REVIEW

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Infection strategies of enteric pathogenic *Escherichia coli*

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Enteric *Escherichia coli* (*E. coli)* are both natural flora of humans and important pathogens causing significant morbidity and mortality worldwide. Traditionally enteric *E. coli* have been divided into 6 pathotypes, with further pathotypes often proposed. In this review we suggest expansion of the enteric *E. coli* into 8 pathotypes to include the emerging pathotypes of adherent invasive *E. coli* (AIEC) and Shiga-toxin producing enteroaggregative *E. coli* (STEAEC). The molecular mechanisms that allow enteric *E. coli* to colonize and cause disease in the human host are examined and for two of the pathotypes that express a type 3 secretion system (T3SS) we discuss the complex interplay between translocated effectors and manipulation of host cell signaling pathways that occurs during infection.

Since its identification in 1885, *Escherichia coli* has become one of the most comprehensively studied bacterial species. *E. coli* strains are comparatively easy to grow and manipulate in the laboratory, are amenable to genetic manipulation, and naturally acquire mobile genetic elements. While *E. coli* isolates form part of the beneficial normal flora of the intestine, some strains have evolved pathogenic mechanisms to cause disease in humans and animals. *E. coli* strains can cause enteric/diarrhogenic or extraintestinal (ExPEC) infections in humans. ExPEC infections are primarily urinary tract (caused by uropathogenic *E. coli*, UPEC) and sepsis/meningitis (caused by neonatal meningitis *E. coli*, NMEC). Only the enteric *E. coli* will be covered in this review.

Enteric *E. coli* infections are traditionally divided into 6 pathotypes based on their pathogenicity profiles (virulence factors, clinical disease and phylogenetic profile): Enteropathogenic *E. coli* (EPEC), Enterohamerrhagic *E. coli* (EHEC), Enteroinvasive *E. coli* (EIEC, including Shigella sp), Enteroaggregative *E. coli* (EAEC), Enterotoxigenic *E. coli* (ETEC) and Diffusely Adherent *E. coli* (DAEC).[1,2] Characteristic features of these pathotypes are shown in **Table 1**. Two further pathotypes have recently emerged; Adherent Invasive *E. coli* (AIEC) which is thought to be associated with Crohn disease but does not cause diarrhogenic infection[3] and the Shiga Toxin (Stx) producing Enteroaggregative *E. coli* (STEAEC) responsible for the 2011 Germany *E. coli* outbreak. *E. coli* strains can also be categorized by their serogroup, e.g., *E. coli* O157 where O refers to the LPS O-antigen or serotype e.g., *E. coli* O157:H7 where H refers to the flagellar antigen. However, as each pathotype contains many serotypes (117 ETEC serotypes have been identified[4]) and some serotypes can belong to more than one pathotype (e.g., O26:H11 can be either EPEC or EHEC), serotyping strains may not provide definitive identification of pathotypes.

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Epidemiology

Enteric *E. coli* are part of the natural flora of many animals. Human infections occur through consumption of contaminated food products (undercooked meat, or contaminated fresh produce such as salad leaves), drinking water contaminated with animal or human waste, or through direct person-to-person spread from poor hygiene.[5] Accurate figures of the incidence of enteric *E. coli* infections worldwide are difficult to determine, as the causative agents of diarrhogenic infections are often not identified. In the developing world ETEC, EPEC and EAEC appear to be major causes of infantile diarrhea with potentially fatal consequences when untreated, while in the developed world these infections are mild and self-limiting. EHEC and more recently EAEC and STEAEC are the main *E. coli* pathotypes associated with food poisoning outbreaks in the developed world.

ETEC is reported to be the most commonly isolated bacterial enteropathogen in children under 5 y of age in developing countries, accounting for approximately 20% of cases, equivalent to several hundred million cases of diarrhea and several tens of thousands of deaths each year.[6] ETEC is also the most common cause of travelers' diarrhea accounting for 10–60% of infections depending on the region visited.[7,8] Extrapolation of these figures suggests there may be 10 million cases of travelers' diarrhea caused by ETEC per year.[9] ETEC also causes disease in animals including cattle and neonatal and post-weaning pigs[10] with host specificity occurring through acquisition of colonization factors (CF) rather than emergence of animal specific lineages.

EAEC is the second most common cause of travelers' diarrhea after ETEC[11] and its prevalence in endemic and epidemic disease is becoming well recognized. It causes persistent diarrhea in children in developing countries[12,13] and has been implicated as an important enteric pathogen affecting AIDS patients.[14] No animal reservoir has been described for EAEC suggesting that it is persisting in the human population. The 2011 German *E. coli* foodborne outbreak was caused by an EAEC strain (O104:H4)

Table 1. Summary of enteric *E. coli* pathotypes

Pathotype	Adhesin	Toxin	T3SS	SPATE	Disease
ETEC	Colonization factors (CF) Porcine A/E associated adhesin (Paa)	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST) Cytolysin A (ClyA)	-	ETEC autotransporter A (EatA)	Acute watery diarrhea (< 5yo) Travelers' diarrhea
EAEC	Aggregative adherence fimbriae (AAF) (I, II, III, Hda) Toxigenic invasion loci A (Tia)	EAEC heat-stable enterotoxin 1 (EAST1) Shigella enterotoxin (ShET)1 Hemolysin E (HlyE)	+/−*	Plasmid-encoded toxin (Pet) Protein involved in intestinal colonization (Pic) Secreted autotransporter toxin (Sat) Shigella IgA-like protease homology (SigA) *E. coli* secreted protein (Esp)P	Travelers' diarrhea Infant diarrhea
STEAEC	AAF IrgA homolog adhesin (Iha)	Shiga toxin (Stx)	-	Pic Pet	Food poisoning
DAEC	afimbrial (Afa) or fimbrial (Dr) adhesins	-	-	Sat	Acute diarrhea (< 5yo)
AIEC	Type 1 pili Long polar fimbriae (LPF)	-	-	-	Crohn disease
EHEC	Intimin Paa Toxin B (ToxB) *E. coli* factor for adherence (Efa)-1 LPF STEC autoagglutinating adhesin (Saa) *E. coli* immunoglobulin-binding protein (EibG) EHEC autotransporter encoding gene A (EhaA) Outer membrane protein A (OmpA) Iha	Stx	LEE encoded	EspP	Food poisoning
EPEC	Intimin Bundle forming pili (BFP) Paa LPF Iha EhaA	-	LEE encoded	EspC	Infant diarrhea
EIEC (Shigella)	-	ShET1/2	pINV encoded	Shigella extracellular protein (Sep)A SigA	Shigellosis

*One potentially functional but as yet uncharacterized T3SS (ETT2) was found in the genome sequence of EAEC O42 (and remnants of a second).

that had acquired typical EHEC phenotypes, most notably Stx production. Infection with STEAEC O104:H4 resulted in a high percentage of patients developing hemolytic uremic syndrome (HUS) and a mortality rate of 1%;[15] 852 cases of HUS, resulting in 32 deaths and 3469 cases of non-HUS STEAEC, resulting in 18 deaths.[16] Taking into account this large outbreak and the previous outbreaks of Stx2-positive O104:H4,[17,18] STEAEC could now be considered an emerging pathotype of enteric *E. coli*. Confirmation of STEAEC as an emerging pathotype will require continued detection of this distinct population of hybrid EAEC/EHEC strains.

The importance of DAEC to enteric disease remains uncertain. Some studies suggest DAEC may be an important contributor to diarrhogenic disease in children, however problems of cross-reactivity of one of the standard detection probes raises questions about this.[19] A correlation with disease may occur in specific age demographics (children aged 18 mo–5 y[20] or 13–24 mo[21]) although further epidemiological studies are required if DAEC is to remain a distinct enteric *E. coli* pathotype.

