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Stress-induced adaptations in *Salmonella: A* ground for shaping its pathogenesis

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ABSTRACT

Microorganisms are able to adapt to multiple adverse environmental conditions that facilitate their survival. These microorganisms including bacteria, viruses, algae, fungi, and protozoans are exposed to different abiotic and biotic challenges throughout their life. Adaptations help these organisms to overcome the challenges and evolve as successful pathogens which at the same time might lead to severe disease outcome. The intracellular gram-negative pathogen *Salmonella,* the causative agent of typhoid fever has evolved into a successful pathogen and shows increasing host mortality and morbidity every year across the globe. *Salmonella* adapts itself in the different extreme host and non-host environments both at genetic and phenotypic level leading to their better survival and propagation. The uncontrolled and improper use of antibiotics against several *Salmonella* serovars has not only given rise to various multidrug resistance strains but also the emergence of hyper-infectious *Salmonella* strains adds to the severity of disease manifestation and treatment. Besides, several disadvantages in the existing *Salmonella* vaccines stand against the current therapeutic interventions against the bug. This review deals with the wide array of stresses that *Salmonella* encounter in its life cycle and outlines the adaptations occurring in *Salmonella* upon exposure to such stresses as well as how adaptations help the pathogen to withstand such extreme conditions. Insights in these aspects will help to understand *Salmonella* pathogenesis and associated consequences which might help in the development of new strategies in combating *Salmonella* infection.

1. Introduction

Salmonella is gram-negative intracellular pathogenic bacteria and its major susceptible target includes young children, pregnant women, immune-compromised and elderly person (Eng et al., 2015). Annually millions of peoples succumb to the infection and significant numbers of new infection are reported worldwide (Pui et al., 2011). Globally around 98.3 million people suffer from gastroenteritis every year with around 155,000 annual death whereas 21 million cases of typhoid fever reports leading to an approximate 200,000 death (Majowicz et al., 2010; Gilchrist et al., 2015). *Salmonella* species can be either host-specific or can infect multiple host types causing different disease pathologies. Taxonomically the genus *Salmonella* comprises of two species namely *Salmonella bongori* with one subspecies V and *Salmonella enterica* with seven subspecies I, II, IIIa, IIIb, IV, VI, and VII (Hurley et al., 2014). The subspecies I infect only warm-blooded animals i.e. mammals and birds, the rest subspecies are restricted to infect the cold-blooded hosts such as reptiles and snakes. Further based upon various biochemical characteristics such as surface antigens, the composition of their carbohydrates, flagellar and lipopolysaccharide (LPS) structures *Salmonella* is differentiated into more than 2500 serovars (Hurley et al., 2014). Majorly, host-specific serovar Typhi (*S.* Typhi), and serovars Typhimurium (*S.* Typhimurium) and Enteritidis (*S.* Enteritidis) with a broad range of host contribute to infection outcome (Gordon et al., 2008; Silva et al., 2012; Kurtz et al., 2017). *S.* Typhi causes typhoid fever in humans and higher primates whereas *S.* Typhimurium infects human, poultry, pigs, cattle, horses, rodents and sheep that causes typhoid-like symptoms and gastroenteritis with diarrhea in animals and humans respectively (Pui et al., 2011; Kurtz et al., 2017). In spite of several measures being taken against *Salmonella* infection, the prevalence of infection still exists across the globe and millions of lives are lost annually. The emergence of various drug-resistant hyperactive *Salmonella* strains in nature, in several host and non-host environments, is a recent concern to the prevailing infection (Raveendran et al., 2010; Mastroeni et al., 2011; Heithoff et al., 2012; Klemm et al., 2016).

Many pathogenic and non-pathogenic bacteria undergo several types of adaptations as it benefits them in multiple ways (Nigg et al., 1956; Somerville et al., 2002; Mastroeni et al., 2011; Heithoff et al.,

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2012; Koskiniemi et al., 2013; Van Ditmarsch et al., 2013; Jansen et al., 2015; Chakroun et al., 2017, 2018). These adaptations help different organisms by providing either the gain of function for survival and propagation or loss of undesired features. The intracellular facultative foodborne pathogen come across a wide variety of stresses in due course of its entry to dissemination in the wide variety of hosts that it infects. How *Salmonella* adapts to these stressful environments balancing with its pathogenesis has been studied by various groups worldwide. Further emergence of highly infectious *Salmonella* strains, development of drug resistance and the emergence of multidrug resistance (MDR) and extremely drug resistance (XDR) *Salmonella* strains have further gained the concern to understand the pathophysiology and molecular pathogenesis of the bug. Here in this review, we discuss a wide array of stresses that *Salmonella* encounters in different environments *in-vitro* or *in-vivo* and how it deals with these situations. Under these conditions, what are the adaptations reported and how they are helping the pathogen to counteract such host responses and conditions ultimately evolving into a successful pathogen? Do these adaptations always give benefit to the bug or not and how the host reciprocate to such evolved pathogen? Most of the reports associated with *Salmonella* adaptation so far have dealt with serovars Typhimurium and there are very few reports on *S.* Typhi like the typhoid toxin evolution (Gao et al., 2017) and also inside host evolution giving to different serovars as well as host restriction phenotype of Typhi (Tanner and Kingsley, 2018). The current review deals with the detailed analysis of the aspect majorly associated to non-typhoidal *Salmonella* Typhimurium until unless specified.

2. *Salmonella* pathogenesis

Virulence factors such as adhesins, toxins, endotoxins, invasins, protein secretion systems, iron uptake systems, etc. are the major pathogenicity factors in pathogenic bacteria that are encoded by horizontally acquired pathogenicity islands (PAIs) (Hacker and Kaper, 2000). PAI was first described in *Escherichia coli* (*E. coli*) belonging to the Enterobacteriaceae family (McDaniel and Kaper, 1997). PAIs are present in the genomes of pathogenic organisms and absent in non-pathogenic organisms or closely related species. In *Salmonella* majority of virulent genes are present in horizontally acquired pathogenicity islands called *Salmonella* pathogenicity islands (SPIs) and plays an important role in infection, their intracellular survival and also there are various regulatory systems present in the *Salmonella*.

2.1. SPIs: the major virulence determinants

Pathogenesis of *Salmonella* is governed by various pathogenicity island i.e. SPIs, the secretion system of the bacterium and virulence plasmids (Marcus et al., 2000; de Jong et al., 2012). These SPIs are acquired through horizontal gene transfer (HGT) during the bacterial evolution and majorly contribute to survival, virulence, and dissemination of pathogens. So far 23 SPIs have been described but SPI-I and SPI-II are majorly important virulence determinant of *Salmonella* (Hurley et al., 2014). These SPIs encode molecular machine called type three secretion system (TTSS) that is involved in translocating these effector proteins across the plasma membrane into the host cell to exploit the host machinery for its survival and pathogenesis (Hensel, Shea et al. 1998; Hurley, McCusker et al. 2014). The key features behind *Salmonella* being one of the successful pathogens are horizontally acquired pathogenicity islands, the TTSS, and its effector proteins. The divergence of *Salmonella* from *E. coli* by acquiring various virulent genes through HGT in the process of evolution indicates the importance of HGT events and evolution as well in pathogenesis. Almost one-fourth of the *Salmonella* genome is acquired through this process (Garai, Gnanadhas et al. 2012). Horizontal gene transfer is accomplished by various processes like conjugation, transformation, and transduction (Jain, Rivera et al. 2003; Burmeister, 2015). Genes that are acquired by HGT confer new phenotypes to the recipient bacteria and are most often the source of adaptive changes that increase fitness in a given niche (Ilyas, Tsai et al. 2017). For such DNA transfer to take place, various factors are required such as Insertion sequence (IS) elements, transposons, plasmids, and bacteriophages, etc. which have been identified in *Salmonella* species as well (Porwollik and McClelland, 2003). Even though HGT plays an important role in the evolutionary adaptation of *Salmonella* and its pathogenesis, many of such foreign DNA acquired are detrimental to it having direct negative impact on the bacteria affecting fundamental cellular and metabolic processes (Navarre, McClelland et al. 2007). Such foreign genes are transcriptionally repressed on the basis of its base composition known as xenogeneic silencing. Xenogeneic silencing protects the bacteria from such laterally acquired genes by silencing these genes (Singh, Milstein et al. 2016).

