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Escherichia coli: The Good, the Bad and the Ugly

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Abstract

The species *Escherichia coli* comprises non-pathogenic commensal strains that form part of the normal flora of humans and virulent strains responsible for acute infections inside and outside the intestine. In addition to these pathotypes, various strains of *E. coli* are suspected of promoting the development or exacerbation of chronic diseases of the intestine such as Crohn's disease and colorectal cancer.

Description

Escherichia coli is a non-sporeforming, facultatively anaerobic Gram negative bacillus. It is an inhabitant of the intestines of warm-blooded animals and is found in over 90 per cent of humans [1]. Although it represents less than 1% of intestinal microbiota, *E. coli* is the predominant aerobic organism in the gut. It is among the first bacterial species to colonize the intestine, establishing itself in the gut early after birth and remaining resident throughout the life of the host. As a commensal, *E. coli* coexists harmoniously with its mammalian host, promoting normal intestinal homeostasis and preventing colonization by pathogens ("The Good") [1]. However, some strains carry a combination of virulence genes that enable them to cause intestinal (InPEC, Intestinal Pathogenic *E. coli*) and extra-intestinal (ExPEC, Extraintestinal Pathogenic *E. coli*) infections ("The Bad") [2]. The characteristic virulence factors of the InPEC pathotypes that play a decisive role in pathogenesis are known and are different from those of non-pathogenic *E. coli* strains and ExPECs. In contrast to InPEC, ExPECs are facultative pathogens belonging to the normal gut microbiota of a fraction of the healthy population that can gain access to niches outside of the gut, efficiently colonize them and cause diseases in humans such as urinary tract infection, septicemia, and meningitis in new-borns [3]. Although several important ExPECs virulence factors and their role during pathogenesis have been described [2,3], many ExPECs cannot be unambiguously distinguished from commensal *E. coli* on the basis of a set of discriminatory virulence factors. ExPECs use multiple virulence factors in a mix-and-match fashion.

In addition to commensal and pathogenic strains, various strains of *E. coli*, which are usually non-pathogenic in healthy subjects, contribute to the development or exacerbation of chronic diseases of the intestine ("The Ugly") [4-8]. These resident strains produce virulence factors that allow them to persist in the intestine and induce deleterious effects when specific genetic and/or environmental conditions are altered in the host. Such strains, referred to as pathobionts, are increasingly thought to be etiopathogenic factors of inflammatory bowel diseases and colorectal cancer. Increased numbers of mucosa-associated *E. coli* are observed in Crohn's disease (CD) and colorectal cancer [9-11].

The *E. coli* prevalent in CD tissue are highly adherent to intestinal epithelial cells (IEC), are able to invade the epithelial layer, and they replicate within both intestinal epithelial cells and macrophages. These properties were used to define a new pathotype of *E. coli* designated adherent-invasive *E. coli* (AIECs) [4,12]. Interestingly, although commensal *E. coli* strains are located in the large intestine, AIECs are more abundant in the ileum than in the colon and have been particularly associated with the ileal form of CD [4]. Studies of the pathogenicity mechanisms of AIECs have shown that AIECs can translocate through the intestinal epithelium into the lamina propria, where the bacteria interact and survive inside macrophages without inducing host cell death. They further exacerbate inflammation by inducing pro-inflammatory cytokines, such as TNFα, IL1β, and IL-6, eventually forming granulomas [4]. AIEC strains are not characterized by particular genetic traits. They carry different sets of virulence genes that are observed in ExPECs [13,14]. However, unlike AIECs, ExPECs are not highly adherent to intestinal epithelial cells [15]. AIECs also share colonization factors with commensal non-AIEC strains. Thus, we still do not know what virulence gene profiles characterize the AIEC pathotype.