It is still under debate whether the association of AIEC with Crohn disease (CD) is causative or symptomatic. A combination of the two is likely with a genetic predisposition to developing CD exacerbated by microbial infection (including AIEC) into active CD. AIEC strains have been found associated with CD lesions in ileal and neo-terminal ileal and colonic specimens.[22] An increased immune response to *E. coli* in CD patients also suggests an involvement of *E. coli* in the pathology of CD.[23]

In the developed world epidemiological data for enteric *E. coli* infections is generally collected based on toxin production rather than pathotypes or serotypes and infections are therefore

commonly referred to as Stx-producing *E. coli* (STEC) or Verotoxigenic *E. coli* (VTEC). These classifications can include all of a pathotype (all EHEC strains are STECs) or part of a pathotype (STEAEC strains are also STECs) and may be further categorized as STEC/VTEC O157 referring to the most prevalent EHEC serogroup. 2011 estimates from the United States suggest 9.4 million foodborne illnesses occur annually, resulting in 55,961 hospitalizations and 1,351 deaths.[24] While STEC O157 infections accounted for only 4% of laboratory confirmed foodborne infections in the US from 1996–2005, STEC O157 had the highest case fatality rate across the population and the highest annual population mortality rate in children 0–4 y.[25] Data from the European Union for 2009 suggests 1% of laboratory confirmed zoonotic infections were attributable to VTEC with 7% of those developing HUS.[26] Therefore while incidence rates of STEC/VTEC are relatively low compared with Campylobacter and Salmonella infection rates, the severity of the disease and high case fatality rates means these infections are of major health concern.

While EPEC was the first strain of *E. coli* generally accepted to cause diarrhogenic outbreaks in the developed world,[27,28] its incidence has declined and EPEC outbreaks are now rare in developed countries. However it does remain an important cause of infant diarrhea in the developing world with recent estimates of EPEC prevalence among children with diarrhea ranging from 6–54%, although high carriage rates among healthy controls makes the contribution of EPEC to disease difficult to assess.[29] Atypical EPEC [i.e., those lacking the EAF plasmid that encodes bundle-forming pili (BFP)] appear to have a propensity to cause persistent diarrhea.[30,31]

EIEC and Shigella can be distinguished by minor biochemical tests but in general have the same virulence mechanisms and disease symptoms. Strains of EIEC and Shigella appear to have evolved independently to share many characteristics,[32] and EIEC strains seen today may simply be intermediates between *E. coli* and Shigella. We therefore direct the reader to the excellent review on Shigella species contained in this issue for in depth analysis of this pathotype.

Molecular Mechanisms of Virulence

Three pathotypes of *E. coli* (EHEC, EPEC and EIEC) employ a T3SS to translocate bacterial proteins, known as effectors, directly into the eukaryotic host cell in order to subvert host cell processes. For these pathotypes the T3SS is a major, but not the only, contributor to virulence. For convenience the pathotypes have been divided into non-T3SS dependent pathotypes (ETEC, EAEC, STEAEC, DAEC and AIEC) and T3SS dependent pathotypes (EHEC, EPEC and EIEC). The non-T3SS dependent pathotypes of enteric *E. coli* have comparatively simple and efficient molecular mechanisms of virulence requiring effective colonization factors followed by secretion of toxins that subsequently enter the host cell (for ETEC, EAEC and STEAEC).

Non-T3SS dependent pathotypes. *ETEC.* At least 25 distinct proteinaceous colonization factors (CFs) have been identified in ETEC strains[33] which mediate adhesion to epithelial cells (**Fig. 1**). Although 30–50% of ETEC isolates have no characterized CF by phenotypic screening,[6] novel CFs are constantly being identified genetically thus reducing the number of isolates with no apparent CF.[34] Two further proteins, the outer membrane protein Tia and the glycosylated autotransporter TibA, have been reported to mediate intimate cell attachment and to induce ETEC invasion into epithelial cells, for the prototype ETEC strain H10407.[35] While ETEC binds to leaf surfaces through the flagellum shaft,[36] a novel adhesin, EtpA, located on the tip of ETEC flagella mediates attachment to mammalian host cells.[37] EtpA is degraded by the serine protease autotransporter of Enterobacteriaceae (SPATE), EatA, thereby modulating bacterial adhesion and accelerating delivery of heat labile (LT) toxin into host cells.[38] A model of sequential attachment is proposed whereby the long-range flagella-EtpA first anchors the bacterium to the host cell and allows shorter CFs to interact. EatA then degrades EtpA and finally intimate attachment is mediated by Tia and TibB.

The main pathology of ETEC occurs through secretion of heat stable (ST) and/or heat labile (LT) toxins. Two small (2,000 Da) distinct heat-stable toxins, STa/STI and STb/STII, exist although only the former is thought to contribute to human disease. STa/STI mimics the native intestinal hormone guanylin, binding to and activating the intestinal brush border guanylate-cyclase-C (GC-C) receptor, increasing intracellular messenger cyclic GMP (cGMP). This activates cGMP-dependent protein kinase II leading to phosphorylation of the cystic fibrosis transmembrane regulator (CFTR) and deregulated ion absorption/secretion and hence diarrhea.[39-41]

The LT toxins can be divided into Type I (LT-I), generally in human isolates and closely related to cholera toxin, and Type II (LT-II), which are mainly from non-human isolates.[6] LT toxins are AB_5 toxins (one A subunit linked to a pentameric B subunit) and are transported across the bacterial outer membrane by the type 2 secretion system.[42] LT remains membrane-associated by binding lipopolysaccharide (LPS)[43] and is secreted in outer membrane vesicles (OMVs) that bind to ganglioside receptors on the mammalian cell (GM1a for LT-I or $GD1_{a/b}$ for LT-II) via the LT-B subunit. The OMVs are then actively endocytosed and the LT transported via the Golgi and endoplasmic reticulum (ER) to the cytosol[44] where the A1 subunit then ADP-ribosylates mammalian guanine nucleotide binding protein α-subunit ($G_{s\alpha}$). This inhibits the GTPase activity of $G_{s\alpha}$ and constitutively activates adenylate cyclase leading to uncontrolled elevation of the intracellular cAMP concentration.[45] This has pleotropic effects within the cell including phosphorylation of the CFTR chloride channel by protein kinase A. The combination of LT and CT ultimately leads to secretion of electrolytes and water resulting in osmotic diarrhea.

Several other putative toxins have been described for ETEC including the pore-forming cytotoxin ClyA,[46] however details of their mechanism of action, frequency among isolates, and importance during infection is unclear.

EAEC. EAEC strains are defined by their aggregative adherence or "stacked brick" phenotype on HEp-2 cells while in the intestinal mucosa EAEC forms a biofilm with bacteria incased in a thick mucus layer. Colonization requires the AAF (**Fig. 2**) and

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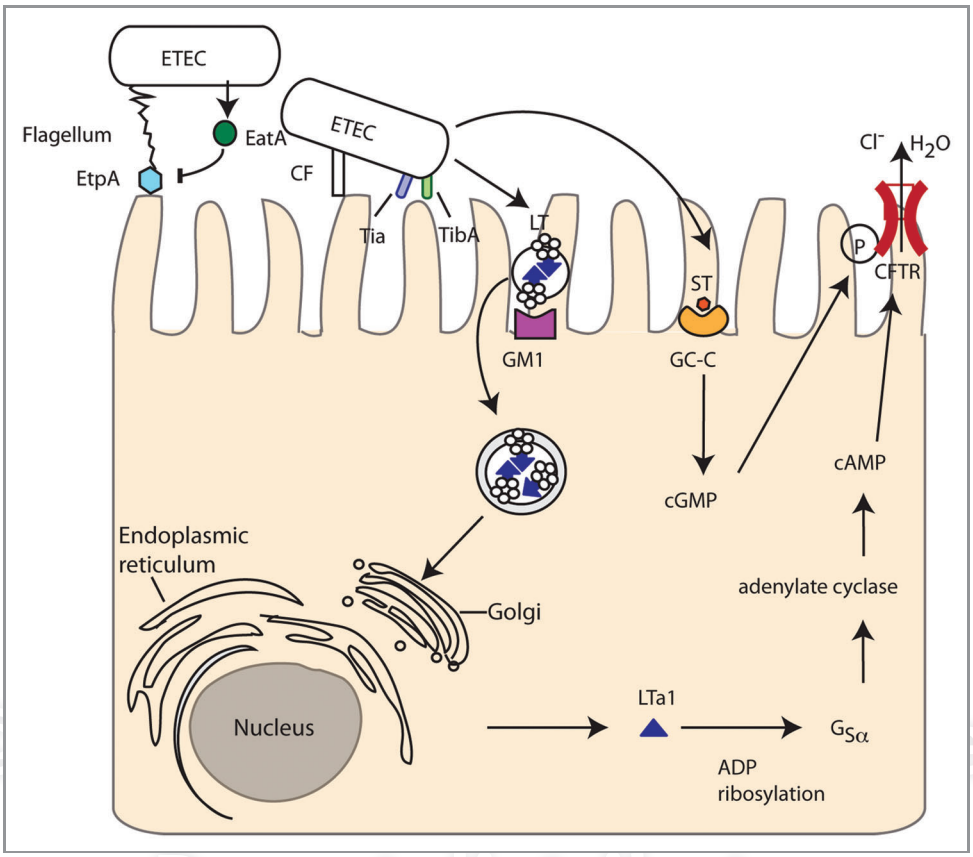

