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Persistent Salmonella Infections: What do we Understand of Typhoid Infections in Man and Other Animals?

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ABSTRACT

For a small number of Salmonella serovars that typically produce serious systemic diseases in man and animals, and which resemble human typhoid, persistent but intermittent post-convalescence shedding is central to the epidemiology of the infection. Persistent infection occurs despite high levels of circulating specific IgG. We have reviewed our understanding of the biological basis of persistence in S. Typhi in man, S. Gallinarum and S. Pullorum in chickens comparing with S. Typhi murium persistence in mice, with some reference to S. Dublin in cattle and S. Abortusovis in sheep and goats. Persistence appears to involve infection of macrophages primarily in the spleen and liver with shedding either from the gall bladder and gut in man or the reproductive tract in poultry and cattle and sheep. There is clearly a host-genetic element involved in mice and poultry albeit much less clear in man. The evidence indicates that the pathogens are able to modulate the immune response for their own benefit away from a clearing Th1-type response towards and anti-inflammatory (Th2) response. There is also some evidence to suggest that modulation of macrophages by the pathogens causes a switch from a M1 to M2 phenotype. The microbiological basis for the modulation has not yet been elucidated. Some experimental work suggests that cytokine therapy may be used to re-modulate the response back to a more-inflammatory response associated with increased tissue clearance.

Keywords: Salmonella; Persistence; Typhoid; Immune Response; Th2, Lymphocytes; Macrophages; Cytokines; Cytokine Therapy

Introduction

Typhoid and typhoid-like diseases of man and animals remain major threats to public and animal health. Although the majority of the more than 2,500 serotypes of Salmonella enterica *subsp enterica* are associated with, in most cases, a self-limiting gastro-enteritis, a small number of serovars typically produce severe systemic disease in a narrow range of host species. These include *S. Typhi* in man, *S. Gallinarum* and *S. Pullorum* in poultry, *S. Dublin* in cattle and *S. Abortusovis* in sheep and goats where the patterns of infection resemble each other. One of the key characteristic features of typhoid serovars is asymptomatic persistent infections in a proportion of convalescents [1-3]. This includes *S. Typhimurium* which, in addition to being one of the most frequently isolated serovars from human food-poisoning, also shows chronic, persistent infection in resistant lines of mice. In this review we will explore the characteristics common to persistent infection in the human and avian serovars, since they resemble each other most closely. The murine *S. Typhimuirum* model will be used for comparison because the availability of immunological reagents has enabled a profound understanding of the nature of murine typhoid. In this review we will use the term persistent infection to avoid confusion with "the carrier state" which is also frequently used to describe intestinal colonisation. Other serovars produce severe, systemic typhoid diseases in different host species, including *S. Paratyphi*, *S. Sendai*, *S. Choleraesuis*, and *S. Abortusequi*, but their involvement in persistent infection is poorly documented and these will not be dealt with further.

Public Health and Economic Significance

Although human typhoid, caused primarily by *S. Typhi*, is controlled in many countries through improved clean water supply, hy-

giene measures and sewage disposal, it is still a cause of morbidity and mortality in Southeast Asia, Africa and South America with an estimated 20 million cases worldwide and 220,000 deaths [4-6]. Treatment is complicated by increasing antibiotic resistance with 60% of strains resistant to more than 4 antibiotics [7-9]. 2-3% of convalescents become persistently infected and shedders, sometimes for decades [1,10-12], although a high proportion never experience acute infection and one study in India suggests that <10% of the normal heathy population may show evidence of *S. Typhi* in their tissues [13]. The avian typhoid pathogens *S. Gallinarum* and *S. Pullorum*, biotypes of the same serovar, are major causes of disease and mortality worldwide especially in small back-yard flocks and in countries where high ambient temperature results in open-sided poultry housing, allowing environmental contamination to occur. Data on the economic effects of the disease are difficult to obtain but mortality can reach 90% depending on bacterial strain and host genetic background. Other serovars of significance in agriculture include S. Dublin, which is the most frequently isolated Salmonella from dairy cattle with prevalence values of between 16-73% in US dairy herds. It causes diarrhea in calves and adults and severe systemic disease in cows accompanied by abortion with mortality occurring in up to 30% calves in infected herds [14,15]. It is also an important zoonotic pathogen. *S. Abortusovis* is the serotype most frequently associated with ovine and caprine salmonellosis and remains an important cause of economic loss in Europe and the Middle East [16,17]. Both these serovars may also localise in the joints and lungs causing pneumonia.

