells, specific types of T- Cells and on non immune cells such as fibroblast and epithelial cells. Their expression is modulated by pathogen infection, cytokine medium and environmental stress (15). There are 13 TLRs (named TLR1-TLR13) identified in humans and mice together, and equivalent form of many of these have been found in other mammalian species. All TLRs activate a common signalling pathway that culminates in the activation of nuclear factor-ƙB (NF-ƙB) transcription factors, as well as the mitogen activated protein kinase (MAPKs) extracellular signal –regulated kinase(ERK), p38, and c-Jun N- terminal kinase (JNK) (17). Upon stimulation by microbial ligands, they elicit inflammatory and anti-microbial responses such as the production of pro-inflammatory cytokines tumour necrosis factor (TNF), interleukin-1β (IL-1β) and IL-6 and the transcription of gene encoding iNOS (18). With respect to Salmonella infection TLR1, TLR2, TLR4, TLR5, TLR6 and TLRs9 are important (19). TLR1/2/6 recognizes lipoproteins on the surface of Salmonella-spp. whereas TLR9 recognizes CpG rich elements in Salmonella DNA. The major TLRs involved in interaction with Salmonella are TLR4 and TLR5 that respond to lipopolysaccharide (LPS) and flagellin respectively.

Salmonella possesses peritrichous flagella that span the bacterial membrane over 500 genes are required for the assembly and functioning of flagella (20). Flagella polymers are the main locomotory apparatus comprised of repeating monomeric units of flagellin. Salmonella flagellin is composed of 494 amino and carboxy termini being conserved among Salmonella serovars. The primary means by which Salmonella is recognized by intestinal epithelial cells is through the detection of flagellin monomers by Toll like receptors (TLR5) (21). S. Typhimurium utilizes genes from the SPI-2 to aid in transcytosis of flagellin across intestinal epithelia from the apical domain to the basolateral domain where TLR5 is expressed. S. Typhimurium is known to repress flagellin transcription after entry into host phagocytes (22).

NOD-like receptors (NLRs)

NOD-like receptors (NLRs) are a subset of pattern recognition receptors (PRRs) located in cytosol that are vital for the identification and initiation of the innate immune response. All NLRs have a central nucleotide / oligomerization domain (NACHT) and most have a variable range of ligand-sensing, leucine-rich repeats at their C-terminal ends. NLRs are initiated by molecules with pathogen-associated molecular patterns (PAMPs) or non-microbial danger signals (DAMPs) released by damaged cells. NOD1 and NOD2 are two well-characterized NLRs of the NLRC subfamily that detect peptidoglycans, the primary structure of the bacterial cell wall γ-d-glutamyl-meso-diaminopimelic acid (iE-DAP) and muramyl dipeptide (MDP) respectively. Upon ligand binding, these receptors recruit serine –threonine kinase RIP2 (Receptor interacting protein 2) to activate transcriptional responses through NF-ƘB and MAP- kinases. Thus, NOD receptors and TLRs might function in an excessive manner to promote production of inflammatory cytokines upon bacterial infection. NOD1 and NOD2 also play an important role in regulation of immune homeostasis. Upon activation, the TLRs homo-oligomerize and recruit signalling molecules that drive the NF-ƙB-/AP-1-dependent expression of pro-inflammatory cytokines. Upon detection of PAMPs or danger associated molecular patterns (DAMPs) in cytosol the TLRs initiate assembly of multiprotein complex called the inflammasome (23). These complexes were initially characterized only in immune cells however recent reports have shown that these might be relevant in epithelial cells as well (24).

Bacteria-mediated endocytosis

The functions of at least five SPI1 T3SS effectors are required for efficient invasion of cultured epithelial cells, although optimal invasion in animal tissues might be more complex and diverse. SopE, SopE2 and SopB activate the host Rho GTPases Cdc42, Rac1, which leads to actin cytoskeletal reorganisation, membrane ruffling and bacterial internalization by micropinocytosis (25). However, evidence suggests that only Rac1 and RhoG are indispensable for the actin remodelling events that are generated by Salmonella spp. during host cell entry (26). SopE, SopE2 and SopB are all essential for the invasion of epithelial cells, as an S.typhimurium mutant that is defective in all three effectors cannot induce actin rearrangements and, therefore, become intracellular (27). Whereas SopE

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and SopE2 are potent guanine nucleotide exchange factors (GEFs) for all three GTPases, SopB only stimulates Cdc42 and RhoG indirectly through its phosphoinositide phosphatase activity (25). Although the mechanism of action of SopB is not yet understood, Patel and colleagues have shown that activation of RhoG by SopB occurs by a cellular exchange factor called Src homology 3 domain-containing Guanine nucleotide exchange factor (SGEF). There are two SPI1 T3SS effectors that promote bacterial internalization by binding to actin and modulating actin dynamics directly. Sip A helps to initiate actin polymerization at the site of S.typhimurium entry by decreasing the critical concentration and increasing the stability of actin filaments, whereas Sip Can effector that also function as a translocon and is inserted in the host cell`s plasma membrane with a cytoplasmic domain that may bind to intermediate filaments, can nucleate and bundle actin (28,29). In addition SipA can enhance the activity of SipC independently of any host cellular protein, which indicates that there might be a unique collaboration between two effectors (30). Although Sip A and SipC might act in concert with SopE, SopE2 and SopB to mediate the cytoskeletal changes that are required for the formation of membrane ruffles, they cannot induce membrane ruffling and invasion by themselves (31). Instead, they seem to facilitate efficient bacterial uptake by directing the spatial localization of actin foci beneath the invading bacteria and, perhaps, preventing disassembly of the S.typhimurium-induced actin structures.

