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Fimbriation and curliation in *Escherichia coli* O157:H7

A paradigm of intestinal and environmental colonization

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Shiga toxin-producing *Escherichia coli* (STEC) serotypes, particularly *E. coli* O157:H7, possess a variety of fimbrial and afimbrial adhesins which have emerged as important contributors to intestinal colonization. *E. coli* O157:H7 possesses two chromosomal operons encoding long polar fimbriae (Lpf), which have been found to influence adherence in vitro and colonization in vivo. In a recent *Infection and Immunity* paper, we further explored the role of Lpf in *E. coli* O157:H7 intestinal colonization by using the infant rabbit model of STEC infection. We found that an *E. coli* O157:H7 Lpf-deficient mutant was outcompeted in the rabbit intestine by its parental strain, which may suggest that Lpf contributes to colonization. In contrast, the Lpf-deficient mutant showed an increased adherence to cultured intestinal epithelial cells, and we discovered that this strain overexpressed curli fibers. In this addendum article, we provide a continued perspective on the predicted roles of Lpf and curli, both in vivo and in vitro.

Key words: long polar fimbriae, curli, *E. coli* O157:H7, enterohemorrhagic *E. coli*, fimbria, colonization

Abbreviations: STEC, Shiga toxin-producing Escherichia coli; Lpf, long polar fimbriae; A/E, attaching and effacing

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Food-borne pathogens are able to survive in a diverse range of environmental niches, including those encountered in the mammalian intestine or on the surfaces of different vegetables. The ability to adhere is a vital first step in the successful colonization of these environments. Thus, organisms have acquired an array of fimbrial and afimbrial adhesins that mediate attachment to biotic and/or abiotic surfaces. A determination of the factors that are important in adhesion and the conditions under which these factors operate and interact will enable us to develop more effective approaches to prevent bacterial attachment to surfaces, and thereby reduce the chance of human infection.

Shiga toxin-producing *E. coli* (STEC) O157:H7 is an important cause of human gastrointestinal disease and the best-studied STEC serotype associated with large outbreaks worldwide. *E. coli* O157:H7 strains are common in the intestines of livestock and can be transmitted to humans following the consumption of fecal-contaminated meat, fruits and vegetables.[1] Like many food-borne pathogens, *E. coli* O157:H7 contains a multitude of putative adhesion factors (reviewed in ref. 2). However, the outer membrane protein, intimin, and the long polar fimbriae (Lpf) are the only two *E. coli* O157:H7 adhesins that have been demonstrated to play a role in the colonization of human intestinal epithelial cells.[3,4] While the role for intimin in *E. coli* O157:H7 attachment to human intestinal explants is well-established,[4,5] the role of Lpf is less clear.

E. coli O157:H7 possesses two *lpf* operons, *lpf1* and *lpf2*, both of which contain genes closely related to the long polar fimbriae of *Salmonella enterica* serovar Typhimurium.[6] Expression of *lpf1* and *lpf2* is induced during the late exponential-phase growth in tissue culture media at pH 6.5 and 37°C[7,8] or under iron restricted conditions,[9] and has been found to influence *E. coli* O157:H7 adherence to cultured epithelial monolayers.[10,11] We have shown that a mutation of the *lpf1* operon results in a significant reduction in *E. coli* O157:H7 adherence to, as well

as a reduction in microcolony formation on, cultured epithelial cells.[7] Similarly, an *lpf2* mutation showed partial reduction in adherence, and a possible role for Lpf2 in early adherence to intestinal cells has been suggested.[9]

Studies in a variety of animal models have supported the role of Lpf in intestinal colonization and persistence. For example, a report on in vivo colonization assays using samples from sheep and pigs demonstrated that the absence of both *lpf1* and *lpf2* loci impair *E. coli* O157:H7 colonization.[11] Yet in contrast to the in vitro study results, the single *lpf1* mutant was found to have performed as well as the parent strain in colonizing the intestines of sheep and pigs.[11] Contrasting results were obtained from a different set of experiments that used a collection of *lpf* mutants constructed in a Shiga toxin-negative *E. coli* O157:H7 strain and were conducted in 6-week-old cross-bred lambs. In this case, the recovery of both the *lpf1* mutant and the double *lpf1 lpf2* mutant in fecal material was significantly attenuated when compared with the findings in the wild type.[10] Further complicating matters are findings from studies using tissue explants. For example, Lpf did not influence the ability of *E. coli* O157:H7 to adhere to intestinal explants obtained from lambs.[10] Similar studies in human tissues showed that *E. coli* O157:H7 strains with *lpf* mutations colonized intestinal regions that were not normally bound by a wild-type strain.[3] Taken all together, all of these studies indicate environmental conditions may dictate which mechanisms control *E. coli* O157:H7 adherence and that there is redundancy between some of these systems examined.

