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Short Communication

RNAs in the Acid Tolerance Response and Virulence of *Salmonella*

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*Salmonellaenterica*serovarTyphimurium is a major enteric pathogen capable of causing severe gastroenteritis as well as systemic infections. The intestinal tracts of a diverse range of domestic and wild animals serve as a reservoir for *Salmonella* and consequently infection mainly occurs through the consumption of food and water contaminated with animal waste. This species is responsible for 93.8 million cases of gastroenteritis (80.3 million estimated food-borne), with 155,000 deaths(Majowicz et al., 2010). *Salmonella* spp. are able to survive a variety of stress conditions (pH, high osmolarity, low oxygen tension and bile salts) in their environmental niche, the gastrointestinal tract and the Salmonella containing vacuole(SCV) within macrophages, reflecting the adaptability of these pathogens. Following ingestion, *S*almonella traversethe intestinal epitheliumutilizing a mechanism encoded by the horizontally acquired *Salmonella* Pathogenicity Island 1 (SPI1) type 3 secretion system (T3SS). In immunocompromised patients, *Salmonella* are able to cause typhoid like fever owing to their ability to replicate within macrophages.This survival is mediated by *Salmonella* Pathogenicity Island 2 (SPI2) genes encoding another T3SS(Fàbrega & Vila, 2013).

The adaptive response of *Salmonella* to acid stress conditions termed the Acid Tolerance Response (ATR) is vital to their ability to survive and ultimately cause infection. The ATR received attention through pioneering work by Foster and Hall (J. W. Foster & Hall, 1990; J. Foster, 1991, 1993) and defines a system that induces resistance to normally lethal pH, termed as acid challenge, following growth under mild acid exposure, termed as acid adaptation. This response could enhance survival of the bacteria in acidic foods as well as increase survival to harsher pH in the stomach and SCV. Depending on the growth phase, the ATR could be induced either during the log phase or the stationary phase both of which are functionally distinct. The log phase ATR was first described by shifting log-phase *S.* Typhimurium cells grown at pH 7.6, to mild acid (pH5.8, adjusted with hydrochloric acid) for one doubling and subsequent challenge at lethal pH (pH3.3, adjusted with hydrochloric acid). Subsequent studies utilized the same procedure while varying the pH values and exposure times for adaptation and challenge (J. Foster, 1993, Wilmes-riesenberg, Bearson, & Foster, 1996, (Baik, Bearson, Dunbar, & Foster, 1996; Bang, Kim, Foster, & Park, 2000). The stationary phase ATR was induced by growing overnight cultures to attain a final pH of 7.4 to 4.3 followed by challenge at pH 3.0(Lin, Lee, Frey, Slonczewski, & Foster, 1995). It was observed that stationary phase cells allowed to grow at a pH<5.0, showed significantly better survival than those adapted at higher pH values.

Salmonella have long served as model organisms for studying pathogenesis, virulence, gene regulation and evolution with most of the focus on proteins and their involvement. However, it is only of recent that *Salmonella* has come to the fore as a model organism for studying non-coding RNA mediated regulation. The diverse families non-coding RNAs may fall into include small RNAs (sRNAs) that are regulatory in nature, cis-regulatory elements (riboswitches and thermometers) and RNAs that bind to and interact with proteins.It is only in the last two decades that sRNAs have started to gain momentum as important

regulators in diverse species. They range in size from 50 to 500 nucleotides, do not contain expressed open reading frames (ORFs) and are largely conserved in related species. They bring about their regulatory effects either by binding (cis or trans) to target mRNA and affecting their translation/stability, or by directly binding to proteins and modulating their activity (Altuvia, 2007). Translational repression is brought about by blocking of the ribosome binding site due to sRNA binding and activation, by unraveling of secondary structure that inhibit ribosome binding.

Both, acid tolerance and virulence are essential to the efficient survival and propagation of *Salmonella* in a host. Various protein coding genes involved in the ATR have also been shown to be essential for virulence such as the Mg^{2+} proton translocating ATPase encoded by *atp*. Consequently an *atp* mutant was found to be avirulent(Garcia-del Portillo, Foster, & Finlay, 1993). Similarly, atrC and fur mutants were found to be less virulent as compared to their wild-types (Wilmes-riesenberg et al., 1996). Similar studies in *Listeria monocytogenes*have shown that some acid tolerant mutants displayed increased virulence when compared to their wild-type(Hill, 1996).Additionally, the glutamate decarboxylase (GAD) system has also been shown to be important for both low pH survival and overall virulence. Similarly, several sRNAs have been shown to be involved in response to acid stress, with probable roles in virulence as well. For example, in *E.coli*the DsrAsRNA is a well known acid resistance regulator, with probable roles in virulence (Lease, Smith, Mcdonough, & Belfort, 2004). Other sRNAssuch as RprA, ArcZ and GcvB have also been shown to play similar roles with still more (IsrM, IsrC, IsrE) being implicated in virulence (Tracy, Gaida, & Papoutsakis, 2010). The link between the different acid tolerance systems and virulence should further be examined particularly in the case of enteric pathogens and with a focus on sRNA regulators involved. This would help provide a clear picture on the regulatory circuits that play roles in survival and pathogenesis.

