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Recent advances in adherence and invasion of pathogenic *Escherichia coli*

Anjana Kalita[1,*], **Jia Hu**[1,*], and **Alfredo G. Torres**[1,2,†]

[1]Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas, 77555, USA

[2]Department of Pathology, University of Texas Medical Branch, Galveston, Texas, 77555, USA

Abstract

Purpose of review—Colonization of the host epithelia by pathogenic *Escherichia coli* is influenced by the ability of the bacteria to interact with host surfaces. Because the initial step of an *E. coli* infection is to adhere, invade, and persist within host cells, some strategies used by intestinal and extra-intestinal *E. coli* to infect host cell are presented.

Recent findings—This review highlights recent progress understanding how extra-intestinal pathogenic *E. coli* strains express specific adhesins/invasins that allow colonization of the urinary tract or the meninges, while intestinal *E. coli* strains are able to colonize different regions of the intestinal tract using other specialized adhesins/invasins. Finally, evaluation of, different diets and environmental conditions regulating the colonization of these pathogens is discussed.

Summary—Discovery of new interactions between pathogenic *E. coli* and the host epithelial cells unravels the need of more mechanistic studies that can provide new clues in how to combat these infections.

Keywords

enterohemorrhagic *E. coli*; enteropathogenic; enterotoxigenic; uropathogenic; enteroaggregative; adherent invasive *E. coli*

Introduction

Escherichia coli are commonly found as part of the gut flora, where it is the predominant aerobic organism, living in symbiosis with its vertebrate host. However, there are several categories of *E. coli* strains that have acquired the ability to cause pathogenic processes in the host (1). These *E. coli* strains can cause intestinal (enteritis, diarrhea, or dysentery), or. extra-intestinal diseases (urinary tract infections, sepsis, or meningitis) (2, 3). To cause infection, pathogenic *E. coli* interact with the mucosa, by either attaching to the epithelial

[†]Corresponding author: Alfredo G. Torres, PhD. UTMB, Department of Microbiology and Immunology, Galveston, Texas, 77555 Phone (409) 747 0189; Fax (409) 747 6869; altorres@utmb.edu.
[*]These authors contributed equally to this work

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cells and in some instances, invading the target host cells. Because bacterial adhesion and/or invasion to/into host cells are the first step during infection, it is necessary to understand at a molecular level the mechanisms mediating these initial interactions. This article focus on reviewing recent progress on the understanding of the adhesion/invasion mechanisms used by intestinal and extra-intestinal pathogenic *E. coli* during colonization of the host cells.

Enterohemorrhagic *E. coli* (EHEC)

EHEC are a category of pathogenic *E. coli* that colonize the human large intestine and which can cause bloody diarrhea, or a systemic process known as hemolytic uremic syndrome (4). EHEC strains are characterized by the production of Shiga toxin and the formation of attaching and effacing intestinal lesions (Figure 1). Cattle are a main reservoir for EHEC strains; however several vegetables and fruits can serve as vehicles for EHEC outbreaks (5).

EHEC colonization is impacted by nutrient availability and dietary choice. Zumbrun et al found that dietary fiber content affects susceptibility to *E. coli* O157:H7 infection in mice (6). They treated BALB/c mice with high fiber diet (10% guar gum) or low fiber diet (2% guar gum) for two weeks and then mice were challenge with 10^9 to 10^{11} cfu of *E. coli* O157:H7. The results showed that mice fed with high fiber diet had enhanced levels of butyrate that temporally increased the expression of the Shiga toxin receptor Gb3. Therefore, mice exhibited greater *E. coli* O157:H7 colonization and reduction in resident *Escherichia spp*. Sheng et al also showed that cattle fed a hay diet are colonized by EHEC for a longer period of time than grain fed cattle (7). Different diets regulate the colonization of *E. coli* O157:H7 by altering the composition of gastrointestinal tract microbiota and the study demonstrated that the bacterial SdiA sensor activates genes conferring EHEC acid resistance, increasing efficient colonization of the cattle mucosa (8).