The Clinical Picture in Acute and Persistent Infection

Acute Infection

To understand the basis of persistent infection we must also understand the course of the more frequently encountered acute form of the disease. For the three model serovars covered in detail in this review; namely *S. Typhi*, *S. Gallinarum*/*Pullorum* and *S. Typhimurium*, the course of infection is remarkably similar. *S. Typhi*, *S. Gallinarum* and *S. Typhimurium* are able to infect animals of all ages. By contrast, *S. Pullorum* produces clinical disease almost exclusively in very young birds usually after horizontal transfer in the hatchery. All involve oral infection, invasion from the alimentary tract, probably mainly via lymphoid tissue including the Peyer's Patch and, in poultry, the *caecal* tonsil [18] and probably via M cells [19]. In mice translocation to the lymph nodes involves CD-18-expressing macrophages [20] and, in all species, from there to the liver, spleen, bone marrow and gall bladder [1,21,22]. Multiplication occurs in the monocyte-macrophage cell types which is followed, during clinical disease, by dispersal to lymphoid tissue in the small intestine from where they are excreted in the faeces. Macrophages are central to the control of Salmonella via the formation of granulomata [23].

The bacteria may proliferate within the Salmonella-containing vacuole (SCV) through the activity of proteins encoded by genes found in Salmonella pathogenicity island-2 (SPI-2) [24,25] and which may lead to cell death [26] or may induce pro-inflammatory mediators [27] which can lead to bacterial killing [26,28]. Control of Salmonella in macrophages is dynamic, with the involvement of reactive oxygen species in acute infections and reactive nitrogen species in more chronic infections [29]. Localisation in the lymphoid tissues in the small intestine leads to shedding in the faeces and may lead to occasional intestinal perforation near the ileo-caecal junction in humans, while urinary tract infection can also occur but is less frequent. Unlike *S. Typhi* and *S. Gallinarum*, *S. Typhi* murium is also able to colonise the alimentary tract of animals very well, which results in carcass contamination and entry into the human food chain resulting in food poisoning. Immunological control of infection requires cellular and antibody responses [30,31]. The production of IFNγ by natural killer cells or by CD8 T cells is important in early host-protection. Clearance of the infection requires CD4 T cells and appears to be dependent on IFNγ [32,33].

Persistent Infection

In human typhoid the gall bladder is frequently infected and is associated with *faecal* shedding although persistence can occur following cholecystectomy and the infection rate of the liver in healthy Indians has been found to be higher than the gall bladder [34]. Although humans are outbred, the low specific frequency of persistence suggests a host genetic element in susceptibility to this characteristic. Under experimental conditions, *S. Gallinarum* only shows long-term persistence in lines of chicken which are relatively resistant (Sal1R phenotype) to systemic disease with the pathogen localising in the liver and spleen. In susceptible chicken lines infection leads inevitably to severe acute infection and death, depending on infection dose. From the point of view of infection biology, *S. Pullorum* may be regarded as a less pathogenic biotype of *S. Gallinarum* and produces persistent infection in Salmonella susceptible (Sal1S phenotype) chickens. The bacteria localise in the spleen and liver and gradually decline in numbers in both sexes until, in females, birds reach sexual maturity at 16-18 weeks of age. At this point the change in hormone balance results in suppression in T cell activity accompanied by bacterial translocation to the reproductive tract and transfer to the progeny via the egg and up to 10% of eggs may be infected. In males' bacterial numbers continue to decline and clear at 20-25 weeks of age.

