Gut Microbiota and Dendritic Cells in Colorectal Cancer

Subjects: Immunology

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Colorectal cancer (CRC) is a malignancy that manifests in serial stages and has been observed to have an escalating incidence in modern societies, causing a significant global health problem. The development of CRC is influenced by various exogenous factors, including lifestyle, diet, nutrition, environment, and microbiota, that can affect host cells, including immune cells.

C-type lectin receptor CRC DCs interleukins

1. Introduction

Colorectal cancer (CRC) significantly contributes to cancer-related deaths and ranks as the third most prevalent cancer globally [1]. CRC is notably high among populations that adopt a Western lifestyle; it is also rising in other locations, primarily low-income nations, creating a worldwide health threat [2]. CRC develops slowly over years, as adenomas originate from tiny, hard-to-see neoplastic foci into malignant carcinomas that may spread throughout the body [3]. CRC is reported to have considerable heterogeneity due to genetic instability [4][5]. It may also be caused by lifestyle, food, nutritional intake, environmental circumstances, and the microbiome. These variables affect non-neoplastic cells, including immune cells, increasing heterogeneity [6][7]. CRC is caused mainly by immune system malfunction, as it begins by impairing the host's anti-tumor immunity, the so-called tumor microenvironment [8]. The tumor microenvironment changes early in neoplastic transformation and progression to promote cell proliferation. Tumor development and metastasis or immune-mediated cancer inhibition may follow. Inflammatory and immunological cells in the tumor microenvironment may accelerate colorectal cancer. These cells may limit tumor development or cause chronic inflammation, suppressing the immune system and promoting CRC progression [9][10].

2. Causes and Symptoms of CRC

Diet and lifestyle have been associated with CRC risk for decades. Modifiable risk factors cause 50–60% of CRC cases [11]. Tobacco use, excessive alcohol use, obesity, lack of exercise, consuming red and processed meat, and insufficient dietary fiber and other nutrients worsen health (**Figure 1**). The microbiome, such as bacteria, viruses, and fungi, is essential to health. Microbiota disturbances may cause CRC. According to Song and Chan [12], environmental risk factors may cause and promote CRC by altering the gut microbiota. Personal or family history of colorectal polyps or CRC, Lynch syndrome, inflammatory bowel disease (IBD), racial/ethnic origin, and type 2

diabetes are all unchangeable risk factors for CRC [13]. CRC can develop in persons as young as in their 20s, if they are predisposed to the disease. Advanced age is the most prominent risk factor [14]. Over 90% of new cases and 94% of CRC-related fatalities occur in people over 50. Medium-risk people over 50 should be examined for CRC, and high-risk people should be monitored. High-risk factors include CRC syndromes, adenomatous polyps, IBD, and personal or family history of CRC [15]. Constipation, diarrhea, stomach pain, and rectal pain precede 70–95% of early-onset CRC. Later, anemia, rectal bleeding, and weight loss occur [16].