Given the relatively subtle effects of *lpf* mutations on adherence in vitro, coupled with the divergent findings from in vivo or organ culture experiments, the precise role of Lpf in *E. coli* O157:H7 adherence remains somewhat unclear. Therefore, in our recent study published in *Infection and Immunity*,[12] the role of the *E. coli* O157:H7 *lpf* loci was further tested in an infant rabbit model which mimics the diarrhea and gut pathology, including the histopathological attaching and effacing lesions, seen in patients with STEC infection.[13] We assessed the importance of Lpf for intestinal colonization by performing competition experiments between *E. coli* O157:H7 and an isogenic *lpf1 lpf2* double mutant and found that the mutant was outcompeted in the ileum, cecum, and mid-colon of rabbits, confirming that Lpf contributes to intestinal colonization.[12] Unexpectedly, we observed that the *lpf1 lpf2* double mutant showed an increased adherence to colonic epithelial cells in vitro, and transmission electron microscopy revealed curli-like structures on the surface of this mutant, as confirmed by immunoblotting and Congo red binding assays, immunogold-labeling electron microscopy, and real-time RT-PCR measuring *csgA* (encoding the major curli subunit) expression. Interestingly, deletion of *csgA* per se did not appear to affect intestinal colonization. Therefore, in addition to conclusively demonstrating that Lpf contribute to *E. coli* O157:H7 intestinal colonization, our observations indicated that the regulatory mechanisms controlling expression of Lpf and curli are interconnected.

Curli fibers are commonly thought to be involved in the colonization of abiotic surfaces and the development of biofilms (reviewed in ref. 14). Curli are thin (2 to 5 nm wide), coiled fibers of varying lengths that self-assemble outside the cell and aggregate to form an amorphous matrix.[15–18] Curli fibers bind Congo red dye and certain host proteins including fibronectin, laminin, and plasminogen.[19,20] The production of curli polymers is environmentally regulated and RpoS-dependent, which means that the transcription of *csgA* is under the control of an environmental program that responds positively to low temperature, low osmolarity, and stationary-phase growth conditions.[21,22]

The role of curli in the pathogenesis associated with different diarrheagenic *E. coli* pathogroups is not clear. For example, in a collection of 49 bovine and human *E. coli* O157:H7 strains, only two human isolates were found to produce curli and exhibit Congo red binding under the conditions tested.[23,24] It has been proposed that natural *E. coli* isolates can be either "on" or "off" for the program controlling curli expression and that different growth conditions may select for these variants in both commensal and pathogenic *E. coli*.[21,25,16] Therefore, the low percentage of curli-positive strains found in the study above may mean that curli production in the human intestine is not common.

The results of several studies have led to a suggestion that curli play an important role in mediating attachment to surfaces other than those found in the intestine. For example, expression of the *E. coli* O157:H7 *csg* operon in laboratory *E. coli* strains increased the ability of these strains to bind to alfalfa sprouts and seed coats.[26] Furthermore, transcriptional analyses revealed that genes involved in curli production were significantly upregulated during *E. coli* O157:H7 attachment to lettuce leaves.[27] Finally, curli-expressing *E. coli* O157:H7 strains appeared to develop stronger associations bound in higher numbers to the surface of spinach leaves than did isogenic curli-deficient mutants.[28] Examination of the inoculated leaves revealed that curli-expressing *E. coli* O157:H7 were embedded in extracellular material that immunostained with anti-curli antibodies, possibly meaning that these structures may offer protection against the harsh desiccating environment found on the surface of leaves.[28]

The prevailing dogma is that curli expression in most *E. coli* strains is inhibited at mammalian body temperatures (i.e., 37°C) (reviewed in ref. 14), conditions which instead favor the transcription of most classes of fimbriae genes (reviewed in refs. 29 and 2). Our findings lead us to suggest that the regulation of these two adherence mechanisms may be linked. In our model, we propose that conditions in the intestine (37°C, pH 6–7, and/or low iron) favor the expression of Lpf, which in turn mediates bacterial colonization (see **Fig. 1**). In the absence of Lpf1 and Lpf2, the bacterium expresses curli, thus providing the organism with an alternative adhesion mechanism. Yet curli is known to be expressed better in low-salt and at 30°C,[30] and to mediate adhesion to surfaces other than the intestine.[26] Thus, deletion of *csgA* does not further attenuate *E. coli* O157:H7 intestinal colonization. It is clear that *E. coli* O157:H7 has evolved multiple adherence mechanisms to maximize bacterial survival fitness in different environments.

