Chapter 14
Interactions of Pathogenic *Escherichia coli* with Host Receptors

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Summary Each *Escherichia coli* pathotype has a unique way to interact with its host. While some of the adhesins that mediate cell adherence and bacteria-to-bacteria interactions are shared among these different categories of pathogenic *E. coli*, other adhesins are pathotype specific. This implies that there are common and unique receptors recognized by this myriad of *E. coli* adhesins, which ultimately determine what host (human, animal, or plant), tissue, or cell type they are colonizing. Notably, both commensal and pathogenic *E. coli* adhere to the gut mucus layer covering and protecting epithelial cells. This is a prerequisite for colonization of the epithelium and establishment of disease. It is then the interaction between surface adhesins and their cognate surface-exposed receptors that determines tropism, unravels mechanisms of pathogenesis, and triggers activation of the local immune responses. Despite our knowledge on the mechanisms of adherence of some pathogenic *E. coli*, much effort is still needed in identifying the eukaryotic receptor counterparts. The most current knowledge on the nature of the receptors involved in the *E. coli*–host interaction is reviewed here.

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1 *E. coli*–Host Interactions

For commensal or any pathogenic *E. coli*, the ability to detect host signals and interact efficiently with host cells is a prerequisite for successful colonization of the gut mucosa and/or establishment of disease. Immediately after entering the host, the bacteria must face the lethal effect of the low pH of the gastric mucosa. Therefore, pH-resistant bacteria, such as Shiga toxin-producing *E. coli* (STEC) and enteroinvasive *E. coli* (EIEC) require lower doses of infection (e.g., 10–50 organisms) than pH-sensitive *E. coli*, such as enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), and enteroaggregative *E. coli* (EAEC), which require over 10^7 bacteria to infect the host. The low acidity of the stomach signals the bacteria to up-regulate necessary genes in preparation for the upcoming encounter with bile salts and other host signals present in the small bowel. For example, virulence genes in ETEC and EPEC required for toxicity and adherence may be turned on by these signals in preparation for colonization of this anatomical site (Fig. 14.1). EHEC and EAEC, on the other hand, transiently travel through the lumen of the small bowel to reach their site of colonization in the large bowel (Kaper et al. 2004) Once there, these bacteria face host-specific factors that prevail in their colonization niche, such as an anaerobic atmosphere, an intense metabolic activity of digestion of nutrients and adsorption, the intestinal microbiota, and an alert humoral and cellular immune system that is prepared to attack the intruding bacteria (Sommer and Backhed 2013).

What determines whether a particular organism will colonize a host niche is in great part the presence of an array of host-cell receptors, which come in different

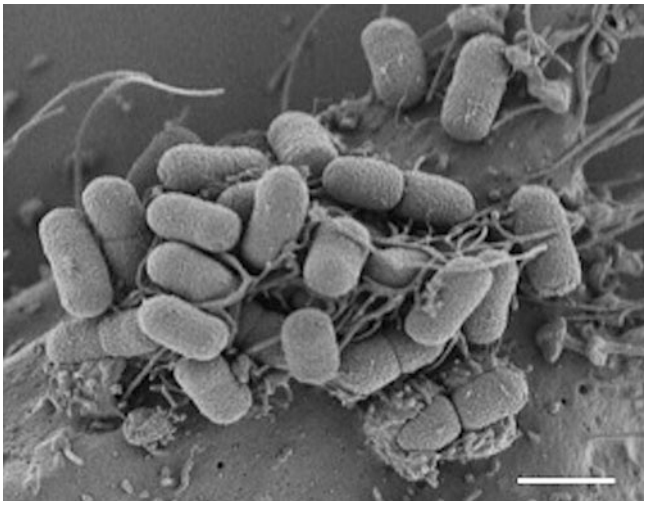

Fig. 14.1 EPEC O127:H6 strain E2348/69 forming localized adherence to a cultured HeLa cell. Several types of interactions occur in this event: (1) Bacteria attaching intimately to the cell surface inducing the formation of pedestals where the bacteria sit atop (*bottom right*). (2) Bacteria tethered through thick cellular pseudopod-like protrusions. (3) Bacteria-to-bacteria interactions through thin and thick pili structures such as ECP and BFP, respectively. Bar, 3 μm

forms and structures. These receptors may be present only on the surface of certain cell types; for example, forming part of the mosaic of surface-exposed molecules on the enterocytes, or secreted in the mucus layer, bathing the epithelium or in the extracellular matrix (EM) of the basal membrane (McGuckin et al. 2011).