Figure 1. Enterotoxigenic *E. coli* (ETEC). EtpA located on the tip of flagella attaches to host cells but is then degraded by the SPATE EatA. Adherence is maintained by colonization factors (CF) and intimate attachment achieved with Tia and the autotransporter TibB. Heat stable toxin (ST) is secreted by ETEC and binds to guanylate cyclase-C receptor increasing cGMP and cGMP-dependent protein kinase II. Heat labile toxin (LT) is contained in outer membrane vesicles, which are endocytosed after interaction with ganglioside receptors (GM1). Retrograde transport through the Golgi and ER leads to the A1 subunit being released in the cytosol where it can ADP ribosylate mammalian guanine nucleotide binding protein α-subunit ($G_{s\alpha}$) inhibiting the GTPase activity of $G_{s\alpha}$ and activating adenylate cyclase resulting in uncontrolled cAMP levels. cAMP and cGMP both contribute to phosphorylation of the cystic fibrosis transmembrane regulator (CFTR) chloride channel and modulation of other ion channels leading to osmotic diarrhea.

the regulator AggR both encoded on a large virulence plasmid pAA. AAF, of which four variants have been described, mediates attachment of EAEC to salad leaves (in combination with flagella),[47] host cells[48] and human intestine ex vivo[49] but were not shown to confer a colonization advantage in a mouse model.[50] Other than AAF and AggR, there is a great deal of genomic diversity among EAEC strains with corresponding heterogeneity in virulence and few conserved virulence factors. Further colonization factors found in some EAEC isolates include Heat-resistant agglutinin (Hra) 1 and 2 and Tia (also found in ETEC).[51] The secreted small hydrophilic protein dispersin (encoded by *aap*) aids colonization by attaching noncovalently to the bacterial cell surface potentially neutralizing the negative charge of the LPS and allowing the positively charged AAF to extend away from the cell.[52]

EAEC strains produce a variety of SPATEs of either class I (cytotoxic) or class II (non-cytotoxic). Pic (protease involved in colonization, also found in *Shigella flexneri* and UPEC) is a class II SPATE with hemagglutinin and mucinolytic activity which may help to penetrate the mucus layer in which EAEC resides on enterocytes.[53] Conversely, Pic can induce mucus hypersecretion and an increase in the number of mucus-producing goblet cells.[54] Pic has also been implicated in immunomodulation by cleaving leukocyte surface glycoproteins and inducing both activation and apoptosis in T cells, but impaired migration, of polymorphonuclear leukocytes (PMNs).[55] Pet is a well characterized class I SPATE that is endocytosed by host cells, undergoes retrograde trafficking and utilizes the ER-associated degradation (ERAD) pathway to be released into the cytosol. Pet then cleaves the actin binding protein spectrin in the host cytosol, disrupting the actin cytoskeleton and causing cell rounding and detachment.[56] Recent evidence has also suggested a role for Pet in disrupting focal adhesions.[57] Pet is only present in a small minority of strains[58] and alternative class I SPATES (Sat, SigA, EspP) may have similar roles. Sat in particular has 52% amino acid identity with Pet and is discussed further under DAEC.

Non-SPATE toxins include the EAEC heat-stable enterotoxin 1 (EAST-1), which is encoded on pAA and is 50% identical to, but antigenetically distinct from, the enterotoxic domain of STa. Like STa, EAST-1 activates guanylate cyclase leading to increased cGMP, although the toxigenic effect appears milder than for STa.[59] The prevalence of EAST-1 among EAEC strains and its contribution to virulence remains unclear.[60,61] Further toxins

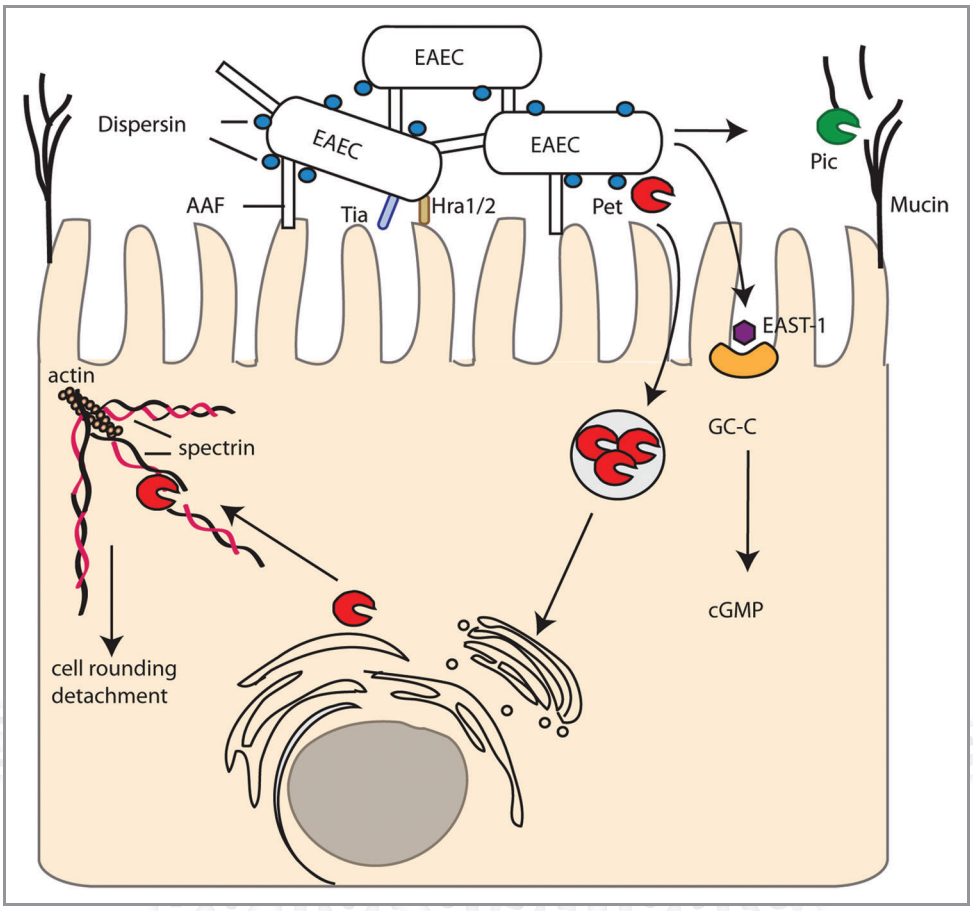

Figure 2. Enteroaggregative *E. coli* (EAEC). EAEC attach to host cells and each other by Aggregative Adherence Fimbriae (AAF) that are kept extended from the bacterial cell by dispersin. Adhesins Tia and Hra1/2 also contribute to intimate attachment. SPATEs include Pic, which digests mucin on host cells, and Pet which is endocytosed, undergoes retrograde trafficking and cleaves spectrin disrupting the actin cytoskeleton and inducing cell rounding and detachment. EAST-1 binds to and activates GC-C resulting in increased cGMP.

include ShET1 (characterized as an AB_5 toxin in *Shigella flexneri*)[62] and HlyE (a pore-forming toxin)[63] have also been proposed to contribute to EAEC virulence.

