Recent Advances in Our Understanding of the Diversity and Roles of Chaperone-Usher Fimbriae in Facilitating Salmonella Host and Tissue Tropism

Rachel A. Cheng* and Martin Wiedmann

Department of Food Science, Cornell University, Ithaca, NY, United States

Salmonella enterica is one of the most diverse and successful pathogens, representing a species with >2,600 serovars with a variety of adaptations that enable colonization and infection of a wide range of hosts. Fimbriae, thin hair-like projections that cover the surface of Salmonella, are thought to be the primary organelles that mediate Salmonella’s interaction with, and adherence to, the host intestinal epithelium, representing an important step in the infection process. The recent expansion in genome sequencing efforts has enabled the discovery of novel fimbriae, thereby providing new perspectives on fimbrial diversity and distribution among a broad number of serovars. In this review, we provide an updated overview of the evolutionary events that shaped the Salmonella chaperone-usher fimbriome in light of recent phylogenetic studies describing the population structure of Salmonella enterica. Furthermore, we discuss the complexities of the chaperone-usher fimbriae-mediated host-pathogen interactions and the apparent redundant roles of chaperone-usher fimbriae in host and tissue tropism.

Keywords: Salmonella, fimbriae, chaperone-usher, host-pathogen interaction, adhesin Salmonella

INTRODUCTION

The World Health Organization reported that Salmonella infections contributed the greatest burden of foodborne disease of any diarrheal disease agent, resulting in an estimated 8.6 million [95% confidence interval (CI) 3.9–17.5 million] disability-adjusted life years (DALYs) (Havelaar et al., 2015). Salmonella includes just two different species (S. bongori and S. enterica), but at least 2,659 known serovars (Issenhuth-Jeanjean et al., 2014). Among the six recognized subspecies of S. enterica (Brenner et al., 2000), the majority of serovars associated with human clinical disease belong to S. enterica subsp. enterica (Centers for Disease Control and Prevention, 2016). Serovars are often divided into typhoidal (serovar Typhi), paratyphoidal (serovars Paratyphi A, B, and C, and Sendai/Miami) and nontyphoidal serovars (e.g., serovars Typhimurium and Enteritidis), to reflect the diseases that they cause, with infection with typhoidal and paratyphoidal serovars resulting in an invasive, extraintestinal infection, and infection with nontyphoidal serovars resulting in a primarily
gastrointestinal illness that is often self-limiting (Crump et al., 2015). An ongoing challenge in the effort to reduce the morbidity and mortality associated with human salmonellosis, is that many Salmonella serovars are known to colonize and infect a wide range of hosts, although some serovars are host-restricted (e.g., Typhi in humans) or host-adapted (e.g., Dublin in cows). Furthermore, potential reservoirs of many nontyphoidal serovars that are commonly associated with human clinical illness, remain largely unknown.

Reflective of its overall success at colonizing a large range of hosts to enhance its distribution throughout many environments, Salmonella uses a variety of strategies to survive passage through the host gastrointestinal tract, enabling its transient or long-term presence, and facilitating its spread to additional host populations. Fimbriae (also known as pili) are the thin, hair-like appendages that mediate bacterial adherence to a surface, such as the intestinal epithelium (Nuccio and Bäumler, 2007), although non-fimbrial adhesins have also been described (Wagner and Hensel, 2011). Given the importance of fimbriae in mediating host interactions for multiple pathogens (Kaper et al., 2004; Nobbs et al., 2009; Paczosa and Mecas, 2016), special attention has been given to characterizing the role that different Salmonella fimbriae play in mediating host and tissue tropism, as well as their potential use in source attribution predictions (Zhang et al., 2019).

The recent increases in the number of Salmonella whole genome sequences (WGS) available has afforded the discovery and characterization of fimbriae encoded by a variety of Salmonella (Nuccio and Bäumler, 2007; Worley et al., 2018), as most fimbriae are poorly expressed under standard culturing conditions (Humphries et al., 2003; Thanassi et al., 2007; Hansmeier et al., 2017). In this review, we discuss recent advances in our understanding of the content and evolution of the Salmonella chaperone-usher fimbriome, and evidence supporting the complexity of fimbriae-mediated interactions in the context of tissue and host tropism.

