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Colorectal Cancer and Gut Microbiota

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Abstract

Colorectal cancer is the third most diagnosed cancer globally, accounts for 9.6% 0f all cancer diagnosed and 9.3% of all cancer deaths. Most cases of colorectal cancer, about 80% are sporadic in origin, and the remaining 20 % are hereditary. Colorectal cancer have the risk factors like family history, diet, comorbities, smoking, alcohol, medication research also shows that there is alteration in the gut microbiota of colorectal cancer. Gold standard investigation for diagnosis of colorectal cancer is colonoscopy with biopsy for histopathology. Human gut microbiota is the colony of comprises more than 10^{14} microbes like bacteria, virus and fungi. The normal commensal microorganism present in the gut microbiota have symbiotic association with the intestine helps in digestion and absorbtion. Colorectal cancer as it involve chronic inflammatory response leads to decrease in the biodiversity of microorganism and presence of pathological microorganism and this is used as a biomarker for the colorectal cancer. Fecal sample metagenomic analysis shown increase in Fusobacterium nucleatum, Parvimonas, Peptostreptococcus, Porphyromonas, and Prevotella, are part of the CRC microbiota. This is a promising noninvasive biomarker for colorectal cancer.

Keywords: Colorectal cancer, Gut microbiota, Fusobacterium nucleatum, Bacteroides fragilis

Introduction

Colorectal cancer is the third most diagnosed cancer globally that is 9.6% 0f all cancer diagnosed and 9.3% of all cancer deaths according to Global cancer statistics of the year 2022. Colorectal cancer is the most common cancer of the gatrointestinal tract (1). Carcinogenesis in colorectal cancer arises mainly from the adenoma (adenomatous polyp). It takes 5-10 years for the conversion of adenoma (neoplastic precursor lesion) into colorectal cancer. Stem cells located in the base of colorectal crypts, due to genetic and epigenetic alteration, are converted progressively to cancer stem cells. This conversion is a critical step in the formation and maintenance of the tumor (2). In most cases of colorectal cancer, about 80% are sporadic in origin, and the remaining 20 % are hereditary. Inherited mutations are nonpolyposis syndrome and polyposis syndrome, most common is hereditary non polyposis syndrome known as Lynch syndrome. Lynch syndrome occurs due to a defect in DNA mismatch repair gene like MSH2, MLH1, MSH6 progress to microsatellite instability in tumor phenotype and also small proportion of somatic APC mutation in advanced stage of lynch syndrome(3). The APC/beta-catenin pathway and microsatellite

instability pathway are two significant pathways in colorectal cancer. Both pathways involve multiple gene mutations. APC/beta-catenin pathway activated in adenoma-carcinoma sequence and microsatellite instability due to defect in DNA mismatch repair. 80% of sporadic colon cancer is due to APC gene mutation then microsatellite instability with CpG island hypermethylation, methylation of MLH1, increased CpG island methylation without microsatellite instability. KRAS mutation seen, uncommon p53 and BRAF mutation also contribute to development of colorectal adenocarcinoma (4,5). Apart from the risk factors like family history, diet, comorbities, smoking, alcohol, medication research also shows that there is alteration in the gut microbiota of colorectal cancer. Gut microbiota includes bacteria, viruses, fungi, yeasts and form the 95% of the total microbes in our body in gut mainly in our large intestine. Environmental factors like diet and lifestyle changes more than 20% of variance in the gut microbiome diversity(6). The genetic diversity of the gut microbiome forms a vast reservoir transcending diversity of its host human DNA(7). Gut microbiome plays a significant role in maintaining the human health, alteration in the microbiome can occurs by antibiotic medication, malnutrition, diet pattern and sleep deprivation(8). There is a symbiotic relationship between human gut microbiota and host, the host provides nutrition and place for growth and multiplication of intestinal microbes, and microbes provide resistance to infection and promote absorption of digested food to host. So the role of the gut microbiota includes protection against pathogenic microorganism by facilitates heathy immune system, regulation of intestinal motility and facilitate metabolisms. There are 3 main categories of gut microbiota in individuals based on the predominance of genera are Bacteroides, Prevotella and Ruminococcus, which varies based on diets (9). In normal conditions, gut homeostasis is maintained by the microbiota retaining mucosal integrity, secreting antimicrobial molecules, renewal of epithelial cell, nutrient synthesis, detoxification, and metabolising indigestible diet components contributing to normal colonic function. Along with other factors, imbalance in the microbiome leads to CRC progression and metastasis via epithelial mesenchymal transition (10).