2.2. Two-component system (TCS)

Besides the pathogenicity islands, virulence in *Salmonella* is also regulated by a gene regulatory system called TCS composed of sensor kinases and transcriptional regulators. *Salmonella* being the intracellular pathogen responds to the extracellular signals by these TCS that detect the physiochemical changes and sends signals to the nucleoid regulating the gene expression. The PhoP/PhoQ TCS is the major virulence regulatory system in regulating more than 120 different genes (Kato and Groisman, 2008). It is composed of response regulator PhoP and sensor kinase PhoQ that senses the environmental signals such as low Mg^{2+} and pH and in turn activates PhoP (Groisman, 2001). It regulates the expression of genes required for invasion, intra-macrophage survival, bacterial Magnesium transport, resistance to anti-microbial peptides, etc. (Lucas, Lostroh et al. 2000; Tang, Cheng et al. 2013). The TCS PmrA /PmrB which is activated at low pH provides resistance against cationic antimicrobial peptide polymyxin B and against Fe^{3+} mediated bacterial killing by chemically altering the LPS present in the outer membrane (Perez and Groisman, 2007; Chen and Groisman, 2013). Besides, it helps in the virulence of *Salmonella* in mice and infection of chicken macrophages (Kato, Latifi et al. 2003). Another TCS PreA/PreB has a role in the *Salmonella* invasion as well as virulence along with regulating the PmrA/PmrB regulon (Merighi, Carroll-Portillo et al. 2006; Merighi, Septer et al. 2009). The SsrA/SsrB TCS that activates the type III secretion system in SPI-II for intracellular survival and is activated by another TCS OmpR/EnvZ (Lee, Detweiler et al. 2000; Kim and Falkow, 2004). BarA/SirA is a global regulator of virulence, motility, and biofilm that directly interacts with the promoters of SPI-I genes like *hilA* and *hilC* (Teplitski, Goodier et al. 2003; Teplitski, Al-Agely et al. 2006). Thus these regulatory systems of *Salmonella* play an important role in pathogenesis and its regulations.

2.3. Entry into the host cell and intracellular life of Salmonella

After entering into the host body *Salmonella* or any other organism encounters a number of barriers such as low gastric pH, intestinal mucosa and intestinal epithelial cell barriers. *Salmonella* is known to survive these barriers and cause infection efficiently. The complex membrane structure of *Salmonella* helps it to survive until reaching the epithelial cell wall of the host in the lower intestine. *Salmonella* enters into the host cells through the Microfold (M) cells of Peyer's patch, the mass of lymphoid tissue found throughout the small intestine (Fig. 1) that analyses and responds to the pathogenic microbes in the intestine (Broz, Ohlson et al. 2012; Mabbott, Donaldson et al. 2013). Approximately 10% cells of the Peyer's patch are M cells having the inner side facing to the intestinal lumen and outer side containing many lymphoid cells such as lymphocytes and phagocytes (Broz, Ohlson et al. 2012). There are two major ways of *Salmonella* entry into the host cell. One is through the M cells by transcytosis, a passive process by which the bacteria are taken up by these cells from the lumen to the basolateral side (Broz, Ohlson et al. 2012). The second way is uptake induced by

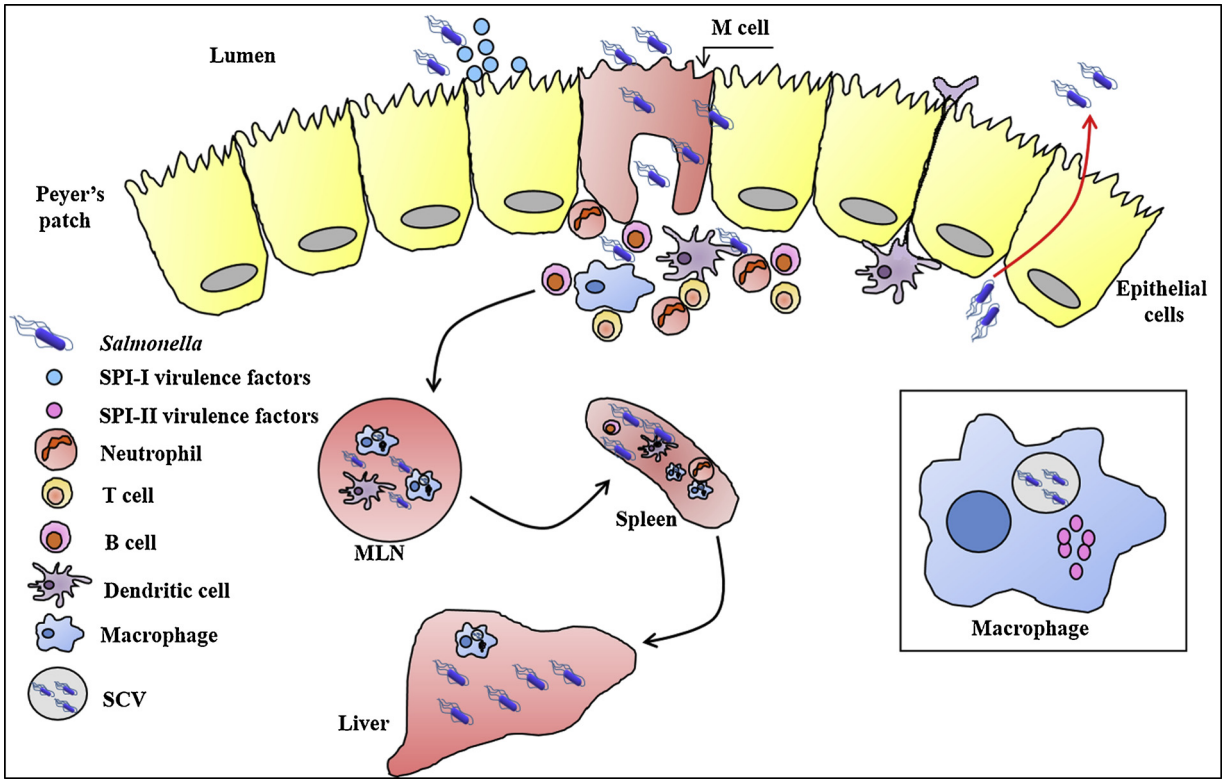

Fig. 1. Basic steps in *Salmonella* pathogenesis: Entry of *Salmonella* takes place through the M cells of the Peyer's patch in the intestinal epithelium, followed by inflammation due to infiltration of the immune cells such as neutrophils, T cells, B cells, macrophages, and dendritic cells. These cells transport the bacteria to MLN, spleen, and liver through blood and lymphatic system. Bacteria can persist in these tissues for years from where relapse of infection can happen. (MLN- Mesenteric lymph node, SCV- *Salmonella*-containing vacuole, SPI- *Salmonella* pathogenicity island).

the bacteria by secreting SPI-I TTSS effector proteins that cause membrane ruffling by the cytoskeletal rearrangement of the epithelial cells (Velge, Wiedemann et al. 2012). In addition to this, antigen-presenting dendritic cells (DCs) sends processes out to the lumen through the epithelial cells without disturbing the cell junctions and help to sample bacteria to nearby mesenteric lymph node (MLN) (Broz, Ohlson et al. 2012). Invasion is mediated by the flagellar motility along with the TTSS-I effector proteins. Various SPI-I proteins act together in facilitating the invasion process e.g. InvG, InvJ, PrgH, PrgI, prgK, SpaO assemble the needle complex, SipB, SipC, SipD translocate effector proteins through this needle apparatus whereas SipA, SopA, SopB, SopD and SopE2 help in the actin cytoskeleton alteration leading to the invasion of *Salmonella* (Raffatellu, Wilson et al. 2005; Garai, Gnanadhas et al. 2012; Thiennimitr, Winter et al. 2012).