Modulation of host signals in the intestinal epithelia also affects EHEC colonization. Intestinal epithelial cells produced SIGIRR, a negative regulator of interleukin (IL)-1 and TLR signaling, that makes the cells hypo-responsive (9, 10). To address whether hypo-responsiveness affects enteric host defense, Sham et al challenge Sigirr deficient (−/−) mice with the murine pathogen, EHEC-related, *Citrobacter rodentium* and showed that Sigirr−/− mice are more susceptible to bacterial infection and had a dramatic loss of microbiota (11). The study showed that this host signaling mechanism promotes commensal dependent resistance to EHEC colonization.

Type III secretion system (TTSS) is required for EHEC colonization and attaching and effacing lesion formation. This syringe-like structure used to inject virulence factors into the host cell is exquisitely regulated. Hansen et al revealed that tyrosine phosphorylation in EHEC mediates signaling of virulence properties, including the type III secretion system (12). SspA is a known regulator of the TTSS (13) and a phosphorylated tyrosine residue of this protein positively affects expression and secretion of type III secretion system proteins. Branchu et al also found a new regulator of the TTSS (14) known as the NO-sensor regulator, NsrR. Nitric oxide (NO) reduced EHEC adherence to intestinal epithelial cells, by causing the detachment of the NsrR activator from the type III secretion system-encoding operons (*LEE1/4/5*), limiting colonization.

Enteropathogenic *E. coli* (EPEC)

EPEC isolates colonize the small intestine and are one of the leading causes of infantile fatal diarrhea (15). In industrialized countries, there are sporadic diarrheal cases in daycare facilities (16, 17). As for EHEC, EPEC uses the type III secretion system to form attaching and effacing lesions (Figure 1). EPEC strains are subdivided into typical (tEPEC) and atypical EPEC (aEPEC) based on the presence of EPEC adherence factor plasmid associated with the tEPEC localized adherence pattern (18). Some aEPEC form diffuse (DA) or aggregative adherence pattern and Hernandes et al (19) found that the DA pattern is associated with the TTSS system and its suggested that the traslocon serves as the DA adhesin.

Regarding the type III secretion system, recent studies have evaluated the role of the effector protein NleB in pathogenesis. Deletion of *nleB1* in *C. rodentium* caused significant reduction in murine intestinal colonization (20), and NleB has also been shown to modulate the host innate immune system by suppressing tumor necrosis factor (TNF)-mediated NF-κB activation (21). Three studies have investigated the role of NleB1 in EPEC. Gao et al focused on how NleB interfere with NF-κB (22). A proteomic screen was used to identify the host GAPDH as NleB-interacting protein, which results in modification of GAPDH and inhibition of NF-κB-dependent innate immune responses. The other two groups discovered that NleB blocks host death receptor signaling (23, 24), by interacting with two death receptor-signaling proteins, TRADD and FADD. NleB is the first known bacterial virulence factor to target death receptor signaling and it has been suggested that blocking this signaling mechanism may facilitate EPEC and EHEC colonization.

Other studies evaluated ways to reduce EPEC adhesion to host cells. Pan et al expressed synthetic tetrameric-branched peptide that enhanced the expression of Mucin 3 (25). They found that Mucin 3 interacted with EPEC and EHEC and reduced their binding to epithelial cells. In other study, Salcedo et al showed that the combination of gangliosides and sialic acid were able to interfere with EPEC and EHEC adhesion to Caco-2 cells (26).

Enterotoxigenic *E. coli* (ETEC)

ETEC colonizes the human small intestine and is responsible for neonatal diarrhea in developing countries as well as “travelers’ diarrhea” (27). ETEC adherence to the intestinal mucosa is mainly mediated by diverse adhesive structures known as colonization factors, which in combination with the heat-labile (LT) and/or heat-stable (ST) enterotoxins, causes disruption of fluid homeostasis in the host, resulting in diarrhea (2, 28) (Figure 1).

Guevara et al recently investigated one colonization factors, the CS21 pilus, and its role in adherence and pathogenesis *in vivo* (29). They found that ETEC CS21 (Longus) adherence to primary intestinal cells was inhibited by anti-LngA sera and the purified LngA protein. *In vivo* intra-stomach administration of CS21-expressing ETEC strain contributes to 100% lethality of newborn mice, which was reduced in the *lngA* mutant. A separate study investigated the role of the LT toxin in ETEC colonization (30). The authors observed enhanced adherence to IPEC-J2 cells by various isogenic ETEC constructs carrying different forms of the LT toxin (K88/LT wild type, attenuated toxin form [K88/LTR192G] and

