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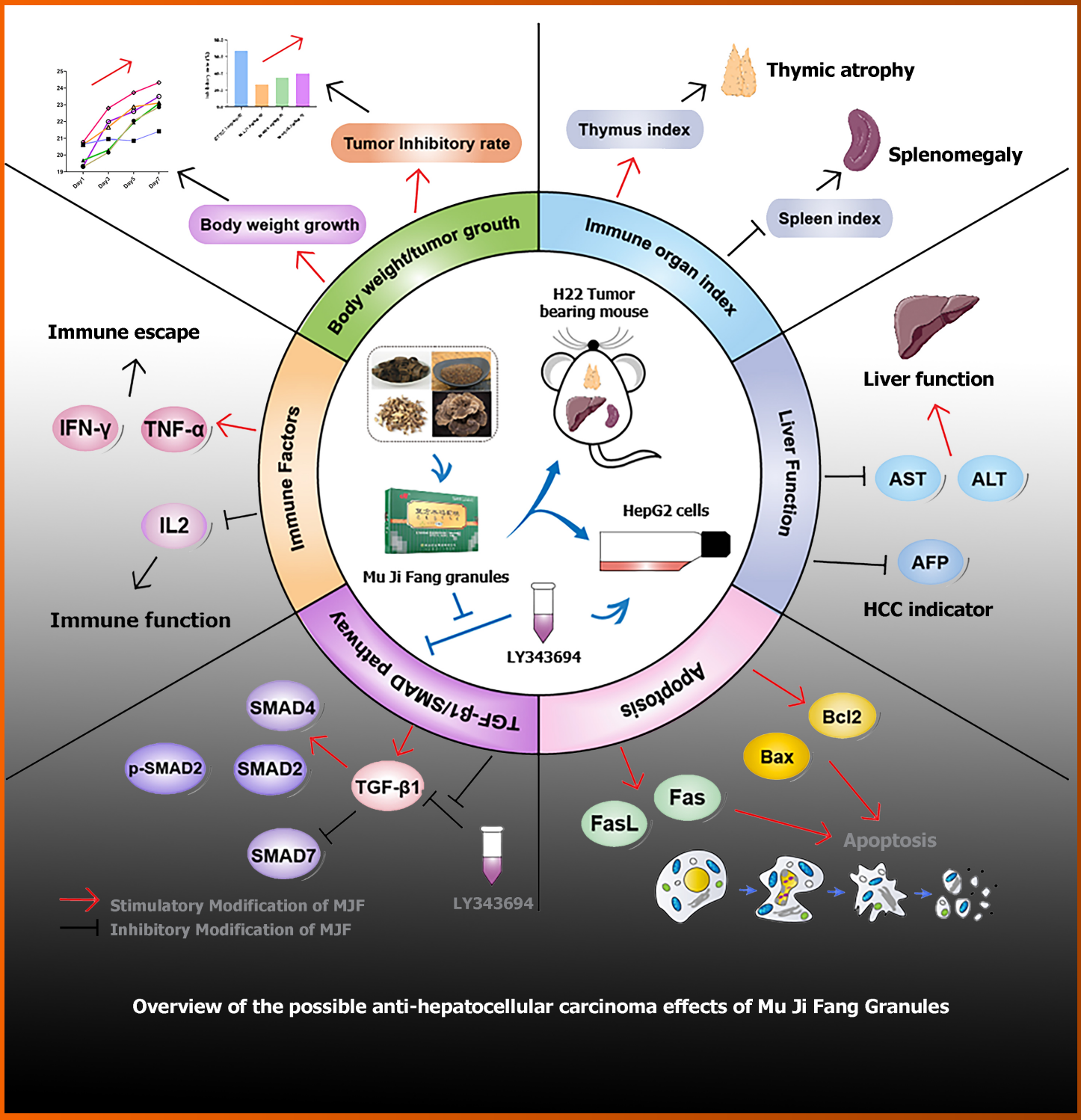

Overview of the possible anti-hepatocellular carcinoma effects of Mu Ji Fang Granules

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Contents

Monthly Volume 15 Number 3 March 15, 2023

FIELD OF VISION

372 Machine learning algorithm to construct cuproptosis- and immune-related prognosis prediction model for colon cancer

Huang YY, Bao TY, Huang XQ, Lan QW, Huang ZM, Chen YH, Hu ZD, Guo XG

REVIEW

389 Prevention of malignant digestive system tumors should focus on the control of chronic inflammation

Zhang YH, Chen XL, Wang YR, Hou YW, Zhang YD, Wang KJ

405 Immunotherapy for advanced or recurrent hepatocellular carcinoma

Luo YZ, Zhu H

425 Molecular methods for colorectal cancer screening: Progress with next-generation sequencing evolution

Abbes S, Baldi S, Sellami H, Amedei A, Keskes L

MINIREVIEWS

443 Genetic heterogeneity of colorectal cancer and the microbiome

Senchukova MA

ORIGINAL ARTICLE

Basic Study

464 Xiaojianzhong decoction prevents gastric precancerous lesions in rats by inhibiting autophagy and glycolysis in gastric mucosal cells