References

1. Altuvia, S. (2007). Identification of bacterial small non-coding RNAs/ : experimental approaches, *10*, 257–261. doi:10.1016/j.mib.2007.05.003
2. Baik, H. S., Bearson, S., Dunbar, S., & Foster, J. W. (1996). The acid tolerance response of Salmonella typhimurium provides protection against organic acids. *Microbiology*, *142*, 3195–3200.
3. Bang, I. E. L. S. O. O., Kim, B. A. E. H., Foster, J. W., & Park, Y. K. (2000). OmpR Regulates the Stationary-Phase Acid Tolerance Response of Salmonella enterica Serovar Typhimurium. *Journal of Bacteriology*, *182*(8), 2245–2252.
4. Fàbrega, A., & Vila, J. (2013). Salmonella enterica serovar Typhimurium skills to succeed in the host: virulence and regulation. *Clinical Microbiology Reviews*, *26*(2), 308–41. doi:10.1128/CMR.00066-12
5. Foster, J. (1991). Salmonella acid shock proteins are required for the adaptive acid tolerance response. *Journal of Bacteriology*, *173*(21), 6896–6902. Retrieved from http://jb.asm.org/content/173/21/6896.short
6. Foster, J. (1993). The acid tolerance response of Salmonella typhimurium involves transient synthesis of key acid shock proteins. *Journal of Bacteriology*, *175*(7), 1981–1987. Retrieved from http://jb.asm.org/content/175/7/1981.short
7. Foster, J. W., & Hall, H. K. (1990). Adaptive Acidification Tolerance Response of Salmonella typhimurium. *Journal of Bacteriology*, *172*(2), 771–778.
8. Garcia-del Portillo, F., Foster, J. W., & Finlay, B. B. (1993). Role of acid tolerance response genes in Salmonella typhimurium virulence. *Infection and Immunity*, *61*(10), 4489–92. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=281185&tool=pmcentrez&rendertype=abstract
9. Hill, C. (1996). Adaptive acid tolerance response in Listeria monocytogenes/ : isolation of an acid-tolerant mutant which demonstrates increased virulence . Adaptive Acid Tolerance Response in Listeria monocytogenes/ : Isolation of an Acid-Tolerant Mutant Which Demonstrates.
10. Lease, R. A., Smith, D., Mcdonough, K., & Belfort, M. (2004). The Small Noncoding DsrA RNA Is an Acid Resistance Regulator in Escherichia coli †. *Journal of Bacteriology*, *186*(18), 6179–6185. doi:10.1128/JB.186.18.6179
11. Lin, J., Lee, I. S., Frey, J., Slonczewski, J. L., & Foster, J. W. (1995). Comparative analysis of extreme acid survival in Salmonella typhimurium, Shigella flexneri, and Escherichia coli. *Journal of Bacteriology*, *177*(14), 4097–104. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=177142&tool=pmcentrez&rendertype=abstract
12. Majowicz, S. E., Musto, J., Scallan, E., Angulo, F. J., Kirk, M., O'Brien, S. J., … Hoekstra, R. M. (2010). The global burden of nontyphoidal Salmonella

gastroenteritis. *Clinical Infectious Diseases/ : An Official Publication of the Infectious Diseases Society of America*, *50*(6), 882–9. doi:10.1086/650733

13. Tracy, B. P., Gaida, S. M., & Papoutsakis, E. T. (2010). Flow cytometry for bacteria: enabling metabolic engineering, synthetic biology and the elucidation of complex phenotypes. *Current Opinion in Biotechnology*, *21*(1), 85–99. doi:10.1016/j.copbio.2010.02.006
14. Wilmes-riesenberg, M. R., Bearson, B., & Foster, J. W. (1996). Role of the Acid Tolerance Response in Virulence of Salmonella typhimurium. *Infection and Immunity*, *64*(4), 1085–1092.