جامعة الانبار

كليه العلوم

قسم علوم الحياة

Bacterial toxins

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Lecture 4

Cholera toxins (O1-O139)

Intestinal Diseases Caused by *E. coli*

سلالات اخرى لسموم الكوليرا

وسموم الاشريشية القولونية

(ii) Other *V. cholerae* O1/O139 toxins. Lec4

The second toxin identified in *V. cholerae* O1 strains is **Zot** (for zonula occludens toxin). The *zot* gene encodes a predicted 44.8-kDa peptide . The *zot* geneis present in most O1 and O139 strains, and if a strain is CT positive, it is almost always *zot* positive. Crude Zot diminishes the resistance of rabbit ileal tissue in Ussing chambers without causing detectable changes in potential difference.

Zot has been reported to cause F-actin rearrangement in rat intestinal epithelial cells (IEC-6 cells) in vitro and rabbit ileum in vivo . In an endothelial cell line, Zot treatment increased the proportion of F to G actin . Together, these observations indicate an effect of Zot on the zonula occludens or epithelial tight junctions, possibly through a rearrangement of F actin, and suggest that Zot may contribute to diarrhea in cholera by altering the permeability of intestinal tissue.

Several signal transduction mechanisms (e.g., calcium, PKC, tyrosine kinase, cyclic AMP) have been shown to regulate tight junctions in intestinal epithelial cells , and current data implicate PKC in the response of intestinal cells to Zot .

The third toxin identified in *V. cholerae* O1 is **Ace** (for accessory cholera enterotoxin), a 11.3-kDa protein encoded by the *ace* gene . Ace is predicted to be an amphipathic molecule, leading to the hypothesis that it forms multimers which insert into the eukaryotic cell membrane, creating an ion-permeable pore. Direct proof of this hypothesis is not yet available. In rabbit ileal tissue mounted in Ussing chambers, crude Ace stimulates a delayed increase in *I*sc and PD.

Inoculation of ligated rabbit ileal segments with a CT- and Zot-negative *V. cholerae* strain containing the cloned *ace* gene results in fluid accumulation. Both of these observations are consistent with Ace stimulating electrogenic chloride secretion, which may contribute, in a limited fashion , to the pathogenicity of *V. cholerae* O1.

V. cholerae O1 and O139 strains also produce a cytotoxic protein, which produces fluid accumulation in animal models.This toxin, known as the El Tor hemolysin or hemolysin-

cytolysin, is cytotoxic for a variety of erythrocytes and mammalian cells in culture and rapidly lethal for mice . Injection of the purified toxin into rabbit ileal loops produces fluid accumulation, and the accumulated fluid is usually bloody with mucus .

Intestinal Diseases Caused by *E. coli*

As a pathogen, *E. coli* is best known for its ability to cause intestinal diseases.

Five classes (virotypes) of *E. coli* that cause diarrheal diseases are now recognized: **enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC), enteropathogenic *E. coli* (EPEC), and enteroaggregative *E. coli* (EAEC)**.

Each class falls within a serological subgroup and manifests distinct features in pathogenesis. A summary of the characteristics of diarrheagenic strains of *E. coli* is given in Table 1.

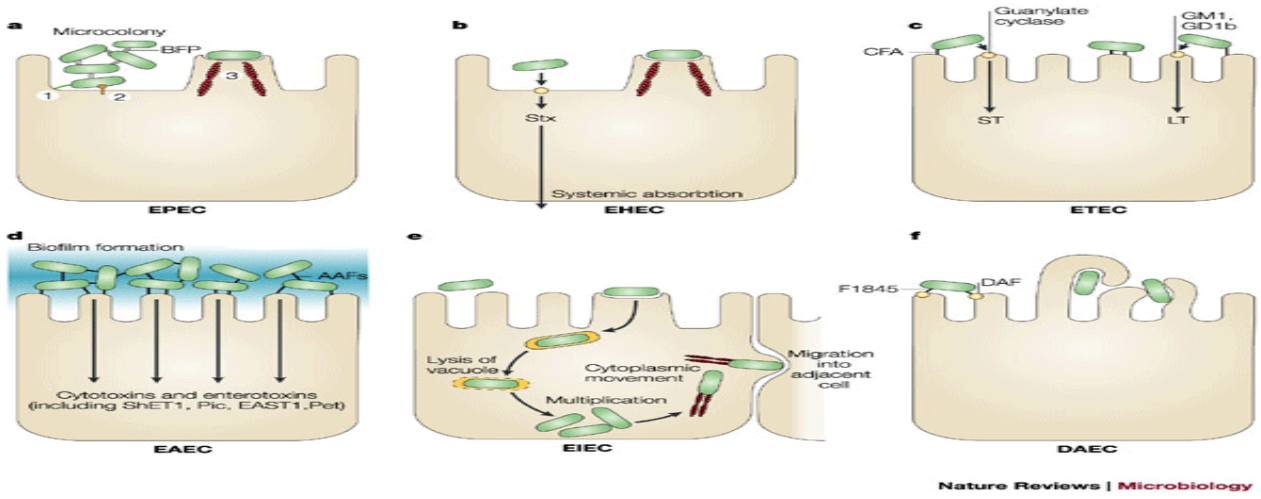
Table-1. Diarrheagenic *E. coli*: virulence determinants and characteristics of disease