In *S. Typhi* and *S. Gallinarum*, colonisation of the alimentary tract is poor and only associated with clinical disease. In slc11a1-/- mice, *S. Typhi* murium produces a typical acute typhoid. In slc11a1+/+ mice persistent infection occurs with the bacteria localised in the liver, spleen and mesenteric lymph nodes with occasional isolation from the gall bladder [35-38] associated with faecal shedding for, in one case, more than 365 days [33]. The infection biology of S. Dublin and S. Abortusovis is much less studied but persistence has been associated with infection of the liver, spleen and gall bladder in S. Dublin with persistent shedding for up to one year in a calf showing an infected gall bladder [39].

Microbiological Features Contributing to Persistence

The members of this group of serovars associated with typhoid-like infections, and for which whole genome analyses have been carried out, are characterised by a reduced number of functional Open Reading Frames (ORF) undoubtedly indicating that the environment in the phagolysosome is nutritionally a very favourable environment. *S. Typhi* has 210 pseudogenes, *S. Gallinarum* 210-240 and *S. Pullorum* 231-263 depending on the strain [40-42] compared with *S. Typhimurium* which has 25. Pseudogenes occur in fimbrial gene clusters and in some nutritional pathways such as the 1,2-propanediol degradation pathway. This involves tetrathionate as a terminal electron acceptor and requires cobalamin and the combination of these operons are thought to be required for intestinal colonisation. However, there are no genomic features that appear to be uniquely characteristic of persistence as opposed to acute infection, both involving intra-macrophage multiplication and survival. Salmonella Pathogenicity Island-2 (SPI-2) is required for both acute and persistent infection but it is difficult to tease apart its role in both. It is thought that persistence is associated with accumulation of neutral mutations [43-45]. There is also no particularly strong evidence that strains associated with persistence are any different to the wider serovar population.

Immunological Features of Persistence

We have a fairly detailed understanding of the immune response to acute Salmonella infection, primarily from *S. Typhimurium* infection in mice. Studies have indicated the critical role of $CD4^+$ Th1 lymphocytes and IL-12 in controlling acute infections in the liver and spleen [46]. Th1-lymphocyte-dependent production of IFNγ [47,48], leads to increases in reactive oxygen species in macrophages countering acute infection and reactive nitrogen species in the more chronic phase of infection [28]. Much less is known of the characteristics of the immune response to the typhoid Salmonella serovars during persistent infection and most of this also comes from work with *S. Typhi* murium in the mouse and more recently with additional data from studies on *S. Pullorum* and *S. Gallinarum* in the chicken. From the studies with these serovars, evidence has accumulated to indicate that the pathogens are able to modulate the host response, away from that observed during clearance of acute infection, to a response which facilitates persistence of the pathogen with minimal host damage, which might arise from a continued inflammatory response [47].