Zhang JX, Bao SC, Chen J, Chen T, Wei HL, Zhou XY, Li JT, Yan SG

490 F-box and leucine-rich repeat 6 promotes gastric cancer progression *via* the promotion of epithelial-mesenchymal transition

Meng L, Hu YT, Xu AM

504 Possible mechanisms associated with immune escape and apoptosis on anti-hepatocellular carcinoma effect of Mu Ji Fang granules

Zhang YB, Bao YR, Wang S, Li TJ, Tai H, Leng JP, Yang XX, Wang BC, Meng XS

Retrospective Cohort Study

523 Risk of pancreatic cancer in individuals with celiac disease in the United States: A population-based matched cohort study

Krishnan A, Hadi YB, Shabih S, Mukherjee D, Patel RA, Patel R, Singh S, Thakkar S

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 3 March 15, 2023

Contents

Retrospective Study

533 Nomogram model predicting the overall survival for patients with primary gastric mucosa-associated lymphoid tissue lymphoma

Wang D, Shi XL, Xu W, Shi RH

546 Mitophagy-related gene signature predicts prognosis, immune infiltration and chemotherapy sensitivity in colorectal cancer

Weng JS, Huang JP, Yu W, Xiao J, Lin F, Lin KN, Zang WD, Ye Y, Lin JP

CASE REPORT

562 Carcinosarcoma of common bile duct: A case report

Yao Y, Xiang HG, Jin L, Xu M, Mao SY

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 3 March 15, 2023

Contents

ABOUT COVER

Zhang YB, Bao YR, Wang S, Li TJ, Tai H, Leng JP, Yang XX, Wang BC, Meng XS. Possible mechanisms associated with immune escape and apoptosis on anti-hepatocellular carcinoma effect of Mu Ji Fang granules. *World J Gastrointest Oncol* 2023; 15(3): 504-522 URL: https://www.wjgnet.com/1948-5204/full/v15/i3/504.htm DOI: https://dx.doi.org/10.4251/wjgo.v15.i3.504

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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MINIREVIEWS

Genetic heterogeneity of colorectal cancer and the microbiome

Marina A Senchukova

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Abstract

In 2020, the International Agency for Research on Cancer and the World Health Organization's GLOBOCAN database ranked colorectal cancer (CRC) as the third most common cancer in the world. Most cases of CRC (> 95%) are sporadic and develop from colorectal polyps that can progress to intramucosal carcinoma and CRC. Increasing evidence is accumulating that the gut microbiota can play a key role in the initiation and progression of CRC, as well as in the treatment of CRC, acting as an important metabolic and immunological regulator. Factors that may determine the microbiota role in CRC carcinogenesis include inflammation, changes in intestinal stem cell function, impact of bacterial metabolites on gut mucosa, accumulation of genetic mutations and other factors. In this review, I discuss the major mechanisms of the development of sporadic CRC, provide detailed characteristics of the bacteria that are most often associated with CRC, and analyze the role of the microbiome and microbial metabolites in inflammation initiation, activation of proliferative activity in intestinal epithelial and stem cells, and the development of genetic and epigenetic changes in CRC. I consider long-term studies in this direction to be very important, as they open up new opportunities for the treatment and prevention of CRC.

Key Words: Gut microbiota; Bacterial metabolites; Colorectal cancer; Colorectal polyp; Stem cells; Epigenetic changes