expressing just the B subunit [K88/LTB]), in contrast to the attenuated phenotype of the LT-negative construct. LT^+ strains blocking binding of wild type ETEC strain to IPEC-J2 cells suggested that LT-driven adherence alters net surface charge on epithelial cells. Another study evaluated the transcriptional pattern of 214 genes at different time points following interaction of prototype ETEC E24377A with epithelial cells (31). The study found a prominent alteration of genes associated with motility, adhesion, toxin production, and global regulatory mechanisms, such as those linked to cAMP receptor protein and c-di-GMP, upon ETEC-host interaction, which suggested that ETEC coordinated its responses to the host environment by sequential activation of different virulence factors.

Among those ETEC strains infecting animals, the most common adhesive fimbriae include K88 or K99 (also called F4 and F5) (28). Recently, Zhou et al have demonstrated that deletion of *fliC* (encoding the major flagellin protein) and/or the *faeG* (encoding the F4 major fimbrial subunit) from ETEC strain C83902 significantly reduced its ability to adhere to porcine epithelia IPEC-J2 cells, but also impacting biofilm formation and quorum sensing (32). Interestingly, another study found an alternative way to block the adherence of ETEC K88 to IPEC-J2 by using ETEC anti-adhesives, including casein glycomacropeptide, exopolysaccharide, and vegetable extract (locust bean or wheat bran) (33). Finally, studies with human milk and commercial infant formulas found that the main gangliosides (GM3, GD3, GM1) and free sialic acid (Neu5Ac) are able to impede the adhesion of several pathogenic bacteria, including ETEC (26). Other dietary supplements, such as plantain NSP, also hampered the adherence of ETEC to Caco-2 cells, and has been suggested that blocking M-cell bacterial translocation can subsequently prevent diarrheal episodes (34).

Enteroaggregative *E. coli* (EAEC)

EAEC are a major cause of acute and persistent diarrhea in the small intestine of children and adults worldwide, including industrialized countries (35). EAEC is also responsible for sporadic cases and several outbreaks (36). At an initial stage of infection, EAEC adhere in a characteristic “stacked-brick” formation to host intestinal mucosa; forming a thick mucoid biofilm. The adherence process is mainly mediated by fimbrial structures called aggregative adherence fimbriae (AAF) (35) (Figure 1). Additionally, several EAEC virulence-related genes have been described but their role in the clinical outcome of infection is not completely defined.

A study recently confirmed a high prevalence, endemicity and heterogeneity of EAEC strains, and found that the plasmid-encoded toxin or AAF/II fimbrial subunit genes were associated significantly with disease (37). However, this study also demonstrated that the pathophysiology of EAEC infections involves a complex and dynamic modulation of several virulence factors. Another study identified an association of the EAEC virulence-encoded *aggR* gene (virulence regulator), pCDV432 plasmid, and additional virulence gene products, including dispersin and the Air adhesin in 90% of the diarrheagenic isolates that distinguished them from non-diarrheagenic EAEC strains, suggesting heterogeneity among highly pathogenic EAEC strains (38).

Another area of study in EAEC pathogenesis is the contribution of the autotransporter proteins. Munera et al evaluated the role of chromosome-encoded autotransporters in colonization and subsequent induction of diarrheal disease in infant rabbits and found that Shiga toxin-producing EAEC O104:H4 autotransporters, but not its virulence plasmid, are critical for robust colonization and disease (39). EAEC has also been associated with urinary tract infections (40, 41). The autotrasporter Pic has been defined as a gene marker associated with spreading of infection to the urinary tract (40). Finally, comparison of EAEC isolates from HIV-positive and non-HIV diarrheal samples showed that HIV-positive isolates are stronger biofilm producers and more resistant to antibiotics than the non-HIV diarrheal isolates, which confirmed the heterogeneity of the EAEC isolates (42).

Adherent and Invasive *E. coli* (AIEC)

Inflammatory bowel disease (IBD), particularly Crohn's disease and ulcerative colitis, are the result of alterations in the intestinal microbiota due to a variety of genetic and environmental factors (43). Interestingly, an increased number of AIEC have been isolated from IBD patients and more frequently found in ileal-Crohn's disease patients than in healthy controls (44). AIEC strains have the ability to adhere and invade intestinal epithelial cells and survive within macrophages (45). Small et al recently established a chronic infection murine model using prototypical AIEC isolates (46), and demonstrated that AIEC infection stimulates chronic inflammation and fibrosis in mice. This study showed for the first time evidence that an infection with AIEC can cause intestinal symptoms similar to those observed in Crohn's disease patients.

