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ENTEROTOXIGENIC ESCHERICHIA COLI INTESTINAL PATHOGENESIS AND COLONIZATION RESISTANCE

[1]Mamatmusayeva F.Sh., [2]Kadirova K.A. [3]Egamberdiyev R.Y.
[1]Associate Professor of Microbiology, Immunology, Virology Department of TTA, PhD, mkomfo@mail.ru, +998909631843
[2]Assistant of the Department of Clinical allergology, immunology, microbiology of the Tashkent Paediatric Medical Institute
[3]Second year student of Treatment faculty of TMA, @e.rasulbek21@gmail.com, +998940942332

Abstract
This review discusses articles in the last 10 years about the etiology, pathogenesis, and clinical manifestations of ETEC, as well as gut microbiota-mediated resistance to colonization, its interactions in human small intestine, prevention strategies and most importantly modern diagnostic methods using cutting-edge technologies which provide new insights in reducing adverse human health impacts.
And also you can see here colonization factors (CFS) of ETEC and heat stable toxin (ST) and/or heat labile toxin (LLT of it , which causes dysregulation of cellular ion transport and water secretion.
Keywords: Enterotoxigenic Escherichia coli; gut microbiota; pathogenesis; enterotoxin; colonization resistance; small intestine, outer membrane vesicles (OMV), enterohemorrhagic E. coli (EHEC), STa, STb, estA (STI), estB (STII), CS30

Аннотация
В этом статьи обсуждаются статьи за последние 10 лет об этиологии, патогенезе и клинических проявлениях ETEC, а также опосредованной кишечной микробиотой устойчивости к колонизации, ее взаимодействиях в тонком кишечнике человека, стратегиях профилактики и, самое главное, современных методах диагностики с использованием передовых технологий, которые дают новое представление о снижении неблагоприятных последствий для человека, воздействие на здоровье.

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А также вы можете узнать факторы колонизации (CFS) ETEC и термостабильный токсин (ST) и /или термолабильный токсин (LLT) it , который вызывает нарушение регуляции клеточного транспорта ионов и секреции воды**.**

Ключевые слова: Энтеротоксигенная кишечная палочка; кишечная микробиота; патогенез; энтеротоксин; колонизационная резистентность; тонкая кишка, везикулы наружной мембраны (OMV), энтерогеморрагическая кишечная палочка (EHEC), STa, STb, estA (STI), estB (STII), CS30

Introduction

Enterotoxigenic Escherichia coli (ETEC) is a major enteric pathogen that accounts for tens of millions of cases of diarrheal disease each year [1]. Children under 5 years of age are susceptible to ETEC, especially in endemic areas, which is estimated to be responsible for 100 million episodes of diarrhea and 60,000 deaths in 2015[1,2]. ETEC is also a key etiology of traveler's diarrhea, which affects travelers visiting low-income regions of the world, and about a third of all patients with traveler's diarrhea who seek medical attention have been diagnosed with gastrointestinal -intestinal disorders [3]. ETEC infection is caused by the consumption of contaminated food and water in developing countries where there is no infrastructure to supply clean drinking water and dispose of excreta. Previous research has shown that ETECs can persist in faeces for over half a year and are commonly found in water as biofilms, providing a greater potential for survival [4]. (Figure 1) In low-income regions, health-related infrastructure and sanitation is difficult to dramatically improve in a short period of time the risk of diarrhea caused by ETEC is difficult to control effectively.