Recent sequencing of the prototype EAEC strain 042 has revealed some interesting potential virulence factors including two T3SS and potential effector proteins as well as a locus encoding a polysaccharide capsule, but these remain to be tested and their frequency among clinical isolates determined.[64] EAEC 042 also encodes three type 6 secretion systems and, like many EAEC clinical isolates, has multiple antibiotic resistance genes,[65] making treatment and eradication difficult.

STEAEC. The chromosome of STEAEC 2011 outbreak strain O104:H4 is most similar to EAEC strain 55989.[15,66] This STEAEC outbreak strain carries Pic on the chromosome and a pAA-like virulence plasmid encoding AAF, AggR, Pet, ShET1 and dispersin (**Fig. 3**). A second virulence plasmid encodes multiple antibiotic resistances. In addition to these standard EAEC virulence determinants STEAEC O104:H4 has an *stx2*-harbouring prophage integrated into the *wrbA* locus, and therefore can produce Stx, a defining characteristic of the EHEC pathotype (discussed under EPEC/EHEC—Non T3SS virulence mechanisms—Toxins). The outbreak strain has also acquired the IrgA homolog adhesin (Iha)[67] and a tellurite resistance cluster, which are common features of EHEC strains.[68] Therefore, there do not appear to be new virulence determinants in this strain, rather a combination of known virulence determinants from two pathotypes. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with EHEC allowing more Stx to be transferred and more resultant pathology.

DAEC. Grouping of DAEC strains is due to their diffusely adherent phenotype on HEp2 cells, which for most strains is due to the action of afimbrial (Afa) or fimbrial (Dr) adhesins (Afa-Dr adhesins) (**Fig. 4**). All Afa/Dr adhesins bind the decay-accelerating factor (DAF), while a subfamily of Afa/Dr adhesins (AfaE-III, Dr and F1845 adhesins) can also bind carcinoembryonic antigen-related molecules (CEACAMs)[69,70] and the Dr adhesin can also bind type IV collagen.[71] A small number of DAEC strains may also express the CS20 colonization factor from ETEC.[72]

Once the Afa/Dr adhesins bind their cellular target on enterocytes (DAF or CEACAMs) they relocalize the target around the site of bacterial attachment. For the Dr adhesin this relocalization has been shown to be dependent on Src kinase

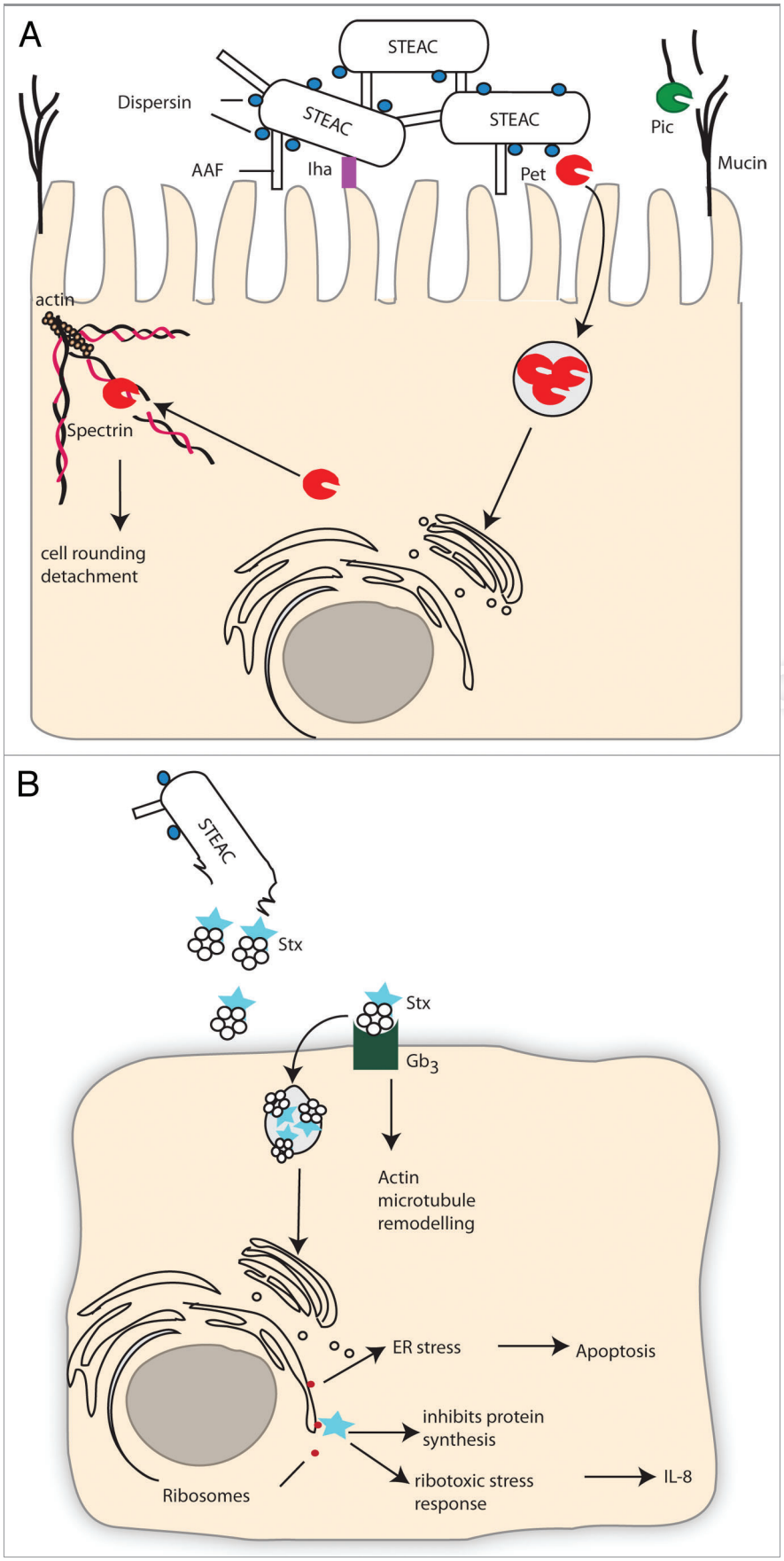

Figure 3. For figure legend, see page 77.

Figure 3. (See opposite page). Shiga Toxin producing Enteroaggregative *E. coli* (STEAEC). (A) STEAEC attach to each other and to enterocytes by AAF and dispersin, as for EAEC. STEAEC also encodes the Iha adhesin and SPATES Pet and Pic, although their contribution to infection is unknown. The action of shiga toxin (Stx) on an endothelial, toxin sensitive cell is shown in (B). The B subunit of Stx interacts with Gb_3 on the host cell and Stx is endocytosed and undergoes retrograde trafficking through the Golgi and ER, the A subunit then cleaves an adenine residue from the 28S rRNA of eukaryotic ribosomes inhibiting protein synthesis and leading to cell death. Stx can also cause cells to undergo a ribotoxic stress response, which leads to release of IL-8, or to undergo ER-dependent apoptosis.

activation.[73] Following target mobilization, enterocyte signaling pathways (e.g., MAPK and PI3K) are activated and IL-8 is synthesized (for the F1845 adhesin this requires HIF-1α[74]) inducing transepithelial migration of human polymorphonuclear neutrophils (PMN). This stimulates the enterocytes to synthesize TNFα and IL-1β and upregulate DAF to strengthen bacterial adhesion.[75] DAEC can interact with the transmigrating PMNs and induce type I pili-dependent IL-8 release.[76] Transmigrated PMNs are also induced to undergo apoptosis after interaction with DAEC and have a diminished phagocytic capacity, prolonging bacterial persistence in the gut.[77]

The only documented secreted factor associated with DAEC infection is the SPATE Sat. Sat can induce rearrangement of the tight junction proteins ZO-1, ZO-3 and occludin increasing paracellular permeability but not transepithelial resistance[78] and can also bind spectrin,[79] rearrange focal adhesion associated proteins vinculin and paxillin, and cause cell detachment and caspase-independent cell death.[80]

AIEC. While AIEC strains are genetically related to ExPEC strains they appear to have acquired novel virulence-specific features which can be characterized phenotypically (adhesion, invasion and intramacrophage replication) but the genetic basis of which is still largely undetermined.[81] This has hampered identification and hence research into the prevalence and importance of AIEC. The majority of AIEC research has used a single strain, LF82, and extrapolation of these results to other AIEC strains is vital as the field progresses.