**A COLLECTOR’S ITEM: SALMONELLA ENCODES A DIVERSE NUMBER OF CHAPERONE-USHER FIMBRIAE**

Since the discovery of fimbriae in *Escherichia coli* in 1955, at least 39 different fimbriae have been described in *Salmonella* (Yue et al., 2012; Desai et al., 2013; Aviv et al., 2017; Cheng et al., 2019; Rehman et al., 2019). Fimbriae belong to four general categories depending on their morphology, function, or assembly pathway: (i) F pili, (ii) type IV fimbriae, (iii) curli, and (iv) chaperone-usher pathway fimbriae (reviewed in [Nuccio and Bäumler, 2007]). Fimbriae of the chaperone-usher pathway represent the majority of fimbriae encoded by Salmonella (Nuccio and Bäumler, 2007; Rehman et al., 2019), and are therefore the focus of our discussion. Chaperone-usher pathway fimbriae, so named because these fimbriae utilize one or more chaperones to transfer folded fimbrial subunits to the usher protein (an integral outer membrane protein) for translocation across the outer membrane (Figure 1A), are categorized phylogenetically based on sequence conservation of the usher protein (Nuccio and Bäumler, 2007; Thanassi et al., 2007). The number of genes within a given chaperone-usher fimbrial gene cluster varies, but all include genes encoding (i) an usher protein, (ii) at least one chaperone, and (iii) a major fimbrial structural subunit; many fimbriae also include a minor fimbrial structural subunit known as a tip adhesin (Nuccio and Bäumler, 2007).

In 2007, Nuccio and Bäumler proposed the current classification scheme for chaperone-usher pathway fimbriae, which groups chaperone-usher fimbriae into three general categories based on the phylogenetic relatedness of the usher protein: (i) alternate, or α-fimbriae, (ii) classical, or β-, γ-, κ-, π-fimbriae; (iii) and archaic, or σ-fimbriae (Nuccio and Bäumler, 2007). Members of the γ-fimbriae are further sub-divided into classes γ₁ through γ₄ (Nuccio and Bäumler, 2007), although some γ₂ fimbriae have not been identified in *Salmonella* (Yue et al., 2012; Rehman et al., 2019). Among the 36 known chaperone-usher fimbriae produced by *Salmonella*, the alternative and archaic fimbriae include just one member each (Yue et al., 2012), and the remaining 34 represent members of the classical fimbriae with 23 belonging to the γ-fimbriae (Figure 1B) (Desai et al., 2013; Rehman et al., 2019). Additional novel fimbriae have since been proposed but the fimbrial gene cluster family for those was not reported (Desai et al., 2013; Aviv et al., 2017).

**EVOLUTION OF THE SALMONELLA CHAPERONE-USHER FIMBRIOME: A STORY OF GAIN AND LOSS**

Recent advances in our understanding of the *Salmonella* chaperone-usher fimbriome have been catalyzed by the appreciable increase in the number of WGS data available. A synthesis of several studies (Fookes et al., 2011; Yue et al., 2012; Desai et al., 2013; Worley et al., 2018) examining the presence of fimbrial gene clusters among serovars belonging to the major lineages of *Salmonella* (Worley et al., 2018) suggests a complex history of multiple gain and loss events (Figure 1B).

**The Ancestral Chaperone-Usher Fimbriome: Fimbrial Gene Clusters Acquired Before the Divergence of *Salmonella* and *Escherichia* **

At least seven *Salmonella* chaperone-usher fimbrial gene clusters are orthologous to fimbriae characterized in *Escherichia* (Nuccio and Bäumler, 2007), suggesting that these fimbrial gene clusters were most likely acquired prior to the divergence of these two genera approx. 140 million years ago (Yue et al., 2012; Desai et al., 2013). The Bcf fimbrial gene cluster [orthologue of Ycb in *E. coli* (De Masi et al., 2017)], originally named for its role in colonization of bovine hosts (Tsolis et al., 1999), is present in *S. bongori* and *S. enterica*, although this fimbrial gene cluster has been lost in subspecies *houtenae* (Desai et al., 2013). The conservation of a Fim (also called Type I fimbriae) orthologous fimbrial gene cluster [called Sfm (for *Salmonella* like fimbriae)
among many lineages in *E. coli* (Wurpel et al., 2013)] supports that this fimbrial gene cluster was acquired prior to the divergence of *Salmonella* and *Escherichia* (Townsend et al., 2001), although this fimbrial gene cluster has since been lost in *S. bongori* (Fookes et al., 2011; Yue et al., 2012; Desai et al., 2013). Long polar fimbria [Lpf (Bäumler and Heffron, 1995)] shows a distinct evolutionary pattern characterized by an apparent acquisition from *E. coli* [also called Lpf in *E. coli* (Torres et al., 2002)] and conservation among *S. bongori* and some isolates of subspecies *salamae* and *enterica* (Worley et al., 2018); however some models based on a smaller set of isolates suggest the independent acquisition of the Lpf gene cluster by *S. bongori* and *S. enterica* subsp. *enterica* clade A serovars (Desai et al., 2013). The Peg fimbrial gene cluster [named for its original discovery in *S. enterica* subsp. *enterica* serovars Paratyphi A, Enteritidis, and Gallinarum (Thomson et al., 2008)] is detected

![Diagram showing the distribution of chaperone-usher fimbriae](https://example.com/diagram.png)
broadly across both species and most *S. enterica* subspecies except for *diarizonae* and *houtenae*. *S. bongori* is predicted to have acquired the Sba fimbrial gene cluster from a most recent common ancestor (MRCA) shared with *E. coli*, although Sba has since been lost in *S. enterica* (Fookes et al., 2011; Yue et al., 2012). Finally, Sta [orthologue of *E. coli* Yad (Townsend et al., 2001; Wurpel et al., 2013)] and Stc [orthologue of *E. coli* Yeh (Townsend et al., 2001; Wurpel et al., 2013)] fimbrial gene clusters are found in *S. bongori* and *S. enterica* but show different distributions among the *S. enterica* subspecies (Figure 1B), suggesting different patterns of loss for these two fimbrial gene clusters (Yue et al., 2012; Desai et al., 2013).