Several families of eukaryotic surface molecules can be targets of pathogenic bacteria for binding and colonization including mucins, proteoglycans, cholesterol, membrane integral proteins, carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), toll-like receptors (TLRs), signaling lymphocytic activation molecule family (SLAMF), integrins, and EM proteins. While host cell receptors are widely distributed in different tissues, they present at the same time certain high degree of variability that enables the tropism for adherence to certain cell types and tissues (Juge 2012). One should be mindful that these receptors play a biological function in the host and do not necessarily exist to serve bacterial pathogens. Pathogenic bacteria have engineered their receptors ligands (adhesins) to recognize these cellular receptors for their benefit. Certain pathogenic *E. coli* strains actually produce and inject their own receptor on host cells. Such is the case of the translocated intimin receptor (Tir), a bacterial 90 kDa-protein that is injected into host cells by the type-3 secretion system of EPEC and enterohemorrhagic *E. coli* (EHEC) (Fig. 14.2). Once inserted and displayed on the host cell membrane, Tir serves as the receptor for the bacterial outer membrane protein called Intimin to produce intimate cell attachment (Kenny et al. 1997). Pathogenic *E. coli* strains display a large capacity to adapt their fimbrial adhesins to diverse ecological niches via charge-driven interactions, congruent with binding to mucosal surfaces displaying an acidic gradient along the intestinal tract (Waksman and Hultgren 2009).

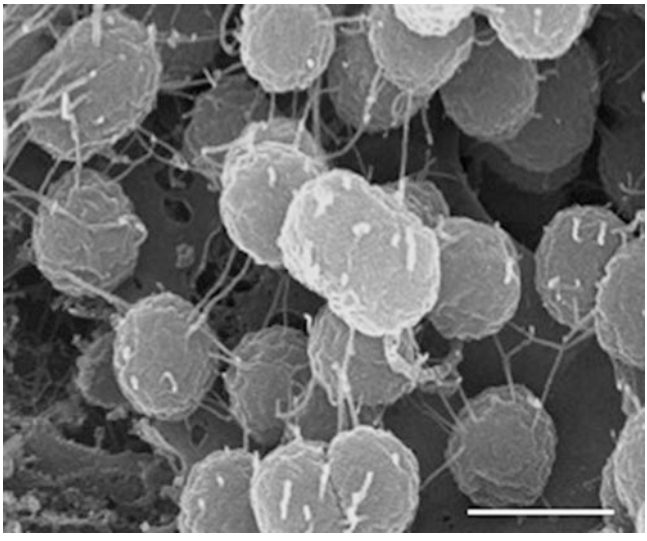

Fig. 14.2 EHEC O157:H7 strain EDL933 attaching to cultured HeLa cells. The bacteria associate with the cell membrane and to each other through peritrichous fibrillar structures that extend out of the bacterial surface. Bar, 1 μm

2 The Intestinal Mucus Barrier

The human intestine is in fact a complex ecosystem where the interrelationship between the microbiota, nutrients, and host epithelial cells has a significant impact upon health and establishment of disease. Gastrointestinal epithelial cells are tightly linked via intracellular junctions that form a contiguous barrier, which is resistant to microbial passage (McGuckin et al. 2011; Juge 2012). The intestinal barrier to infection is constituted by secreted mucus, the apical glycocalyx, and epithelial tight junctions. All along the gastrointestinal tract, a thick mucus layer covers the underlying mucosa, which protects it from harmful organisms present in the lumen content or from incoming enteric pathogens. Thus, the intestinal mucus represents the first line of defense in gut epithelium against dangerous bacteria. Two layers with different composition and function can be distinguished in the gut mucus. The outer loose section of the mucus layer provides a sanctuary for the natural microbiota constituted by thousands of different bacterial species, which play important roles in the physiology and homeostasis of the intestine. The inner mucus layer is firmly attached to the epithelial lining and protects it from possible microbial intruders (McGuckin et al. 2011; Juge 2012).

This biochemically complex gel varies in thickness with the region of the gastrointestinal tract, being thicker in the colon and the rectum. The gastrointestinal tract's mucus is rich in glycoproteins, antimicrobial peptides (e.g., β-defensins), immunoglobulins, lipids, electrolytes, and water. The viscous nature of mucus makes it capable of aggregating and removing microorganisms. The importance of the mucus barrier is underlined by recent reports that mice deficient in MUC2 develop severe, life-threatening disease when infected with the attaching and effacing pathogen *Citrobacter rodentium*. These mice also develop spontaneous intestinal inflammation, consistent with the previously demonstrated nonphysiological exposure of the commensal microbiota to the epithelium when mucus is depleted (McGuckin et al. 2011; Juge 2012).