Specific studies have been made of certain virulence factors in AIEC strains related to pathogenesis of CD. AIECs usually express FimH adhesin variants that confer a high binding affinity to the mannose residues exposed at the surface of carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), which is abnormally expressed in the ileal mucosa of CD patients [13,16]. The binding of type I pili to CEACAM6 in intestinal epithelial cells activates the NF-κB pathway and inflammatory response. The endoplasmic reticulum stress response glycoprotein 96 (Gp96), which is overexpressed on the apical surface of ileal epithelial cells of CD patients, facilitates invasion via recognition of the bacterial outer membrane protein OmpA of AIECs [17]. It was recently shown that AIECs can invade the lamina propria not only via epithelial cells but by targeting the M cells of the Peyer's patches. Adhesion of AIECs to M cells involves long polar fimbriae, which are surface appendages [18]. This could be the missing link between AIECs colonization and the presence of early lesions in the Peyer's patches of CD patients.

The inability of CD patients to control AIECs infection may be due to genetic or environment-derived host defects. These defects are probably caused by impaired allelic innate immunity effectors such as the nucleotide-binding oligomerization domain-containing protein 2 (NOD2), which is an intracellular sensor of pathogen/microbe-

associated molecular patterns and the autophagy-related 16-like 1 (ATG16L1) and immunity-related GTPase family M protein (IRGM) genes, which are involved in autophagy [19,20]. However, the autophagy process can be modulated by AIECs [21,22]. These bacteria induce the up-regulation of microRNAs (MIR30C and MIR130A), which control the expression of the autophagy proteins ATG5 and ATG16L1. This leads to increased numbers of intracellular AIECs and increased inflammatory response [22]. Hence, the ileal implantation of AIECs and their impact on intestinal inflammation are the result of a complex combination between host deficiency factors and AIECs virulence factors.

The ugly strains of *E. coli* are also found in colorectal cancer (CRC) biopsies. Colonic adenoma and carcinoma tissues are highly colonized by mucosa-associated *E. coli* compared to controls [9,10,23,24]. Mucosa-associated *E. coli* isolated from patients with CRC, but not Crohn's disease, share pathogenicity islands with urinary pathogenic *E. coli* [25]. CRC-associated *E. coli* frequently express afimbrial adhesin (Afa)-1, which can bind the CRC makers CEACAM-5/6 [24]. CRC-associated *E. coli* also frequently encode toxins referred to as cyclomodulins because they modulate the cell cycle of host cells [26], especially colibactin, cytotoxic necrotizing factor 1 (CNF-1) and cytolethal distending toxins (CDT) (10). Colibactin-producing *E. coli* (*E. coli* clb+) induce double-strand DNA breaks, chromosomal instability, cell cycle arrest and megalocytosis [27,28]. Furthermore, *E. coli* clb+ has a protumoral effect in CRC mouse models independent of inflammation [29,30]. This dual effect of colibactin (cell cycle arrest and protumoral effect) has recently been elucidated [7]. *E. coli* clb+ infections contribute to the emergence of senescent cells that acquire a secretory phenotype, characterized by a high production of growth factors, notably hepatocyte growth factor (HGF), that promote the proliferation of uninfected cells and, subsequently, tumor growth [30]. The mechanism underlying *E. coli* clb+ induced senescence involves an up-regulation of microRNA-20a-5p expression in infected cells, which bind to SENP1 mRNA 3'-untranslated region (UTR), resulting in the downregulation of SENP1. SENP1 is a negative regulator of p53 SUMOylation; its downregulation leads to the accumulation of a stabilized SUMO-conjugated form of p53 that induces cellular senescence. Interestingly, these in vitro findings are consistent with the expression of SENP1, miR-20a-5p and growth factors in human CRC biopsies colonized by *E. coli* clb+ [30]. All these results suggest that *E. coli* clb+ might play an important role in CRC development. This therefore prompted as to target colibactin synthesis, as recently reported using a structural approach [31]. Several drug-like compounds were shown to suppress the genotoxic activity of *E. coli* clb+ both in vitro and in vivo. One compound, the 3-aminophenyl boronic acid, also prevented cell proliferation and *E. coli* clb+-induced tumourigenesis in mice. In a CRC murine model colonized by *E. coli* clb+, the number of tumors decreased by 3.5-fold in animals receiving the compound in drinking water [31]. These results show that targeting microbiota may be useful in reducing the carcinogenesis induced by bacteria.