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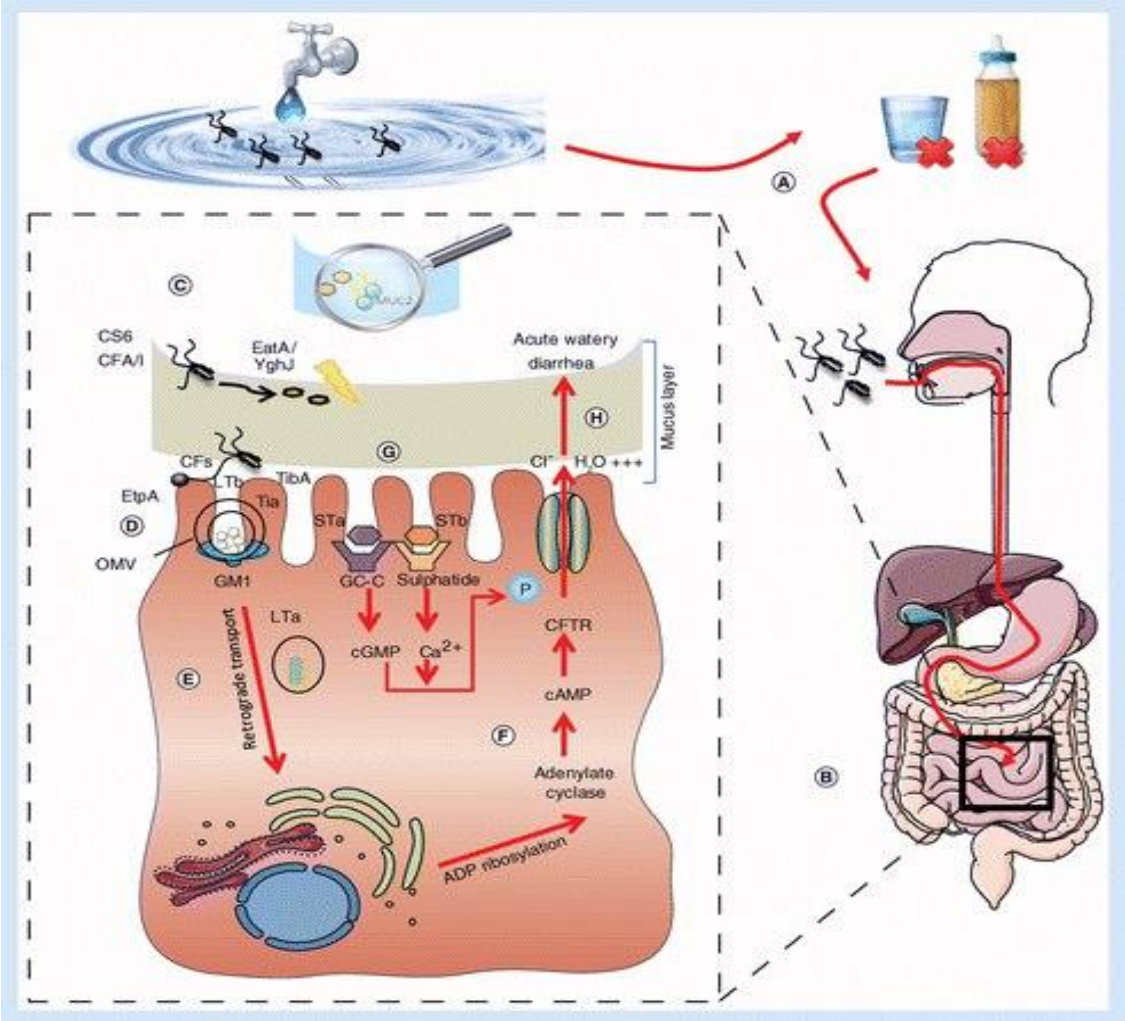

Figure 1. Characteristics of the ETEC infection. ETEC is the major enteric pathogen that account for the diarrhea that occurs in travelers and children in developing countries. ETEC infection is caused by ingestion of contaminated food and water, ETEC through the gastrointestinal tract, and eventually colonization in the small intestine. When ETEC is exposed in the small intestine, it colonizes intestinal epithelial cells via CFs, and ETEC proliferates on the intestinal epithelial after colonization. ETEC produces and delivers heat-labile (LT) and/or heat-stable (ST) enterotoxins to exert toxic e錦ect. Image created with BioRender.

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Outer membrane vesicles (OMVs) are nanoscale proteoliposomes secreted from the cell wall of all Gram-negative bacteria [6]. They are formed by controlled erosion of the bacterial outer membrane due to membrane disruption by various Rueter and Belashevskaya mechanisms [7]. As a result, OMVs are surrounded by a single membrane layer and contain mainly components from the bacterial outer membrane (outer membrane proteins, lipopolysaccharide, phospholipids, peptidoglycan) and periplasm (periplasmic proteins) [8]. Initially thought to be a cell wall artifact, OMVs are now recognized as a common secretion system, [9] which serves to improve bacterial fitness and facilitate interactions between cells in the context of mixed bacterial communities and between host and microbe [10]. Membrane vesicle release is a ubiquitous process and has been observed in a wide range of bacteria. sticky-invasive E. coli and extra-intestinal pathogenic E. coli, but also non-pathogenic bacteria such as E.coli Nissle 1917, secrete membranous vesicles during growth [11,12,13].