3 Mucins

The major structural components of the mucus layers are high-molecular-weight proline-, threonine-, and serine-rich glycoproteins called "mucins." These amino acidic residues are heavily glycosylated producing a myriad of oligomeric mucins that provide specificity and programmed function to host cells. There are two types of mucins: membrane-bound and secreted mucins. All mucosal epithelial cells produce and display surface-exposed mucins. These are transmembrane glycoproteins characterized by a cytoplasmic domain involved in signal transduction and an extensively O-glycosylated extracellular domain that may reach up to 800 nm away from the cell surface, which is important in cell adhesion. The outer surface-exposed portion of the glycosylated mucins can be secreted or

shed from the cell and it is thought that this could represent a mechanism to distract bacterial pathogens consequently limiting their access to their target receptors on the epithelium.

The intestine produces membrane-bound mucins: MUC1, MUC3, MUC4, MUC12, MUC13, and MUC17; and secreted mucins: MUC2, MUC5B, MUC5AC, and MUC6 (Juge 2012; Etzold and Juge 2014). The main mucins in the stomach are MUC1, MUC5AC, and MUC6, while in the small intestine and colon, MUC2 is the major component of the mucus layer. More than 100 complex oligosaccharides (mono-, di-, or trisialylated) can be found in colonic MUC2 mucin. This complex diversity of colon glycans is relatively conserved between individuals and highlights the biological importance of these glycans in dictating, through ligand-receptor binding, which bacterial species will conform the commensal microbiota. Bacterial pathogens have learned to recognize mucin glycans as receptors and even regulate changes in production of mucins and their glycosylation. A large body of evidence supports the role of intestinal mucins in maintenance of the gut homeostasis, protecting the host from intruding and invasive pathogens, and regulating immune responses. For example, the lack of MUC2 in mice leads to spontaneous colitis, intestinal inflammation, and development of colorectal cancer (Juge 2012).

4 Bacterial Strategies to Overcome the Gut Mucus Barrier

Enteric pathogens have evolved a wide range of specific strategies to either penetrate or circumvent the secreted and cellular barriers to infection. These strategies include mechanisms allowing efficient penetration of the mucus by producing enzymes that degrade mucus components, through production of flagella that mediates swimming across the dense mucus, using pathways that allow evasion of the barrier, and by disruption of the cells that produce such barrier. Intestinal *E. coli* are capable of swimming across the mucus layer using flagella to reach their target sites on epithelial cells for efficient delivery of toxins and effectors through any of the secretion systems so far described (see Chap. 10). Pathogens with disturbed flagellar function have reduced pathogenicity, underlining the importance of motility in disease. It should be recognized that flagella are also involved in adhesion and activation of immune responses through recognition of TLR-5. Furthermore, some pathogens can alter the integrity of the mucus, affecting its viscoelasticity to their benefit (Giron et al. 2002).

EAEC is a good example of an organism that induces mucus production in the colon favoring attachment and formation of biofilms, a mechanism that has been associated with the characteristic mucoid and persistent diarrhea that distinguishes this pathogen from other diarrheagenic *E. coli* (DEC) strains (Nataro and Kaper 1998).

Many microorganisms have evolved enzymes to degrade mucus. These enzymes include glycosidases that breakdown mucin oligosaccharides, exposing the mucin peptide backbone to proteases, while also removing decoy carbohydrates from

microbial adhesins. Proteolytic cleavage of mucins causes disassembly of the oligomerized mucin macromolecules, resulting in substantially diminished mucus viscosity, dispersal of the mucus, and diffusion and dilution of antimicrobial molecules (McGuckin et al. 2011). For example, EAEC has the mucolytic activity that is required for translocation through mucin-containing gels in the intestine. It produces a mucinase called Pic (Protein involved in colonization), which targets O-glycosylated residues on surface-exposed mucins in different cell types (Harrington et al. 2009; Ayala-Lujan et al. 2014).

EHEC produces StcE, a zinc metalloprotease/mucinase with activity on the intestinal mucin MUC7. It was suggested that this enzyme contributes to intimate adherence of this organism and also functions as an anti-inflammatory molecule, by localizing complement regulator C1-INH to cell membranes (Grys et al. 2006).

A highly conserved metalloprotease encoded by the chromosomal gene *yghJ* was recently reported to influence the ability of ETEC to colonize the small intestine, by degrading the major MUC2 and MUC3 mucins. This gene is also widely spread in other enteric pathogens including *Vibrio cholerae* and other DECs (Luo et al. 2014).