The Modern Chaperone-Usher Fimbriome: Fimbrial Gene Clusters (Likely) Acquired After Divergence From *Escherichia*

Following *Salmonella*’s divergence from *Escherichia*, the remaining chaperone-usher fimbrial gene clusters are hypothesized to have been acquired *via* horizontal gene transfer. While the exact mechanisms responsible for acquisition of the majority of *Salmonella* fimbrial gene clusters remain elusive, the presence of orthologous clusters in other Gammaproteobacteria (Nuccio and Bäumler, 2007; Desai et al., 2013; Stubenrauch et al., 2017), and the observation that multiple chaperone-usher fimbrial gene clusters are carried on plasmids [e.g., Pef and *κ*-fimbriae (Bäumler et al., 1996a; Nuccio and Bäumler, 2007; Aviv et al., 2017)] support their horizontal acquisition from other genera.

Although originally characterized in *S. enterica* subsp. *enterica* serovars Typhi [Stb, Std, Ste, Sf, Stg, and Sth (Townsend et al., 2001)] and Typhimurium [Stj (McClelland et al., 2001)], these fimbriae are distributed widely across multiple different *Salmonella* lineages (Figure 1B). The Stb and Std fimbrial gene clusters were likely acquired by subspecies *diarizonae* (Yue et al., 2012) and maintained in the majority of subspecies *enterica* isolates. The evolutionary history of Sdf, Ste, Sf, Stg, and Stj fimbrial gene clusters likely involved multiple acquisition events or a combination of acquisition and loss/retenion by some subspecies (Yue et al., 2012; Desai et al., 2013). Last, the Sth fimbrial gene cluster is present in *S. bongori* and in most *S. enterica* subspecies (missing in subspecies *arizonae* and *diarizonae*); this fimbrial gene cluster was most likely acquired by *S. bongori* following its divergence from *Escherichia* (Desai et al., 2013) as this genomic region is missing from *E. coli* (Townsend et al., 2001) and no known *E. coli* fimbrial gene clusters with similar sequence homology have been identified (Nuccio and Bäumler, 2007).

The remaining *Salmonella* chaperone-usher fimbriae include those that have only been characterized in one species or subspecies. Multiple fimbrial gene clusters are found exclusively in non-subsp. *enterica* isolates: (i) Sbb and Sbc in *S. bongori* (Fookes et al., 2011; Yue et al., 2012), (ii) Sdd and Sdc, the only known *σ*-fimbria, in *S. enterica* subsp. *arizonae*, (iii) Sdi, Sdj, Sdl, and Sdk in *S. enterica* subsp. *diarizonae* (Yue et al., 2012), and (iv) Sib, a novel *β*-fimbria, in *S. enterica* subsp. *indica* (Desai et al., 2013). *S. enterica* subsp. *enterica* encodes 12 fimbriae that are not found in *S. bongori* or other *S. enterica* subspecies (Figure 1B). Tcf [for Typhi colonization factor (Folkesson et al., 1999)] and Saf are present in isolates representing all currently known subsp. *enterica* clades except for clade C. Sti, Peh, Sdg, and Sdh fimbrial gene clusters are found in multiple subsp. *enterica* clades, but are largely missing from section Typhi isolates (Sti is present in one serovar, Kintambo, in section Typhi), suggesting the selective loss of these fimbriae in section Typhi isolates. Conversely, Stk and Fae fimbrial gene clusters are found in some isolates representing subsp. *enterica* clades B, A1, Typhi, and A2. The plasmid-encoded Pef fimbrial gene cluster was only detected in a handful of serovars including Nottingham (clade B) and four serovars in clade A2 that had previously been shown to carry the *Salmonella* virulence plasmid (i.e., serovars Choleraesuis, Enteritisidis, Bovismorbiﬁcans, and Typhimurium) (Cheng et al., 2019). The Sef [*Salmonella* Enteritidis fimbriae (Clouthier et al., 1993)] fimbrial gene cluster is found in multiple clade A2 serovars as well as in some section Typhi isolates (Yue et al., 2012). Finally, the Sde and Mrk [Mannose resistant *Klebsiella*-like fimbriae (Wilksch et al., 2011)] fimbrial gene clusters have only been reported in serovars Tennessee (clade A1) and Montevideo (clade B), respectively (Yue et al., 2012).

