Chapter

Virulence Factors of *Salmonella Typhi*

Noor S.K. Al-Khafaji, Ali M.K. Al-Bayati and Hussein O.M. Al-Dahmoshi

Abstract

S. Typhi is an enteric bacillus which belongs,to the genus *Salmonella* in the family Enterobacteriacaea and it is a multi–organs pathogen which inhibits the lymphatic tissues of the small intestine, liver, spleen, and blood stream of infected humans. S. Typhi has a mixture of features that make it an efficient pathogen. This species contains an endotoxin that is characteristic of Gram-negative organisms, as well as the virulence-enhancing Vi antigen. Many of the S. Typhi virulence factors are clustered in some areas of the chromosome known as *Salmonella* pathogenicity islands (SPI), such as adhesion, invasion, and toxin genes. A protein known as invasin that permits non-phagocytic cells is also produced and excreted by the bacterium., Where it is capable of intracellular living. The oxidative burst of leukocytes may also be inhibited, making innate immune reaction ineffective.

Keywords: S. Typhi-virulence factors -endotoxin, enterotoxin, cytotoxin

1. Introduction

It was quite a long time before typhoid fever was differentiated from other febrile disorders. Pierre Louis was the first who used the word " typhoid " and give the classical picture of typhoid in 1829 and described in detail post-mortem finding, especially the enlargement and ulceration of peyer's patches. However, he did not clearly differentiate between typhoid and typhus. In 1837, Gerhard was the first who clearly differentiate typhoid from typhus fever and William Budd described the contagious nature of the disease and Incriminated transmission of facially polluted water supplies in 1873 [1].

In 1873, William Budd, a physician in Bristol who was interested in cholera and intestinal fever, showed that typhoid fever could be transmitted by a particular toxin found in the excrement and that this propagation was responsible for the contamination of water by the feces of patients. Each case was linked to another anterior case, according to Budd. A significant number of doctors and scientists have attempted to discover the nature of the disease-causing microorganism and have experienced considerable difficulty in isolating the bacillus. It was Karl Joseph Eberth, Rudolf Virchow's doctor and pupil, who discovered the bacillus in the abdominal lymph nodes and the spleen in 1879. In 1880 and 1881, he reported his findings. The genus '*Salmonella*' was named after Daniel Elmer Salmon, an American veterinary pathologist, who was the administrator of the USDA (United States Department of Agriculture) research program. His discovery was then tested and confirmed by German and English bacteriologists, including Robert Koch., Thus, despite the fact

that a number of scientists had contributed to the quest [2, 3], the organism was named after him. *Salmonella* has thus become new scientific knowledge and thus the mechanisms of infection and the presence of healthy carriers have been relatively nascent [4]. Recent reports suggest that there are approximately 20 million cases of typhoid each year, resulting in deaths of 100,000-200,000 [5]. Karl J. Eberth, who isolated the bacterium from spleen parts and lymph nodes from a patient who died of typhoid fever and discovered the typhoid agglutinins and their diagnostic application, first isolated S. Typhi in 1880. In 1881, Robert Koch succeeded in cultivating the bacterium. However the isolation of typhoid bacillus from other enteric bacteria was unclear due to the lack of differential characters [6, 7].

Salmonella is a genus of rod shaped (bacillus) gram negative bacteria related to family Enterobacteriaceae. They have two species which are *Salmonella enterica* and *Salmonella bongori*. *S. enterica* is the kind species and is further divided into sex subspecies [8]. that contain over 2,600 serotypes [9]. *Salmonella* species are non spore forming, predominantly motile enterobacteria for cell diameters between on 0.7 and 1.5 μm, lengths for 2 to 5 μm, and peritrichous flagella (all concerning the cell body [10]. exceptions *S. Gallinarum* and *S. Pullorum* [11, 12]. The bacterial strain was named after the American pathologist, Dr. Daniel Elmer Salmon, who collaborated with Smith. The *Salmonella* nomenclature is controversial and still changing. The Centers for Disease Control and Prevention (CDC) is currently using the *Salmonella* nomenclature system suggested by the World Health Organization (WHO) Collaborating Centre as a nomenclature system.: Species: *Salmonella enterica* serotype Typhi. [13].