The membrane-bound mucin MUC17 is highly expressed on the apical surface of intestinal epithelia and is thought to play a role in epithelial restitution, in maintaining epithelial barrier function, and protection of the mucosa against luminal pathogens. Reduction of endogenous MUC17 is associated with increased permeability, inducible nitric oxide synthase, and cyclooxygenase 2 induction, as well as enhanced bacterial invasion in response to EIEC exposure, while bacterial adhesion is not affected. These data suggest that MUC17 plays a role in attachment and invasion of EIEC in colonic cell lines and in maintaining a normal epithelial barrier function (Resta-Lenert et al. 2011).

Mucus degradation is not limited to pathogens, as some commensal intestinal bacteria are also mucolytic, and can use mucin glycoproteins as an energy source and also to provide substrates for other nonpathogenic bacteria in the outer mucus layer (McGuckin et al. 2011).

5 *E. coli* Mucin Glycan Receptors

Both commensal and pathogenic *E. coli* compete for binding sites on gastrointestinal mucus. While a number of enteric pathogens interact with mucins at different levels in the gut mucosa, as a prerequisite for colonization, not much is known about the types of mucins that function as receptors for most *E. coli* pathotypes and what adhesins are involved in this process. A few studies described later highlight the importance of mucins in the attachment or anti-inflammatory activity of pathogenic *E. coli* molecules. EAEC binds to intestinal mucins, a property associated with biofilm formation in the colonic outer layer mucus. These bacteria produce Pic that recognizes O-glycosylated serine in mucins (Henderson et al. 1999; Ayala-Lujan et al. 2014) and was shown to promote colonization in a mouse model of

infection (Harrington et al. 2009). The role of flagella in the binding of EPEC and EHEC to host receptors such as mucins and bovine mucus has been documented (Giron et al. 2002; Erdem et al. 2007).

Although many fimbrial and nonfimbrial adhesins have been identified in human pathogenic *E. coli*, the structure of the receptors for only a handful of bacterial fimbrial adhesins is known. The FimH tip adhesin of the type 1 fimbriae is the most widely studied glycan-recognizing protein adhesin with specificity for cellular structures containing α-D-mannosylated proteins and mannose in different conformations leading to different tissue tropism (Sokurenko et al. 1992). The recognition of mannose-rich uroplakin on bladder epithelial cells by uropathogenic *E. coli* (UPEC)'s type 1 fimbriae is a mechanism of colonization of the urinary tract (Kaper et al. 2004). The P fimbriae tip adhesin PapD of UPEC recognizes α-D-galactopyranosyl-(1,4)-β-D-galactopyranoside receptor epitope present on erythrocytes and kidney epithelial cells favoring colonization and production of pyelonephritis (Lindberg et al. 1987). The F17G tip adhesin of the F17 fimbriae of animal ETEC binds to glycoprotein glycan receptors and recognizes terminal *N*-acetyl-glucosamine on intestinal mucins (Mouricout et al. 1995; Lonardi et al. 2013). The F4 fimbriae of animal ETEC recognizes porcine intestinal glycosphingolipids (Coddens et al. 2011). The CS6 fibrillae of human ETEC recognizes the sulfatide (SO3-3Gal β1Cer) glycosphingolipid (Jansson et al. 2009). Arabinans present in plant cell walls function as receptors for the EcpD tip adhesin-mediated adherence of ECP-producing *E. coli* (Rossez et al. 2014). However, the nature of the mammalian cell receptor for ECP is unknown. Most recently, it was reported that CfaE, the tip adhesin of the CFA/I fimbriae, binds to asialo-GM1 on Caco2 cells and erythrocytes demonstrating that asialo-glycosphingolipids are implicated as receptors for this important pilus of ETEC and in mediating binding and colonization of intestinal epithelial cells (Madhavan et al. 2016). The alpha bundlin of the bundle-forming pilus (BFP) of EPEC possesses lectin-like properties that are responsible for N-acetyllactosamine (LacNAc)-specific initial adherence to host intestinal epithelial cells (Hyland et al. 2008). There is a need for more research on the identification of receptor structures for a large number of *E. coli* adhesins.