With a more complete picture of the *Salmonella* chaperone-usher fimbriome, several key themes arise. First, many chaperone-usher fimbrial gene clusters are detected broadly across both *S. bongori* and *S. enterica*, suggesting the early acquisition of these chaperone-usher fimbrial gene clusters. Second, very few chaperone-usher fimbrial gene clusters are serovar-specific. While this may be a reflection of the specific bioinformatic approaches used (i.e., identity cut-off used) or the isolates in the comparison, it suggests that while fimbriae may contribute to host/niche adaptation, they are likely only a part of the process as many other factors also play a role (e.g., changes in metabolic pathways (Nuccio and Bäumler, 2014), immunological naivety of the host (Bäumler et al., 2000), etc.). Last, the currently available data highlight multiple “rare” fimbrial gene clusters, where future characterizations including a broader range of isolates will be necessary to extend our knowledge of the evolutionary events associated with these fimbriae.

**MAKING AN ENTRANCE—EXAMINING A ROLE FOR CHAPERON-USHER FIMBRIAE IN MEDIATING INTERACTIONS WITHIN AND BETWEEN HOSTS**

As reviewed previously (Rivera-Chavez and Bäumler, 2015), *Salmonella* is ill-suited to compete with the resident anaerobic microbiota within the lumen of the gut (Tsolis and Bäumler, 2020). Therefore, *Salmonella* uses different strategies upon entering the gut to either escape to a slightly less competitive environment or modify the environment to one that favors its expansion (Tsolis and Bäumler, 2020). Fimbriae are proposed to play a key role in mediating initial interactions with host cells.
The majority of the host cell surface receptors that are recognized and bound by fimbriae remain elusive, although several surface glycans have been identified as facilitating adhesion (Table 1): Std (¢-fimbriae) binds to terminal α-1,2 fucose (Chessa et al., 2009; Suvandi et al., 2019), Fim (γ1-fimbriae) binds to mannose (Duguid et al., 1966), and Pef (κ- fimbriae) binds Galβ1-4(Fucα1-3)GlcNAc [also called the Lea histo-blood group antigen (Chessa et al., 2008)]. These observations suggest that fimbriae may mediate preferential binding to different glycans, thereby facilitating Salmonella’s ability to bind to different host cell surfaces either within the same host (tissue tropism) or in different hosts (host tropism).

### A Role for Chaperone-Usher Fimbriae in Tissue Tropism?

*Salmonella* strains encode an average of 5–14 different fimbrial gene clusters (McClelland et al., 2001; Townsend et al., 2001; Yue et al., 2012; Worley et al., 2018) with multiple fimbriae being co-expressed in vivo (Humphries et al., 2003; Laniekis et al., 2017). During an infection, nontyphoidal *Salmonella* (e.g., *S. Typhimurium*) capitalize on a pro-inflammatory response to generate host-derived nitrate released by immune cells (Rivera-Chavez and Bäumler, 2015) to favor their expansion in the gut lumen. In contrast, *S. Typhi* favors an anti-inflammatory approach by evading (Winter et al., 2015) immune surveillance and colonizing extraintestinal sites such as the gallbladder (Gunn et al., 2014). Reflective of these strategies, different fimbriae are proposed to facilitate nontyphoidal *Salmonella*’s preferential binding to M cells (Hase et al., 2009) and typhoidal *Salmonella*’s preferential binding to enterocytes (Gonzales et al., 2017). *S. Typhimurium* FimH, the tip adhesin of Fim, binds glycoprotein 2 (GP2) on M cells in a mannose-dependent manner (Hase et al., 2009), while Lpf facilitates binding to M-like cells (Gonzales et al., 2017) and murine Peyer’s patches (Table 1 (Bäumler et al., 1996b)). Conversely, Stg fimbriae in *S. Typhi* are thought to promote binding to enterocytes (Gonzales et al., 2017), although in at least some *S. Typhi* the Stg usher protein is likely non-functional due to frame shift mutations leading to pseudogene formation (Townsend et al., 2001; Dufresne et al., 2018).