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Core Tip: Most cases of colorectal cancer (CRC) develop from colorectal polyps that can progress to intramucosal carcinoma and CRC. A large number of studies have indicated that the gut microbiota may play a key role in the initiation and progression of CRC. The mini-review discusses current ideas about the role of the microbiome and microbial metabolites in inflammation initiation, activation of proliferative activity in intestinal epithelial and stem cells and development of genetic and epigenetic changes in CRC. Further research in this direction is of great interest since these studies may contribute to the development of new CRC prevention and treatment methods.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer type worldwide and the second most common cause of cancer death[1]. Risk factors for developing CRC include age, male sex[2-4], family history of CRC, and genetic predisposition (for example, polyposis and nonpolyposis CRC, including Lynch syndrome), which are detected in 5% of patients with CRC[2,5,6]; benign tumors (adenomatous polyps and sessile serrated polyps) associated with sporadic CRC[3]; inflammatory bowel diseases[7,8]; obesity and type 2 diabetes[9-11]; smoking[3,4,12]; and alcohol consumption[13]. Currently, increasing evidence is accumulating that the intestinal microbiome plays a key role in the initiation and progression of CRC and affects the effectiveness of this pathology treatment. Moreover, intestinal dysbiosis, which is characterized by a decrease in the microbiota diversity and an overgrowth of pathogenic and conditionally pathogenic flora, is associated with many risk factors for CRC, such as inflammatory bowel disease, obesity, type 2 diabetes, and a diet characterized by a high intake of fat, red meat and processed meat [14-16]. To discuss the role of the gut microbiota in the development and progression of CRC, as well as in the development of genetic and epigenetic changes in CRC, a search was made in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) and Reference Citation Analysis (https://www.referencecitationanalysis.com/) for studies published up to December 31, 2022, using a combination of text keywords "gut microbiota", "bacterial metabolites", "CRC", "colorectal polyp", "stem cells", and "epigenetic changes". A total of 2042 unique results were identified, which were screened individually by title and abstract, and 222 references were included in this review based on the role of the microbiome and microbial metabolites in inflammation initiation, activation of proliferative activity in intestinal epithelial and stem cells, in the development and progression of CRC, and development of genetic and epigenetic changes in CRC.

CHANGES IN THE GUT MICROBIOTA IN CRC

Accumulating evidence indicates that the gut microbiota may play a key role in the initiation and progression of CRC, acting as an important metabolic and immunological regulator[7,17-20] and influencing both the efficacy and toxicity of cancer treatment[21]. A number of studies have shown that patients with CRC and polyps had a significant increase in *Bacteroides massiliensis*, *Bacteroides ovatus*, *Bacteroides vulgatus* and *Escherichia coli (E. coli)*[22], *Atopobium parvulum* and *Actinomyces odontolyticus* [23], *Fusobacterium nucleatum (F. nucleatum)*[24,25] and *Bacteroides fragilis (B. fragilis)*[25,26], as well as *Porphyromonas asaccharolytica*, *Parvimonas micra (P. micra)*, *Prevotella intermedia*, *Alistipes Finegoldii* and *Thermanaerovibrio acidaminovorans*[25]. Other authors have established an association of CRC and adenomas with *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Butyricimonas*, *Alistipes* and *Odoribacter*[27-29]. Coker *et al*[30], in addition, noted dysbiosis of the intestinal fungal microflora and archaea in patients with CRC, namely, a decrease in methanogenic archaea, Saccharomycetes, and Pneumocystidomycetes but enrichment of halophilic archaea and Malasseziomycetes in fecal samples[30].

A recent study by Liu W in 2020 found a significant reduction in the richness and diversity of the intestinal flora in patients with CRC and polyps compared with healthy individuals[31]. In healthy individuals, *Bacteroidetes* (52.14%) and *Firmicutes* (35.88%) predominated. When analyzing the microbiome in healthy individuals, patients with polyps, adenomas and CRC, a decrease in *Bacteroidetes* (from 52.14% - 53.92% - 52.46% to 47.06%) and *Firmicutes* (from 35.88% - 29.73% - 24.27% - up to 25.36%) and an increase in the share of *Proteobacteria* (from 9.33% - 12.31% - 16.51% - to 22.37%) were revealed. In addition, in patients with CRC, there was a decrease in the number of *Clostridium butyricum*, producing butyrate, *Streptococcus thermophiles*, producing lactic acid[32], and other intestinal symbiotic bacteria, such as *Bifidobacterium animalis* and *Streptococcus thermophiles*[33]. In African Americans with a high risk

of developing CRC, the main representatives of the intestinal microbiome were *Bacteroides*, with a high level of microbial gene expression, which encode the production of secondary bile acids (BAs). At the same time, in the intestinal microbiome of indigenous inhabitants of rural Africa with a low risk of developing CRC, the main representative was *Prevotella*, with a high level of expression of genes encoding methanogenesis and production of hydrogen sulfide[34].

It has been established that bacteria with proven pro-carcinogenic activity are capable of forming biofilms, which are communities of microorganisms embedded in the matrix of extracellular polymeric substances that are produced by the biofilm bacteria themselves and include proteins, polysaccharides and nucleotides in different proportions. Bacterial biofilms reduce the penetration of antibiotics, increase the permeability of the epithelium due to the loss of E-cadherin, and promote the contact of bacteria with epithelial cells and bacterial translocation[35,36]. Dejea *et al*[37] demonstrated that invasive polymicrobial bacterial biofilms are detected in 89% of cases in right-sided CRC[37]. They were more often determined in areas of normal mucosa remote from the tumor, and their composition was identical to the microbial composition in the tumor tissue. The presence of biofilms has been associated with increased levels of interleukin 6 (IL-6) and activation of signal transducer and activator of transcription 3 (STAT3), a decrease in epithelial cell E-cadherin, and increased proliferation of crypt epithelial cells in normal colonic mucosa[37]. Drewes *et al*[38] showed that these biofilms are enriched in *B. fragilis*, *F. nucleatum*, *P. micra*, and *Peptostreptococcus stomatis*[38].