6 The Proteoglycans

The proteoglycans (PG) are complex ubiquitous molecules which have a different tissue-depending distribution and composition (Garcia and Gerardo 2014). The basic core of proteoglycans consists of different types of proteins modified with chains of anionic polysaccharides called glycosaminoglycans (GAGs). The GAGs are made up of repeated disaccharide units which can be classified as either heparin/heparan sulfate (glucoronic acid plus N-acetylglucosamine [NAG]), chondroitin/dermatan sulfate (glucoronic acid plus N-acetylgalactosamine), keratan sulfate (glucoronic acid plus NAG), and hyaluronic acid (glucoronic acid plus NAG). Among these molecules, heparan sulfate is the most widespread and physiologically relevant

GAG. Heparan-sulfate-containing PGs have multiple functions, some of them related to the core proteins but most certainly to the GAG chains. It is this structural diversity that allow heparin sulfate PGs to play important roles in many cellular processes, such as organization of the basement membrane structure, regulation of proliferation, cell adhesion and migration, cytoskeleton organization, differentiation and morphogenesis, among others. Several bacterial pathogens, including pathogenic *E. coli*, interact with heparin sulfate PGs to achieve adherence and even invade and disseminate (Duan et al. 2013).

However, bacterial glycans such as lipooligosaccharides and lipopolysaccharides were shown recently to interact with host cell glycans with high affinity demonstrating that glycan–glycan interactions mediate binding of pathogenic bacteria to host cells (Day et al. 2015). The recognition of host glycans by pathogenic *E. coli* glycans has yet to be determined but considering the high degree of LPS variants among the *E. coli*, it wouldn't be surprising to find such interactions.

7 Membrane-Associated Cholesterol in Pathogen–Host Interaction

Pathogen–host interactions involve several key components at the cell surface of both the host and the pathogen. Cholesterol is an essential lipid in higher eukaryotic cell membranes and is unique in terms of the functional role it plays in cellular physiology (Simons and Ikonen 2000; Kumar et al. 2016). This lipid is an important player in the entry of intracellular pathogens. EIEC, like *Shigella*, uses T3SS and its effectors to penetrate enterocytes (Kaper et al. 2004). Whether EIEC uses also cholesterol in lipid rafts to gain access to the host cell cytoplasm is unknown.

8 CEACAMs

The carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) comprise a group of immunoglobulin-related glycoproteins, some of which are found at the surface of epithelial cells (Tchoupa et al. 2014). Several biological functions have been associated to CEACAMs and they may be recognized as receptors by pathogenic and nonpathogenic bacteria. Pathogenic *E. coli* strains such as adherent and invasive *E. coli* (AIEC) and diffuse adherent *E. coli* (DAEC) have been shown to interact with CEACAMs (Berger et al. 2004; Barnich et al. 2007).

AIEC strains have been linked to the pathogenesis of Crohn's Disease (CD) characterized by high levels of inflammation of the gut mucosa, presumably triggered by AIEC and influenced by the composition of the intestinal microbiota. Studies with transgenic mice expressing human CEACAMs demonstrated that the FimH tip adhesin is involved in the recognition of CEACAM6 by AIEC (Carvalho et al.

2009). It has been shown that CD patients have increased levels of CEACAM6 expression, which would explain, at least in part, the association of AIEC with this disease. Further, AIEC adherence to enterocytes obtained from CD patients was blocked with anti-CEACAM6 monoclonal antibody. Similar observations were found when IFN-γ-stimulated Caco-2 cells were transfected with siRNA-blocking CEACAM6 (Barnich et al. 2007). Sequence analysis of *fimH* genes from AIEC and non-AIEC strains revealed that point mutations in *fimH* confer AIEC a significantly higher ability to adhere to CEACAM-expressing intestinal epithelial cells in vivo and in vitro (Dreux et al. 2013). These results suggest that in the evolution of pathogenic AIEC strains the selection of FimH polymorphism was key for AIEC pathogenesis in CD patients.

DAEC strains associated to urinary infections express Afa/Dr adhesins, a family of molecules with receptor specificity for the Dr blood group antigen. These adhesins are responsible for the attachment of the bacteria to the surface of epithelial cells. DAEC adherence to epithelial intestinal cells was blocked using antibodies against CEACAM5 (CD66e) (Guignot et al. 2000). Later, experiments carried out with different cell types expressing CEACAM demonstrated that Afa/Dr adhesins F1845 and AfaE-III have the ability to bind to CEACAM1, CEACAM5, or CEACAM6 (Berger et al. 2004). To date, several members of the Dr adhesins are known to bind to CEACAM receptors (Servin 2014), but the significance of the recognition of these receptors in DAEC pathogenesis still needs further investigation.

9 The Extracellular Matrix: One Target Fits All *E. coli*

The extracellular matrix (EM) is a complex protein structure involved in several biological processes and may be recognized as a receptor by many bacterial pathogens (Patti and Hook 1994). The composition of the EM varies with the tissue; in the case of the gastrointestinal tract, fibronectin, laminin, and type I and IV collagens are the main protein constituents (Dubreuil et al. 2002). Given the abundance and adhesive properties of the EM, several research groups have studied the involvement of EM proteins in the recognition of adhesins of several bacterial pathogens, including pathogenic *E. coli* strains (Abraham et al. 1983; Froman et al. 1984; Castaneda-Roldan et al. 2004; Alteri and Mobley 2007; Wells et al. 2009; Christner et al. 2010; Nallapareddy et al. 2011). Although several *E. coli* strains have the ability to bind to EM proteins, the majority of studies focus on the interaction of DECs with EM proteins.

