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(REVIEW ARTICLE)

Relationship between *Escherichia coli* and colon cancer

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Abstract

Microbiota in the intestine provides major benefits to human health. The development of these microbiota depends on the individual's diet and lifestyle and is reflected in the impact of the microbiota on the body's energy and metabolism. In a normal healthy environment, *Escherichia coli* grows healthy and reflecting in the human body's metabolism. However, it has been known that there is linking the community of bacterial structure factors of the intestinal microbiota to colorectal cancer development and progression, *E. coli* can infect and cause changes in the gut that can finally lead to cellular transformation. Thus, chronic inflammation induced by *E. coli* during inflammatory bowel disease predisposes an individual to colorectal cancer. *E. coli* is a type species of the genus Escherichia. *E. coli* is a Gram-negative bacillus, facultative anaerobe, motile. *E. coli* producing many of toxin such as colibactin is a hybrid nonribosomal peptide-polyketide encoded by polyketide synthase (pks) can induce DNA double-strand breaks leading to chromosomal aberrations and increases the frequency of gene mutations and able to induce senescence-associated secretome to contribute to colon cancer development. Therefore, the study aims to investigate the bioactivity of *E. coli* on colon cell that has transformed to a cancer cell and to understand the *E. coli* as microbiota behavior in a certain environment the effect of this new environment on its activities.

Keywords: Colon cancer; *E. coli*- bioactivity; Adhesion- invasion

1. Introduction

E. coli is the most microorganisms studied worldwide, commonly found as normal flora in the intestines of humans. Colonization of *E. coli* begins with the digestive system since the early hours of birth. *E. coli* is a type species of the genus Escherichia. *E. coli* is a Gram-negative bacillus, oxidase-negative, commonly found as normal flora in the intestines of human, facultative anaerobe with the ability to respire oxygen preferably at 37°C, motile with peritrichous flagella, use alternative anaerobic electron acceptors, or ferment, depending on electron acceptor availability. As lactose-positive *E. coli* colonies will appear red or pink on media such as MacConkey agar. Central metabolism in *E. coli* consists of the Embden-Meyerhof-Parnas glycolytic pathway (EMP), the pentose phosphate pathway (PP), the Entner-Doudoroff pathway (ED), the TCA cycle, and diverse fermentation pathways [1-2]. *E. coli* has been classified into five phylogenetic groups (A, B1, B2, D, and E), also classified according to serotyped based on three types of somatic (O), capsular (K) and flagellar (H) antigens, and more than 700 *E. coli* serotypes have been identified based on the combination of O and H antigens [3]. *E. coli* follows a strategy for infection by: (i) colonization of a mucosal site, (ii) evasion of host defenses, (iii) multiplication, and (iv) host damage [4-5]. Where it was also classified according to the causative agents of diseases, Six well-known intestinal pathogenic *E. coli* types are enteropathogenic *E. coli* (EPEC), Shiga toxin-producing *E. coli* (STEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC). Some *E. coli* strains can also cause extraintestinal diseases and are called extraintestinal

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pathogenic *E. coli* (ExPEC). The ExPEC, which were defined by disease association, include uropathogenic *E. coli*, neonatal meningitis-associated *E. coli* and sepsis-causing *E. coli* [5, 6-12].

2. Gastrointestinal tract environment

Gastrointestinal tract is an organ system within humans and other animals which takes in food, digests it to extract and absorb energy and nutrients, and expels the remaining waste as feces. The GI system extends from the mouth and esophagus to the rectum and can be divided into the upper (mouth and stomach) and lower tracts (small and large intestine). The composition of the microbial community in the digestive tract is different, as there are about 1000 types of bacteria, diversity is due to physicochemical conditions such as intestinal motility, pH, nutrients, host secretions; e.g., gastric acid, bile, digestive enzymes, and mucus [13]. Bacteria colonies the GI tract after birth, most of which are residing in the lower intestine. These bacteria survive within the GI tract, receiving nutrients from the host, while providing the host with essential nutrients and benefits and produce more heat than any other organism per weight unit, and it is estimated that 70% of the body heat at rest results from bacterial metabolism in the gut. Microbial environments face factors and abnormal changes (Dysbiosis) such as the use of antibiotics, illness, stress, aging, bad dietary habits and lifestyle, and diseases like inflammatory bowel disease (IBD), obesity, diabetes, and even cancer.

The human colon is known for its overall microbiota composition, which consists of many different organisms that interfere with the host, usually in a symbiotic relation. These microorganisms convert the undigested nutrients that reach the colon as substrates for their metabolism into some useful metabolic products, such as vitamins, among others [14-15]. The bacteria are present that known as intestinal microflora, most gut microorganisms are strictly anaerobic bacteria, these bacteria interact with, and colonies the epithelial cells. The dominant bacterial species in the human gastrointestinal tract are divided into three phyla: the phylum Bacteroidetes; e.g., *Porphyromonas*, *Prevotella*, *etc*., the phylum Firmicutes; e.g., *Ruminococcus*, *Clostridium*, *Eubacteria etc*. and the phylum Actinobacteria; *Bifidobacterium*. Other bacteria such as *Lactobacilli*, *Streptococci*, and *E. coli* are found in small numbers. These species represent only a small subset of all of the bacterial taxa on Earth. Many factors can impact the homeostasis of GI tract bacteria, such as diet, physical stressors, and degenerative and infectious diseases. Food is a source for new bacterial species to enter the body such as yogurt contain healthy bacteria known as probiotics which have a protective role in the gut While there are bacteria are healthy flora in the intestines responsible of some infections is *E. coli* [16-22].