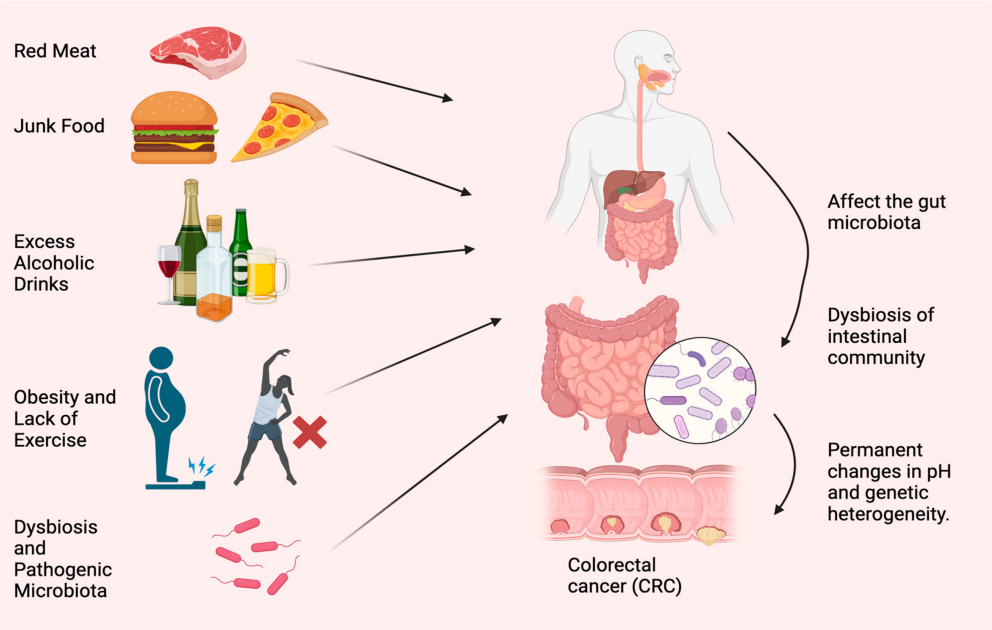

Figure 1. Most typical causes of CRC. Red meat, junk food, excess alcoholic drinks, obesity, lack of exercise, dysbiosis, and accumulation of pathogenic microorganisms are the main reasons for CRC.

2.1. Effect of Red Meat and Junk Food

Research by the World Cancer Committee [17] demonstrated that the regular consumption of 100 g of red and processed meat heightens the likelihood of developing CRC by 12%. This heightened susceptibility is attributable to the presence of heme iron, sulfur, and choline, in addition to nitrates, nitrites, emulsifiers, and heterocyclic amines and polycyclic aromatic hydrocarbons, which emanate from processing and cooking techniques and may stimulate the onset of cancer [18]. These meals may fuel gut microbes that generate carcinogens. Red meat provides choline and carnitine. Red meat elevated blood and urine trimethylamine-N-oxide (TMAO) in a random controlled experiment. TMAO increases heart disease and mortality. Two bacterial genes, cutC (choline TMA-lyase) and cutD (choline TMA-lyase-activating enzyme), were discovered in extremely high numbers, supporting the concept that the choline-TMAO pathway may modify metagenomes and cause CRC. *Hungatella hathaway*, *Clostridium asparagiforme*, *Klebsiella oxytoca*, and *E. coli* increased in CRC patients with sequence changes in these two genes. Several prospective studies have linked high dietary and blood choline levels to CRC [19]. DNA methylation and synthesis require choline, folate, and vitamin B12. TMAO only increased CRC risk in vitamin B12-deficient people. Its effects may vary, depending on whether it is in the carbon metabolism cycle or in the stomach for microbial TMAO synthesis [20]. CRC is connected to bacterial secondary bile acids, processed foods, red meat,

and free radicals [21]. Bile acid content and concentration variations in metabolic diseases and infectious bowel disease (IBD) enhance CRC risk. Several analyses of eight geographically and methodologically diverse fecal shotgun genomic studies found that higher secondary bile acid was produced [22]. According to a study, high-fat diets may contribute to the epidemic of CRC in young people. It has been found that high-fat diets alter the gut bacteria and alter the digestive substances, called bile acids, in mice. Consequently, inflammation occurs, increasing the chance of developing colorectal cancer, a disease that is notoriously difficult to treat [23]. When the body consumes fat, bile acids are synthesized in the liver, and they play a role in facilitating lipid absorption by the small intestine. Bile acids are reabsorbed and subjected to enterohepatic circulation in the small intestine. Bile acids undergo complex biotransformation in the colon by gut bacteria, resulting in secondary bile acids that promote tumor growth. Excessive dietary fat intake leads to a high level of secondary bile acids in feces and primes the gut microbiota to produce bile acids. It is believed that this promotes an altered overall bile acid pool, resulting in an altered intestinal and hepatic cross-signaling of the farnesoid X receptor (FXR), the receptor for bile acids. The FXR gene is a main regulator of bile acid-mediated effects on intestinal tumorigenesis, integrating dietary, microbial, and genetic risk factors. In healthy and tumorigenic conditions in the intestine, selective FXR agonist or antagonist activity is determined by additional factors such as bile acid concentration, composition, and genetic instability of the cells [24].