Taken together, these data show that commensal microbiota, notably *E. coli*, by hijacking cellular functions and modulating signal transduction pathways, play an important part in the development or exacerbation of chronic intestinal disease. *E. coli* strains such as AIECs or *E. coli* clb+, may be implicated in the initiation/progression of Crohn's Disease and CRC [4]. However, the deleterious effects of pathobionts have been mainly observed in mouse models whose intestinal mucosal barrier function is altered, clear evidence that a direct bacteria–host cell contact is necessary [6,29]. Consequently, in healthy epithelium, which is protected by a mucus layer and the production of antibacterial peptides, these *E. coli* strains might not instigate pathology unless they produce virulence factors, such as mucolytic proteases, which allow them to cross the intestinal mucus layer. Additionally, although transient colonization by AIECs or *E. coli* clb+ is sufficient to develop intestinal disease in mouse models, it can still be supposed that in humans, on the basis of epidemiological data (percentage of "healthy carriers" with pathobionts and prevalence of CD and CRC), chronic exposure to slow-acting bacteria and/or host susceptibility is required to trigger disease. Pathobionts open up new research avenues in the field of medical microbiology.

References

1. Tenaillon O, Skurnik D, Picard B, Denamur E (2010) The population genetics of commensal Escherichia coli. Nat Rev Microbiol 8: 207-217.
2. Kaper JB, Nataro JP, Mobley HL (2004) Pathogenic Escherichia coli. Nat Rev Microbiol 2: 123-140.
3. Köhler CD, Dobrindt U (2011) What defines extraintestinal pathogenic Escherichia coli? Int J Med Microbiol 301: 642-647.
4. Agus A, Massier S, Darfeuille-Michaud A, Billard E, Barnich N2 (2014) Understanding host-adherent-invasive Escherichia coli interaction in Crohn's disease: opening up new therapeutic strategies. Biomed Res Int 2014: 567929.
5. Carvalho FA, Barnich N, Sauvanet P, Darcha C, Gelot A, et al. (2008) Crohn's disease-associated Escherichia coli LF82 aggravates colitis in injured mouse colon via signaling by flagellin. Inflamm Bowel Dis 14: 1051-1060.
6. Chassaing B, Koren O, Carvalho FA, Ley RE, Gewirtz AT (2014) AIEC pathobiont instigates chronic colitis in susceptible hosts by altering microbiota composition. Gut 63: 1069-1080.
7. Dalmasso G, Cougnoux A, Delmas J, Darfeuille-Michaud A, Bonnet R (2014) The bacterial genotoxin colibactin promotes colon tumor growth by modifying the tumor microenvironment. Gut Microbes 5: 675-680.
8. Yang Y, Jobin C2 (2014) Microbial imbalance and intestinal pathologies: connections and contributions. Dis Model Mech 7: 1131-1142.
9. Bonnet M, Buc E, Sauvanet P, Darcha C, Dubois D, et al. (2014) Colonization of the human gut by E. coli and colorectal cancer risk. Clin Cancer Res 20: 859-867.
10. Buc E, Dubois D, Sauvanet P, Raisch J, Delmas J, et al. (2013) High prevalence of mucosa-associated E. coli producing cyclomodulin and genotoxin in colon cancer. PLoS One 8: e56964.
11. Carrière J, Darfeuille-Michaud A, Nguyen HT1 (2014) Infectious etiopathogenesis of Crohn's disease. World J Gastroenterol 20: 12102-12117.
12. Barnich N, Darfeuille-Michaud A (2007) Adherent-invasive Escherichia coli and Crohn's disease. Curr Opin Gastroenterol 23: 16-20.
13. Dreux N, Denizot J, Martinez-Medina M, Mellmann A, Billig M, et al. (2013) Point mutations in FimH adhesin of Crohn's disease-associated adherent-invasive Escherichia coli enhance intestinal inflammatory response. PLoS Pathog 9: e1003141.
14. Vejborg RM, Hancock V, Petersen AM, Krogfelt KA, Klemm P (2011) Comparative genomics of Escherichia coli isolated from patients with inflammatory bowel disease. BMC Genomics 12: 316.
15. Martinez-Medina M, Mora A, Blanco M, López C, Alonso MP, et al. (2009) Similarity and divergence among adherent-invasive Escherichia coli and extraintestinal pathogenic E. coli strains. J Clin Microbiol 47: 3968-3979.
16. Barnich N, Carvalho FA, Glasser AL, Darcha C, Jantscheff P, et al. (2007) CEACAM6 acts as a receptor for adherent-invasive E. coli, supporting ileal mucosa colonization in Crohn disease. J Clin Invest 117: 1566-1574.
17. Rolhion N, Barnich N, Bringer MA, Glasser AL, Ranc J, et al. (2010) Abnormally expressed ER stress response chaperone Gp96 in CD favours adherent-invasive Escherichia coli invasion. Gut 59: 1355-1362.