Diarrheagenic *E. coli*	**virulence determinants**	**toxin**	**characteristics of disease**
ETEC	fimbrial adhesins e.g. the K-88 fimbrial Ag is found on strains from piglets; K-99 Ag is found on strains from calves and lambs; CFA I, and CFA II, are found on strains from humans non invasive. The infectious dose 10^8 cells	produce LT and/or ST toxin (plasmid-encoded toxins)	watery diarrhea in infants and travelers; no inflammation, no fever
EIEC	nonfimbrial adhesins, possibly outer membrane protein , invasive (penetrate and multiply within epithelial cells).	does not produce shiga toxin	dysentery-like diarrhea (mucous, blood), severe inflammation, fever

	The infectious dose 10^6 organisms . Unlike typical *E. coli*, EIEC are non-motile, do not decarboxylate lysine and do not ferment lactose. Both plasmid and chromosomal genes are involved in conferring pathogenicity. The invasion phenotype, encoded by a high molecular weight plasmid		
EPEC	non fimbrial adhesin (intimin) a plasmid-encoded protein referred to as EPECadherence factor (EAF) enables localized adherence of bacteria to intestinal cells. Moderately invasive (not as invasive as *Shigella* or EIEC). Some types of EPEC are referred to as diffusely adherent *E. coli* (DAEC). The infectious dose 10^6 organisms	does not produce LT or ST; some reports of shiga-like toxin	usually infantile diarrhea; watery diarrhea with blood, some inflammation, no fever; symptoms probably result mainly from invasion rather than toxigenesis
EAEC	adhesins not characterized non invasive. Attach to tissue culture cells in	produce ST-like toxin (EnteroAggregative ST) (EAST) and a	persistent diarrhea in young children without inflammation or

	an aggregative manner	hemolysin	fever
EHEC	adhesins not characterized, probably fimbriae , *E. coli* O157:H7 is the prototypic EHEC and most often implicated in illness worldwide The bacteria do not invade mucosal cells. The infectious dose10 - 100 cells	does not produce LT or ST but does produce shiga toxin [Verocytotoxin-producing *E.coli* (VTEC) Shiga-toxin-producing *E.coli* (STEC)]. The toxin is phage encoded and its production is enhanced by iron deficiency. The EHEC plasmid is known to encode the enterohemolysin (*ehx*) as well as a fimbrial antigen potentially involved in colonization.	pediatric diarrhea, copious bloody discharge (hemorrhagic colitis), intense inflammatory response, may be complicated by hemolytic uremia syndrome (HUS).

Pathogenic schema of diarrhoeagenic E. coli.



The six recognized categories of diarrhoeagenic E. coli each have unique features in their interaction with eukaryotic cells. Here, the interaction of each category with a typical target cell is schematically represented.

a | EPEC adhere to small bowel enterocytes, but destroy the normal microvillar architecture, inducing the characteristic attaching and effacing lesion. Cytoskeletal derangements are accompanied by an inflammatory response and diarrhoea.

1. Initial adhesion, 2. Protein translocation by type III secretion, 3. Pedestal formation.
Adherence of EPEC strains to the intestinal mucosa is resulting in rearrangements of actin in the vicinity of adherent bacteria. The phenomenon is sometimes called "attachment and effacing"**(A/E)** of cells.Adherence of EPEC to epithelial cells results in the phosphorylation of several epithelial cell proteins on serine and threonine residues, the most prominent of which is myosin light chain .Activation of at least two kinases, PKC and myosin light chain kinase, has been shown. Activation of PKC induces rapid changes in intestinal water and electrolyte secretion in vivo and in vitro and phosphorylation of myosin light chain can lead to increased permeability of tight junctions,

b | EHEC also induce the attaching and effacing lesion, but in the colon. The distinguishing feature of EHEC is the elaboration of Shiga toxin (Stx), systemic absorption of which leads to potentially life-threatening complications.

c | Similarly, ETEC adhere to small bowel enterocytes and induce watery diarrhoea by the secretion of heat-labile (LT) and/or heat-stable (ST) enterotoxins.

d | EAEC adheres to small and large bowel epithelia in a thick biofilm and elaborates secretory enterotoxins and cytotoxins.

e | EIEC invades the colonic epithelial cell, lyses the phagosome and moves through the cell by nucleating actin microfilaments. The bacteria might move laterally through the epithelium by direct cell-to-cell spread or might exit and re-enter the baso-lateral plasma membrane.

f | DAEC elicits a characteristic signal transduction effect in small bowel enterocytes that manifests as the growth of long finger-like cellular projections, which wrap around the bacteria. AAF, aggregative adherence fimbriae; BFP, bundle-forming pilus; CFA, colonization factor antigen; DAF, decay-accelerating factor; EAST1, enteroaggregative E. coli ST1; LT, heat-labile enterotoxin; ShET1, Shigella enterotoxin 1; ST, heat-stable enterotoxin

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