Entry is followed by the inflammation leading to the infiltration of immune cells such as neutrophils, T cells, B cells, dendritic cells, and macrophages, etc. to the site of entry (Kaur and Jain, 2012). T3SS-II effector proteins such as SifA, SpiB, SpiC, SpiD, SseA, SseF, SseG, PipB, etc. encoded by SPI-II helps in the survival of these invaded bacteria in these cells (Hurley, McCusker et al. 2014). From the M cells, these bacteria translocate into the nearby enterocytes as shown in Fig. 1 by crossing the intestinal epithelium barrier (Velge, Wiedemann et al. 2012). Bacteria further are engulfed by the immune cells in the lamina propria and reach the MLN through the blood and lymphatic system from where they travel to deeper tissues such as spleen, liver and even to bone marrow (Kaur and Jain, 2012). In all these tissues bacteria resides inside the macrophages, in specialized modified endosomal compartments called *Salmonella*-containing vacuole (SCV), as depicted in Fig. 1, where they proliferate since it is known to be devoid of host antimicrobial defense mechanisms (Eswarappa et al., 2010). SCV acquires early endosomal markers like EEA1, Rab4, and Rab5 that are short-lived and replaced by late endosomal markers such as Rab7, Rab11, LAMPs, and vATPase 30–60 min s post-invasion (Tuli and Sharma, 2019). SCV biogenesis and maturation require both TTSS-I and TTSS-II effector proteins, SPI-II effector proteins that play a major role in the survival and proliferation in the SCV (LaRock, Chaudhary et al. 2015). *Salmonella* gets the access of membrane components and nutrients from the host endocytic compartments to SCV by establishing a network of interconnected tubules called *Salmonella* inducing filaments (Sifs) (Sindhwani, Arya et al. 2017). *Salmonella* avoids fusion of SCV with lysosome hence providing a better niche for its survival and propagation (Garvis, Beuzón et al. 2001). Finally, apoptosis of macrophage releases the *Salmonella* which then reinvades nearby epithelial cells or other phagocytic cells of the host immune system (Kaur and Jain, 2012; Hurley, McCusker et al. 2014). *Salmonella* can persist in MLN, spleen, and liver for years from where the recurrence of infection takes place (Kaur and Jain, 2012; Gunn, Marshall et al. 2014; Hurley, McCusker et al. 2014).

2.4. Clinical manifestation

The clinical manifestations of salmonellosis include enteric fever otherwise called Typhoid fever, gastroenteritis or gastrointestinal inflammations, bacteremia where the bacteria enter the bloodstream and a chronic carrier state which is mostly the result of untreated *Salmonella* infections (Pui, Wong et al. 2011). The severity of *Salmonella* infection depends upon the health status of the individual as well as the serotypes causing the infection (Eng, Pusparajah et al. 2015). Enteric fever is caused by *S*. Typhi and *S*. Paratyphi collectively called typhoidal *Salmonella* strains. Humans are the only reservoir of typhoidal *Salmonella* and are transmitted by faeco-oral route upon ingestion of contaminated food and water. Enteric fever is characterized by symptoms like fever ranging from one to two weeks associated with headache, abdominal pain, and diarrhea (Pui, Wong et al. 2011). Sometimes the patients may

show bradycardia, splenomegaly, hepatomegaly and rose spots on chest and abdomen (Parry, 2006). Besides in most severe infection conditions, hemorrhage happens due to perforations in Peyer's patches resulting in bloody diarrhea (Eng, Pusparajah et al. 2015). Gastroenteritis or gastrointestinal inflammations is caused by at least 150 *Salmonella* serotypes collectively known as nontyphoidal *Salmonella* strains (NTS) (Pui, Wong et al. 2011). NTS infections are characterized by inflammatory conditions of the stomach often associated with non-bloody diarrhea, vomiting, nausea, headache, and abdominal cramps (Acheson and Hohmann, 2001). The infection has a shorter incubation period of 6–12 hours lasting for 10 days or less (Eng, Pusparajah et al. 2015). Bacteremia is a condition where *Salmonella* enters the bloodstream after invading the intestinal barrier which is characterized by high fever. All the *Salmonella* strains can cause bacteremia, *S.* Dublin and *S*. Choleraesuis being majorly associated with the same (Pui, Wong et al. 2011; Eng, Pusparajah et al. 2015). In chronic carrier, state bacteria are shredded in stools for more than a year (Bhan, Bahl et al. 2005). This is more prevalent in typhoidal *Salmonella* strains as compared to the nontyphoidal one (Acheson and Hohmann, 2001).

2.5. Host evasion strategies by Salmonella

Like any other pathogens, *Salmonella* comes across a wide range of environmental conditions such as pH in gastrointestinal (GI) tract and SCV, AMPs, reactive oxygen and nitrogen radicals, inflammatory responses, etc. These stresses are sensed by the response regulators present in *Salmonella* and regulate the expression of a particular set of proteins to sustain the stresses and hence evading the immune system (Garai, Gnanadhas et al. 2012). Acid tolerance response (ATR) regulating alternate sigma factor RpoS and PhoP helps in acid survival whereas membrane remodeling by LPS modifications help to avoid from pathogen recognition by toll-like receptor 4 (TLR-4) and increase resistance against host AMPs (Ye, He et al. 2019). Similarly, RNS is counteracted by various mechanisms such as arginase production that compete with inducible nitric oxide synthase (iNOS) for arginine (Das, Lahiri et al. 2010). *Salmonella* is known to block not only SCV-lysosome fusion thereby evading lysosomal degradation (Chakravortty, Hansen-Wester et al. 2002) but also inhibits antigen presentation via dendritic cells (Tobar, Carreno et al. 2006; Bueno, Gonzalez et al. 2007). *Salmonella* employs SPI-II T3SS to subvert NLR family CARD-domain containing protein 4 (NLRC4) and NLR family PYRIN-domain containing protein 3 (NLRP3) inflammasome responses leading to their survival (Bierschenk, Monteleone et al. 2019).