2.2. Correlation between Healthy Diet and CRC

Many epidemiological inquiries remain to be conducted to substantiate this concept. Based on a meta-analysis of 21 studies, there appears to be no link between fiber consumption and CRC risk. Nevertheless, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort has persistently demonstrated that a higher fiber intake can lower susceptibility to CRC [25]. Europeans eat cereals, but Americans eat fruits and vegetables, which may explain the observed behavior. US cohorts stated that low fiber consumption might have prevented efficacy. According to numerous studies, whole grains reduce the risk of CRC. A meta-analysis found that increasing a whole grain diet by 90 g/day reduced CRC risk by 17% [17].

2.3. Role of Obesity and Physical Activity on CRC

A meta-analysis revealed that a rise in body mass index (BMI) of 5 kg/m^2 raised the risk of CRC by 5%. Additionally, obesity may potentially escalate the incidence of early-onset CRC [26]. Obesity is linked to inflammatory and metabolic changes in adipokines, insulin-like growth factor 1 signaling, systemic inflammation, sex hormones, and CRC risk. Obesity-induced gut microbiota alterations and metabolic byproducts may affect cancer development. Obesity decreases gut microbiota diversity [27].

Obesity-induced intestinal barrier dysfunction may worsen systemic inflammation. Leaking microbiota products such as lipopolysaccharide (LPS) causes metabolic endotoxemia. Greater BMIs are related to greater LPS-binding protein (LBP) and LPS levels. Losing weight decreases blood LBP and LPS [28]. Adenomas were associated with increased LPS levels in cross-sectional research. Villous adenomas had higher LPS levels than tubular ones. An LBP gene polymorphism (rs2232596) has been associated with CRC [29].

According to cohort data, high exercisers decrease CRC risk by 19% compared with non-exercisers. Exercise has not been linked to rectal cancer. In many cross-sectional studies, exercise influences the gut microbiome's composition and function [17].

A 6-week intervention of endurance-based exercise was provided to a population of 32 people who lived sedentary lifestyles, after 2 weeks of the baseline study. The subjects then had a 6-week exercise-free washout period. The study found that only skinny participants had short-chain fatty acid concentrations in their stools after exercise. The number of butyrate-producing bacterial taxa increased, linked to body composition changes in lean people [30].

2.4. The Role of GUT Microbiota in Dysbiosis and CRC

Specific nutritional components can regulate the gut microbiome and promote a persistent inflammatory state by modulating immune and inflammatory pathways, making diet a significant factor in CRC onset, progression, and prevention. Human microbiota includes bacteria in the gastrointestinal, genitourinary, oral, respiratory, and cutaneous systems, among others. These bacteria interact with the body in various mechanisms and are essential for several physiological routes, including immunology, tissue growth, nutrition absorption, metabolism, and cancer [31]. Recent research showed that nutritional, genetic, and environmental factors affect the microbiome. Gut microorganisms also affect food metabolism. Nutrition affects microbiota in populations with various diets. According to the study, "healthy" diets like the Mediterranean diet increase microbial biodiversity. Dietary fiber, polyphenols, and lipids are crucial food–gut microbiome interactions. Different dietary lipids may affect gut microbiota variety, microorganisms, and activity. Metabolic effects may modulate systemic low-grade inflammation. Many pathways link dysbiosis to illnesses, including cancer [32]. Oncogenesis may also result from microbiota-induced mucosal inflammation or systemic metabolic and immunological disruption. The microbiome may indirectly alter cancer treatment and immunity. The inhibition of programmed cell death (PD-1) is associated with antitumor effects of epithelial malignancies in hepatocellular carcinoma and is also linked to *Akkermansia muciniphila* frequency [33]. Lower levels of this bacterium in rats and humans are connected to obesity, insulin resistance, type 2 diabetes, and other cardiometabolic diseases. CRC patients' fecal and mucosal microbiota change during the disease, reducing bacterial diversity [34].