2. Virulence factors of *Salmonella Typhi*

Virulence factors in *Salmonella Typhi* are involved in the various stages of infection, namely: the production of toxins (LPS) endotoxin, enterotoxin, cytotoxin), colonization, adhesion and invasion, as well as survival inside the host cells [14] (**Figure 1**).

2.1 Vi antigen

The capsular Vi antigen is a linear homopolymer of alpha 1–4 linked to galactose aminouronic acid which is variably acetylated at the C3 position. This antigen is

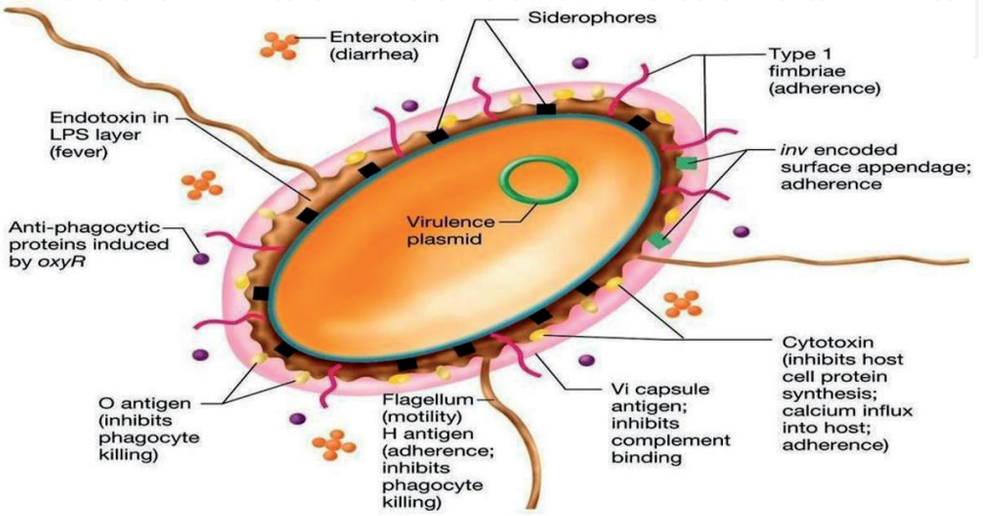

Figure 1.
Salmonella *virulence factors [14].*

believed to inhibit phagocytosis and complement C3 activation thus inhibiting non-specific opsonization, "[15] One of the main characteristics that distinguishes *S.* Typhi from (non typhoid *Salmonella*) NTS is the production of a polysaccharide capsule named the Vi antigen. The Vi capsule inhibits phagocytosis and confers serum resistance [16, 17], likely by shielding the O-antigen from antibodies [16]. The genes encoding the Vi capsule comprise the viaB locus within *Salmonella* pathogenicity island (SPI)-7, which also encodes the type III secretion system (T3SS) effector SopE and a type IVB pilus [18].

2.2 The SPI-1, SPI-2 and type III secretion systems

Common to both typhoidal and NTS are two pathogenicity-island encoded type III secretion systems (T3SS): the SPI-1 and SPI-2 T3SS, which are essential for *Salmonella* virulence. In S. Typhi, the SPI-1 T3SS is also required for invasion of nonphagocytic cells [19], but the importance of the SPI-2 T3SS is less clear. Disruption of the SPI-2 T3SS did not influence the survival of *S*. Typhi in THP-1 and human monocyte-derived macrophages [20]; however, S. Typhi strains with transposon insertions in the SPI-2 components ssaQ, ssaP, or ssaN were negatively selected against during competitive growth in human macrophages [21]. The role of SPI-2 during the intracellular lifestyle of typhoidal serovars therefore warrants further investigation.