3. Antibiotic resistance in *Salmonella*

Antibiotic resistance is a serious yet common phenomenon in the recent past that can be acquired naturally or induced. In many pathogenic bacteria including *Salmonella* resistance can be natural, when bacteria evolve without any drug exposure or induced with respect to usage of drugs/antibiotics. Easy accessibility, increased and uncontrolled use of antibiotics in animal-based food products as well as to control human salmonellosis has worsened the situation worldwide giving a platform for induced resistance (Threlfall, 2002). The continuous evolution of *Salmonella* at genomic levels contributes to the increased virulence and resistance to multiple antibiotics leading to a significant increase in the emergence of MDR strains. Till date various MDR strains and the strains with increase in the minimum inhibitory concentration (MIC) to various antibiotics have been reported from different parts of the globe (Gross, Tschäpe et al. 1998; Raveendran, Datta et al. 2010; Singh, Yadav et al. 2010; Pui, Wong et al. 2011; Chiou, Lauderdale et al. 2014; Kemal, Sibhat et al. 2016). Multidrug resistance has been reported in various *Salmonella* serotypes such as Typhi, Typhimurium, Paratyphi, Havana, Albany, Anatum and London, Choleraesuis, etc. (Van, Moutafis et al. 2007; Pui, Wong et al. 2011; Chiou, Lauderdale et al. 2014). The first report of *Salmonella* resistance to a single antibiotic came in the early 1960s (Pui, Wong et al. 2011). Subsequently, resistance towards the first-line antibiotics such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was reported at the end of the 1980s and 1990s (Raveendran, Datta et al. 2010). Further resistance to second-line treatment of MDR strains such as cephalosporin and fluoroquinolone was reported in *S*. Choleraesuis strain in swine in Taiwan and Thailand (Asai, Namimatsu et al. 2010). *Salmonella* isolates of chicken eggs collected from poultry farms and marketing, channels predominantly Typhimurium serovar was reported to be resistant to bacitracin, colistin, and polymyxin B in north India (Singh, Yadav et al. 2010). Recently Kemal et.al have reported *Salmonella* strains resistant to erythromycin and clindamycin from chicken egg isolates in Ethiopia (Kemal, Sibhat et al. 2016). Interestingly again in 2016, XDR strains of *Salmonella* were reported in Pakistan and the United Kingdom (Klemm, Shakoor et al. 2018). Not only *Salmonella,* but MDR and XDR have also been reported in many other pathogens such as *Mycobacteria*, *Staphylococcus*, *Pseudomonas,* etc. that poses a major threat to treatment and cause increased mortality and morbidity. This multidrug resistance phenomenon indicates the versatility of the pathogen in altering the genetic repertoire against the various challenges it faces in its life cycle (Porwollik and McClelland, 2003).

The enteric pathogens including *Salmonella* are not only restricted to the inside host environment but stay and are transmitted in various hostile non-host environments that dramatically influence the virulence of the pathogen and provide resistance to survive in that specific environment (Diard and Hardt, 2017).

4. Stress encountered by Salmonella during its life span

Salmonella being transmitted via faeco-oral route, encounters various microenvironments while enrouting from its natural human or animal hosts to various aquatic and terrestrial microcosms, where they are faced with a number of stress such as temperature, pH, salinity, metal ion stress, osmolarity, limiting nutrients, and most importantly the host immune defenses etc. (Fig. 2) which can either inhibit their growth or can be lethal (Spector, del Portillo et al. 1999). *Salmonella* has to be efficient enough to sense and respond to these stresses as well as to adapt to these environments not only to survive but also to disseminate and retain its pathogenicity. In the subsequent section, we have tried to bring together the information associated with various type of stresses bacteria may generally face.

4.1. Temperature

Studies have shown the temperature to be one of the major factor regulating metabolic, growth, and virulent gene expressions in bacteria (White-Ziegler, Malhowski et al. 2007; Sirsat, Burkholder et al. 2011; Shah, Desai et al. 2013). *Salmonella* experiences alteration of temperature during its transition from the host body to the environment or vice versa as it is constantly released from the infected host like human, animals, and pets to the immediate surrounding. Low-temperature exposure i.e. cold stress during freeze storage of various food items suppress the growth. Improper cooking of frozen or contaminated fresh food by inadequate temperature is reported to contribute to *Salmonella* infection (Smadi, Sargeant et al. 2012). High temperature affects cytoplasm and cell envelope in gram-negative bacteria including *Salmonella* (Spector and Kenyon, 2012). Thus temperature plays an important role in bacterial survival, adaptation, and transmission among hosts.

4.2. Osmotic stress

Turgidity of the bacterial cell, the driving force for cell extension, growth and division is regulated by maintaining the osmotic pressure (Sleator and Hill, 2002). Osmotic stress causes the flow of water either out of the cells or into the cells causing changes in its structure, function, and viability also. The foodborne intracellular pathogen

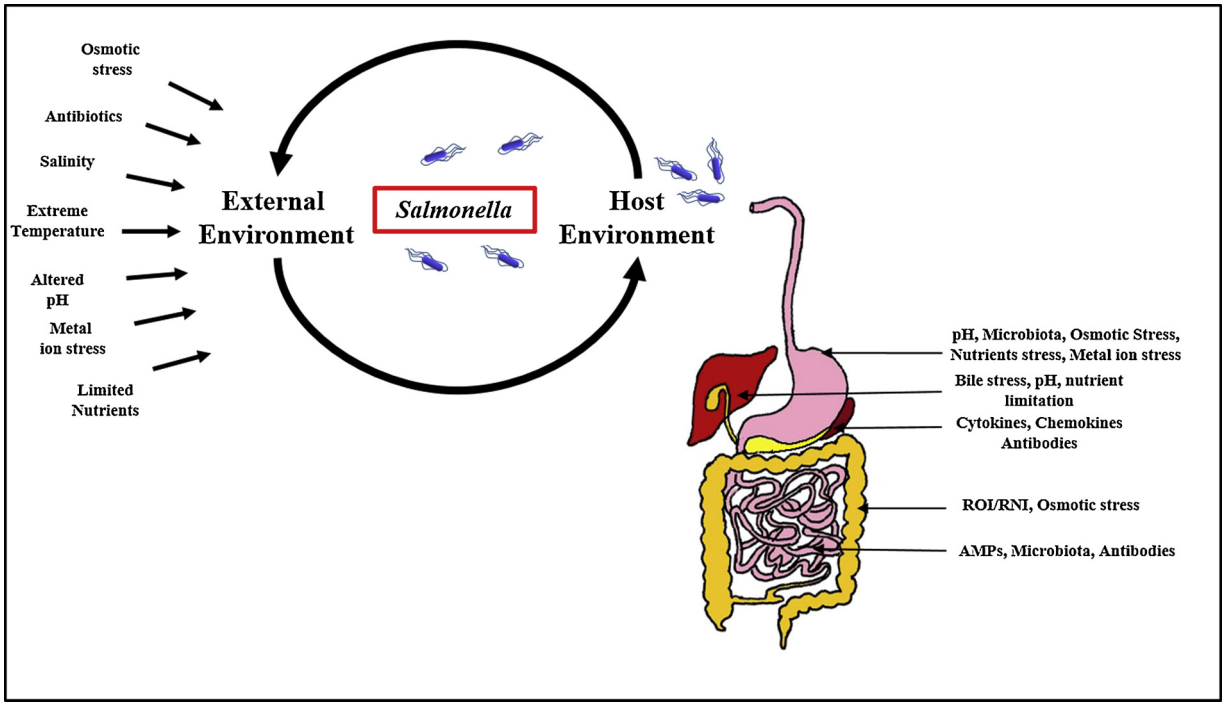

Fig. 2. Stress encountered by *Salmonella* in its life cycle: *Salmonella* transits between host and the non-host environment i.e. in the external environment. The external environment includes various aquatic and terrestrial environments, chemical and dry preservation of foods as well as freeze storage whereas the various animals and human are the hosts. In all these environments *Salmonella* faces several stress conditions as shown above to which it tries to adapt differently and sustains itself until the favorable conditions are available at the same time maintaining its pathogenicity. (ROI- Reactive oxygen intermediate, RNI- Reactive nitrogen intermediate, AMPs-Antimicrobial peptides).