It is important to note that LPS is an important component of the outer layer of bacteria and has a strong pathogenic effect [35]. Inflammation and immune responses in the hosts can be triggered through TLR activation (one of the pattern recognition receptors), among which TLR4 and TLR2 are the most important receptors [36]. The FimA and Mfa1 subunits of bacterial fimbriae are important in promoting bacterial adhesion to host tissues and their invasion [37]. A TLR on endothelial cells [38], macrophages [39], and DCs [40] can also recognize it, activating the cells and causing them to produce cytokines and adhesion molecules. These cytokines stimulate the proliferation and differentiation of DCs. A link between innate and adaptive immunity is established when inflamed endothelial cells trigger macrophages and immature tissue DCs to present the bacterial cell wall on their surface for T cells called major histocompatibility molecules (MHC-I). DCs recognize pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) [41]. As DCs mature, metabolic, cellular, and gene transcription programs are activated, allowing them to migrate from peripheral tissues to secondary lymphoid organs, where T

lymphocyte-activating antigen presentation may occur in response to CCL19 and CCL21 [42]. The maturation of DCs is characterized by the loss of adhesive structures, the reorganization of the cytoskeleton, and an increase in motility. As a result of DC maturation, the level of endocytic activity declines; however, the expression of MHC-II and co-stimulatory molecules such as CD80 and CD86, as well as the chemokine receptor CCR7, is increased, as are the levels of pro-inflammatory cytokines such as TNF-α and IL-12 [43]. A mature DC expresses higher levels of the chemokine receptor, CCR7 [44], and secretes cytokines required for T-cell activation [45]. Consequently, mature DCs interact with antigen-specific T cells to trigger antigen-specific immune responses [46]. By interacting with $CD4^+$ T cells (called MHC-II), DCs may induce differentiation into different T helper (Th) cells [47], Th2 cells [48], Th17 cells [49], or other $CD4^+$ T cells [50]. This way, DCs can trigger responses against intracellular antigens from various cell types [51] and even prime $CD8^+$ lymphocytes without $CD4^+$ T cells [52]. Cross-presentation also introduces tolerance to intracellular self-antigens not expressed by APC, called cross-tolerance [53]. The “immature” cells are, however, extremely effective at capturing antigens due to their high endocytic capacity via receptor-mediated endocytosis, including lectins [54], Toll-like receptors [55], FC receptors, and complement receptors [56]. Thus, immature DCs act as sentinels against invading pathogens and as tissue scavengers, capturing apoptotic and necrotic cells [57]. Accordingly, immature DCs are essential for inducing and maintaining immune tolerance [58]. DCs internalize cell apoptosis and the loss of critical details in polyps, such as tissue turnover. However, they do not induce DCs maturation [59]. In this way, their antigens are presented to T cells without the activating co-stimulatory signals delivered by a mature DC, resulting in the apoptosis of T cells and the development of regulatory T cells. It has been demonstrated that a “tolerogenic DC” expresses fewer co-stimulatory molecules and proinflammatory cytokines. Still, it upregulates the expression of inhibitory molecules (such as PD-L1 and CTLA-4) and secretes anti-inflammatory cytokines (IL-10, tumor growth factor beta, for example). In this situation, the DC fails to increase the co-stimulatory molecules required to activate T cells, meaning that the immune system leaves uncontrolled disease despite recognizing pathogens or changes in the tumor microenvironment [52][58].

2.4.1. *Fusobacterium nucleatum*

Cohort studies showed that colorectal neoplasia patients have more *Fusobacterium nucleatum* (*F. nucleatum*) in their feces than controls. This was connected to more advanced disease, less T-cell infiltration, a higher risk of recurrence, and a worse prognosis. This was linked to serrated pathway molecular characteristics. The inhibition of Myeloid-derived suppressor cells and natural killer (NK) and T cells enhances tumor growth. Modifying E-cadherin/-catenin may affect this mechanism [35]. According to recent studies, *F. nucleatum* stimulates the production of reactive oxygen species (ROS) and inflammatory cytokines (e.g., IL-6 and TNF) in colorectal cancer [38][60]. MLH1 is epigenetically silenced due to inflammation and ROS, reducing mismatch repair protein’s enzymatic activity (MMR) activity. In addition, virulence factors derived from *F. nucleatum* also inhibit T cell proliferation [33][61]. This may be consistent with a recent study finding that a greater abundance of *F. nucleatum* in colorectal carcinoma tissue was associated with a lower density of T cells in the tumor microenvironment. Based on these findings, *F. nucleatum* may downregulate antitumor T-cell-mediated adaptive immunity [62].