AIEC adherence depends on the expression of the type 1 pili, long polar fimbriae and the presence of the carcinoembryonic antigen (CEACAM6) as a host cell receptor (47, 48) (Figure 1). Crohn's disease patients showed abnormal expression of CEACAM6 (48) and as such, Martinez-Medina et al used a model of transgenic mice expressing CEACAMs to assess the effects of a high fat/high sugar western diet on gut microbiota composition, barrier integrity and susceptibility to infection (49). They found that the diet induces changes in gut microbiota composition, altering host homeostasis and promoting AIEC murine gut colonization. With respect to the type 1 pili, a study sequenced the *fimH* gene (FimH is the adhesin protein located on the tip of the pili) from 45 AIEC strains and 47 non-AIEC *E. coli* strains. Phylogenetic analysis found that AIEC strains predominantly express FimH with amino acid mutations of a recent evolutionary origin as compared to non-AIEC strains, which represents a feature of pathoadaptive changes in several bacterial pathogens (50). The accumulation of these mutations confers AIEC the ability to adhere to CEACAM-expressing intestinal epithelial cells and to participate in the development of chronic inflammation in a genetically susceptible host. Finally, it is known that the long polar fimbriae help AIEC to interact with intestinal Peyer's patches and M cells (51). A recent study analyzed the effect of gastrointestinal conditions on AIEC long polar fimbriae expression. The authors found that bile salts strongly enhanced fimbriae expression, causing a higher level of interaction of AIEC with Peyer's patches and a higher level of translocation through M cell monolayers (52).

Regarding the clinical implications of AIEC recent investigation indicates that colonization of AIEC results in chronic colitis in mice lacking the flagellin receptor TLR5. Transient AIEC colonization drove intestinal inflammation which is associated with altering microbiota composition (53). Proteases and protease inhibitors control microbiota composition, immune response and intestinal function to maintain gut homeostasis. CYLD is a de-ubiquitinase that is significantly downregulated in the intestine of Crohn's disease patients (54). Decrease CYLD expression results in an enhanced intracellular replication of AIEC (54). Therefore, protection against AIEC during microbiota acquisition might be a strategy to control IBD in genetically susceptible individuals (53).

Uropathogenic *E. coli* (UPEC)

UPEC are among the most prevalent extra-intestinal bacteria, accounting for 90% of all urinary tract infection (UTI) (2). The most predominant chaperone-usher fimbriae in UPEC strains is the type 1 fimbriae, which is an important determinant for pathogenicity, allowing the interaction of UPEC with urinary tract host epithelia (55, 56). FimH within the type 1 fimbriae bound to α-D-mannosylated uroplakin, facilitating bacterial invasion, colonization and formation of biofilm-like structures called intracellular bacterial communities (IBCs) (57) (Figure 1). A high-throughput *insilico* analysis and *in-vitro* binding study discovered that pathoadaptive alleles of FimH, with variant residues outside the binding pocket, affect FimH-mediated acute and chronic pathogenesis of two prototype UPEC strains (56). The study argues that FimH variants, which maintain a high-affinity conformation, were attenuated during chronic bladder infection, implying FimH's ability to switch between conformations is important during pathogenesis.

With respect to the regulatory mechanisms controlling UPEC colonization, Mitra et al found UvrY as a key regulator modulating phase variation during UPEC pathogenesis, down-regulating the expression of type 1 fimbrial structural genes, and influencing biofilm formation, virulence and motility in UPEC strain CFT073 (58). Cpx is another key regulator involved in bacterial adhesion. The deletion of *cpxRA* impaired the ability of UPEC strain UTI89 to invade and colonize bladder epithelial cells, suggesting that the Cpx system is needed for UPEC persistence in the urinary tract (59). Similarly, mutation in *cpxRA* and *cpxP* in CFT073 also greatly reduced virulence tested the zebrafish infection model (59). Finally, natural medicinal plants and secondary metabolites have being study because asiatic acid and ursolic acid decreased expression of P fimbriae and curli fibers, altering cell morphology and adhesion of UPEC to uroepithelial cells (60). Finally, Rafsanjany et al also demonstrated anti-adhesive effects of various medicinal plant extracts against UPEC strains (61).