After breaching the gut epithelium, *S. Typhimurium* uses Sti, Saf, Agf (curli, non-chaperone-usher fimbriae), and Stc fimbriae at extraintestinal sites, as quadruple deletion mutants show a reduced colonization of the spleen and liver compared to wild type strains (Laniekis et al., 2017). *S. Typhi* Agf has also been shown to enable binding to the gallbladder epithelium (Gonzalez-Escobedo and Gunn, 2013), supporting a role for this fimbria in promoting chronic colonization of *S. Typhi* in the gallbladder (Gonzalez-Escobedo et al., 2011). Several fimbriae have been implicated in facilitating long-term intestinal colonization of 129X1/Sv [Saf, Bcf, Sti, and Std (Lawley et al., 2006)] and CBA mice [Lpf, Bcf, Stb, Stc, Std, and Sth (Weening et al., 2005)]; as deletion of these fimbriae did not result in a reduced recovery of *S. Typhimurium* from fecal samples of BALB/c mice at five days post infection (Weening et al., 2005), it appears that these fimbriae instead affect colonization in a temporal-manner, at different stages over the course of an infection. Finally, multiple studies have shown that chaperone-usher fimbriae undergo phase variation, a process in which expression of fimbriae in the bacterial population is heterogeneous (Humphries et al., 2001; Humphries et al., 2005; Kolenda et al., 2019). Together, these observations support a role for multiple chaperone-usher fimbriae in facilitating tissue tropism in both acute and chronic infections for both typhoidal and nontyphoidal *Salmonella*, but also suggest redundant roles for many fimbriae as deletion/inactivation of a single fimbrial gene cluster often has negligible effects on virulence in vivo.

### It Is Complicated—A Combination of Fimbrial Adhesin Allelic Diversity, Pseudogene Formation, and Differential Fimbrial Expression Support a Role for Chaperone-Usher Fimbriae in Host Tropism

Together with the observation that many chaperone-usher fimbriae are distributed across multiple lineages (and serovars), several studies have suggested that the mere presence of fimbrial gene clusters cannot fully explain the observed patterns of host tropism (Chaudhuri et al., 2013; Zhang et al., 2019), highlighting the complexity of the relationship between fimbriae and virulence (Humphries et al., 2001). One possible explanation is that analyses that only consider presence/absence data do not account for pseudogene formation among fimbrial genes, which has been demonstrated previously for multiple host-adapted/restricted serovars Typhi (Townsend et al., 2001), Dublin (Nuccio and Bäumler, 2014; Langridge et al., 2015), Gallinarum (Clayton et al., 2008), Choleraesuis and Paratyphi C (Nuccio and Bäumler, 2014) (Figure 1C). Another possibility is that the conformation of the tip adhesin mediates binding to different host cells, as several studies have documented that different alleles of fimbrial adhesins are associated with isolation from different hosts (Kisiela et al., 2012; Yue et al., 2018).

### TABLE 1 | Summary of fimbriae with known host receptors.

| Chaperone-usher clade | Fimbria | Host cell receptor | Cell types bound | References |
|-----------------------|---------|--------------------|------------------|-----------|
| γ1                   | Fim     | Mannose residues on glycoprotein 2 | M cells | (Duguid et al., 1966; Hase et al., 2009) |
| γ1                   | Lpf     | Unknown            | M-like cells     | (Bäumler et al., 1996b) |
| γ1                   | Stg     | Unknown            | Enterocytes      | (Gonzales et al., 2017) |
| κ                    | Pef     | Galβ1-4(Fucα1-3)GlcNAc | Unknown | (Chessa et al., 2008) |
| π                    | Std     | α-1,2 fucose       | Colonic and cecal intestinal epithelial cells | (Chessa et al., 2008; Suvandi et al., 2019) |

1 Types of host cells predicted to be the preferential binding target of the fimbria.
MISSING PIECES OF THE SALMONELLA CHAPERONE-USHER FIMBRIOME PUZZLE

The appreciable diversity of Salmonella serovars is mirrored by its diverse chaperone-usher fimbriome. While some fimbriae, such as Fim and Agf, have been studied extensively due in part to their expression under certain standard lab culturing conditions (Laniewski et al., 2017; Kolenda et al., 2019), discovery of novel fimbrial gene clusters continues with the expanded use of whole genome sequencing in public health and research efforts. With current initiatives aimed at utilizing genomic data for source prediction to facilitate foodborne outbreak investigations (Zhang et al., 2019; Merlotti et al., 2020), an enhanced understanding of the role that diverse chaperone-usher fimbriae, and potentially different conformations of their adhesins, play in the colonization of a wide range of hosts is warranted. Future investigations to understand the sequence diversity and conservation of chaperone-usher fimbriae among lesser studied Salmonella subspecies and serovars will be important for determining patterns of chaperone-usher fimbriae associated with different hosts. Furthermore, structural data of fimbrial components that facilitate interactions with host receptors will require the development and characterization of additional cell culture/organoids and animal models to expand our understanding of the role of chaperone-usher fimbriae in a broader range of tissues and hosts. These, combined with more basic inquiries to understand transcriptional and translational regulatory mechanisms to identify which host signals govern expression of different fimbriae, represent important missing pieces in our understanding of the Salmonella chaperone-usher fimbriome puzzle.

AUTHOR CONTRIBUTIONS

This review article was conceptualized by RC and MW. RC and MW wrote, reviewed, and edited the original and final drafts. Funding was secured by RC. All authors contributed to the article and approved the submitted version.

FUNDING

Funding for this review was provided by USDA 2020-67034-31905 awarded to RC.