3. Adhesions and Invasive of *E. coli*

Infection of epithelial cells begins to cause disease by attaching bacteria to those cells by fimbrial and pili, located on the surface of bacteria where they interact with the host cell membrane and affect cell functions, however, over the years, a large number of monomeric surface-bound adhesive proteins have been identified [23-24]. It was studied Filagelin in the bacterium *E. coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC), which is composed of several thousand copies of flagellin subunits, which cause diarrheal diseases and death worldwide. Recently, the EPEC E2348/69 (O127: H6) and EHEC EDL933 (O157: H7) flagella and their flagellin monomers were shown to possess adhesive properties to a range of host receptors including mucins and bovine mucus. These results suggest that the flagellin proteins are involved in the attachment of pathogenic bacteria to the mucus layer of the intestine, the first barrier encountered during colonization [25].

4. Colorectal cancer (CRC)

Cancer is a disease characterized by the unchecked division and survival of abnormal cells. When this growth occurs in the colon, it is called colorectal cancer (CRC).

Colorectal cancer, like gastric cancer, is one of the leading neoplastic diseases worldwide the third most common cancer in the world after breast, lung, and prostate and the second most common cause of cancer death after lung in the United States and is responsible for more than 600,000 deaths every year. Colon cancer is the virtually only cancer that occurs with approximately equal frequency in men and women [26-27]. Although many cancers, including CRC, are known to have genetic and environmental components, its development occurs in a highly complex and poorly characterized bacterial environment. There are indications of the role of bacteria in colorectal cancer [28-30].

Bacteria and dietary factors could participate in the development of CRC including the induction of pro-inflammatory and procarcinogenic pathway in epithelial cells, the production of genotoxins and reactive oxygen species, and the conversion of procarcinogenic dietary factors into carcinogens [31-32]. Two theories indicate inflammation and gut microbial communities development CRC: (1) the "alpha bug" concept, wherein select members of a microbial

community with virulence and pro-carcinogenic features are capable of remodeling the microbiome as a whole to drive pro-inflammatory immune responses and colonic epithelial cell transformation leading to cancer; and (2) the "driver-passenger" concept, wherein certain indigenous intestinal bacteria, termed "bacteria drivers," initiate CRC by inducing epithelial DNA damages. The resulting tumorigenesis induces intestinal niche alterations that promote the proliferation of opportunistic passenger bacteria with a growth advantage in the tumor microenvironment [33]. The vast majority of colorectal cancers are not inherited, but sporadic and what a person eats can have a profound effect on the initiation, promotion, and progression of the neoplastic process. The rate of carcinogenesis is determined by the penetrance of the genetic defect and by the aggressiveness of the environmental insult. Evidence indicates that colorectal cancer arises from a stepwise disturbance of the composition of the gut microbiota, induced by food components or diet, plus genetic alterations in oncogenes and tumor-suppressor genes [34].

5. *Escherichia coli* and colorectal cancer

The bacterial density in the large intestine ($\sim 10^{12}$ cells per ml) is much higher than that in the small intestine ($\sim 10^{2}$ cells per ml), and this is paralleled by an approximately 12-fold increase in cancer risk for the large intestine compared with the small intestine. These two observations combined point towards the hypothesis that colon cancer may be induced by bacteria [35]. Some factors lead to colorectal cancer, such as *E. coli* the first bacteria to be associated with CRC, that producing colibactin which is a hybrid nonribosomal, peptide-polyketide encoded by polyketide synthase (pks), genotoxicity island [36-39]. Some strains of *E. coli* from phylogroup B2 are associated with Crohn disease (CD), known to be a risk factor for colorectal cancer (CRC) [40-41]. Two groups of *E. coli* have been of particular interest concerning the pathogenesis of CRC, genotoxic *E. coli*, and tightly adherent *E. coli*. phylogenetic group B2 *E. coli* induces double-strand DNA breaks through the polyketide synthase (pks) island containing the genotoxin colibactin [42-44].

Annually, *E. coli* causes mortality infant diarrhea and extraintestinal infection (septicemia derived from urinary tract infection) and also responsible 150 million causes of uncomplicated cystitis. Now, the focus was on the pathogenic strain, particularly group B2 [45]. The relationship between *E. coli* and CRC began to monitor the accumulation of *E. coli* on the epithelium cell [46]. In an early study, *E. coli* was recovered from 82% of adenoma/carcinoma biopsies, compared with none of the controls. Evidence for a contributory role of *E. coli* in CRC is emerging. Further studies have consistently found disrupted microbial homeostasis in CRC patients. For example, several studies have found a decrease in butyrate-producing species and an increase in potential pathogens in the lumen or fecal matter of CRC cases [47].

E. coli are more frequently identified in colon tissue from patients with CRC. Even if *E. coli* is a commensal bacterium, some pathogenic strains have acquired some virulence factors including toxins, such as cyclomodulins, Studies have shown the ability of *E. coli* to synthesize isolated toxins from cyclomodulins, such as cytolethal distending toxins (CDT), cytotoxic necrotizing factor (CNF), cycle inhibiting factor and colibactin, which were genotoxic or interfering with the cell cycle and introduce DNA damage. (*Fusobacterium nucleatum*, *Streptococcus gallolyticus*, *Enterococcus faecalis*, *Bacteroides fragilis* and *E. coli*) were described for their pro-tumoural activities, including the induction of chronic inflammation or the production of carcinogenic metabolites and toxins [48-49]. Collibactin has a critical role in cellular senescence, Colibactin-producing bacteria induce the emergence of senescent cells to promote the proliferation of uninfected cells and, subsequently, tumor growth [50].

6. Conclusion

We conclude that *E.coli* can infect and cause changes in the gut that can finally lead to cellular transformation, and it has different mechanisms that they use to affect colon cancer development. Moreover, the association of *E.coli* with cancerous lesions may put into consideration as evidence of a causal relationship that is reverse.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares there are no conflicts of interest in this article.

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