Conclusion

The recent progress understanding the adhesion/invasion properties of intestinal and extra-intestinal pathogenic *E. coli* during colonization of host cells reveals that there is a need of further mechanistic studies that can be used for development of specific therapeutic approaches.

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Key points

- Recent studies revealed how host signaling responses alter pathogenic *E. coli* colonization.
- Advances in the understanding for the role of pathoadaptive mutations on fimbrial adhesins and their contribution to the pathogenic process.
- Development of new murine model of chronic *E. coli* infection and the study of novel *E. coli* pathotypes.

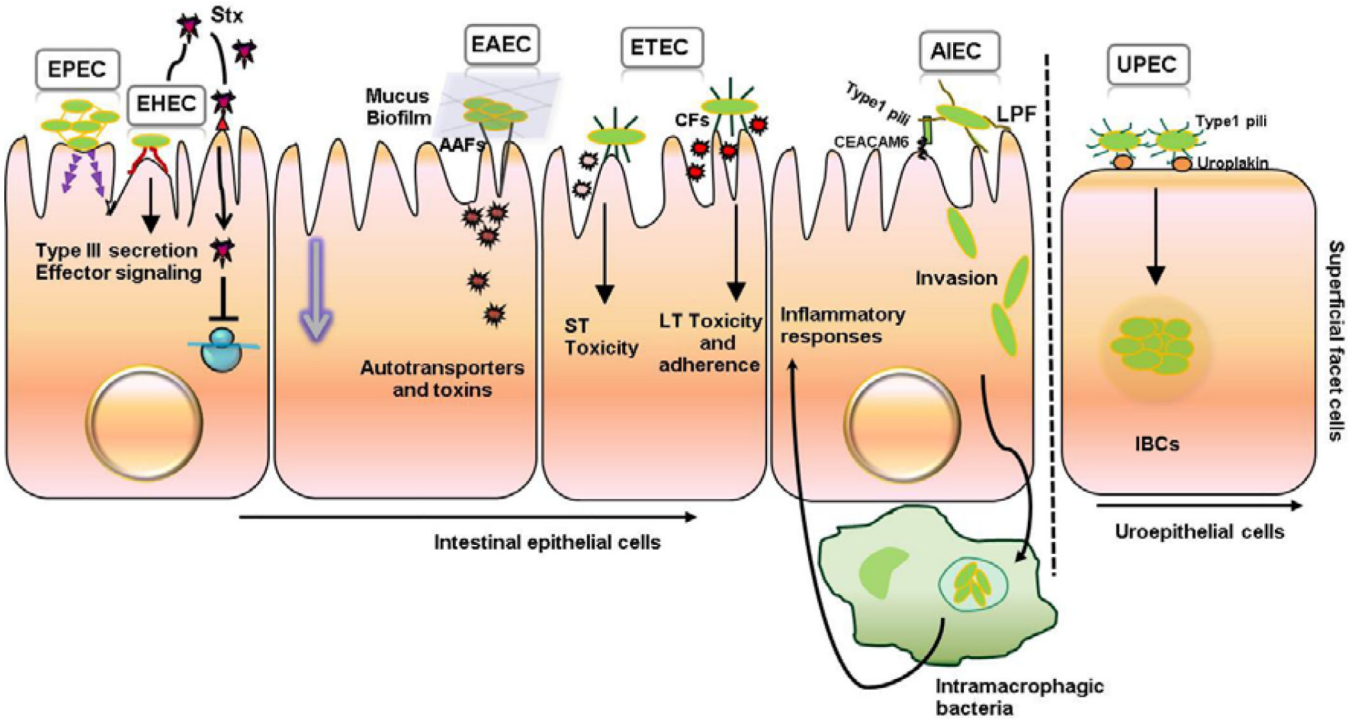

Figure 1.

Pathogenic *Escherichia coli* colonization of intestinal epithelial cells and uroepithelium. Adherence and/or invasion of intestinal (EPEC, EHEC, EAEC, ETEC, AIEC) and extraintestinal (UPEC) pathogenic *Escherichia coli* to epithelial cells (See text for details).