ACKNOWLEDGMENTS

The authors wish to acknowledge members of the Cornell Food Safety Lab for helpful discussions pertaining to the content of this review.

REFERENCES

Aviv, G., Elpers, L., Mikblin, S., Cohen, H., Vitman Zilber, S., Grasl, G. A., et al. (2017). The plasmid-encoded Ipf and Klf fimbriae display different expression and varying roles in the virulence of Salmonella enterica serovar Infantis in mouse vs. avian hosts. PLoS Path. 13, e1006559–e1006559. doi: 10.1371/journal.ppat.1006559
Azriel, S., Goren, A., Shomer, I., Aviv, G., Rahav, G., and Gal-Mor, O. (2017). The Typhi colonization factor (Tcf) is encoded by multiple non-typhoidal Salmonella serovars but exhibits a varying expression profile and interchanging contribution to intestinal colonization. Virulence 8, 1791–1807. doi: 10.1080/21505594.2017.1380766
Bäumler, A. J., Tsolis, R. M., Bowe, F. A., Kusters, J. G., Hoffmann, S., and Heffron, F. (1996a). The pef fimbrial operon of Salmonella Typhimurium mediates adhesion to murine small intestine and is necessary for fluid accumulation in the infant mouse. Infect. Immun. 64, 61–68. doi: 10.1128/IAI.64.1.61-68.1996
Bäumler, A. J., Tsolis, R. M., and Heffron, F. (1996b). The Ipf fimbrial operon mediates adhesion of Salmonella Typhimurium to murine Peyer’s patches. Proc. Natl. Acad. Sci. U. S. A. 93, 279–283. doi: 10.1073/pnas.93.1.279
Bäumler, A. J., Harigs, B. M., and Tsolis, R. M. (2000). Tracing the origins of Salmonella outbreaks. Science 287, 50–52. doi: 10.1126/science.287.5450.50
Bäumler, A. J., and Heffron, F. (1995). Identification and sequence analysis of lpfABCDEF, a putative fimbrial operon of Salmonella Typhimurium. J. Bacteriol. 177, 2087–2097. doi: 10.1128/JB.177.8.2087-2097.1995
Bodicker, J. D., Ledeboer, N. A., Jagnow, J., Jones, B. D., and Clegg, S. (2002). Differential binding to and biofilm formation on, HEP-2 cells by Salmonella enterica serovar Typhimurium is dependent upon allelic variation in the fimH gene of the fim gene cluster. Mol. Microbiol. 45, 1255–1265. doi: 10.1046/j.1365-2958.2002.03121.x
Brenner, F., Villar, R., Angulo, F., Tauxe, R., and Swaminathan, B. (2000). Salmonella nomenclature. J. Clin. Microbiol. 38, 2465–2467. doi: 10.1128/JCM.38.7.2465-2467.2000
Centers for Disease Control and Prevention (2016). National Enteric Disease Surveillance: Salmonella Annual Report 2016. https://www.cdc.gov/ncsrnsurveillance/pdfs/2016-Salmonella-report-508.pdf
Chaudhuri, R. R., Morgan, E., Peters, S. E., Pleasance, S. J., Hudson, D. L., Davies, H. M., et al. (2013). Comprehensive assignment of roles for Salmonella Typhimurium genes in intestinal colonization of food-producing animals. PLoS Genet. 9, e1003456. doi: 10.1371/journal.pgen.1003456
Cheng and Wiedmann Revisiting the evolution of the Salmonellae. Nature 496, 243–246. doi: 10.1038/nature12007
Gonzales, A. M., Wilde, S., and Roland, K. L. (2017). New insights into the roles of long polar fimbriae and Stg fimbriae in Salmonella interactions with enterocytes and M cells. Infect. Immun. 85, e00127–e00117. doi: 10.1128/IAI.00172-17
Gonzalez-Cescobeo, G., Marshall, J. M., and Gunn, J. S. (2011). Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. Nat. Rev. Microbiol. 9, 9–14. doi: 10.1038/nrmicro2490
Hoelzer, K., Marshall, J., Baker, S., Dongol, S., Charles, R. C., and Ryan, E. T. (2014). Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends Microbiol. 22, 648–655. doi: 10.1016/j.tim.2014.06.007
Humphries, A. D., Townsend, S. M., Kingsley, R. A., Nicholson, T. L., Tsolis, R. M., et al. (2011). Animal contact as a source of human non-typhoidal salmonellosis. Vet. Microbiol. 166, 530–557. doi: 10.1016/j.vetmic.2013.07.004
Humphries, A. D., Rafailovitch, M., Laffin, A. E., Brotas, M., Cisaros, M., and Dresler, K., et al. (2017). Functional expression of the entire adhesiome of Salmonella enterica serotype Typhimurium. Sci. Rep. 7, 1–12. doi: 10.1038/s41598-017-10998-2
