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Review

Host specific differences alter the requirement for certain *Salmonella* genes during swine colonization

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ABSTRACT

The pathogenic potential of *Salmonella* is determined during the complex interaction between pathogen and host, requiring optimal regulation of multiple bacterial genetic systems within variable *in vivo* environments. The mouse model of systemic disease has been an extremely productive model to investigate the pathogenesis of *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium). Although the mouse model is a widely used paradigm for studying the pathogenesis of systemic disease caused by *Salmonella*, investigations concerning food safety interventions should employ natural hosts to examine gastrointestinal colonization by *Salmonella*. Recent research has demonstrated specific differences in the attenuation of certain *S.* Typhimurium mutants in mice compared to swine. This variation in pathogenesis between the mouse model and pigs for the *S.* Typhimurium mutants is presumably dependent upon either the requirements for specific gene products during systemic disease (mouse) versus gastrointestinal colonization (pig) or host specific differences. In addition, host specific diversity in *Salmonella* colonization of swine has also been described in comparison to other food-producing animals, including cattle and chickens. Differences in *Salmonella* colonization and pathogenesis across diverse animal species highlight the importance of species-specific studies of gastrointestinal colonization for the development of *Salmonella* interventions to enhance pork safety.

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1. Introduction

The pathogenicity of *Salmonella* has been extensively studied, especially using the mouse model of systemic disease (Mastroeni and Sheppard, 2004; Grassl and Finlay, 2008). The combination of the frequently employed mouse model and *in vitro* cell culture analyses has been extremely important in elucidating virulence mechanisms of *Salmonella enterica*, especially serovar Typhimurium (*S.* Typhimurium) (Haraga et al., 2008). These investigations have revealed that a complex repertoire of virulence genes is required for *S.* Typhimurium pathogenicity, including gene products encoded in the *Salmonella P*athogenicity *I*slands (SPI) (Coburn et al., 2007; Bakowski et al., 2008). For example, a subset of SPI-1 gene products is required for bacterial invasion of epithelial cells in the gastrointestinal tract, whereas SPI-2 gene products are required for systemic infection and intracellular survival (Zhou and Galan, 2001; Waterman and Holden, 2003).

While septicemic episodes have been reported for *S.* Typhimurium in natural hosts, colonization by most *Salmonella* serovars (including Typhimurium) in food-producing animals is usually limited to the gastrointestinal tract (Stevens et al., 2009). Furthermore, pigs are typically asymptomatic carriers of broad host-range serovars of *Salmonella*, such as Typhimurium and Derby (Boyen et al., 2008a,b; NAHMS, 2009). This commensal-like state in *Salmonella*-carrier pigs establishes a significant reservoir for *Salmonella* contamination of pork products during harvest and processing, and a source of foodborne risks to consumers. Not only is *Salmonella* contaminated meat a concern, but *Salmonella*-contaminated manure used as a soil amendment (fertilizer) has the potential to adulterate water sources via field run-off into streams and rivers and contaminate edible crops that may not be cooked prior to consumption (Hanning et al., 2009). The importance of pigs as a source of *Salmonella* in the food chain is highlighted in a prediction model that estimated 100,000 human cases of salmonellosis associated with pork annually with a social cost of $82 million (Miller et al., 2005). Furthermore, the top ten most prevalent *Salmonella* serovars isolated from pigs based on the USDA, NAHMS surveys (http://www.aphis.usda.gov/vs/ceah/ncahs/nahms/swine/index.htm) partially overlap with the CDC's top ten list of *Salmonella* serovars isolated from humans (CDC, 2008). Therefore, developing intervention strategies against *Salmonella* in pigs (and other food-producing animals) will contribute to protect our food supply in the farm-to-fork continuum.

The search for potential *Salmonella* vaccine candidates in swine and the investigation of *Salmonella* pathogenesis in pigs has revealed differences in virulence mechanisms, pathogen colonization and disease susceptibility compared to studies in the murine model of systemic disease (Boyen et al., 2006, 2008a,b; Brumme et al., 2007; Carnell et al., 2007; Bearson et al., 2008). In addition, a comparison of *Salmonella* signature-tagged mutagenesis screens in swine, cattle and poultry has indicated a variable requirement for individual *Salmonella* genes during host colonization (Morgan et al., 2004; Carnell et al., 2007). This review will highlight a few of the recently identified differences in genetic mechanisms required for *Salmonella* pathogenesis in swine compared to other animal models and natural hosts.

2. Differences in virulence phenotypes of *Salmonella* mutants between the porcine host and murine model

The murine model has provided an extensive amount of knowledge on *Salmonella* pathogenesis. The function and requirement of many *Salmonella* genes are similar between the murine model and other hosts of *Salmonella*. However, certain attenuated mutants of *S.* Typhimurium investigated in the murine model for vaccine potential have been shown not to be attenuated in the natural swine host.

2.1. Iron acquisition via the siderophores enterochelin and salmochelin

Iron is an essential element for bacterial growth but is toxic at high concentrations; therefore, the acquisition of iron is tightly controlled by the bacterial cell (Andrews et al., 2003). Iron availability is limited in many environments including within mammalian hosts. An elegant interplay between iron sequestration by the host and iron scavenging by bacterial pathogens has recently emerged. The mammalian host sequesters iron using iron-binding proteins such as transferrin. To overcome iron limitation, bacteria utilize iron chelators termed siderophores to bind iron for transport into the bacterial cell (Faraldo-Gomez and Sansom, 2003). *S.* Typhimurium produces a catecholate siderophore, enterochelin, with high affinity for iron (Andrews et al., 2003). However, the mammalian host synthesizes lipocalin 2 which sequesters enterochelin, thereby limiting the siderophore's function of iron acquisition for the bacterium (Goetz et al., 2002). The presence of the *iroA* gene cluster in *Salmonella* spp. circumvents the limitations of enterochelin via glucosylation of enterochelin by IroB to produce salmochelin to serve as the siderophore for iron acquisition (Bister et al., 2004; Fischbach et al., 2006a,b; Luo et al., 2006).

The *fepA*, *iroN*, and *cirA* genes encode the outer membrane proteins FepA, IroN and CirA for the transport of the siderophores enterochelin, salmochelin and their breakdown products across the bacterial outer membrane, respectively (Neilands, 1982; Hantke et al., 2003). These iron acquisition genes were identified in investigations of gene products required for norepinephrine-enhanced growth of *S.* Typhimurium in serum-containing medium (Rabsch et al., 2003; Bearson et al., 2008). In challenge studies, a *fepA iroN cirA* mutant of *S.* Typhimurium was demonstrated in the BALB/c mouse model to be significantly attenuated compared to wild-type *S.* Typhimurium (Rabsch et al., 2003). The *fepA iroN cirA* mutant also elicited significant protection against subsequent challenge with wild-type *S.* Typhimurium in BALB/c mice, suggesting a possible vaccine application (Williams et al., 2006). In contrast to results in the mouse model, no significant difference in gastrointestinal colonization or fecal shedding was found comparing a *S.* Typhimurium *fepA iroN cirA* mutant to the wild-type strain in the natural swine host (Bearson et al., 2008). Thus, these studies suggest that *fepA*, *iroN*, and *cirA* gene products are not required for