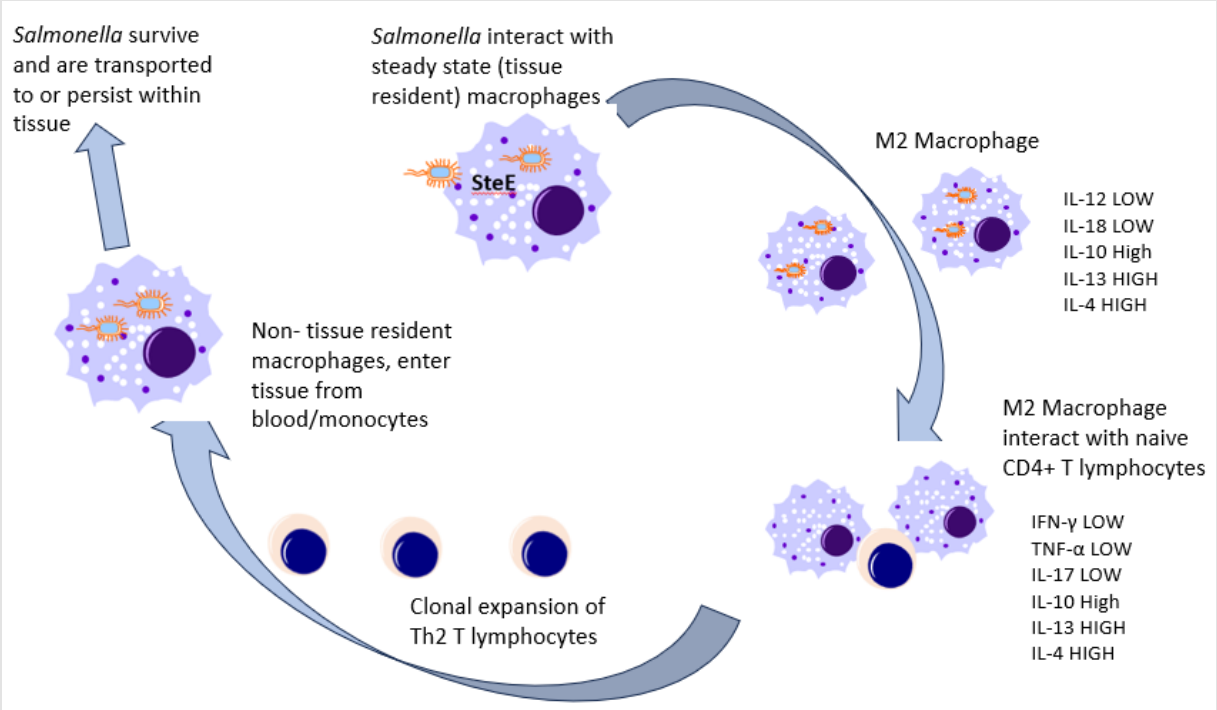

Figure 1: A tentative role for the role of SteE in Salmonella in the development of persistent infection in typhoid infections caused by S. Typhimurium, S. Gallinarum and S. Typhi. Typhoid serovar infects resident steady state macrophages. Effector proteins such as SteE are secreted intracellularly which causes macrophage differentiation into M2 macrophages. The patterns of cytokine production induce proliferation of Th2 lymphocytes leading to clonal expansion. This leads to a move away from production of IFNγ, TNF-α and IL-17 towards IL-10, IL-4 and IL-13 which are suppressive signals for macrophages which are unable to kill the intracellular Salmonellae.

In chickens infected with *S. Gallinarum*, down-regulation of the inflammatory response and up-regulation of IL-10 is correlated with transit from the intestine to the liver [49]. *S. Typhi* murium is found to be preferentially associated with anti-inflammatory M2 macrophages during the later stages of splenic infection; M2 macrophages were identified by CD301 and IL-4Rα markers [50,51]. The Salmonella bacteria persist in splenic granulomas, populated by $CD11b^+C-D11c^+Ly6C^+$ macrophages which have been reprogrammed from the M1 to M2 phenotype, possibly induced by the bacterial effector protein SteE, which modulates STAT3 activity promoting the alternative M2 phenotype [52] (Figure 1). Reprogramming is thought to occur during infection and is limited by TNF production. A key question is therefore the cause of the switch and reprogramming from M1 to M2 macrophages during infection and whether this is associated with a temporal change in SteE expression in *S. Typhi* murium. The steE gene is present in 18/24 *S. Gallinarum* and 2/4 *S. Pullorum* strains (*A. Berchieri* and V. Benevenides, unpublished results). Higher bacterial numbers certainly lead to an increase in the number of $IFN\gamma^+$ $CD4^+$ T cells, neutrophils and CD301- granuloma macrophages which produce more IFNγ and inducible nitric oxide synthase (iNOS).