Havelaar, A. H., Kirk, M. D., Torgerson, P. R., Gibb, H. J., Hald, T., Lake, R. J., et al. (2015). World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. PLoS Med. 12, e1001923. doi: 10.1371/journal.pmed.1001923
Hoelzer, K., Moreno Switt, A. I., and Wiedmann, M. (2011). Animal contact as a source of human non-typhoidal salmonellosis. Vet. Res. 42, 34. doi: 10.1186/1297-9716-42-34
Humphries, A. D., Townsend, S. M., Kingsley, R. A., Nicholson, T. L., Tsolis, R. M., and Bäumler, A. J. (2001). Role of fimbriae as antigens and intestinal colonization factors of Salmonella serovars. FEMS Microbiol. Lett. 201, 212–215. doi: 10.1111/1574-6988.2001.b10744.x
Humphries, A. D., Rafailovitch, M., Winter, S., Weening, E. H., Kingsley, R. A., Nicholson, T. L., Tsolis, R. M., et al. (2011). Animal contact as a source of human non-typhoidal salmonellosis. Vet. Res. 42, 34. doi: 10.1186/1297-9716-42-34
Kisiela, D. I., Chattopadhyay, S., Libby, S. J., Karlinsey, J. E., Fang, F. C., Tchesnokova, V., et al. (2012). Evolution of Salmonella enterica virulence via point mutations in the fimbrial adhesin. PLoS Path. 8, e1002733–e1002733. doi: 10.1371/journal.ppat.1002733
Kapfer, B. C., Nataro, J. P., and Mobbly, H. L. (2004). Pathogenic Escherichia coli. Nat. Rev. Microbiol. 2, 123–140. doi: 10.1038/nrmicro818
Kisiela, D. I., Chattopadhyay, S., Libby, S. J., Karlinsey, J. E., Fang, F. C., Tchesnokova, V., et al. (2012). Evolution of Salmonella enterica virulence via point mutations in the fimbrial operon. FEMS Microbiol. Lett. 326, 326–332. doi: 10.1111/j.1574-6968.2012.02370.x
Kisiela, D. I., Chattopadhyay, S., Libby, S. J., Karlinsey, J. E., Fang, F. C., Tchesnokova, V., et al. (2012). Evolution of Salmonella enterica virulence via point mutations in the fimbrial adhesin. PLoS Path. 8, e1002733–e1002733. doi: 10.1371/journal.ppat.1002733
Kolenda, R., Ugorski, M., and Gryzmajoł, K. (2019). Everything you always wanted to know about Salmonella type 1 fimbriae, but were afraid to ask. Front. Microbiol. 10. doi: 10.3389/fmicb.2019.001017
Langridge, G. C., Fookes, M., Connor, T. R., Feltwell, T., Feasey, N., Parsons, B. N., et al. (2015). Patterns of genome evolution that have accompanied host adaptation in Salmonella. Proc. Natl. Acad. Sci. 112, 863–868. doi: 10.1073/pnas.1416707112
Laniewski, P., Baek, C. H., Roland, K. L., and Curtiss, R.3. (2017). Analysis of spleen-induced fimbra production in recombinant attenuated Salmonella enterica serovar Typhimurium vaccine strains. mBio 8, e01189–e01117. doi: 10.1128/mBio.01189–17
Lawley, T. D., Chan, K., Thompson, L. J., Kim, C. C., Govoni, G. R., and Monack, D. M. (2006). Genome-wide screen for Salmonella genes required for long-term systemic infection of the mouse. PLoS Pathog. 2, e11. doi: 10.1371/journal.ppat.0020011
Mcclelland, M., Sanderson, K. E., Spieth, J., Clifton, S. W., Latreille, P., Courtney, L., et al. (2001). Complete genome sequence of Salmonella enterica serovar Typhimurium LT2. Nature 413, 852–856. doi: 10.1038/35101614
Merlotti, A., Manfreda, G., Muncy, N., Hald, T., Litrup, E., Nielsen, E. M., et al. (2020). Network approach to source attribution of Salmonella Typhimurium and its monophasic variant. Front. Microbiol. 11, 1205. doi: 10.3389/fmicb.2020.01205
Nobbs, A. H., Lamont, R. J., and Jenkinson, H. F. (2009). Streptococcus adherence and colonization. Microb. Mol. Biol. Rev. 73, 407–450. doi: 10.1128/MMBR.00014-09
Nuccio, S. P., and Bäumler, A. J. (2007). Evolution of the chaperone/usher paradigm: fimbrial classification goes Greek. Microb. Mol. Biol. Rev. 71, 551–575. doi: 10.1128/MMBR.00014-07
Nuccio, S.-P., and Bäumler, A. J. (2014). Comparative analysis of Salmonella genomes identifies a metabolic network for escalating growth in the inflamed gut. mBio 5, e00929. doi: 10.1128/mBio.00929-14