Interactions in Human Small Intestine

Enterotoxigenic strains of Escherichia Coli (ETEC) are ubiquitous pathogens in low- and middle-income regions, where they are a major cause of diarrheal disease morbidity and mortality, especially among young children [15]. In the classical ETEC virulence paradigm, microorganisms attach to the epithelial cells of the small intestine by plasmid-encoded colonization factors where they deliver heat-resistant (LT) and/or heat-stable (ST) enterotoxins that promote a net efflux of salt and water into the intestinal lumen, followed by watery diarrhea. However, some features of ETEC disease suggest that this classical paradigm of molecular pathogenesis is far from complete.16 Notably, strains of ETEC cause diseases that can range from mild disease to severe diarrhea accompanied by rapid dehydration clinically indistinguishable from cholera [17,18,19,20]. In addition, ETEC and other bacterial enteric pathogens, including shigella, have been repeatedly associated with poorly understood non-diarrheal outcomes, [21] including environmental enteropathy, [22] growth retardation, [23,24,25,26] malnutrition, and [27] cognitive Impairment [28,29,30].

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Once ETEC is colonized in the epithelium of the small intestine via CFS, efficient delivery of enterotoxins begins, which is responsible for the secretion of water and electrolytes in the intestinal lumen [5].

Enterotoxigenic E. coli is spread by the fecal-oral route among hosts, and several virulence factors such as adhesins and enterotoxins play an important role in its pathogenesis. When administered orally and after entering the gastrointestinal tract, ETECs colonize the small intestine through the interaction of fimbrial and non-fimbrial adhesins with specific receptors present in the apical membrane of the small intestinal epithelium [31].

However, the addition of mucin resulted in a slight increase in the number of viable bacteria 120 minutes before the end of digestion in the duodenum. Then, in the distal small intestine, less stringent conditions (i.e. near neutral pH, lower bile salt concentrations due to reabsorption and/or longer residence time) allowed ETEC to rise, as previously shown for other strains. E. coli [32,33,34].

Most nutrient transport takes place in the small intestine, while the large intestine is usually responsible for water and ion exchange [35].

IL-33 has been shown to stimulate intestinal IgA responses in the colon, which may seem to contradict the results presented here. It should be noted that our results show that ST induces IL-33 in small intestine tissue and not in colon tissue. Moreover, LT has been shown to induce TH17 responses[36] and IL-33 controls TH17-Treg balance in the small intestine, suggesting a difference between Motyka et al. Infection and Immunity April 2021 Volume 89 Issue 4 e00707-20 iai.asm.org 12. monitoring immune responses in various tissue types.

This result was similar for other global ETEC isolates, highlighting the universal effectiveness of this strategy. Importantly, these data were determined using four different enteroid strains from the small intestine, three from the ileum, and one from the jejunum, with all blood groups represented, highlighting the genetic diversity of the host model used [37].

In the present study, the potential recognition of CS30 carbohydrates was investigated by binding ETEC-expressing CS30 to glycosphingolipids from various sources on thin layer chromatograms. Clear binding to the rapidly

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migrating acidic glycosphingolipid of the human and porcine small intestine was found [38].

This suggests that SslE enhances the virulence of E. coli pathotypes through its ability to stimulate biofilm maturation and/or through interaction with mucosal defenses. Both enterotoxigenic and enteropathogenic strains of E. coli cause infection in the small intestine 1 where intraluminal pH ranges between ~6.0 and 7,55 [39].

Heat-Stable Enterotoxins of ETEC from Human and Animal Origin

The thermostable enterotoxins produced by ETEC are secreted peptides that can be divided into two types: STa and STb. While the latter is more virulent in animals, and especially in weaned piglets, STa enterotoxin is more important for the induction of diarrhea in humans, newborn piglets, and calves [53]. These peptides are encoded by two genes, estA (STI) and estB (STII), which located on plasmids and can be distinguished from each other by their solubility in methanol and sensitivity to proteases. Enterotoxin STa is soluble in methanol and resistant to proteases, while STb is insoluble in methanol and sensitive to proteases. Depending on the host species, STa is further classified into two subtypes known as STp and STh, which were originally isolated from porcine and human ETEC strains, respectively [54]. While STp is widely found in porcine, bovine, and human ETEC strains, STh produced only by human ETEC strains [43].