EAEC adhesion to human intestinal mucosa requires the participation of the aggregative adherence fimbriae (AAFs), which promotes the formation of a biofilm on the epithelial surface (Nataro et al. 1992). EAEC has the ability to bind to different components of the EM such as fibronectin, laminin, and collagen IV, a process dependent on the expression of AAFs. Previous studies have shown that preincubation of cultured intestinal epithelial cells with fibronectin increases the adhesion of EAEC (Farfan et al. 2008). Recent studies focused on elucidating the mechanism of

Table 14.1 *E. coli* adhesins recognizing EM proteins

Adhesin	*E. coli* type	Ligand	Reference
AAF fimbria	EAEC	Fn, Lm, CIV	Farfan et al. (2008), Konar et al. (2012)
P fimbriae	UPEC	Fn	Westerlund et al. (1993), Roberts et al. (1997)
Curli	All	Fn, Lm	Olsen et al. (1989), Farfan et al. (2011)
FimH	All	Fn, Lm	Sokurenko et al. (1992), Kukkonen et al. (1993)
Bfp fimbriae	EPEC	Fn, Lm, CIV	Giron et al. (1993)
S fimbriae	MAEC	Fn	Saren et al. (1999)
Tsh autotransporter	APEC	Fn, CIV	Kostakioti and Stathopoulos (2004)
Flagella	EPEC, STEC	Fn, Lm	Erdem et al. (2007)
HCP	STEC	Fn, Lm	Xicohtencatl-Cortes et al. (2009)
ELF fimbriae	STEC	Lm	Samadder et al. (2009)
Ehly hemolysin	EPEC	Fn	Magalhaes et al. (2011)
Lpf fimbriae	STEC	Fn, Lm, CIV	Farfan et al. (2011)
GroEL	aEPEC	Fn	Moraes et al. (2015)
CS6	ETEC	Fn	Ghosal et al. (2009)

Fn, Fibronectin; Lm, Laminin; CIV, Collagen IV

EAEC adherence mediated by AAF-fibronectin have shown that the interaction between these two proteins involves electrostatic interactions attributed to the presence of basic residues in the AAF (Berry et al. 2014).

Similar to EAEC, several pathogenic *E. coli* adhesins have the ability to bind to EM proteins (Table 14.1). Thus, it is not surprising that a particular adhesin has the ability to bind to one or several EM proteins. However, one of the main questions regarding the ability of *E. coli* to adhere to these proteins is the biological significance of this binding. Future studies should address the importance of this interaction and its implication in the establishment of disease.

10 Toll-Like Receptors

Toll-like receptors (TLR) are a family of transmembrane immune receptors that trigger an inflammatory cascade reaction in response to pathogen-associated molecular patterns (PAMPs). Currently, there are ten TLRs described and agonists for nine of them have been determined (Takeda and Akira 2004). This family of proteins constitutes a network that functions as an alarm system that alerts the immune system of the presence of microorganisms. For example, some TLRs recognize

viruses, other recognize Gram-positive or Gram-negative bacteria, and so on. The LPS and flagellin are classical bacterial agonists that bind to TLR4 and TLR5, respectively, although there are other factors that participate in the activation of TLR by bacteria. Upon activation of TLRs, a signal cascade is initiated which results in the activation of expression of genes encoding proinflammatory molecules. The type 1 and P fimbriae of UPEC trigger mucosal inflammation through the stimulation of a TLR4-dependent pathway (Frendeus et al. 2001; Mian et al. 2010). The interaction of a particular bacterial adhesin with the surface of epithelial cells promotes the engagement of bacterial TLR agonists, such as LPS, triggering intracellular cascades involved in the inflammatory response originated as a consequence of the infection process.