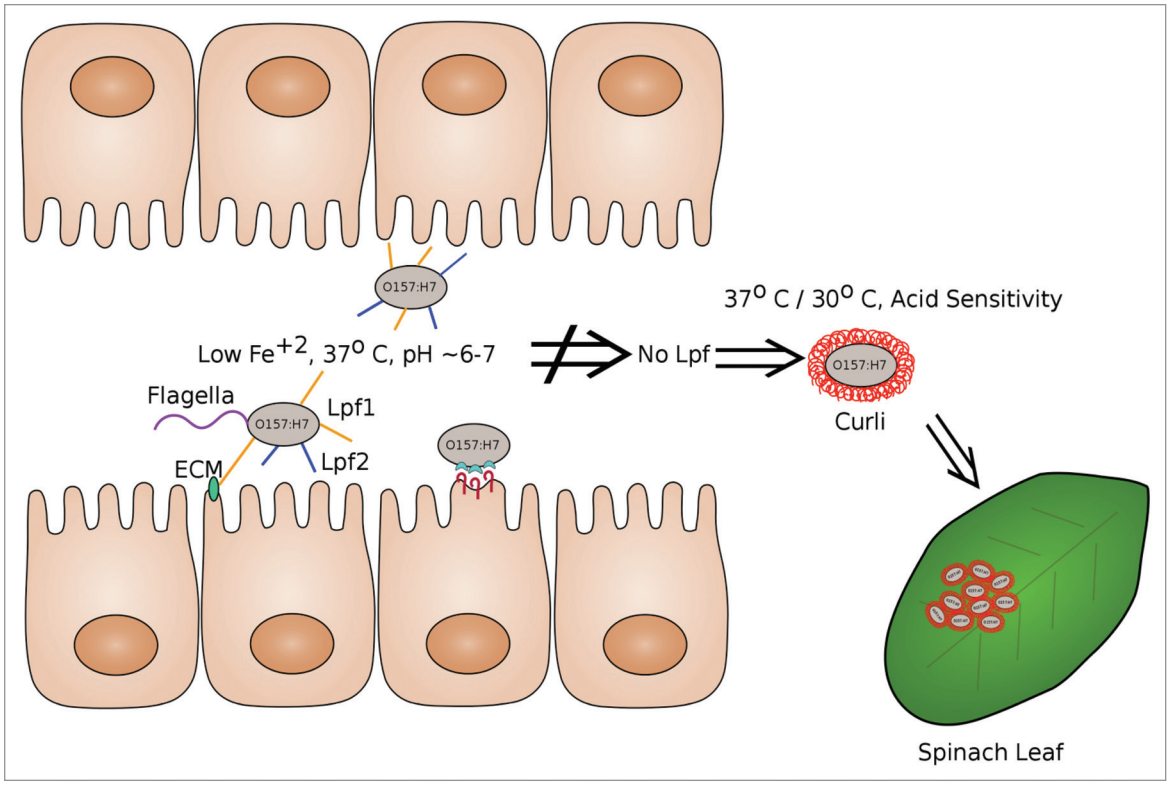

Figure 1. Model of intestinal expression of Lpf and environmental expression of curli. Long polar fimbriae (Lpf1 in yellow and Lpf2 in blue) are induced in conditions that mimic the intestine (pH 6.5, 37°C and low iron) and are proposed to participate in early attachment to intestinal cells and binding to extracellular matrix proteins (ECM). Intimin (light blue) and Tir (dark red), along with other Type III secreted effector proteins mediate the pedestal formation and the intimate attachment (attaching and effacing lesion, A/E) characteristic of *E. coli* O157:H7 and other A/E-producing bacteria. Curli (bright red) is expressed in the absence of Lpf at 30°C and 37°C, and curliated variants of *E. coli* O157:H7 are known to display acid sensitivity. Curli was shown not to contribute to intestinal colonization[12] and thus is thought to play a role in attachment to plant surfaces, such as in the case of spinach leaves, or other environmental substrates.