AIEC infection requires both a susceptible host as well as bacterial virulence determinants. The first step in AIEC infection is abnormal colonization of the intestinal epithelium via type I pili binding to the CEACAM6 receptor, which is overexpressed in the ileal mucosa of CD patients.[82,83] In addition to type I pili, long

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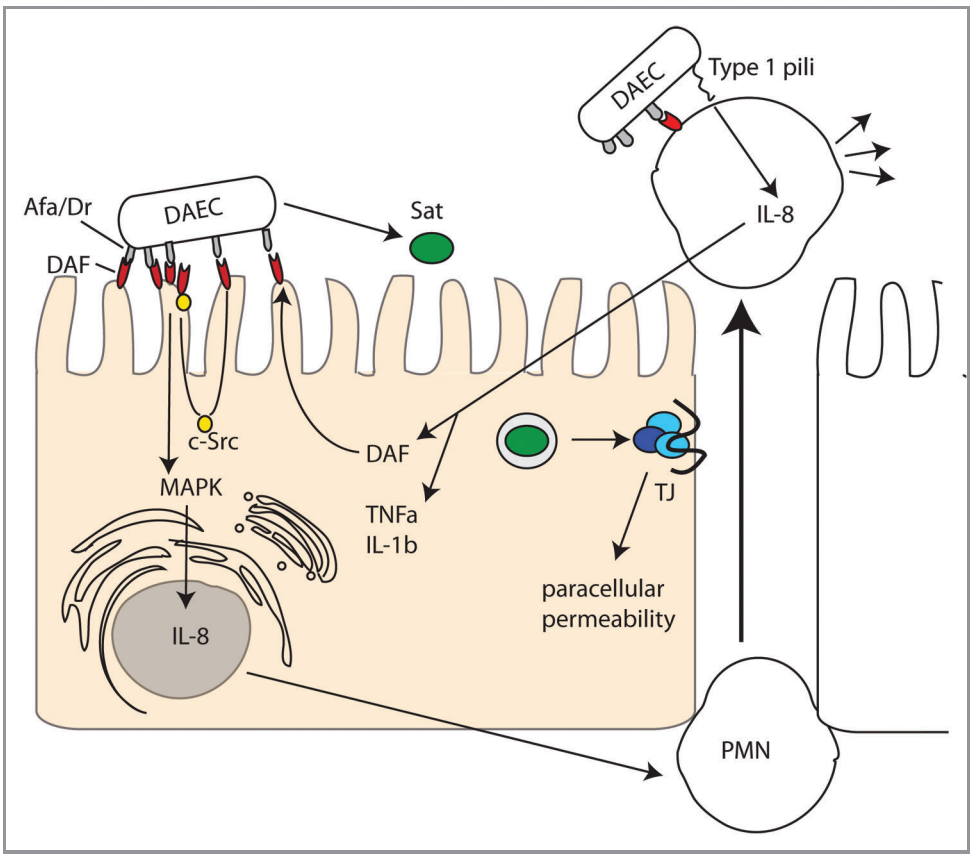

Figure 4. Diffusely Adherent *E. coli* (DAEC). AFA/Dr adhesins interact with the decay-accelerating factor (DAF) on host cells. Src kinase activation mobilizes DAF around the attachment site mediating stronger attachment and MAPK and PI3K pathway activation culminating in IL-8 synthesis, which induces transmigration of PMNs. PMN transmigration stimulates upregulation of DAF and TNFα and Il-1β synthesis. DAEC Type 1 pili induces IL-8 release from PMNs and apoptosis. Sat induces rearrangement of the tight junction proteins ZO-1, ZO-2 and occludin leading to paracellular permeability.

polar fimbriae were recently shown to also be required for AIEC to bind to M cells in Peyers patches.[84] This suggests that AIEC may utilize the transcytic characteristics of M cells to cross the intestinal barrier, as is the case for many other intestinal pathogens (e.g., Yersinia sp).

AIEC secrete OMVs that appear to be required for AIEC to invade intestinal epithelial cells (IECs),[85] potentially by delivering effector proteins into the host cell. The OMVs contain OmpA which interacts with the ER-localized stress response protein Gp96 which has been shown to be overexpressed on the apical surface of ileal epithelial cells in Crohn disease patients.[86] Other than OmpF/C and OmpA the composition of these OMVs and potential effector proteins delivered by this mechanism are unknown. While AIEC invasion into epithelial cells requires actin and microtubule involvement[87] the molecular mechanisms remain unknown. AIEC can survive and replicate in phagolysomes of infected macrophages in the lamina propria, resulting in increased TNFα secretion[88] which may lead to the inflammation associated with Crohn disease.

T3SS-dependent pathotypes. Of the T3SS-dependent pathotypes EHEC and EPEC primarily remain extracellular during infection while EIEC are found intracellular. Despite these very different lifestyles and the different T3SS origins (LEE encoded or pINV encoded, respectively) EPEC/EHEC and EIEC/*Shigella* actually share a number of T3SS translocated proteins, e.g., EspG/VirA, EspO/OspE, NleE/OspZ reflecting similar infection strategies.

EPEC/EHEC. The EPEC and EHEC T3SS is encoded on a pathogenicity island termed the locus of enterocyte effacement (LEE), a region highly conserved between the attaching/effacing (A/E) pathogens EPEC, EHEC, rabbit enteropathogenic *E. coli* (REPEC) and murine pathogen *Citrobacter rodentium*.[89] The LEE encodes gene regulators, structural components of the T3SS, chaperones, the bacterial surface protein intimin and a number of translocated proteins.[90]

EHEC O157:H7 appears to have evolved from EPEC O55:H7[91] and non-O157:H7 EHEC strains to have evolved by parallel evolution.[92] Defining characteristics of EHEC are the presence of *stx* genes, leading to more serious disease pathology and complications (HUS), and absence of BFP, leading to different adherence mechanisms. EPEC and EHEC are primarily human pathogens; although a range of ruminants carry EHEC it is generally asymptomatic in these animals. This host restriction makes modeling EPEC/EHEC infections difficult and so the related A/E pathogens REPEC and *C. rodentium* are commonly used as infection models.

Non T3SS virulence mechanisms. *Adherence.* EPEC/EHEC encode several well-characterized fimbrial (pili) adhesins. Human EPEC strains are divided into typical or atypical strains according to the presence or absence of the EPEC adherence factor (EAF) plasmid[93] which encodes the BFP. BFP is responsible for the formation of microcolonies through bacterial-bacterial interactions and a binding pattern known as localized adherence.[94,95] Long polar fimbria (LPF) play a significant role in EHEC adherence to epithelial cells, although they are not present in all strains.[96]

A variety of non-fimbrial adhesins have been identified for both EPEC and EHEC (**Table 1**). EHEC factor for adherence (Efa-1), found in some EHEC strains, contributes to in vitro adherence.[97] The major outer membrane protein OmpA has been reported to interact with cultured human intestinal cells in O157 EHEC infections.[98] Porcine attaching and effacing associated adhesin (Paa), found in EHEC, EPEC and ETEC strains, contributes to A/E lesions in pig ileal explants.[99] Additionally, there is a growing list of autotransporters involved in adherence in some EPEC/EHEC strains including STEC autoagglutinating adhesin (Saa),[100] *E. coli* immunoglobulin-binding protein (EibG)[101] and EhaA.[102] Intimate attachment of the bacteria to the host cell is T3SS-dependent and is described in detail below (Intimate attachment and A/E lesion).