Lower bacterial numbers could therefore reduce the production of inflammatory mediators and may lead to the switch from the M1 phenotype to an M2 phenotype in order to reduce the long-term damaging effect of the inflammatory response. It is also possible that dendritic cells (DCs) may play an important role in Salmonella persistence. DCs are present in substantial numbers in the sub-epithelial dome of murine Peyer's patches and, following invasion, bacteria are found within DCs [53]. DCs are also able to phagocytose Salmonella by penetrating the epithelial cell monolayer tight junctions in order to sample the intestinal environment directly [54]. Salmonellae are able to inhibit MHC II expression by murine DCs and are able to suppress $CD4^+$ lymphocyte activation [55-57]. Different DC subsets (which may be immunogenic or tolerogenic) have been detected in intestinal tissue [58-60] so it is possible that different DC subsets may be involved in persistence and acute infection. Transcriptional changes associated with a switch from a Th1 immune response to a Th2 response have also been recorded during persistent gall bladder infection in mice by *S. Typhi* murium [61,62], associated with increases in immunoglobulins and transcription of the IL-4, Stat6 and the Th2 transcriptional regulator GATA3. We have used *S. Pullorum* to study persistence in chickens. *In vitro*, both *S. Gallinarum* and *S. Pullorum* persist in host macrophages and cause less cell death in comparison to more inflammatory serovars, such as *S. Typhi* murium and the taxonomically closely related *S. Enteritidis* [48]. The basis of this is unknown but this may be possibly linked to persistence.

In vivo work with *S. Gallinarum* and *S. Pullorum* infection involved a susceptible (Sal1S) line of chickens. In the spleen, *S. Gallinarum* induced significantly lower levels of iNOS and IFNγ and consistently lower levels of IL-18 and IL-12 but significantly greater expression of anti-inflammatory IL-10 when compared to S. Enteritidis [63]. Chickens infected with *S. Gallinarum* also had a reduced expression of inflammatory mediators and increased levels of anti-inflammatory IL-10 production. The work with *S. Gallinarum* must be interpreted in the context of the use of susceptible lines of chickens where the main outcome is clinical disease and death rather than persistence which occurs in more resistant lines of bird. In comparison with S. Enteritidis, *S. Pullorum*-infected monocyte-derived macrophages show reduced mRNA expression levels of IL-12α and IL-18 and stimulated the proliferation of Th2 lymphocytes, with reduced expression of gamma interferon (IFNγ) and IL-17 and increased expression levels of IL-4 and IL-13. *In vivo S. Pullorum* also increased the levels of expression of IL-4 and decreased the levels of IFNγ in the spleen and caecal tonsil of infected birds. There was little evidence of clonal anergy or immune suppression induced by *S. Pullorum in vitro*. These studies suggest that *S. Pullorum* is able to modulate host immunity from a dominant IFNγ-producing Th17 response toward a Th2 response [64,65] with associated poorer cell mediated tissue clearing but with high levels of circulating antibody.

As yet, we have not elucidated whether either of these avian serovars become localised in M2 macrophages during chronic infection but the fact that *S. Pullorum*-infected macrophages produce low levels of IL-12α/IL-18 but much higher levels of IL-4/IL-13, suggest that *S. Pullorum* infection may induce an M2 phenotype. In human typhoid one study has reported that there are decreased levels of the inflammatory mediators IFNγ and IL-17 in the serum of patients with acute typhoid compared to levels from convalescent patients [66], suggesting that the inflammatory response is inhibited during the acute phase but that this is overcome, leading to reduced clinical symptoms and disease convalescence. The Vi capsular antigen by *S. Typhi* is thought to contribute to inhibition of the inflammatory response, to reduced opsonisation, phagocytosis, and production of oxidative killing pathways [67] and IL-8 production via inhibition of Toll-like receptor signalling. Transcriptional changes in blood [68] suggest that carriers showing persistent infection exist in two populations with a third of individuals showing patterns of raised levels of gene expression more closely resembling post-acute patients and with the remainder showing much lower levels. This latter group also showed a reduction in lymphocyte numbers, transcripts associated with CD8+ cytotoxic T lymphocytes, several neurotransmitter transcripts and glutamate receptor SLC1 A6 found in Kupfer cells [69].