Colorectal Cancer

According to the GLOBOCAN 2022 report, Colorectal cancer is the third most diagnosed cancer globally, accounting for 9.6% of all cancers diagnosed. Among that, 10.4% and 8.9% of all cancers were diagnosed in males and females, respectively. It is the second most common cancer, which constitutes 9.3% of all cancer deaths. In males and females, 9.2% and 9.4% of all cancer deaths are due to colon cancer, respectively. In Asian continent, colorectal cancer constitutes 0.96 million(1). Protrusion in the colonic lumen are colonic polyp might be associated with sporadic or as apart of genetic syndromes. Polyp arising from mucosa are adenomatous, serrated and nonneoplastic, adenomatous are main polyp arising from mucosa of which 80% are tubular, 10% villous and 10% mixed, serrated are sessile or traditional and nonneoplastic are hyperplastic and juvenile. Sessile serrated polyp with dysplasia and traditional serrated polyp have significant malignant potential. Mostly that is more 95% colon adenocarcinoma arises from polyps(11)

Gut Microbiota

Gut microbiota comprises more than 10^{14} cells primarly formed by the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Throughout life gut microbiota changes dynamically. After birth, vaginally born babies inherit the mother's vaginal and fecal microbiota. Bacteroides and Bifidobacterium species first invade gut that creates an anaerobic environment support the growth of obligate anaerobes. While babies born by cesarean section initially have skin-associated microbiota. Breastfed babies often have higher levels of Bifidobacterium species variety and abundance than their formula-fed counterparts; once solid foods are introduced, the diversity of the gut microbiota rises (12).

Specific changes in the microbiome are seen according to the level of colorectal cancer progression. In CRC patients Fusobacterium nucleatum, Bacteroides fragilis, and E. coli are enriched in the intestinal lumen and mucosa compared to healthy controls (13). In chronic inflammatory response before the progression of CRC that promote availability of oxygen, reduction in the biodiversity of bacteria and abundance of pathological microorganism , abundance of Fusobacterium nucleatum correlates with poor prognosis metastatic CRC, abundance Streptococcus gallolyticus promote the transcription factor of colorectal cancer, enterotoxigenic Bacteriodes fragilis promote c-myc expression, epipthelial barrier damage, immune response activation to CRC (14). Bacteriodes fragilis toxin that target E- cadherin protein cleaves it breaks the intestinal epithelial barrier. E.coli produces colibactin that causes DNA damage and more inflammatory pathway activation occurs in a loop drives to more mutation, genomic instabilities ,proliferation and progress to CRC(15).

Fusobacterium Nucleatum

It is symbiotic anaerobic Gram-negative bacteria present in the human oral cavity. Bacteria forms a biofilm and mounting evidence that F. nucleatum impacts many phases of colorectal cancer development.There are 3 mechanism in which Fusobacterium nucleatum might promote the growth of cancer cells: First mechanism is the β-catenin and Wnt pathway are activated by the interaction of FadA and E-cadherin. Second mechanismis the carcinogenic miR21 is expressed more when TLR4 and NF-κB are activated.third mechanism via upregulating the histone modification of ENO1 thus promoting glycolytic pathway promoting carcinogenesis of colorectal cancer(16).

Bacteroides Fragilis

It is a symbiotic anerobic gram negative bacterium. The majority of bacteria promote gut health and aid in food digestion. But occasionally, these bacteria release a toxin that damages the gut's surface cells, which encourages colorectal cancer. Toxin produced target E-cadherin to cleave and the epithelial barrier to be destroyed, trigger mucosal inflammation, activate the Wnt signal transduction pathway, and encourage the development of colon tumors.Toxin also target STAT3 pathway activation which create an inflammatory tumor microenvironment in intestine. Ultimately cytokine release and DNA damage promoting development of CRC(17).