Toxins. The major toxin produced by EHEC is the phage encoded Stx of which there are two subgroups, Stx1 and Stx2 (and variants thereof), with Stx2 more common among human isolates. Antibiotic treatment of Stx-producing bacteria is not recommended as it induces both expression of the toxin and allows release and dissemination (Stx does not appear to be actively transported from the cell).[103] For a review of Stx activity and intracellular trafficking see Johannes et al.[104]

Stx are AB_5 toxins with the B subunit mediating binding to the membrane glycolipid globotriaosylceramide (Gb_3). The B subunit induces endocytic plasma membrane invaginations[105]and vesicles traffic to early endosomes where, in toxin sensitive cells, Stx leaves the endocytic pathway[106] and travels through the Golgi apparatus and ER by retrograde transport. The catalytic A-subunit is translocated to the cytosol to reach its molecular target, rRNA, where it cleaves an adenine residue from the 28S rRNA of eukaryotic ribosomes, inhibiting protein synthesis and eventually leading to cell death.[107] In toxin resistant cells (e.g., Monocytes, macrophages) Stx does not leave the endocytic pathway but is degraded by lysosomes.[108] In these cells Stx activates the MAPK pathway and produces IL-6 and TNFα, which can in turn increase Gb_3 expression on endothelial cells.

Once Stx is released into the gut lumen it is translocated across the intestinal epithelium into the underlying tissues and bloodstream and then targets host cells expressing Gb_3. In humans, high concentrations of Gb_3 are found in renal tubular cells and microvascular endothelial cells, particularly those in the kidney, gut and brain, explaining the clinical manifestations of HUS. Stx has also been shown to induce apoptosis in various cell types which may contribute to disease pathology.[109,110]

Some EHEC and EPEC strains also produce SPATEs, the two best characterized being EspP from EHEC and EspC from EPEC. EspC shares 70% amino acid similarity with Pet (EAEC) and also cleaves spectrin, although at a different site than Pet. Unlike Pet which is internalized by receptor-mediated endocytosis EspC internalization requires EPEC contact with the host cell and production of a T3SS.[111] Four subtypes of EspP have been described with subtype α associated with highly pathogenic strains.[112] EspP has recently been described to cleave complement factors C3/C3b and C5 and impair complement function in vitro.[113]

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The T3SS and delivered effectors. The general T3SS is comprised of a cytosolic ATPase, inner and outer membrane rings, a periplasmic shaft and an extracellular needle protein (reviewed in ref. 114). The EPEC and EHEC systems have an additional filament of ~260 nm protruding from the T3SS needle which is generated by polymerization of EspA subunits.[115] This filament functions in initial attachment to the host cell before secretion of the translocators, EspB and EspD, which form the translocation pore in the host cell membrane.[116,117] EHEC and EPEC use the T3SS to inject dozens of effector proteins into the eukaryotic cell cytoplasm. Once translocated, these effector proteins are targeted to different subcellular compartments and affect diverse signaling pathways and physiological processes. In addition to the seven effectors encoded in the LEE, there are other effectors encoded within prophages and other integrative elements.[118] Although EPEC and EHEC show high levels of conservation between the LEE encoded effectors, there is significant diversity in their non-LEE effector (NLE) repertoire; EPEC E2348/69 has been shown to have 21 intact effector genes whereas the EHEC O157 strain Sakai is estimated to have closer to 50 T3SS effectors.[118,119] For a recent detailed review of EPEC/EHEC effectors see Wong et al.[120]

Intimate attachment and A/E lesion. EPEC/EHEC colonization results in the formation of A/E lesions on the apical surfaces of enterocytes (**Fig. 5A**). These characteristic T3SS-dependent lesions describe the effacement of microvilli and intimate bacterial attachment with actin accumulation at the bacterial host cell interface; in vitro the actin polymerization activity results in formation of raised pedestal-like structures underneath the attached bacteria.[121] The outer membrane adhesin, intimin was the first bacterial gene product found to be essential for the intimate attachment of bacteria to epithelial cells.[122] The intimin encoding *eae* gene was later found on the LEE and its product was shown to be secreted via the general secretory pathway and inserted into the bacterial outer membrane.[123,124] Four distinct intimin types were originally reported (α, β, γ and δ),[125] although more than 20 types are now recognized.[126] Intimin shares homology (31% identity) with invasin from *Yersinia pseudotuberculosis* and further studies on the intimin/invasin family have shown that the C-terminal 280 amino acids (Int280/Inv280) are required for binding β1-chain integrins.[127,128] The transmembrane intimin receptor (Tir) is a LEE-encoded effector translocated via the T3SS,[129] which resides in the host cell plasma membrane and interacts with intimin to allow intimate attachment of the bacteria with the host cell. EPEC/EHEC therefore delivers its own adhesin into the host to ensure intimate attachment is achieved. Intimin can also interact with the host protein nucleolin, which is upregulated by Stx.[130]

In addition to the role of Tir as a receptor for intimin, it is also an important mediator of protein signaling within epithelial cells. In EPEC, Tir is phosphorylated at tyrosine 474 (Y474p) to promote its interaction with the adaptor protein Nck leading to the recruitment of neural Wiskott-Aldrich syndrome protein (N-WASP).[131,132] This initiates actin polymerization mediated by the actin-related protein 2/3 (Arp 2/3) complex.[131,133] However, EHEC Tir lacks a tyrosine 474 equivalent and the process of actin polymerization is mediated via the T3SS translocated effector protein, TccP (Tir-cytoskeleton coupling protein)[134] also known as $EspF_U$ (*E. coli* secreted protein F in prophage U).[135] TccP/$EspF_U$ interacts with the IRSp53/MIM proteins, IRTKS and IRSp53, which also bind Tir at an Asn-Pro-Tyr (NPY458) tripeptide in the Tir C-terminal domain thereby linking TccP/$EspF_U$ indirectly to Tir.[136-138] TccP/$EspF_U$ interacts with and activates N-WASP preventing its autoinhibition fold and thus, initiating an Nck-independent actin polymerization pathway.[139] The NPY motif is conserved in EPEC Tir (NPY454) but in EPEC belonging to lineage 1 this pathway accounts only for low levels of pedestal formation in the absence of TccP/$EspF_U$.[138] Previous studies have demonstrated the conservation of the Nck and TccP/$EspF_U$ pathways in EPEC lineage 1 and EHEC O157 respectively.[140] Interestingly, both pathways are utilized simultaneously in vitro for most non-O157 EHEC strains, EPEC O119:H6[141] and EPEC lineage 2 strains.[140] Unexpectedly neither pathway appears to be necessary for A/E lesion formation in vivo in *C. rodentium* infections, in EPEC and EHEC infection of human intestinal in vitro organ cultures (IVOC),[142,143] or for EHEC colonization in the infant rabbits and gnotobiotic piglets models,[144] indicating the molecular mechanisms of A/E formation and their functions are far from understood.