Salmonella is exposed to osmotic stress in food, water, soil, and host body during its life cycle. Exposure to salt, especially during food preservation, causes water loss causing an imbalance of intracellular metabolites and hence affecting various physiological processes like nutrient uptake, DNA replication, cell division, etc. (Burgess, Gianotti et al. 2016).

4.3. Metal ion stress

Acquisition of metal ions is very much essential for microorganisms as ions of metals such as Iron (Fe), Copper (Cu), Zinc (Zn), Manganese (Mn), etc. are involved in several cellular activities including metabolism, constituents of proteins, serves as cofactors or structural elements for enzymes, virulent protein expression etc. (Porcheron, Garénaux et al. 2013). At the same time excess of few metal ions such as Cobalt (Co) becomes toxic and detrimental for the growth of enteric bacteria like *E. coli* and *Salmonella enterica* (Barras and Fontecave, 2011). One of the most important metal is the Iron (Fe^{3+}) that acts as a cofactor and are involved in a number of cellular activities such as gene regulation, cellular respiration, DNA replication, and repair (Spector and Kenyon, 2012). Although Iron is an abundant element the availability of free Fe^{3+} to *Salmonella* in many conditions including mammalian host is less than its required amount which further put stress on bacteria to survive in low Fe^{3+} condition (Foster and Spector, 1995).

4.4. pH

Acidity, as measured by the pH value, has a deleterious effect on the growth and viability of many microbes including bacteria. Acid stress is often encountered by *Salmonella* naturally in foods where organic acids are used as food preservatives (Spector and Kenyon, 2012). Acids are also used to decontaminate food ingredients (Koyuncu, Andersson et al. 2013). *Salmonella* encounter acid stress inside the host in the gut and different cells (explained in section 4.8). Such exposures help bacteria to acquire spontaneous mutations and help to survive under such acidic conditions.

4.5. Nutritional stress

Otherwise known as starvation stress, limiting essential nutrients can lead to many changes in the bacterium including cell metabolism, gene expression pattern collectively called starvation stress response (SSR) (Spector, del Portillo et al. 1999). *Salmonella* encounters nutrient starvation of essential nutrients such as Carbon (C), Nitrogen (N) and Phosphorous (P) Sulphur (S), Potassium (K), Magnesium (Mg) both inside and outside the host in natural environments (Harder and Dijkhuizen, 1983; Spector and Cubitt, 1992). Host microbiota further restricts the availability of carbohydrates, amino acids and proteins (Fang, Frawley et al. 2016). SCV, the replicative niche of *Salmonella* limits the access of the cytosolic nutrients (Tuli and Sharma, 2019). Availability of these nutrients plays an important role particularly for the bacterial viability and persistence hence pathogenicity.

4.6. Salinity

Most often *Salmonella* is disseminated to water sources including marine coastal water where it is exposed to different biotic and abiotic challenges including high salt concentration. This poses a danger to the bacterium because of the osmotic up-shift (Rozen and Belkin, 2001). Salt is usually used in the food industries as a preservative, as an antibacterial agent to prevent bacterial growth in preserved food items. Most of the *Salmonella* outbreaks happen because of the consumption of such contaminated preserved food of animal origins such as meat, eggs, and poultry. Besides, *Salmonella* is also found in many of the ready to eat food items such as chocolates, flour, cereals, sausage, seeds, egg powder, dried mushrooms, spices, black pepper, dried herbs, soybean meal etc. (Pui, Wong et al. 2011; Burgess, Gianotti et al. 2016; Siala, Barbana et al. 2017). Therefore, salt content in these preservation

conditions affects *Salmonella* for its growth and survival and various occasions the surviving bacteria cause the infection.

4.7. Antibiotics

Antibiotics are being used to treat many infectious organisms in human and animals. Resistance to those antibiotics plays a pivotal role in bacterial survival in the modern era where there is a tremendous development in the health and medicine sector. Various antibiotic-resistant strains are being detected and further strategies in treating these strains are being developed. Recently based upon mortality, health care burden, the prevalence of resistance, 10-year trend of resistance, transmissibility, preventability, and treatability, *Salmonella* is categorized in the high priority list by WHO (Tacconelli, Carrara et al. 2018). Till date, several antibiotics named as first-line antibiotics (Ampicillin, Trimethoprim-sulfamethoxazole, Chloramphenicol), second-line antibiotics (Fluoroquinolones) and third-line antibiotics such as Cephalosporin and Azithromycin are being used to control the bacterial manifestations (Crump, Sjölund-Karlsson et al. 2015; Klemm, Shakoor et al. 2018). High and prolonged usage is providing resistance to the pathogen against these antibiotics which makes treating them an alarming challenge and also causes severe disease manifestations.

4.8. Stress inside the host

After entering into the host, *Salmonella* has to survive in the highly acidic pH of stomach i.e. around 2 which acts as the first line of defense before it colonizes (Berk, De Jonge et al. 2005). Gastric juice secreted by the parietal cells of the stomach along with pepsin is known to kill bacteria within 30 min as pH is less than 3 (Giannella, Broitman et al. 1972). Further acidification of phagosome containing *Salmonella* occurs after lysosome fusion in the macrophages where they are also exposed to low pH (Rathman, Sjaastad et al. 1996; Spector and Kenyon, 2012). Mice deficient in producing gastric HCl are more susceptible to *Salmonella* infection than normal counterpart (Tennant, Hartland et al. 2008) indicating the acidic stress-related *in-vivo* susceptibility of *Salmonella*.

Gastrointestinal lumen is rich in various salt concentration that causes osmotic shock in the pathogens like *Salmonella* which spends part of its life cycle in this region. Ability to adapt this osmotic stress is very much important and is required for the growth, division and the survival of bacteria (Sleator and Hill, 2002).

The bile salts present in bile secreted from the gall bladder acts as a detergent and have potent antimicrobial properties, by acting on the cell membrane and hamper its integrity and permeability. Besides, it also induces DNA damage, alters protein conformation leading to their misfolding or denaturation, causes oxidative stress by production of oxygen free radicals, etc.(Begley, Gahan et al. 2005; Álvarez-Ordóñez, Begley et al. 2011). Several genetic regulators have been reported to be involved in *Salmonella* to resist the bile, such as two-component system, efflux pumps, DNA repair mechanism and genes involved in the maintenance of membrane integrity, helping directly or indirectly in its survival and pathogenesis (Álvarez-Ordóñez, Begley et al. 2011). *Salmonella* grown in presence of bile shows reduced invasion in epithelial cells than grown in the absence of bile (Prouty and Gunn, 2000). Also, bile can act as a signal molecule to modulate gene expression required for survival and repress the other genes (Álvarez-Ordóñez, Begley et al. 2011).

Salmonella inside the gut interacts with numerous complex gastrointestinal microflorae also which are part of the gut commensals. These microbes also affect the outcome of the infection process in numerous ways. Most important is the competition for nutrients as well as for adhesion to the gut epithelium. Gut commensals are also reported to produce metabolites and short-chain fatty acids having anti *Salmonella* activity and induce stress responses (Nava, Bielke et al. 2005; Rychlik and Barrow, 2005; Álvarez-Ordóñez, Begley et al. 2011).