2.3 Somatic O antigen (cell wall Ag or LPS)

The outer L-layer underlying the capsular material has the lipopolysaccharide (LPS) called the '0' antigen. This'L' layer also has certain proteins called outer membrane proteins (OMP) which are antigenic. These OMPs include both porin (OMP F and OMP C) and non-porin substances. Porins are pore-forming channels which help in solute uptake and non-porin proteins are structural proteins (**Figure 2**) [23]. These antigens are highly immunogenic and there is a good antibody response to all these antigens in patients with typhoid fever.". [24, 25]. The somatic antigens represent the side chains of repeating sugar unit projecting outwards from the lipopolysaccharide layer and the surface of the bacterial cell wall; they are hydrophilic and heat stable. It is used for serological diagnosis [26].

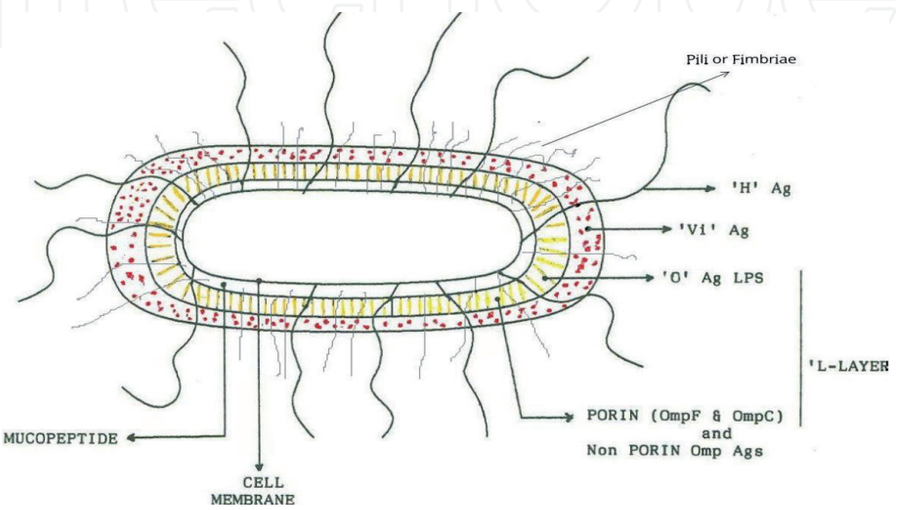

Figure 2.
Antigenic structure of Salmonella Typhi *[22].*

2.4 Flagella(H antigen)

Flagella, while contributing to virulence, are also important activators of innate immune responses via recognition of monomeric flagellin by TLR5 and NAIP receptors [27, 28], H antigen may occur in either or both of two forms, called phase 1 and phase 2. The organism tends to change from one phase to the other. H antigen also provides a useful epidemiologic tool with which to determine the source of infection and its mode of spread [29]; While most NTS display phase variation through the alternate expression of two genes of flagellin (fliC and fljB), most S. Typhi strains are monophasic, expressing FliC of the antigen H: d directly. Interestingly, some Indonesian S. Typhi strains transmit H: j, due to an in-frame deletion in fliC, a variant of H:d. [30], and/or are biphasic, expressing a plasmid-encoded FljB analogue of the H:z66 antigen [31], H:j and H:z66 antigenic variants are thought to have recently emerged during S. Typhi evolution [32], driven by immune selection in this high incidence region [31]. This additional variation seems to play a role in *S*. Typhi interactions with host epithelial cells and macrophages and partly in immune evasion [33].

2.5 Fimbriae (adhesion protein) and pili

The significant adhesion factors for S. Typhi are fimbriae and pili. These elements of virulence are employed by S. Typhi during infection and host colonization for its various cellular interactions [34]. The Operon Stg, one of the six Operons Fimbriae found in S. Typhi, But not S. Typhimurium has recently been shown to be involved in cellular invasion and in vitro destruction of epithelial cells [34]. In addition, the STG operon was found to assist S. Typhi targets enterocytes more preferentially than M cells, which promotes S. Typhi By passing the Peyer patches, eludes the innate immune system [35].

2.6 Virulence plasmid

Certain *Salmonella* carry a large, low copy number plasmid that contains virulence genes. Virulence plasmids are required to trigger systemic disease; their involvement in the enteric stage of the infection is unclear. *Salmonella* virulence plasmids are heterogeneous (50–90) kb in size, but all share a 7.8 kb area, SPV, necessary for reticuloendothelial system bacterial multiplication [36, 37].