Immune responses during Salmonella infection

Innate immune response

The innate immune system has the basic function of identifying and eradicating microbial invaders and alerting the adaptive immune system to their presence (32,33). Epithelial cells provide the first line of defence against orally invading pathogens. They recognize pathogenic bacteria and initiate an inflammatory response and recruit a variety of bone-marrow-derived phagocytes. The early immune response to Salmonella in payer`s patches and mesenteric lymph nodes (MLNS) involve the recruitment of neutrophils and inflammatory monocytes and these response are important for delaying the spread of bacteria to systemic infection. Salmonella enables its entry into enterocytes by activating localized cytoskeleton rearrangements characterized by membrane ruffling followed by engulfing of bacteria into the vesicles. Salmonella invasion process is mediated by the action of SPI-1 effectors SipA, SipC, SopE and SptP. Salmonella sensing induce secretion of soluble chemokines and cytokines including MCP-1, IL-6, IL-8, IL-10, IFN-$_{\gamma}$, TNF-α, as a primary innate defence response. After breaching gut epithelial barrier, invasive Salmonella encounter phagocytic cells like monocytes/macrophages with gut associated lymphoid tissue. Macrophages play a major role in controlling and clearing Salmonella. Presence of bacteria in macrophages brings about the change in mRNA expression of host genes responsible for secretion of pro-inflammatory cytokines (IL-1, TNF-α and IL-6) and anti-inflammatory molecules.

Adaptive immune response

The adaptive immune response is composed of highly specialized, systemic cells that eliminate pathogens or prevent their growth. Adaptive immunity comprises of humoral and cellular immune components. The salmonella pathogen successfully colonizes the host by reducing, evading or exploiting the immune response mount by host immune system against it. The exact mechanism of resistance is not known clearly but it is in knowledge that the T cells act as critical component of immunity against salmonella infection. So, for primary infection clearance and subsequent challenge of resistance a robust T-cell response is required. For generation of adaptive immunity B-cell functions are also required which are not limited to just antibody production. In addition interaction is essential among host cells. For example APC's release cytokines which activates and differentiate CD^{4+} cells. These differentiated CD4+ cells release cytokines which functions as both autocrine and paracrine which include phagocyte activation and recruitment, affinity maturation and B-cell isotype class switching. In order to reduce its susceptibility to host immune surveillance many bacterium-directed mechanisms which include altered interference with APC's activation and function and antigen expression and bioavailability, combine to modify Salmonella's "pathogenic signature". So a deep understanding of adaptive immune response will provide more information of pathogenic bacterial function which is required to resist the infections against salmonella and vaccine development.

II. DISCUSSION

Salmonella enterica serovar typhi causes systemic infection typhoid in humans while as Salmonella serovar typhimurium causes self

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limiting gastroenteritis in humans and typhoid like illness in mice. The reason for different clinical outcomes produced by S. Typhi and S. Typhimurium, and for the host specificity exhibited by these two closely related Salmonella serovars are not completely understood. Most of the protein and antigenic molecules have similarities like S. Typhi belongs to serogroup D and shares O-antigens 9 and 12 with S. Enteritidis. S. Typhimurium that belongs to serogroup B and shares O12 with S. Typhi or with S. Paratyphi A that belongs to serogroup A and also shares O12 with S. Enteritidis. Anti-Salmonella antibodies present in human immune sera cross-reacted with different Salmonella serovar in ELISA and western blot analysis due to similarity at the level of antigenic molecules. These antibodies are against cell surface determinants present on the bacteria.

This was seen with the antibody binding analysis with intact S. Typhi and S. Typhimurium. These determinants may, 40 therefore, be involved in interactions with the host and would therefore qualify as targets of protective immunity. Indeed, in vitro analysis showed that antibodies directed against these determinants could inhibit bacterial invasion of epithelial cells. Interestingly, bacteria coated with these antibodies were cleared better, which may be due to the engagement of TRIM21 that binds Fc region of the antibody and has been shown to bring about clearance of intracellular bacteria through autophagy. It is also possible that these antibodies neutralize the inhibitory effect that O-antigens have been shown to exert on antibacterial host defense in intestinal epithelial cells.

III. CONCLUSION

Our results are consistent with previous studies that have shown protection against Salmonella infection with vaccine candidates which were designed based on surface antigens. These findings have significant implications for immunity against pathogenic Salmonella.

Salmonella Infection remains a distressing public health concern worldwide. The genetic make-up of theSalmonellastrains permits their adaptation in various environments, including human, animal and non-animal hosts.

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