Escherecia Coli

It is a symbiotic anerobic gram negative bacteria. They colonises the gut soon after the birth, most prevalent pathogenic strains with virulence factors are found in groups B2 and D, whereas fecal strains often fall into groups A and B1. E. coli is the primary producer of it and colibactin is closely linked to colorectal cancer (CRC) and can cause chromosome abnormalities, eukaryotic cell cycle halt, and double-strand DNA breaking. In human colorectal cancer cells, DNA rich in AT-enriched hexamer sequence motifs are selectively destroyed by colibactin. Colibactin-binding sequences were identified in colorectal cancer (CRC) after somatic mutations of colibactin targets(18,19).

Immune Response of Intestinal Microbiota

Intestinal microbiota supports the development and control of the mucosal and systemic immune systems via innate and adaptive immune cells. They have a significant influence on the activation of macrophages, pattern recognition receptors, intestinal cells and specialized receptors on the surface of T cells and B cells in the intestinal mucosa. Helper T cells, B cells, and T cells contribute to the development of tumors by secreting immunoglobulin A (IgA). T cells mainly influence the makeup of intestinal microorganisms by helping B cells in the intestine and secrete IgA, which is primarily secreted into the intestinal cavity and has the ability to bind and cover intestinal microorganisms thereby contribute to the development of the intestinal microbiota(20,21). Cytokines including IL-6, IL-8, IL-17, and TNF-α are released by inflammatory cells that are crucial in promoting CRC. Enterococcus faecalis induces colitis and cause intestinal epithelial cells to secrete TGF-β and activates

Smad4 signaling, also secrete reaction oxygen species and hydrogen peroxide that damage DNA leading to colorectal cancer. NFκB and STAT3 transcription factor are required for inflammation to encourage the occurrence and progression of cancer. IL-17 dependent NFκB and Wnt pathways are triggered to create an inflammatory tumor microenvironment in the gut because ETBF Enterotoxigenic Bacteroides fragilis can quickly activate the STAT3 signaling pathway and encourage Th17 cells to release IL-17(16).

Diagnosis of Colorectal Cancer with Gut Microbiota

Metagenomic analysis of feces reveal intestinal microbiota in diagnosis of CRC. Fusobacterium, Porphyromonas, Parvimonas, and other bacteria, were discovered feces in metagenomic analysis of individuals from various nations with varying lifestyles and eating habits. The identification of F. nucleatum, a unique bacteria that is prevalent in the respiratory and oral cavities, in CRC patients. F. nucleatum is more prevalent in CRC patients than in healthy people. Genes of microbial enzymes choline trimethylamine lyase (cutC) gene is found in the CRC patient feces can break down choline in meat and release acetaldehyde(22). The bacterial strains that are specifically linked to colorectal cancer (CRC) are Bacteroides fragilis, Streptococcus gallolyticus, Enterococcus faecalis, and Escherichia coli, along with that recently discovered strains of bacteria linked to CRC, such as Fusobacterium nucleatum, Parvimonas, Peptostreptococcus, Porphyromonas, and Prevotella, are part of the CRC microbiota. Increased levels of these bacterial strains in tumor and fecal samples from CRC patients may act as biomarkers for the CRC(23).

Conclusion

Colorectal cancer is the most common cancer of the gatrointestinal tract. Colorectal cancer is the third most diagnosed cancer globally, accounting for 9.6% of all cancers diagnosed. Colorectal cancer have the risk factors like family history, diet, comorbities, smoking, alcohol, medication research also shows that there is alteration in the gut microbiota of colorectal cancer. Gut microbiota of CRC patients shows alteration CRC associated bacteria that indidually linked to CRC are Escherichia coli, Bacteroides fragilis, Enterococcus faecalis and Streptococcus gallolyticus. CRC associated bacteria with increased abundance in fecal and tumour samples are Fusobacterium nucleatum, parvimonas, peptostreptococcus, porphyro - monas and prevotella. These microorganism have its own mechanism that lead to colorectal cancer. Production of certain metabolites that promote carcinogenesis and involve association to the immune response. When it comes to CRC patient predictive and prognostic biomarkers are crucial. Among these is the gut microbiota, which can predict the prognosis and response of CRC patients to a particular systemic therapy, as well as play a role in the development of CRC.

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