After its passage through the acidic stomach, *Salmonella* reaches the intestine where the mucosal lining is protected by host immune components like small peptides of 15–30 amino acids long known as antimicrobial peptides (AMPs) and secreted antibodies also (Rychlik and Barrow, 2005). These cationic AMPs produced by many organisms are part of host innate immune defense having bactericidal activities. In human AMPs are produced by many cells such as keratinocytes, neutrophils, mast cells, and T cells and cationic AMPs binds to surface of gram-negative bacteria *Salmonella* (Otto, 2010; Matamouros and Miller, 2015). In addition to its antibacterial properties, AMPs also acts as a signaling molecule to activate the acquired immune system such as T cells and dendritic cells (Oppenheim, Biragyn et al. 2003). Negi.et.al have reported the anti-*Salmonella* activity of mouse AMP cryptdine in the Balb/c mouse model (Negi, Nagarajan et al. 2010). Furthermore, they have found out that vaccine strain of *Salmonella* could retain the cryptdine level in the vaccinated pregnant mice leading to bacterial clearance as well as efficient antigen presentation as compared to the mice infected with the wild type *Salmonella*. In the worm model i.e. *Caenorhabditis elegans* (*C. elegans*) it is also reported that *Salmonella* infection leads to induction of two AMP genes, *spp-1,* and *abf-2* that limits bacterial proliferation (Alegado and Tan, 2008). These immune responses further provide an environment to bacteria to counteract and survive under these conditions by membrane remodeling and efflux pumps in order to avoid attack by AMPs by enzymatic degradation of the AMPs (Eswarappa, Panguluri et al. 2008; Matamouros and Miller, 2015).

The anti-*salmonella* activity of both reactive oxygen and nitrogen species in the professional phagocytes has already been established (Vazquez-Torres, Jones-Carson et al. 2000; Mantena, Wijburg et al. 2008; Fang, Frawley et al. 2016). *Salmonella* is exposed to reactive oxygen species such as H_2O_2 and O_2^- in the phagocytic cells from respiratory burst by electron transport system causing damage to the biomolecules of the invading microbes like nucleic acids, carbohydrates, proteins, and lipids (Fang, 2004; Spector and Kenyon, 2012; Fang, Frawley et al. 2016). Similarly, they might get exposed to reactive nitrogen species such as nitric oxide (NO), peroxynitrite ($ONOO^-$) in the host cell. Production of NO is induced by the interaction of *Salmonella* with the phagocytes where the translation of inducible nitric oxide synthase takes place which in turn produce NO from L-arginine, O_2 and nicotinamide adenine dinucleotide phosphate (NADPH) (MacMicking, Xie et al. 1997). NO is reported to affect DNA replication, transcription, translation, cell division, synthesis of biomolecules such as fatty acids, lipopolysaccharides, peptidoglycans, etc. thereby restricting bacterial growth (Fitzsimmons, Liu et al. 2018).

Further *Salmonella* also faces various inflammatory responses acting against it as well as autophagy that comes into action against it by the host immune system once it starts invading the cells. The adaptive immune response of B cells and T cells also plays an important role against this pathogen. The pathogen-associated molecular patterns (PAMPs) present on the microbial surfaces are recognized by pattern recognition receptors (PRRs) present on the cytoplasmic membrane of phagocytic cells which in turn produce several cytokines and chemokines that enhancing the immune response against the pathogen (Behnsen, Perez-Lopez et al. 2015; Bernal-Bayard and Ramos-Morales, 2017). This recognition and binding also lead to activation of inflammatory response pathways such as nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK) signaling pathways and members of interferon-regulated factor (IRF) family of transcription factors against *Salmonella* (Bernal-Bayard and Ramos-Morales, 2017). Further, the autophagy degradation pathway whereby the SCV is targeted for lysosomal degradation also poses a threat to the invading *Salmonella* (Castanheira and Garca-del Portillo, 2017). In addition to this the adaptive immunity comprising of B cells and T cells that recognize the specific antigens and develop an immune response against it. While B cells produce antibodies against it, the T cells are involved to control intracellular infection (Cummings, Deatherage et al. 2009).

Microbial pathogens adopt at physiological as well as genetic level in order to counteract the above-mentioned stresses in a number of possible ways in order to survive better and to retain their pathogenesis. *Salmonella* is also reported to show adaptive behavior to survive and cause pathogenesis as discussed in the subsequent section.

5. Bacterial adaptations to counteract the stresses

Experimental evolution is increasingly gaining attention to investigate adaptation processes in various microbial species. How the pathogenic microbial species acquire adaptation and what is the outcome of these adaptations is the primary concern of these studies.

5.1. Adaptations observed in different bacterial species

Serial passage experiments are conducted in the laboratory at the micro-evolutionary scale in different microbial species to understand evolutionary adaptation. The serial passage can result in increased genomic diversity as compared to parental strains which might be the outcome of the accumulation of mutations due to DNA deletions or insertions or changes in repetitive sequences (Somerville, Beres et al. 2002). An experimental adaptation was studied by Lenski and group by serial passaging *E. coli* in glucose-limited minimal media and reported that adaptation was associated with increasing fitness, cell size, and altered gene expression pattern (Lenski and Travisano, 1994; Lenski, Mongold et al. 1998; Lenski, Winkworth et al. 2003). A similar study in *Staphylococcus aureus (S. aureus)* has shown that *in-vitro* passage of the strain has decreased the aconitase activity that in turn regulates the synthesis of various virulence factor (Somerville, Beres et al. 2002). Recently Bin Ni et.al have observed an evolutionary enhancement in motility behavior in *E.coli* after passaging for many generations which were due to adaptive mutations in the functionally very different genes that encode either flagellar motor and export apparatus or various transcriptional and translational regulators (Ni, Ghosh et al. 2017). They found point mutations in around 14 genes, the transposable sequence in 5 genes and one gene deletion in the adapted strains (Ni, Ghosh et al. 2017). In another evolutionary study in *Pseudomonas aeruginosa* (*P. aeruginosa*) reflected the tradeoff between motility and biofilm formation (Van Ditmarsch, Boyle et al. 2013). Repeated rounds of swarming in *P. aeruginosa* has led to the evolution of a hyperswarmer phenotype caused by a point mutation in the flagellar synthesis regulator *FleN*. But showed poor biofilm production than the ancestral type (Van Ditmarsch, Boyle et al. 2013). An earlier study on *Burkholderia pseudomallei* (*B. pseudomallei*) has shown multiple passages in mouse results in a highly pathogenic strain comparing to the parental strain (Nigg, Ruch et al. 1956). Further adaptation towards an attenuated phenotype has been seen in *P. aeruginosa* (Jansen, Crummenerl et al. 2015). These groups have reported that a double fitness advantage i.e. increased within-host fitness and availability of a larger number of a host population to infect leads to the evolution of a commensal phenotype in *P. aeruginosa* by losing virulence in a metazoan host *C. elegans*. All these studies suggest that repeated exposure to the host or any non-host environment can cause genetic variations leading to different phenotypes in them.

5.2. Adaptations reported in Salmonella in response to stresses

Adaptations have also been studied in *Salmonella* experimentally in different environmental and laboratory conditions and also inside the host body.