11 SLAMF Receptors

The signaling lymphocytic activation molecule family (SLAMF) is comprised of nine surface glycoproteins receptors expressed mostly in hematopoietic cells. Most SLAMF receptors are self-ligands with signaling motifs, which function in cell–cell communication and can also bind bacterial structures (van Driel et al. 2016). The *E. coli* outer membrane porin C (OmpC) and OmpF have the ability to bind to SLAMF1 and SLAMF6. The interaction of SLAMF1 with nonpathogenic *E. coli* strains expressing Omps C and F results in a more effective phagocytosis of these bacteria by macrophages (Berger et al. 2010). Similarly, *E. coli* expressing FimH binds to SLAMF2 and antibodies against this receptor inhibit the phagocytosis of the *E. coli* by mast cells and macrophages, a process mediated by cellular caveolae (Shin et al. 2000). Further studies are necessary to elucidate the involvement of SLAMF in the innate and adaptive immune responses to *E. coli*, in order to design new strategy to control the host immune response to *E. coli*.

12 Integrins

Integrins are heterodimeric glycoproteins that are critical for a variety of cell–cell and cell–matrix binding events. Once a particular ligand binds to integrin it triggers a specific signaling pathway depending on the type of integrin that is modulated (Hauck and Ohlsen 2006). Bacteria can bind directly and indirectly to integrin. UPEC's type 1 fimbriae bind to integrins β1 and α3 and to the heterodimers formed between these proteins (Eto et al. 2007). Integrin α5β1 participates in the fibronectin-mediated adherence of EAEC to intestinal cells. Fibronectin-associated bacteria can be recognized by integrin α5β1 through the RGD (Arginine-Glycine-Aspartic acid) region, and this engagement increases the adherence of EAEC to intestinal cells (Izquierdo et al. 2014a).

13 The Mosaic of *E. coli* Adhesins

DEC have interacted with their host(s) for thousands of years and have developed multiple strategies to overcome the bactericidal and inhibitory effects of the resident microbiota and the specific and nonspecific factors of the immune system, as well as to produce an arsenal of surface molecules that allow them to recognize host cell receptors present in mucus layers or embedded in the epithelium. Ultimately, DEC strains display surface proteinaceous structures present as polymerized hair-like filaments called fimbriae or pili, or as nonfimbrial adhesins that attach to the gut mucosal epithelium. Different adhesins can coexist in the same pathogen, all of which may act in concert at different stages during infection to successfully colonize the host. The expression and production of these adherence factors are tightly regulated by complex regulatory networks influenced by niche-specific host factors.

Several different fimbrial and nonfimbrial adhesins have been described for the various *E. coli* pathotypes (Farfan and Torres 2012). While some adhesins are unique to an individual pathogenic category, other adhesins may be present and shared in the various groups. For example, the colonization factors (CFs) of ETEC strains are found only in ETEC, the production of the bundle-forming pilus (BFP) is a phenotypic characteristic of EPEC strains only, and the AAF are found only in EAEC strains (Giron et al. 1991; Kaper et al. 2004; Qadri et al. 2005). On the other hand, genes encoding for expression of the long-polar fimbriae (Lpf) may be found in multiple *E. coli* pathotypes (Torres et al. 2009; Galli et al. 2010).

The genetic core of the *E. coli* may contain 12–16 distinct pili operons, depending on the strain, some of which may be produced under certain growth in vitro conditions (Perna et al. 2001; Pouttu et al. 2001; Rendon et al. 2007). Classic examples of core-encoded fimbriae are type 1 fimbriae and curli. While these pili may or may not be important for or even produced by some pathogenic *E. coli*, in general they confer increased adhesiveness and survival fitness in different niches in or outside the host to the bacteria that produce them. Production of other core-encoded fimbrial structures in EHEC and other pathogenic *E. coli* has been reported (Figs. 14.1 and 14.2). The meningitis-associated temperature-dependent fimbriae (MAT) also called *E. coli* common pilus (ECP) are produced by all pathogenic *E. coli* including human and animal strains and they are important for cell adherence and biofilm formation (Pouttu et al. 2001; Rendon et al. 2007; Avelino et al. 2010; Saldana et al. 2014). Receptor recognition is presumably mediated by the tip adhesin protein EcpD (Garnett et al. 2012). The assembly of the *E. coli* laminin-binding fimbriae (ELF) is driven from the chromosomal *ycbQ* operon and the pilin of the hemorrhagic coli type IV pilus (HCP) is encoded by the *ppdD* gene as demonstrated in EHEC (Samadder et al. 2009).

Several outbreaks of diarrheal disease associated with the consumption of EHEC-tainted agricultural products have been reported worldwide. This strongly indicated that EHEC interacts with different salad leaves and vegetables. The interaction of EHEC with spinach leaves involves the participation of several adhesins including the type3 secretion system, flagella, curli, ECP, and HCP (Saldana et al.

2011). It is not far-fetched to think that these fimbrial adhesins mediate colonization to different cell receptors in different hosts at different stages during infection although some may be host specific.