18. Chassaing B, Rolhion N, de Vallée A, Salim SY, Prorok-Hamon M, et al. (2011) Crohn disease--associated adherent-invasive E. coli bacteria target mouse and human Peyer's patches via long polar fimbriae. J Clin Invest 121: 966-975.
19. Gersemann M, Wehkamp J, Stange EF (2012) Innate immune dysfunction in inflammatory bowel disease. J Intern Med 271: 421-428.
20. Nguyen HT, Lapaquette P, Bringer MA, Darfeuille-Michaud A (2013) Autophagy and Crohn's disease. J Innate Immun 5: 434-443.
21. Lapaquette P, Glasser AL, Huett A, Xavier RJ, Darfeuille-Michaud A (2010) Crohn's disease-associated adherent-invasive E. coli are selectively favoured by impaired autophagy to replicate intracellularly. Cell Microbiol 12: 99-113.
22. Nguyen HT, Dalmasso G, Müller S, Carrière J, Seibold F, et al. (2014) Crohn's disease-associated adherent invasive Escherichia coli modulate levels of microRNAs in intestinal epithelial cells to reduce autophagy. Gastroenterology 146: 508-519.
23. Martin HM, Campbell BJ, Hart CA, Mpofu C, Nayar M, et al. (2004) Enhanced Escherichia coli adherence and invasion in Crohn's disease and colon cancer. Gastroenterology 127: 80-93.
24. Prorok-Hamon M, Friswell MK, Alswied A, Roberts CL, Song F, et al. (2014) Colonic mucosa-associated diffusely adherent afaC+ Escherichia coli expressing lpfA and pks are increased in inflammatory bowel disease and colon cancer. Gut 63: 761-770.
25. Bronowski C, Smith SL, Yokota K, Corkill JE, Martin HM, et al. (2008) A subset of mucosa-associated Escherichia coli isolates from patients with colon cancer, but not Crohn's disease, share pathogenicity islands with urinary pathogenic E. coli. Microbiology 154: 571-583.
26. Nougayrède JP, Taieb F, De Rycke J, Oswald E (2005) Cyclomodulins: bacterial effectors that modulate the eukaryotic cell cycle. Trends Microbiol 13: 103-110.
27. Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, et al. (2010) Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proc Natl Acad Sci U S A 107: 11537-11542.
28. Nougayrède JP, Homburg S, Taieb F, Boury M, Brzuszkiewicz E, et al. (2006) Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 313: 848-851.
29. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, et al. (2012) Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 338: 120-123.
30. Cougnoux A, Dalmasso G, Martinez R, Buc E, Delmas J, et al. (2014) Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. Gut 63: 1932-1942.
31. Cougnoux A, Delmas J, Gibold L, Faïs T, Romagnoli C, et al. (2015) Small-molecule inhibitors prevent the genotoxic and protumoural effects induced by colibactin-producing bacteria. Gut.