2.7 Invasiveness

Unlike most bacteria that rely on endocytosis mediated by receptors in order to invade a target cell, S. Typhi uses a complex mechanism known as bacterial mediated endocytosis, in which bacterial proteins enter the host cell and control signaling cascades that regulate the trafficking of cytoskeletal membrane architecture and gene expression, both of which force endocytosis S. Typhi into the host [37, 38]. The target cell for *S*. Typhi is the macrophage. The ability of S. Typhi to survive in macrophages is due to the development of bacterial proteins that allow the organism to with strand both the oxygen-dependent and the non oxygen-dependent killing mechanisms of these professional phagocytic cells [36, 37].

2.8 Biofilm

Biofilm cells manufacture proteinaceous substances that allows synergic growth and protection from possible harsh environments it may encounter [39, 40]. In the

seventeenth horn, a Dutch scientist Van Leeuwenhoek was the first individual to discover biofilm cells which he described as "animacules" on his dental plaque. The biofilm development process is initiated with single cells attaching to a surface or to each other, this is then followed by the formation of clustered cells or microcolonies. Over time, the microcolonies are surrounded by a protective layer of protein-rich substances referred to as extracellular polymeric substances (EPS) [37]. The development and genetic signaling pathways involved in a *Salmonella* biofilm formation are complex. There are four major components to the structure of the *Salmonella* biofilm: curli, cellulose, capsular polysaccharides and lipopolysaccharides. Curli fibers, referred to as thin very aggregative fibers (Tafi) are one of the main components of the extracellular polysaccharide (EPS) matrix [40, 37].

Enea et al. [41] were found biofilm production by *S.* Typhi may represent a key factor for the promotion of a persistent infection in the gallbladder, thus sustaining a chronic local inflammatory response and exposing the epithelium to repeated damage cau*sed* by carcinogenic toxins. **Figure 3** demonstrates the potential role of biofilm-producing S. Typhi, in the development of gallbladder cancer. (A) Chronic S. infection. Typhi strains and gallstone presence strongly correlate with the development of gallbladder cancer (GC); The presence of gallstones (B) could provide