Actin remodeling. Several EPEC T3SS effectors disrupt Rho GTPase signaling and hence subvert actin dynamics (**Fig. 5B**).[145] The Rho family small G proteins are crucial in the regulation of key cellular functions and the best characterized are Cdc42, Rac1 and RhoA, which trigger filopodia, lamellipodia/ruffles and stress fibers respectively.[146] T3SS effectors have been shown to regulate Rho GTPases by functioning as guanine exchange factors (GEFs), which control the switch from GDP-bound (inactive) to the GTP-bound (active) state,[147] or GTPase-activating proteins (GAPs), which increase the hydrolysis of GTP leading to the inactive state of the Rho GTPases.[148]

Alto et al. grouped 24 bacterial effector proteins in the WxxxE family based on a conserved motif of two invariant amino acids, Trp and Glu separated by three variable amino acids.[149] Members of the family include Map, EspM, EspT from EPEC/EHEC, IpgB1 and IpgB2 from Shigella spp, SopE and SifA from Salmonella spp Map and EspM function as GEFs on Cdc42 and RhoA respectively, leading to filopodia[150] and stress fibers formation.[151] In the case of EspT, Rac1 and Cdc42 are both activated which results in the formation of membrane ruffles and lamellipodia and bacterial internalization.[152] Map and SopE have been shown to have similar crystal structures when resolved in complex with Cdc42.[147] Despite the lack of sequence or structural similarity bacterial WxxxE effectors and eukaryotic GEFs appear to form the same conformational complex with Cdc42. The T3SS effector EspH was shown to subvert actin dynamics affecting filopodia and pedestal formation.[153] EspH inactivates mammalian Dbl-homology and pleckstrin-homology (DH-PH) Rho GEFs,[154] but not the bacterial Rho GEFs. This suggests that EspH might clear the cell of endogenous Rho GEFs allowing the bacterial Rho GEFs (WxxxE effectors) to take over cell signaling to fulfill the bacterial infection strategy.

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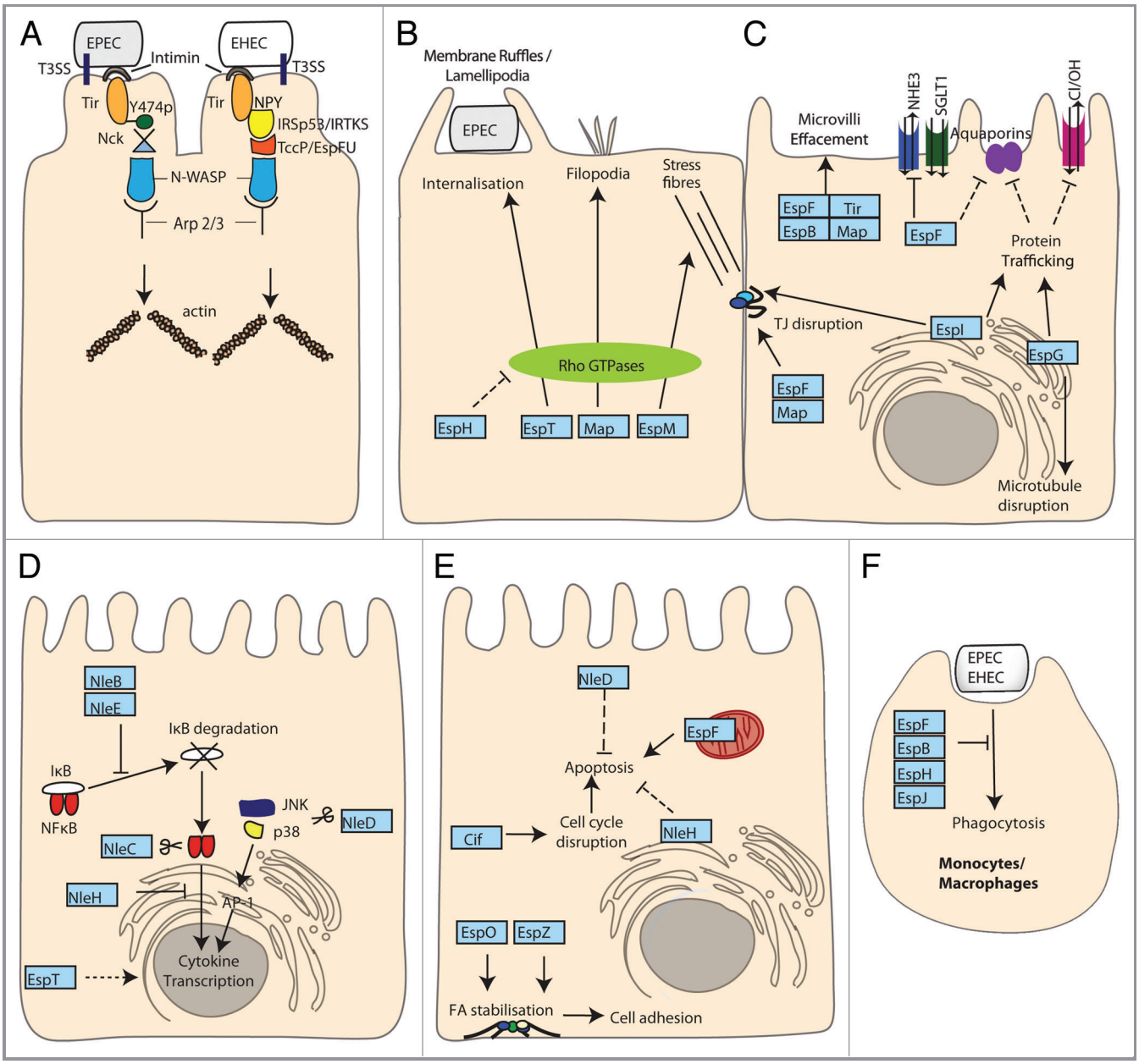

Figure 5. Enteropathogenic *E. coli* and Enterohamerrhagic *E. coli* (EPEC and EHEC). EPEC/EHEC inject an array of T3SS effector proteins to mediate intimate attachment and subvert host cell processes. In addition EHEC produces Stx, the action of which is described in **Figure 3B**. (A) Intimate adherence. The translocated intimin receptor (Tir) binds intimin on the bacterial surface to initiate intimate attachment, actin accumulation and pedestal formation. Tir^{EPEC} is phosphorylated at Y474 resulting in Nck and N-WASP recruitment. Tir^{EHEC} signaling proceeds independently of Nck via the T3SS effector TccP/$EspF_U$ that interacts with IRTKS/IRSp53 and N-WASP. Both pathways lead to Arp2/3 mediated initiation of actin polymerization. (B) Actin remodeling. Map, EspM and EspT activate Rho GTPases leading to filopodia, stress fibers and ruffles/lamellipodia respectively. Additionally, EspT can induce internalization of EPEC. EspH disrupts Rho GTPase signaling by targeting host DH-PH GEFs. (C) Disruption of gut integrity. Tir, Map, EspF and EspB contribute to effacement of the normal absorptive microvilli. Map, EspF and EspI disrupt tight junction (TJ) integrity and epithelial barrier function. EspG disrupts microtubules while EspI and EspG both modulate protein trafficking and affect TJs and the DRA Cl^-/OH^- exchanger respectively. EspG and EspF alter aquaporin levels disrupting water and ion absorption. EspF reduces the activity of the NHE3 Na^+/H^+ exchanger and multiple effectors target the SGLT1 Na^+/glucose co-transporter. (D) Manipulating immune responses. NleB, NleC, NleD NleE and NleH inhibit inflammatory responses through targeting NFκB, JNK and p38 pathways. NleB and NleE inhibit IκB degradation and subsequent nuclear translocation of NFκB. NleH can also block NFκB nuclear translocation. NleC and NleD function as metalloproteases acting on NFκB and JNK/p38 respectively blocking transcription of pro-inflammatory genes initiated by NFκB and AP-1 transcription factors. EspT promotes expression of inflammatory genes through Erk, JNK and NFκB pathways. (E) Balancing apoptosis and survival. Pro-apoptotic EspF causes mitochondrial dysfunction leading to activation of apoptotic pathways while Cif causes cell cycle disruption. Anti-apoptotic NleH interacts with Bl-1 at the ER and NleD inhibition of AP-1 dependent gene expression (shown in C) reduces pro-apoptotic gene expression. EspO and EspZ promote integrin mediated cell adhesion and survival through interacting with ILK and CD98 respectively. (F) Inhibiting phagocytosis. EspF, EspB, EspH and EspJ inhibit phagocytosis by macrophages through disruption of PI3K signaling, myosin-actin interactions, Rho GTPase signaling and an unknown mechanism respectively.