Inside the intestine, the luminal surface consists of a dynamic layer of epithelial cells. It acts as a barrier between luminal materials and their underlying neuronal and immune systems, also supporting nutrient, fluid, and ion transport [56]. This barrier is maintained by connections between adjacent enterocytes. These are the intercellular junctions known as adhesive junctions (AJs) and tight junctions (TJs). TJs are multiprotein complexes that form a continuous loop around cells in the apical and lateral membrane domains. These proteins function as a selective paracellular barrier, facilitating the flow of solutes and ions through the lateral intercellular space. They prevent entry and transport of intestinal antigens, microorganisms, and their potentially harmful products [57]. TJs consist of four unique groups of transmembrane proteins: claudins, occludin, zonula occludens (ZOs), and junctional adhesion molecules (JAMs) [58]. Transmembrane claudins and occlusion are supported

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by scaffolds. ZO proteins. The ZO complex provides intracellular structural support to the multiprotein complex of claudin and occludin on the surface of the cytoplasm [59].

Isolation of the CS30 binding glycosphingolipid from human small intestine

The total acid fraction of glycosphingolipids (43.2 mg) from the human small intestine was first isolated on a 10g Iatrobeads column (Iatron Laboratories Inc.; 6RS-8060) eluted with chloroform/methanol/water (60:35:8, v/v) 30 × 1 ml. The obtained fractions were analyzed by thin layer chromatography and staining with anisaldehyde and combined into four subfractions in accordance with the mobility on thin layer chromatograms. The binding activity of E. coli CS30 of these four fractions was evaluated using a chromatographic binding assay. After this first separation, one fraction (18.6 mg) was obtained containing CS30 binding fast migrating compounds. This fraction was further separated on a second column with 10 g Iatrobeads eluted with chloroform/methanol/water (60:35:8 v/v), 40 ± 0.5 ml. The obtained fractions were again analyzed by thin layer chromatography and anisaldehyde staining and combined into three subfractions in accordance with the mobility on thin layer chromatograms. The obtained first and third fractions had distinctly different mobility on thin layer chromatograms, indicating different compositions of ceramides. To isolate pure ceramide species for testing for CS30 binding, these two fractions (approximately 4 mg each) were further separated on 10 gram Iatrobeads columns, eluted and pooled as above [60].

Generation of L. reuteri CO21 strain producing LFCA and biological activity of LFCA

As seen under a microscope, strains of L. reuteri isolated from the intestinal mucosa were Gram-positive, catalase-negative rod-shaped bacteria. CE1, CO21, CE12 and J31 were identified as L. reuteri by ERIC-PCR and 16 s-rRNA gene sequencing with 99% similarity. We got 4 an isolate of L. reuteri from the intestinal mucosa of a piglet. Further isolate analysis showed that L. reuteri CO21 has the greatest ability to resist lysozyme, bile, low pH (pH 2.0 and 3.0). The L. reuteri CO21 isolate also showed the highest percentage of

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hydrophobicity and autoaggregation ratee1956281-6 W. SE AND DR. Therefore, we used L. reuteri CO21 as mucosal delivery vehicles. L. reuteri CO21 was kept at the China Type Culture Center (Save number: CCTCC NO: M2019601). In this study, we have developed a recombinant L. reuteri CO21 strains with a plasmid expressing LFCA (LR-LFCA). Immunoblotting cell lysates of LR-LFCA and supernatant confirmed the expression-formation and secretion of LFCA by detection 4,6 kDa range (Fig. 1a). Expression level of LRLFCA was highest in culture medium after 18 h. The ability of LR-LFCA cell lysates to inhibit the growth of S. aureus strains, ETEC K88, P. multocida and S. enteritidis. LR-LFCA lysates but not LR-con lysates, significantly inhibited the growth S. aureus, E. coli K88, P. multocida and S. enteritidis (55.07%, 48.65%, 38.31% and 37.79%, respectively) when cultured with lysate for 24 h. Negative staining and electron microscopy showed that LR-LFCA cell lysates damaged morphology of S. aureus, E. coli K88, P. multocida and S. enteritidis, and bacteria treated LR-LFCA lysate contained more atypical bubbles, protrusions and seals than untreated cells (control) and cells treated with Cell Lysate LR-con [61].