Paczosa, M. K., and Mecsas, J. (2016). Klebsiella pneumoniae: going on the offense with a strong defense. Microbiol. Mol. Biol. Rev. 80, 629–661. doi: 10.1128/MMBR.00078-15
Rehman, T., Yin, L., Latif, M. B., Chen, J., Wang, K., Geng, Y., et al. (2019). Adhesive mechanism of different Salmonella fimbrial adhesins. Microb. Path. 137, 103748. doi: 10.1016/j.micpath.2019.103748
Rivera-Chavez, F., and Bäumler, A. J. (2015). The pyromaniac inside you: Salmonella metabolism in the host gut. Annu. Rev. Microbiol. 69, 31–48. doi: 10.1146/annurev-micro-090114-104108
Slaterenbach, T., Nguyen, K. T., Nuccio, S. P., Winter, M. G., Vakulskas, C. A., Clegg, S., et al. (2013). A novel CsrA titration mechanism regulates fimbrial gene expression in Salmonella Typhimurium. EMBO J. 32, 2872–2883. doi: 10.1038/emboj.2013.206
Stubenrauch, C. J., Dougan, G., Lithgow, T., and Heinz, E. (2017). Constraints on lateral gene transfer in promoting fimbrial usher protein diversity and function. Open Biol. 7, 170044. doi: 10.1098/rsob.170044
Suwandi, A., Galeev, A., Riedel, R., Sharma, S., Seeger, K., Sterzenbach, T., et al. (2019). Std fimbriae-fucose interaction increases Salmonella-induced intestinal inflammation and prolongs colonization. PLoS Path. 15, e1007915. doi: 10.1371/journal.ppat.1007915
Thanasi, D. G., Nuccio, S. P., Shu, S. K. S., and Bäumler, A. (2007). Fimbriae: Classification and Biochemistry. EcolSal. Plus 2. doi: 10.1128/ecosal.2.4.2.1
Thompson, N. R., Clayton, D. J., Windhorst, D., Vernikos, G., Davidson, S., Churcher, C., et al. (2008). Comparative genome analysis of Salmonella Enteritidis PT4 and Salmonella Gallinarum 287/91 provides insights into evolutionary and host adaptation pathways. Genome Res. 18, 1624–1637. doi: 10.1101/gr.077404.108
Torres, A. G., Giron, J. A., Perna, N. T., Burland, V., Blattner, F. R., Avelino-Flores, F., et al. (2002). Identification and Characterization of IpgABC/DE, a fimbrial operon of Enterohemorrhagic Escherichia coli O157:H7. Infect. Immun. 70, 5416–5427. doi: 10.1128/IAI.70.10.5416-5427.2002
Townsend, S. M., Kramer, N. E., Edwards, R., Baker, S., Hamlin, N., Simmonds, M., et al. (2001). Salmonella enterica serovar Typhi possesses a unique repertoire of fimbrial gene sequences. Infect. Immun. 69, 2894–2901. doi: 10.1128/IAI.69.5.2894-2901.2001
Tsolis, R. M., Townsend, S. M., Miao, E. A., Miller, S. L., Ficht, T. A., Adams, L. G., et al. (1999). Identification of a putative Salmonella enterica serotype Typhimurium host range factor with homology to IpaH and YopM by signature-tagged mutagenesis. Infect. Immun. 67, 6385–6393. doi: 10.1128/IAI.67.12.6385-6393.1999
Wagner, C., and Hensel, M. (2011). “Adhesive mechanisms of Salmonella enterica,” in Bacterial adhesion Eds. A. Goldman (Heidelberg, Germany: Springer), vol. 17-34. doi: 10.1128/978-84-9007-0490-9_2
Weening, E. H., Barker, J. D., Laarakkers, M. C., Humphries, A. D., Tsolis, R. M., and Bäumler, A. J. (2005). The Salmonella enterica serotype Typhimurium T3p operons are required for intestinal persistence in mice. Infect. Immun. 73, 3358–3366. doi: 10.1128/IAI.73.6.3358-3366.2005
Winter, S. E., Winter, M. G., Atluri, V., Poon, V., Romão, E. L., Tsolis, R. M., et al. (2015). The flagellar regulator TviA reduces pyroptosis by Salmonella enterica serovar Typhi. Infect. Immun. 83, 1546–1555. doi: 10.1128/IAI.02803-14
Worley, J., Meng, J., Allard, M. W., Brown, E. W., and Timme, R. E. (2018). Salmonella enterica phylogeny based on whole-genome sequencing reveals two new clades and novel patterns of horizontally acquired genetic elements. mBio 9, e02303–e02318. doi: 10.1128/mBio.02303–18
Zoonotic source attribution of Salmonella enterica serovar Typhi in the age of microbiome research. Curr. Opin. Microbiol. 53, 78–89. doi: 10.1016/j.mib.2020.03.002
Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.