5.2.1. In different environmental conditions and stress

Upon exposure to various challenges, both inside and outside the host, various pathogens activate their stress response to survive the challenges. These survival strategies employed by the pathogens play a crucial role in promoting its virulence and propagation in the host. Being a waterborne pathogen, *Salmonella* is disseminated in various water bodies such as freshwater, sewage, marine coastal water, and contaminated groundwater, etc. (Baudart, Lemarchand et al. 2000). In these environments, *Salmonella* encounters with many biotic and abiotic challenges and in response, it adapts both genotypically and phenotypically (Srinivasan and Kjelleberg, 1998; Rozen and Belkin, 2001). Studies have reported that pre-exposure of *S.* Typhimurium to NaCl increased the invasion in Caco-2 cells, increased resistance to heat and decreased the sensitivity to antibiotics like chloramphenicol, gentamycin, and oxytetracycline (Yoon, Park et al. 2013). Chakroun et.al has reported that *Salmonella* Typhimurium can survive in the hostile marine water for a longer period of time. One-year-long exposure increased resistant to antibiotics such as cefotaxime and nalidixic acid and showed cytotoxic in Caco-2 cells. Further, the strains also showed greater invasive and adhesive property to Caco-2 cells by altering cytokine production (Chakroun, Cordero et al. 2017). The same group has reported that seawater exposure of *S.* Typhimurium increased tolerance to NaCl and showed better biofilm, swimming and swarming behavior as compared to the non-stressed strain. Various SPI-I virulence gene expression upregulated in the stressed strains than the normal strains under differing NaCl conditions and upon infection in Caco-2 cells (Chakroun, Mahdhi et al. 2018). Similarly, exposure to sublethal heat stress promoted the virulence by altered virulent gene expression in *S.* Typhimurium and pre-exposure to cold stress i.e. 5 °C for 5 h significantly enhanced survival of *Salmonella* during subsequent acid stress by inducing gene expression associated with amino acid metabolism, DNA repair, oxidative stress, etc. (Sirsat, Burkholder et al. 2011; Shah, Desai et al. 2013). Although the pathogenesis of different *Salmonella* serovars is different, we have not come across any reports comparing the adaptive behavior of these serovars. The serovars Typhimurium and Enteritidis has shown very similar adaptation upon preexposure to moderate acidic conditions, resulting in enhanced resistance to more extreme acid conditions as well as to low and high temperatures stress by inducing acid tolerance response (Xu, Lee et al. 2008; Álvarez-Ordóñez, Fernández et al. 2010; Owusu-Kwarteng, Nanewortor et al. 2014). To note thousands of *Salmonella* variants reported till now is also the outcome of within-host evolution leading to diverse disease outcome (Tanner and Kingsley, 2018). Besides, *in-vitro* vitamin B_{12} synthesis differed in different serovars like Typhimurium, Pullorum, Gallinarum, and Enteritidis (Paiva, Penha Filho et al. 2009; Arguello, De Paiva et al. 2010; Paiva, Penha Filho et al. 2011). Thus stress exposure can lead to tolerance and various adaptations in the bacteria that help to survive the subsequent encounter with either similar or different stresses.

5.2.2. In-vivo stress-induced adaptations

Adaptations to host are reported to play a key role in the pathogenesis of many bacteria, viruses, and parasites. As stated before also, after ingestion through contaminated food or water, the challenges encountered by the bacteria inside the host body are pH variations, low oxygen levels, nutrient limitations, osmotic stress, metal ion stresses, etc. (Chowdhury, Sahu et al. 1996). To survive in such environments various virulence factors, as well as stress response genes get activated. Microbes depend on the host for essential nutrients and energy uptake which regulates and alter the expression of various virulence genes in the pathogens, like Magnesium and phosphate limitation induces the expression of SPI-II genes in *Salmonella* (Deiwick, Nikolaus et al. 1999). Besides, in the gastrointestinal tract, the invading pathogen interacts with the host microbiota comprising symbiotic and commensal microorganisms (Schaible, Collins et al. 1998; Endt, Stecher et al. 2010; Yurist-Doutsch, Arrieta et al. 2014). This gut microbiota plays an important role in the pathogen clearance after infection (Endt, Stecher et al. 2010). During its life cycle at various stages, pathogen might experience the nutrient deprivation. Pre-exposure of *Salmonella* to minimal media reduced its efficiency to invade the intestinal epithelial cells whereas did not affect the survival and replication inside the cells

(Yurist-Doutsch, Arrieta et al. 2016). But in the *in-vivo* mouse model nutrient deprivation didn't affect its ability to colonize in spleen, colon, and cecum (Yurist-Doutsch, Arrieta et al. 2016). Moreover, infection with *S.* Typhimurium grown in nutrient-limited conditions had shown to altered the microbiota composition as bacteroidetes species and the Enterobacteriaceae members had increased after the infection of *Salmonella* cultured in the minimal media (Yurist-Doutsch, Arrieta et al. 2016). Being an intracellular pathogen-host environment plays a very important role in its survival and adaptation so that the bug is able to survive and evade the host immune response. Emergence of hyper-infectious strains of *Salmonella* has been reported both from animal passage studies and in nature as well leading to enhanced growth rate, motility i.e. flagellar activity, altered biofilm behaviour etc. (Mastroeni, Morgan et al. 2011; Heithoff, Shimp et al. 2012; Koskiniemi, Gibbons et al. 2013; Klemm, Gkrania-Klotsas et al. 2016; Chakroun, Mahdhi et al. 2018). Mastroeni P et.al have reported in their animal study that *S.* Typhimurium after an *in-vivo* passage in mouse becomes hypervirulent by increasing the net growth rate when infected in naïve mice. However, the enhanced growth rate was lost upon *in-vitro* growth (Mastroeni, Morgan et al. 2011). Host adaptation is also seen in an immunocompromised host caused due to IL-12 β1 receptor deficiency. Persistent infection in this immunocompromised human host has resulted in several changes in *Salmonella* Enteriditis including harboring many SNPs in genes like quinolone resistance gene and several genes involved in LPS biosynthesis and mutation in the mismatch repair gene i.e. *mutS* (Klemm, Gkrania-Klotsas et al. 2016). Serial passage of *S.* Typhimurium in mice has shown to be adapted for an increase in fitness in terms of increase in the growth rate as calculated by increased competitive index compared to the parental strain. Contradict to a transient phenotype of *Salmonella* after passaging in mouse, the evolved lineages did not show loss of fitness when passaged in a secondary environment i.e. LB at different conditions of temperature 30 °C, 37 °C and 42 °C incubations (Nilsson, Kugelberg et al. 2004; Mastroeni, Morgan et al. 2011). Whole-genome sequencing revealed that increased growth rate was associated with mutations in the *stpA* and *phoQ*, global regulators of virulence and also the flagellar inversion from *FljB* type in the parental strain to *FliC* type in the adapted strain (Koskiniemi, Gibbons et al. 2013). From their observation as well as from the previous reports they suggested that in addition to *phoQ* and *stpA* mutations the switch from $fljB^{ON}$ to $fljB^{OFF}$ contributed to the increased growth rate of the evolved strains (Aricó, Miller et al. 1989; Ernst, Guina et al. 1999; Nilsson, Kugelberg et al. 2004; Heithoff, Shimp et al. 2012). *Salmonella* has the capability to survive and proliferate in the environment, in different animal and food products, that provides a reservoir for the animal and human infections. *Salmonella* clinical isolates from patients with gastroenteritis and bacteremia and animal isolates derived from different outbreaks or individual cases showed hypervirulence after an animal passage that could override the immunity conferred in vaccinated animals (Heithoff, Shimp et al. 2012). Some of the hypervirulent strains showed 100 fold decreased LD_{50} along with increased colonization, cytotoxin production, and cytocidal activity and altered host innate immune cytokine response. Gene expression analysis in the emerged strains revealed altered transcription of the gene in the PhoP/PhoQ, PhoR/PhoB and ArgR regulon that affects the expression of SPI-I and SPI-II effectors (Heithoff, Shimp et al. 2012). All these studies provide elaborated information about the genetic regulation and manipulation helping to adapt *Salmonella* under various stress condition and that might also help the bug to survive better and cause subsequent infection as well.