Another T3SS effector, EspV present in EPEC strains E110019 and E22 is able to cause nuclear condensation, cell rounding and actin-rich dendrite-like projections upon overexpression in mammalian cells[155] although the mechanisms involved in this actin rearrangement are not yet known.

Disrupting gut integrity. EPEC induces diarrhea through a variety of mechanisms (**Fig. 5C**). First, the effacement of the microvilli, a defining feature of the A/E lesion, results in a reduced surface area for normal absorptive processes. EspB, Map, EspF, Tir and intimin have all been shown to be involved in microvillus effacement.[156,157] EPEC also inhibits ion and water exchange through more targeted mechanisms. For example, Cl^- absorption is reduced by targeting the DRA Cl^-/OH^- exchanger through reducing the exchanger cell surface levels in an EspG and EspG2 dependent manner.[158] While EspG was originally described to degrade microtubules it can also bind the Golgi matrix protein GM130, p21-activated kinases (PAKs) and ADP-ribosylation factors (ARFs)[159,160] acting as a molecular scaffold to regulate host signaling cascades, leading to decreased protein secretion and receptor trafficking. Consequences of this manipulation of protein trafficking within the host cell include altering the paracellular permeability and membrane channel expression in enterocytes.[161,162]

In addition, the effector EspF is responsible for reducing the activity of Na^+/H^+ exchanger 3[163] and EPEC infection leads to a significant reduction in the activity of the SGLT1 Na^+/glucose cotransporter.[156] EspF and EspG have both been implicated in affecting water transport by altering aquaporin levels on apical and lateral membranes.[164] EPEC infections also affect the integrity of the epithelial monolayer and so disrupt barrier function. EspF, Map and intimin have all been shown to contribute to diarrhea through the disruption of tight junction integrity.[165] EspI (NleA) also disrupts intestinal tight junctions[166] and like EspG is able to decrease protein transport. EspI does so by binding to SEC24 through a PDZ binding motif and inhibiting COPII vesicle fusion[167,168] indicating EPEC/EHEC have developed multiple mechanisms to modulate the intestinal barrier function and integrity during infection.

Manipulating the immune response. Manipulation of the host immune system is a common theme in bacterial infections and a requirement for successful colonization and dissemination. EPEC and EHEC infections lead to an inflammatory response predominantly initiated by recognition of the bacterial flagella[169]. The production of pro-inflammatory cytokines is subsequently dampened by the bacteria with increased bacterial loads leading to reduced IL-8 production[170] with several effector proteins acting in concert to illicit this effect (**Fig. 5D**). The transcription factor NFκB is central to the initiation of inflammatory responses; NFκB dimers are held inactive in the cytoplasm by IκB until IκB is phosphorylated and degraded allowing NFκB to translocate to the nucleus and initiate transcription. The effector proteins NleB and NleE inhibit IκB degradation and therefore the nuclear translocation of NFκB subunits.[171,172] Additionally, the effectors NleC and NleD have been shown to function as metalloproteases downregulating inflammatory responses by targeting NFκB (NleC) and the mitogen activated protein kinases c-Jun N-terminal Kinase (JNK) and p38 (NleD).[173,174] NleH effectors have an uncertain role in immune modulation as they have been shown to enhance inflammatory responses[175] and conversely attenuate NFκB activation[176] with NleH1 able to block nuclear translocation of the RPS3 subunit of NFκB while NleH2 can induce expression of RPS3 dependent genes.[177,178] Interestingly the WxxxE effector EspT, triggers the expression of pro-inflammatory genes through Erk, JNK and NFκB pathways[179] suggesting a careful balance between pro- and anti-inflammatory actions exists.

Balancing apoptosis and maintaining cell survival. Like many enteric pathogens EPEC and EHEC are able to induce apoptosis upon infection.[180,181] However, apoptosis induction needs to be modulated in order to maintain an infective niche within a host, by balancing pro and anti-apoptotic effectors (**Fig. 5E**). In EPEC and EHEC, two T3SS effectors are currently known to act as inducers of apoptosis, EspF[182] and Cycle inhibitory factor (Cif).[183] EspF is targeted to the mitochondria via an N-terminal mitochondrion-targeting sequence and interferes with the mitochondrial membrane potential.[184] EspF has specifically been shown to induce the release of cytochrome *c* and cleavage of caspases 9 and 3[182] while Cif acts mainly as a bacterial cyclomodulin subverting the eukaryotic cell cycle by blocking both the G_1/S and G_2/M transitions resulting in apoptosis.[182] The action of these pro-apoptotic effectors is balanced by the translocation of anti-apoptotic effectors such as NleH and NleD. NleH inhibits intrinsic apoptotic pathways via its direct interaction with the anti-apoptotic protein Bax inhibitor-1 (BI-1)[185] while NleD inactivates JNK leading to the suppression of the downstream transcription factor AP-1 which activates several pro-apoptotic proteins.[186]

Additionally, other T3SS effectors indirectly contribute to the inhibition of apoptosis through their ability to promote host cell survival mechanisms. The LEE encoded effector EspZ interacts with CD98, a host protein involved in integrin mediated cell adhesion and cell survival[187] while the non-LEE encoded effector EspO increases cell adhesion and survival through its direct binding with integrin-linked kinase (ILK).[188] EPEC and EHEC also activate several other signaling pathways known to inhibit apoptosis including the protein kinase C, tyrosine kinases and phosphatidylinositol 3-kinase[189-191] suggesting other effectors might also be involved in manipulation of apoptosis.

Inhibiting phagocytosis. During infection EPEC and EHEC primarily survive extracellularly and have developed mechanisms to inhibit internalization by phagocytic cells (**Fig. 5F**). Phagocytosis involves rearrangement of the actin cytoskeleton and additional membrane recruitment and is initiated by the engagement of surface receptors, which recognize a variety of ligands including pathogen-associated lipids and sugars as well as immunoglobulin (Ig) and components of the complement cascade. EPEC and EHEC inhibit internalization of unopsonized (cis-phagocytosis) and opsonized bacteria (trans-phagocytosis) through the actions of a number of effector proteins. EspF targets PI3K signaling, inhibiting its activation rather than recruitment to the site of attachment, preventing cis-phagocytosis and internalization of IgG opsonized particles.[192] EspB has been shown to

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bind several members of the myosin superfamily preventing the interaction of Myosin -1c and actin, inhibiting cis-phagocytosis.[193] Recently the effector EspH, which inactivates Rho GTPase signaling, was also shown to inhibit both cis-phagocytosis and trans-phagocytosis,[154] while, EspJ has been shown to inhibit trans-phagocytosis through an unknown mechanism. EspJ is capable of preventing phagocytosis of both IgG and complement opsonized particles despite significant differences between these FcγR and CR3 mediated phagocytic pathways.[194]

The T3SS is obviously of fundamental importance to EPEC and EHEC infection. Some effectors appear redundant and others to have multiple functions. The challenge is now to move away from studying effector proteins in isolation and to apply more holistic approaches to study the function of individual effectors in the context of the whole effector repertoire and to determine the significance of the many different effector phenotypes in vivo with respect to the temporal-spatial kinetics of infection.

Conclusions

E. coli are a remarkably versatile and diverse genus of bacteria, which includes both commensals and pathogens. Despite more than 100 years of research we still do not understand all of the pathogenic mechanisms utilized by the different *E. coli* pathotypes. Making research on *E. coli* more challenging is the fact that the species is constantly evolving, as is evident by the recent emergence of a new pathotype (STEAEC). Emergence of novel pathotypes is likely due to selective pressure, changes to human behavior and demographics and to the environment, allowing these strains to present within the human population (e.g., changes in food growing, harvesting and consumption). The rapid growth and easy acquisition of new traits by these pathotypes means researchers and clinicians are forced to play 'catch-up' in treatments and preventative methods. However better understanding of the emergence and changes in pathotypes may help us to predict and potentially prevent the next round of adaptations. The role of *E. coli* and other bacteria in complex disease processes such as Crohn disease is only beginning to be studied and requires much further research to unravel the contributions and interplay between the host, microbiota and pathogen.

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