

Figure 1 - Interaction of AIEC with intestinal mucosa in the context of IBD.

(1) AIEC crossing the mucus layer and resisting antimicrobial peptides:

AIEC first has to overcome the protective mucus barrier that lines the surface of the intestinal epithelium. The protease VAT-AIEC secreted by AIEC promotes the degradation of human secretory mucins leading to a reduced mucus layer thickness that could affect secretion of antimicrobial peptides and promote survival of AIEC. The host defense antimicrobial peptides secreted by colonocytes and Paneth cells can be ineffective against AIEC due to presence of two genes *arlA*, encoding a defensin resistance protein, and *arlC*, encoding an outer membrane protease, that facilitates AIEC attachment to the epithelium during inflammation.

(2) AIEC adhering to IECs and leading to colonization of the gut mucosa:

AIEC adhere and colonize the gastrointestinal tract using FimH type 1 pili variants that bind to mannose residues expressed by glycoproteins such as CEACAM6. OMVs, carrying the transmembrane protein OmpA and released by AIEC, bind the endoplasmic reticulum stress response factor Gp96 which is associated with inflammation, in order to fuse with IEC and promote invasion of the mucosa. CEACAM6 and Gp96 are both overexpressed on the apical surface of ileal epithelial cells in patients with ileal CD. AIEC are also able to adhere to CHI3L1 *via* the chitin-binding domain of ChiA bacterial protein. AIEC has the ability to form biofilms on IECs. AIEC colonization leads to an increase in permeability of the IEC monolayer by promoting a reorganization of apical tight junctions by inducing the expression of the pore-forming tight junction protein claudin-2 and displacing ZO-1 and E-cadherin. AIEC flagellin target TLR5 which elicits the epithelial IL-8 inflammatory response, promoting the internalization of AIEC into the intestinal mucosa.

(3) AIEC entering lamina propria and Peyer's Patches via M cells and interacting with immune cells:

AIEC express long polar fimbriae (LPF), which allow the bacteria to interact with Peyer's patches (PPs) and to translocate across membranous M cells. This translocation is also mediated by type 1 pili which are recognized by GP2 surface proteins and CEACAM receptors. LpfA and GipA factors are required for efficient colonization of PPs. AIEC infection stimulates TNF- α expression by macrophages, which promote their intracellular replication. Activated neutrophils, lymphocytes, dendritic cells and macrophages are recruited into the *lamina propria* and amplify the local immune response. AIEC-infected neutrophils undergo autophagic cell death and NETosis. Intracellular AIEC replicate uncontrollably in host cells with autophagy defects caused by variants of ATG16L1, IRGM, or NOD2.

AIEC: Adherent-Invasive *Escherichia Coli*; DC: Dendritic Cell; GC: Gobelet Cell; IECs: Intraepithelial cells; IEL: Intraepithelial Lymphocyte; IESC: Intraepithelial Stem Cell; LT: Lymphocyte T, M cell: Microfold cell; NT: Neutrophil; PC: Paneth Cell.