6. Possible mechanisms of adaptation

Adaptation to host is central to pathogens evolution and understanding the mechanism can help not only to reveal the process of *Salmonella* evolution but also in controlling the mortality and morbidity caused by *Salmonella* infection. After pathogens entry into the host, cascade of inflammatory and immune responses gets activated against the pathogen. NF-κB system that regulates transcription of a number of genes involved in inflammation and immune responses are shown to be affected by environmental factors like pH (Chakroun, Cordero et al. 2017). Besides cytokine expression in the host cells is also shown to be regulated by environmental conditions (Bahrami, Child et al. 2011). In response to the heightened immune response, the bacteria also activate various stress response genes and regulatory genes to counteract. In due course, the bacteria adapt itself and makes its own protective niche for their own survival. Though there are various reports showing that the adaptation happens in *Salmonella* at different conditions, but very few reflects the exact mechanism responsible for the same. To a transient enhanced growth phenotype observed in *S.* Typhimurium after an animal passage, Mastroeni P et.al have reported that few of the early host responses such as ROS, RNS, TNF-α that recruits phagocytes into the tissues and INF- γ that activate phagocytes do not play role in the particular phenotype (Mastroeni, Morgan et al. 2011). However, there are no reports regarding the effect of several other immune defence mechanism of the host against the pathogen that might play a role in microbial adaptation mechanism. Genome degradation caused by gene inactivation and deletion or insertion is the key feature contributing to adaptation in pathogen (Klemm, Gkrania-Klotsas et al., 2016). Divergence of different serovars into host restricted and host generalised and their adaptation in the host is due to horizontal gene transfer and mutations that include frameshift, point mutations, insertional inactivation or rearrangements (McClelland, Sanderson et al. 2004; Holt, Thomson et al. 2009). *S.* Choleraesuis is known to be highly invasive strains as compared to the other non-typhoidal strains of *Salmonella* (*S.* Typhi CT18 and *S.* Typhimurium LT2) and is reported to have acquired highest number of pseudogenes (151) which are involved in chemotaxis and signal transduction pathways leading to the higher virulence in this strain (Chiu, Tang et al. 2005). In addition to the horizontal gene transfer and genome degradation, point mutations leading to single amino acid replacement also contributes to different pathoadaptive evolution in *Salmonella* that arise by the acquisition of specific structural mutations in mannose-sensitive fimbrial adhesin *FimH* gene (Kisiela, Chattopadhyay et al. 2012). Majority of the pathogens have evolved by undergoing various genetic manipulations to survive and propagate better than the parental strains. If such beneficial adaptive genetic manipulation does not occur, they even tend to lose virulence and become commensal to survive.

7. The outcome of evolutionary adaptation in *Salmonella*

The current scenario of the emergence of MDR, XDR, and hyper-infectious *Salmonella* strains in nature as well as in the host reflects the role of evolutionary adaptation in *Salmonella*. In response to host and environmental stresses, *Salmonella* adapts itself in multiple ways for its benefit. As discussed above *Salmonella* are exposed to various stresses of biotic and abiotic to which it adapts in multiple ways having relevance in its pathogenesis (Fig. 3). These adaptations are associated with the genotypic and phenotypic changes occurring due to various kinds of mutations such as point and frameshift, insertion and deletions of genes and DNA rearrangements in the course of adaptation is reflected in increased virulence of *Salmonella* ultimately leading to increased severity of disease manifestation (Fig. 3). These adaptations lead to increased survival of the evolved bacteria and the phenotype is regulated at the genetic level in a complex manner that is essential for the bug. In absence of the adaptations, *Salmonella* will not be able to resist the host response and the stress and will be cleared from nature, which does not happen as the constant natural as well induced adaptation leads to the survival of the pathogen.

8. Conclusion

Till date, various studies have been done elucidating *Salmonella*

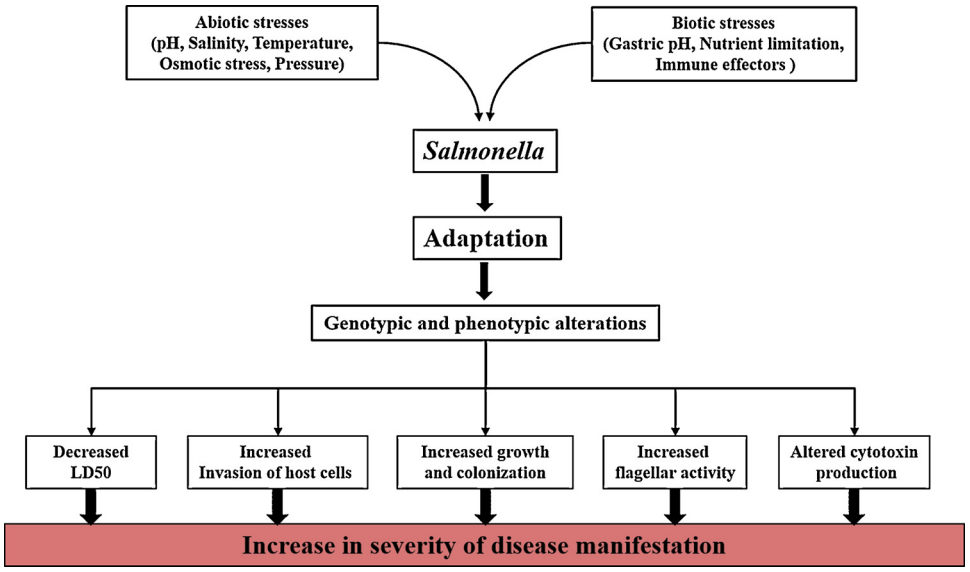

Fig. 3. Overview of evolutionary adaptation in *Salmonella*: *Salmonella* undergoes various adaptations in the phenotypic and genotypic level when exposed to several biotic and abiotic factors both inside as well as outside the host body in its life cycle. These adaptations lead to the emergence of hyper-infectious *Salmonella* strain ultimately increasing the disease severity.

pathogenesis, transmission, prevention and control of infection and developing potent therapeutics. But the outbreaks of *Salmonella* infection still persistent throughout the globe with millions of people succumbing to infection annually. The emergence of multidrug-resistant strains and hyper infective strains and associated morbidity and mortality is the current global health issue. All experimental adaptation reported so far can further become deleterious when they will be acquired in the host and the challenge will be to combat the pathophysiology modulated by such evolved strains. Further at present there are only two licensed vaccines against *Salmonella* as Vi capsular polysaccharide (Vi CPS) and Ty21a (live attenuated *S*. Typhi strain) available which still have many disadvantages such as not licensed for infants, requiring multiple doses, lack of memory response, lack of affinity maturation and Vi CPS giving protection only against *S*. Typhi (Marathe, Lahiri et al. 2012; MacLennan, Martin et al. 2014). Therefore, knowledge about *Salmonella* adaptation in the different host and non-host environments and its impact on its pathogenesis can help in the direction of developing therapeutics against the bug. Genetic regulation of the adaptation can be an interesting aspect and target to design the strategies against *Salmonella* infection. So overall we can conclude that the adaptations found if *Salmonella* under various stress conditions is good for the bug but at the same time, the deleterious outcome in the host is not beneficial for the host. The stress-induced adaptations and evolution discussed in this review potentially can increase the pathogenesis of *Salmonella* as reported by the various researcher and lead to severe disease outcome in the host. So the current challenge still remains to design certain therapeutic measure to control the disease and target the potential regulation system of the bug for the same. We still need further study to develop an effective measure against this evolving enteric pathogen *Salmonella.*

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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