Bacterial adhesins are not restricted to fimbrial structures. Many surface-exposed, membrane-associated proteins, and even secreted proteins have been proposed as adhesins. These adhesins may be associated with any of the six secretion systems so far identified in bacteria (see Chap. 10). While the primordial function of these proteins may not be to directly mediate adherence, they definitely contribute to host mucosal colonization. We cannot ignore the contribution of polysaccharide-containing structures such as capsules, LPS, glycocalyx, and extracellular polysaccharides to bacterial adherence and biofilm formation on biological and nonbiological surfaces. Therefore, high affinity biomolecular interactions can mediate binding of pathogenic bacteria to host cells. The different fimbrial and nonfimbrial adhesins of the several *E. coli* pathotypes have been recently reviewed elsewhere and will not be individually discussed here (Qadri et al. 2005; Farfan and Torres 2012; Madhavan and Sakellaris 2015) (see Chaps. 1–6, and 9).

14 *E. coli*–Host Interaction Studies in Latin America (LA)

Most of the studies on *coli*–host interaction performed in LA focused on the molecular epidemiology of pathogenic *E. coli*, specifically DEC strains. The main reason that drives the investigation in this research area is the epidemiological importance of diarrheal diseases in LA and the high prevalence of hemolytic uremic syndrome (HUS) associated to STEC infections in certain regions of South America. The majority of these studies focused on the prevalence and characterization of virulence factors in DEC clinical isolates, as well as on the identification of newly discovered adherence factors and their participation in the infection process. These studies have contributed significantly to the understanding of the mechanisms of pathogenicity of DECs and will help to develop new tools to control these infections in LA and the rest of the world. In relation to the mechanism of *E. coli*–host interaction, there are several research groups in LA focused on the identification and characterization of receptors for *E. coli*. A brief description of some of these findings is discussed as follows.

15 Participation of EM Proteins in *E. coli* Adherence

Given the large number of adhesins present in the different pathogenic *E. coli* strains, it is reasonable to state that a subset of them may recognize EM proteins. For example, fibronectin proteins participate in the adherence of EAEC to epithelial cells (Farfan et al. 2008; Konar et al. 2012). Integrin α5β1 is the major integrin involved in the indirect recognition of bacterial pathogens that possess ability to

bind to fibronectin. *Staphylococcus aureus*, for example, binds to epithelial cells in the respiratory tract, using surface fibronectin-binding proteins. The fibronectin in this complex binds to cellular integrin acting as a "molecular bridge" connecting the bacteria to the cell surface. Similarly, EAEC attaches to the epithelial cells through an AAF-fibronectin-integrin binding mechanism (Izquierdo et al. 2014b). In contrast to typical EPEC, the mechanisms of adherence of atypical EPEC (aEPEC) to epithelial cell are poorly characterized. The binding of a clinical isolate of aEPEC (strain BA2103) to EM proteins, including fibronectin, was reported. A proteomic approach employing supernatants obtained from cultures of BA2013 and purified fibronectin allows the identification of several candidates responsible of the binding of this EM protein. Further characterization of these candidates demonstrated that H11 flagellin and GroEL protein were associated to the ability of this aEPEC isolate to bind to fibronectin (Moraes et al. 2015).

16 Stx and Central Nervous System Complications

Argentina holds the highest record worldwide of HUS with an incidence of 17/100,000 cases in children less than 5 years old (Masana et al. 2010). Considering that around 30 % of the affected population manifests central nervous system complications, several research groups had focused on the mechanisms of Stx-mediated HUS pathogenesis. It was shown that the intracellular administration of Stx in rat brains induced the expression of Gb3, the Stx receptor, in neurons and the microscopy analysis detected Stx in neurons that expressed Gb3 (Tironi-Farinati et al. 2010), as described in humans (Obata et al. 2008).

17 Novel Receptors

Keratins or cytokeratins are the largest subgroup of intermediate filament proteins and are important constituents of the cell cytoskeleton. These proteins are indispensable for the mechanical stability and integrity of epithelial cells and tissues. To date, 19 human cytokeratins have been identified and all of them are expressed on epithelial cells. The composition of cytokeratins differs among tissues, but CK8, CK18, and CK19 are common constituents of the intestinal epithelia. Using a proteomic approach, cytokeratin-8 (CK8) was found to be a potential receptor for the AAF/II fimbriae and Pet autotransporter of EAEC in intestinal epithelial cells. Anti-CK8 and *ck8* small interfering RNA (siRNA) reduced the adherence of EAEC strains and blocked the cytotoxic effect induced by Pet to epithelial cells, respectively (Nava-Acosta and Navarro-Garcia 2013; Izquierdo et al. 2014b).

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