2.4.2. Enterotoxigenic *Bacteroides fragilis* (ETBF)

Among the symbiotic bacteria in the intestinal tract is *Bacteroides fragilis*. The majority of bacteria in the human body aid in the digestion of food and maintain intestinal health. Occasionally, however, these bacteria produce a toxin that disrupts the cells on the surface of the gut, resulting in the development of CRC. B fragilis has two subtypes, nontoxic B fragilis and enterotoxigenic *B. fragilis* (ETBF), which produce *B. fragilis* toxin (BFT). ETBFs produce a 20 kDa metalloprotease, *B. fragilis* toxin (BFT), which disturbs the intestinal environment and promotes inflammation [63]. BFT destroys the epithelial barrier and E-cadherin cleavage. Additionally, cleavage of E-cadherin can activate the Wnt signal transduction pathway, cause mucosal inflammation, and promote colon cancer development. Further, the STAT3 pathway is required to develop Th17 cells and colon transformation. Th17 cells are stimulated to produce IL-17 after ETBF stimulates the STAT3 pathway, which activates the NF-κB and Wnt pathways, creating intestinal inflammatory tumor microenvironments. Through its rapid activation of the STAT3 pathway, ETBF is involved in the production of IL-17 by Th17 cells. Injection of an anti-IL-17 antibody in mice can inhibit tumor formation by inhibiting IL-17 production [64]. ETBF can also upregulate the expression of spermine oxidase (SMO) in colonic epithelial cells, thus increasing the generation of SMO-dependent reactive oxygen species (ROS), causing DNA damage and, ultimately, leading to CRC development [65].

2.4.3. *Escherichia coli* (*E. coli*)

IBD and CRC patients have higher mucosa-associated *E. coli* levels. In CRC, *E. coli* invades the intestinal wall and becomes intracellular. Polyketide synthase gene complex (pks) bacteria generate genotoxin colibactin, more commonly in CRC patients. Later-stage tumors have more *pks+ E. coli* strains. Ki-67 expression correlates with internalized and mucosa-associated *E. coli*. One fecal microbiome investigation found *E. coli* enrichment in CRC patients. *E. coli* prefers to colonize the mucosal lining and, intracellularly, occupy intestinal cells rather than the lumen, impeding feces removal [66].

3. Pathogenesis and Genetic Alteration of CRC

CRC originates in pre-cancerous polyps. The term “polyp” refers to localized outgrowths or clusters of aberrant cells that extend into the intestinal cavity from the gut’s mucosal layer. CRC exhibits either sessile or pedunculated polyps [67]. If these polyps have enough genetic alterations, their multiplying cells may be able to permeate the intestinal wall, a characteristic of colorectal cancer. These cells may then alter, move to nearby lymph nodes, and reach distant metastatic locations. When the polyp grows, it may acquire genetic mutations and epigenetic alterations that cause cytologic and histologic dysplasia [68]. Slow cellular DNA damage may cause high-grade dysplasia, which increases the risk of invasive cancer [69]. Without removal, these polyps can invade the colon and rectal wall and spread. New blood arteries allow cancer cells to access the lymphatic and circulatory systems and metastasize to distant organs. Pre-cancerous polyps must be removed quickly to break the adenoma-carcinoma cycle and prevent colorectal cancer. Histologically, genetic and epigenetic alterations cause a polyp to become a malignancy (**Figure 2**). DNA alteration can be either inherited or acquired. Inherited mutations, including APC (adenomatous polyposis coli), PMS2, MSH2, MLH1and gene changes, cause 5% of CRC cases. Hereditary mutations with spontaneous APC and DNA divergence repair metamorphoses have illuminated the genetic path from premalignant polyps to cancer [70]. Sessile serrated polyps (SSPs) and adenomas polyps often cause CRC.