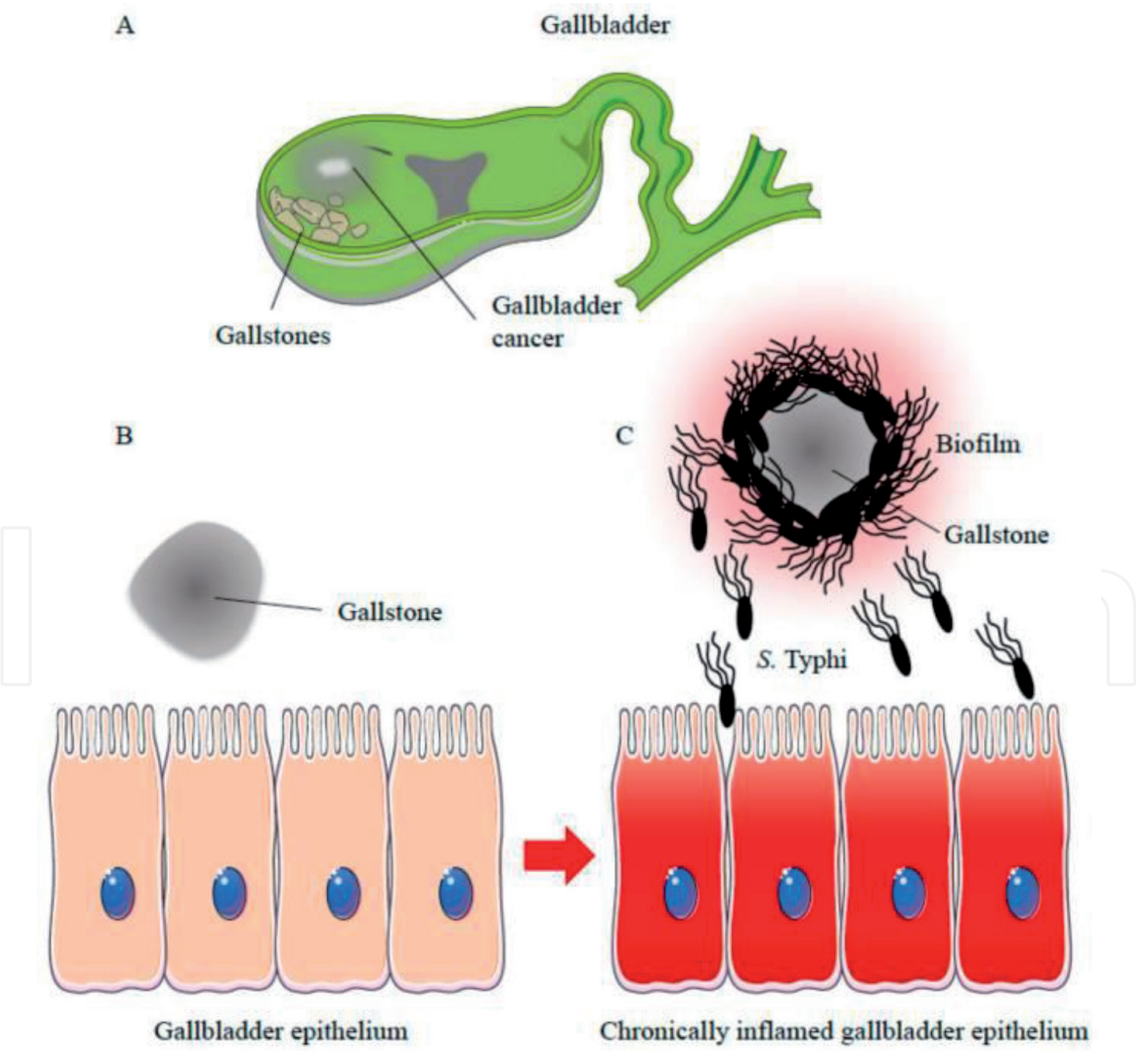

Figure 3.
Showing the potential role of biofilm-producing S. Typhi in the development of gallbladder cancer. (A) Chronic S. infection. Typhi strains and gallstone presence strongly correlate with the development of gallbladder cancer (GC); The presence of gallstones (B) could provide S. Typhi strains with the ideal substrate. (C) Once the biofilm is established, bacterial cells are separated from the gallstones that release carcinogenic molecules [41].

S. Typhi strains with the ideal substrate. (C) Once the biofilm is established, bacterial cells are separated from the gallstones that release carcinogenic molecules that induce genomic instability and chronic inflammation, which are key prerequisites for the onset of GC. with an increased biofilm forming capacity.

2.9 Endotoxin of *Salmonella* Typhi

Endotoxin is a big part of Gram-negative bacteria's outer membrane (OM). Endotoxins have been found to play an important function in the pathogenicity of Gram-negative bacterial infections. It is a powerful mediator of a wide range of pathophysiological effects in humans, mainly in the gasterointestinal tracts. Therefore, these are also known as enterotoxins. These toxic behaviors, as well as many beneficial ones linked to immunostimulation, include lethal toxicity, pyrogenicity and tissue necrotizing activity [42]. Endotoxins are high-molecular weight complexes, of lipopolysaccharides (LPS) which is the major component of bacterial cell wall [42]. It's a heat stable toxic substance released by gram negative bacteria's after disruption of cell envelopes [43, 44]. The role of endotoxins in bacterial pathogenesis and their chemical characterization as lipopolysaccharide (LPS) have been studied earlier [45, 46]. Chemically, LPS consist of a hydrophilic polysaccharide covalently linked to a hydrophobic lipid portion which is termed as lipid A, which anchors the molecules in the outer membrane (OM) [47]. Endotoxins play a major role in human disease states that created interest to investigate the pathogenicity of the producing bacteria [42]. Lipopolysaccharide found to be an important activator for the activation of immune system that leads to non- specific inflammatory immune response [48].

3. Conclusions

According to above review we put highlights on the role of the *Salmonella* virulence factors. In addition, we mentioned some strategies that could be explored in order to take control of *Salmonella* infections.

Conflict of interest

There is no 'conflict of interest' for this work.

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