Proteomic analysis [70] of blood from chronic typhoid carriers compared with healthy individuals indicated increased proprotein convertase, subtilin and furin, the latter of which has also been shown to act as a TGF-β1 converting enzyme leading to biologically active TGF-β 1 [71,72] which, in murine *S. Typhi* murium infection, is also associated with decreased Salmonella numbers in liver and spleen [73]. It seems clear that persistent infection produced by these well studied serovars involves bacterial-mediated immune-modulation to re-

duce the harmful anti-bacterial effects of the inflammatory response through the production anti-inflammatory chemokines and modulation towards a Th2-type response. The mouse model of persistence with *S. Typhimurium* infection has been particularly useful and it seems likely that *S. Typhi* and *S. Pullorum* will follow the same model. How far this model will also transfer to other Salmonella pathogens of livestock particularly S. Dublin and S. Abortusovis remains to be seen. The bacterial factors that are likely to lead to transformation of M1 macrophages to a M2 phenotype are not yet known.

An Immunological Approach to Ameliorating Persistent Infection in the Typhoid Serovars

Experimental evidence for other infection models, involving different pathogens, indicates immunological flexibility and the scope for remodulating the nature and direction of the immune response by administration of immunological signalling proteins, particularly cytokines. Thus, for example, intradermal IFNγ administration has been shown to change local leprosy infection from the lepromatous to tuberculoid form, with increases in the numbers of CD4+ T-cells and reductions in bacterial numbers in dermal biopsies [74]. IL-12 administration can also change the course of Leishmania major infection [75]. Finkelman, et al. [76] were able to modulate the mouse response to Nippostrongylus braziliensis infection, away from a Th2 dominant response, which is characterised by IL-3 and IL-4 production, by parenteral administration of IL-12. This suggests that something similar might be done to ameliorate persistent typhoid-like Salmonella infections. We set up a persistent *S. Pullorum* infection in chickens and administered a single large dose of recombinant chicken IFNγ by the intravenous route. This led to a reduction in the total number of infected spleens: 4/18 (22%) spleens positive for *S. Pullorum* in the IFNγ-treated animals and 7/13 (54%) in the untreated controls ($P < 0.01$) (Barrow, unpublished data). In another study, recombinant chicken IFNγ was also able to enhance NO production in avian peripheral blood monocyte-derived macrophages and reduce the intracellular replication of *S. Typhimurium* and Enteritidis [77,78].

Discussion

The use of the *S. Typhi* murium mouse model together with our current understanding of the behaviour of *S. Pullorum* in chickens has contributed to a better understanding of human typhoid. It remains to be seen how far the explanation of the immunological basis of persistent infection in one species relates exactly to another host species. The M1 to M2 transformation in the mouse induced in part by the SteE protein has suggested a similar approach elucidating its role in other serovar-host combinations might be appropriate. The presence of the steE gene in a proportion, but not all, strains of *S. Pullorum* and *S. Gallinarum* suggests that the situation is probably more complex. How far this has relevant to *S. Typhi* persistence in man also remains to be seen. The work by Finkelman's group [75] prompted this group to explore this approach to reduce persistence in *S. Pullorum* in chickens with some success. For practical and economic reasons, cytokine therapy is highly unlikely to be used for *S. Pullorum* infection in susceptible commercial chickens and is unlikely to be effective against *S. Gallinarum*, which shows persistence in SAL1R chickens similar to *S. Typhi* murium in slc11a1$^{+/+}$ mice which requires IFNγ activity [4]. However, it is conceivable that if administered therapeutically, it may have some application in reducing persistence in the liver and spleen in human typhoid carriers or may reduce gall bladder infection if administered during acute infection. There may also be benefits from applying this approach to some key Salmonella species that cause major economic problems in livestock. It is conceivable that live vaccines, many of which stimulate IFNγ production, and which can be used therapeutically under some circumstances, might also be used in this way to the same effect [79].

Conclusion

Our understanding of the nature and basis of persistent infection, which is a key feature of typhoid-like Salmonella infections is beginning to be understood in immunological terms. While the microbial basis for this phenomenon is not clear there are indications that there is scope for further investigation of the administration of cytokines to modulate the nature of the immune response which could reduce faecal shedding and the associated public health problems in human typhoid and improve animal health in key livestock species.

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