The chromosomal instability route affects 65–70% of sporadic malignancies, which are often linked to conventional adenomas. Many mutations distinguish this method. Two genes cause CRC APC gene mutations to alter chromosomal segregation during cell division, while *KRAS* oncogene changes affect cellular proliferation, differentiation, motility, and survival. Mutations may affect transcription and apoptotic regulator *p53*. This may affect cellular processes and cause cancer [71]. However, *BRAF* gene mutations that disrupt growth signals and impede apoptosis typically cause sessile serrated polyps (SSPs). SSPs have *KRAS* mutations at 23, 21, 24, and 13, but less than adenomatous polyps (**Figure 2**). Serrated lesions cause gene promoter hypermethylation in CRC [72]. Methylation of the promoter region may inhibit gene transcription and function. Inactivating this gene affects many genes, including development-promoting genes [73]. CpG island methylators contain abnormally methylated genes such as *BMP3* and *NDRG4* [74]. Microsatellite instability (MSI) disrupts DNA repair genes, promoting genetic diversity in CRC. MSI may cause short, non-coding, repetitive DNA sequences to replicate unevenly, making bodies more sensitive to genetic alterations [75]. MSI is a phenomenon that can manifest in adenomatous and serrated polyps (**Figure 2**). It is closely associated with alterations in DNA mismatch repair genes resulting from either germline mutations, such as those observed in hereditary nonpolyposis colorectal cancer, or sporadic mutations resulting from abnormal methylation of the MLH1 promoter region. The latter is closely linked with the CpG island methylator phenotype [76].

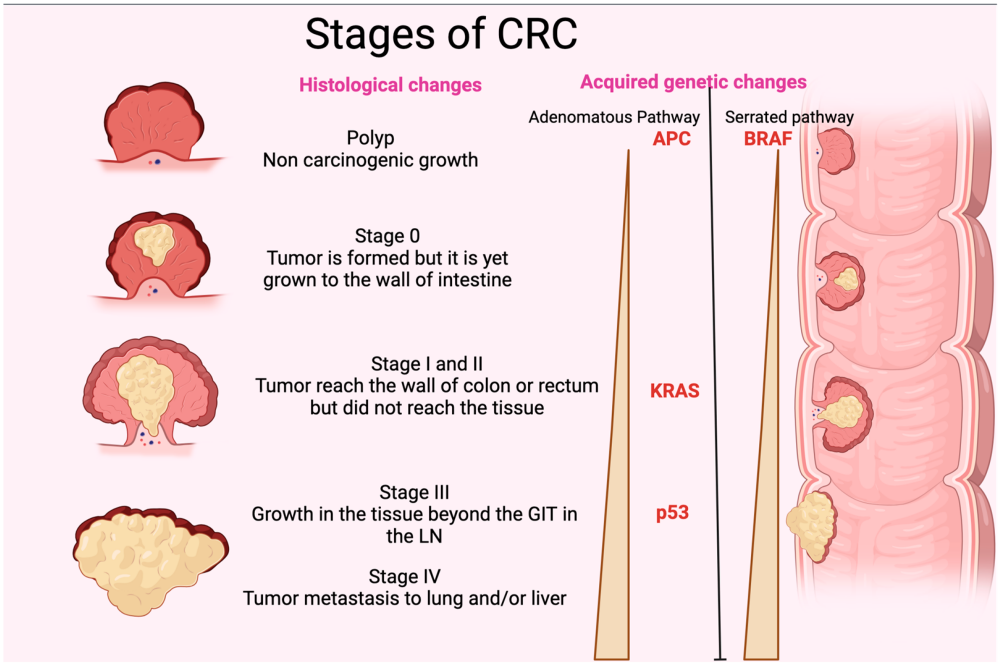

Figure 2. Stages of CRC. The figure shows the different histological stages of CRC. It also represents the gradual increase in p35, KRAS, and APC (adenomatous polyposis coli) in the adenomatous pathway and BRAF in the serrated pathway of acquired genetic changes. GIT: gastrointestinal tract; LN: lymph node.

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