Results

Although the mucin layer in the small intestine is more permeable than the colon [68], perhaps this is enough to exclude direct interaction intestinal epithelial cells with ETEC required for efficient toxin delivery [69]. In addition, research rat intestine [70, 71] and cell lines derived from colon cancer [32] have shown that cholera, a LT homologue, can stimulate mucin secretion by goblet cells. Respectively, treatment with enteroids derived from the human small intestine has resulted in significant increased transcription of the MUC2 gene, while processing spheroids cells of the small intestine, in which the apical surface of the cells is oriented towards the inner lumen cavity, led to the release of a significant amount of mucin MUC2 in lumen compared to untreated control. Similarly, the processing of polarized enteroid monolayers of the small intestine LT and cholera toxin, but not the mutant E112K, enzymatically inactive version of LT (mLT), led to a significant increase in secretionmucin MUC2 formation and a corresponding increase in integrity. Enteroid monolayers treated with either forskolin or LT, but not

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untreated monolayers, excluded the migration of fluorescent beads to the surface of the epithelium, which suggests that induced mucin represents a significant barrier. In general, these data indicate that both LT and cholera toxin provoke the intestinal epithelium to strengthen protective mucin barrier in the small intestine.

Effective delivery of ETEC enterotoxin requires close interaction of bacteria with surface of targeted intestinal epithelial cells (IECs) [69]. We found that in the absence of eatA, ETEC bacteria were unable to efficiently migrate through MUC2 purified from enteroids of the small intestine, and were as attenuated as the immobile mutant (fliC), while how MUC2 pretreatment with rEatAp restored migration. Likewise, adhesionacta ETC mutant to enteroid epithelial cells of the small intestine was significantly attenuated compared to wild-type ETEC, as was delivery of heat-resistant toxin . Taken together, these data suggest that eatA plays an important role in providing effective interaction of the ETEC pathogen with the host.

Discussion

In this study, we determined the signaling pathways and effects on NHE3 of thermostable E. coli ST enterotoxin in two ion transport models: mouse small intestine and polarized Caco-2/BBe cells. In both models, as expected, ST inhibited NHE3, and in both cases this was predominantly due to changes in surface expression. In fact, assessing the surface-specific activity of NHE3 (by dividing NHE3 activity by surface expression: for mouse jejunum, NHE3 separation data in Fig. 1A from that shown in Fig. 1C and for NHE3 activity in a Caco-2 cell, by separating data in Fig. 1D from what is shown in Fig. 1E) showed no change in this estimate of transport per NH3 molecule on the apical membrane. Since the data shown in these figures was not obtained from the same experiments, the figures are only a rough estimate. Although the initial stages of signal transduction and the subsequent effect on the NHE3 Na/H exchanger were the same, the intracellular second messengers involved after the increase in cGMP levels were different.

Given that understanding of signal transduction in gut pathophysiology has relied heavily on studies using mouse gut and polarized human colon cancer cell lines, the differences identified in these studies and, most importantly,

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differences in the second messengers mediating inhibition of cGMP NHE3, must be considered in the study of pathophysiology, which attempts to understand human disorders, including intestinal diseases. These results are also highly relevant to attempts to develop drug therapy for diarrheal diseases, which remains an unmet clinical need. Drug targeting strategies for diarrhea include reversing changes in transport proteins that increase fecal Cl and Na, which are the immediate causes of increased fecal water, a major determinant of diarrhea, and interfering with changes in signaling that occur when diarrheal disease [62,63,64,65]. Current research demonstrates that there are differences in intracellular signaling in one disease model studied in the mouse intestine and a human colon cancer cell line. These results make it important to determine whether the diarrhea models tested in rodent and colon cancer cell lines behave similarly in the normal human intestine, and also whether there are differences in other aspects of the diarrheal disease models, for example, whether there are differences in the transport proteins involved. In addition, we suggest that it should not be assumed a priori that all of the numerous gut models currently being studied have the same intracellular signaling that occurs when exposed to a common diarrhea-inducing ligand or virulence factor [66].

Conclusion

To conclude, we 've reviewed all about ETEC's etiology, pathogenesis and clinical manifestations and various diagnostic methods as well as its preventive measures which makes people more aware about this disease resulting a decline in the number of ETEC patients along with reducing numbers of potential transmission of this disease.

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