In other pathogenic scenarios, curli has been implicated in the pathogenesis of sepsis and uropathogenic *E. coli* (UPEC) infections.[31,32] However, in vivo curli production or an in vivo role for curliated *E. coli* O157:H7 has not yet been demonstrated, although some strains of *E. coli* O157:H7 do produce curli at 37°C and have been shown to adhere to or invade cultured cells or bovine intestinal explants.[33,34] Thus, we can only speculate that curli may act as an alternative adhesin in vivo in the Lpf-deficient mutant. Instead, curliated strains of *E. coli* O157:H7 exhibit characteristics that may provide a better fitness advantage in soils, sediments and on plant tissues.[35] A recent report indicates environmental stages of the life history of *E. coli* are more important than previously thought and that the mammalian intestine may not be the primary or even preferred environment for some *E. coli* strains.[36,37] For example, White et al. found curli production was more prevalent in host-generalist strains of *E. coli* (strains that are likely to be better adapted to the environment) than in predicted host-adapted strains.[36] In addition, Carter et al. found that curli-producing variants of *E. coli* O157:H7 were more sensitive to acid than were curli-negative variants, while the curli-negative variants were less fit in nutrient-limited conditions.[35] These results support the idea that curliated *E. coli* O157:H7 variants are more fit in conditions that mimic the environment, while non-curliated *E. coli* O157:H7 are better adapted to the host.

Heterogeneity of adhesin expression within a genetically homogeneous population during infection is thought to be important for niche colonization and immune evasion.[38] *E. coli* O157:H7 strains grown in vitro show heterogeneity of curli production, and subpopulations of curliated *E. coli* O157:H7 may also be present during host colonization or in the environment. In the study by Carter et al., the curli-producing phenotype was found to be stable at the population level in vitro and in all conditions tested, with infrequent conversion to a non-curliated phenotype.[35] The Lpf-deficient mutant described in our paper also exhibited stable curli production. At both 30°C and 37°C on LB plates containing Congo red and no-salt, following 48 h incubation, the majority of the Lpf-deficient colonies produced curli, while the wild-type strain showed a heterogeneous population with a majority of white colonies (data not shown). There is some evidence that both *lpf1* and *lpf2* are capable of phase variation,[39] so it may be that the wild-type colonies that produce curli are in the "off" phase for Lpf production. An example of such mutually exclusive expression has been demonstrated in UPEC in the regulation of Ag43 and type 1 fimbriae.[40] Ag43 (*flu*) mRNA levels increased

in the absence of type 1 fimbriae (*fim*) and decreased when type 1 fimbriae were overexpressed.[40] A similar relationship in *E. coli* O157:H7 in which curli production is dependent on the absence of Lpf would provide strong support for our model. A possible mechanism for interdependent regulation of Lpf and curli may be through the differential action of transcriptional activators that regulate the global repressor, histone-like nucleoid structuring protein (H-NS). In *E. coli* O157:H7, both curli and Lpf expression is silenced by H-NS.[41–44] In order for *lpf1* transcription to occur, the *E. coli* O157:H7 Ler regulator anti-silences H-NS, activating the *lpf1* locus as well as inducing the expression of other virulence factors, such as the intimin adhesin.[44,8] In contrast, activation of the stress/stationary phase response and RpoS de-represses H-NS, resulting in transcription of the curli operons.[21,42] Ler is activated by conditions that mimic the intestine, such as pH, carbon source and temperature (37°C), while RpoS is activated by conditions found outside the host such as low temperature and nutrient limitation.[45] However, the highly complex regulatory network involving H-NS, RpoS and Ler may obscure the effects of any one regulator, much as the effect of particular fimbriae may be masked by the compensatory and/or interdependent expression of other fimbriae. Therefore, the Lpf-deficient mutant may serve as a useful tool in determining whether interdependence occurs between Lpf and curli expression.

Finally, *E. coli* are ubiquitous in the intestines of mammals and other animals, and an environmental role has been recently brought to light in the wake of produce-associated outbreaks of infection by STEC O157:H7 and other STEC serotypes.[46] Thus it is not surprising to discover that *E. coli* possess redundant and/or compensatory mechanisms for colonization both in and out of the intestine. Although we propose that Lpf is preferred over curli in the colonization of the intestine, and the likely primary role for curli is in the environment, we may well discover that, true to the plasticity of *E. coli*, curli fibers are able to mediate adherence and/or survival in multiple host and environmental niches.

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