Of particular interest are the causes of dysbiosis in patients with CRC. It is known that the qualitative and quantitative composition of the microbiome can be influenced by various factors, such as age, infection, diet, stress, inflammation, and drugs[39,40]. Genetic changes (congenital or acquired) with age can contribute to a change in the microenvironment, which leads to a change in the microbiome[39]. The gut microbiota can change under the influence of chemotherapy and immunotherapy for CRC, which, in the end, can affect its effectiveness[41]. In addition, inflammatory changes associated with colorectal carcinogenesis can also alter the gut microbiome[40]. The use of resveratrol, an anti-inflammatory stilbenoid, in a mouse model of CRC not only reduced inflammation and CRC development but also altered the gut microbiota, leading to an increase in colonic butyrate, which has antitumor effects[42]. It is possible that the anti-inflammatory effect underlies the reduction in the risk of CRC with regular use of aspirin[43].

It is believed that the specific tumor microenvironment can also influence the microbiome. This is indirectly evidenced by the fact that the populations of intestinal bacteria “on the tumor” and “outside the tumor”, as well as in the intestinal lumen, associated with the intestinal mucosa and associated with the tumor tissue, differ within the tumor host[39,44]. It is believed that pro-oncogenic "bacteria drivers" associated with colorectal carcinogenesis induce epithelial DNA damage, which leads to a change in the microenvironment of bacteria. In the future, a change in the microenvironment can lead to a decrease or disappearance of “bacteria drivers” and the population of the formed niche by “bacteria passengers”[45-48]. In a number of experimental studies, it was noted that genetic disorders of gastric mucosal cells, for example, in mice with gene knockouts (*e.g.,* Tlr5, Il10, T-bet and Rag2), led to changes in the microbiome in the colon[49]. In patients with CRC with deficient DNA mismatch repair (dMMR) and proficient MMR (pMMR), there were significant differences in the composition of the intestinal microbiome. The dMMR group was dominated by *Fusobacteria, Firmicutes, Verrucomicrobia*, and *Actinobacteria* at the phylum level and *Fusobacterium, Akkermansia, Bifidobacterium, Faecalibacterium, Streptococcus*, and *Prevotella bacteria* at the genus level, while the pMMR group was dominated by *Proteobacteria* at the phylum level and *Serratia, Cupriavidus* and *Sphingobium* at the genus level[50]. Table 1 shows the characteristics of a number of bacteria associated with the development of CRC.

Notably, CRC rarely develops in the small intestine. To some extent, this may be due to the peculiarities of their epithelial and mucosal barrier[51], as well as differences in the quantitative and qualitative gut microbiota composition[52-54]. In particular, the small intestine has (1) A higher density of natural killer T cells, intraepithelial lymphocytes, eosinophils and dendritic cells[51]; (2) A higher oxygen concentration[52]; and (3) A higher concentration of antibacterial substances[55]. At the same time, in the small intestine, the expression of multiple Toll-like receptors (TLRs)[56,57] and microbial cell concentrations are lower[52,53] than those in the large intestine. In addition, a number of authors have noted significant differences in the immune system of the large and small intestines[58,59]. It is believed that tolerance to food and bacterial antigens is formed in the proximal small intestine, which has a thinner layer of mucus, providing closer contact with epithelial and immune cells, and the immune system is aimed at stopping local and systemic inflammation[59]. The duodenum and upper jejunum contain a class of CD103+CD11b+ dendritic cells unique to the gut that are involved in the formation of regulatory T cells[60]. It has been established that in response to food and bacterial antigens, lymph nodes draining the small intestine predominantly induce tolerogenic responses, while lymph nodes draining the large intestine activate proinflammatory T-cell responses[59,61]. The tolerogenic effect of oral administration of antigens was comparable to the systemic anti-inflammatory effect of dexamethasone[59]. These data suggest that the low incidence of CRC in the small intestine may be associated with a low level of inflammatory reactions in response to the intestinal microbiota, given that inflammation is one of the key players in colorectal carcinogenesis.

Table 1 Features of some bacteria associated with colorectal cancer

Virulence factors, clinical and experimental data	CRC pathways
B. fragilis	
- Contains B. fragilis toxin (BFT) that is zinc-dependent metalloprotease toxin[185,186]; -Associated with colitis[186], low-grade dysplasia, tubular adenomas, and serrated polyps[163], Lynch syndrome and familial adenomatous polyposis[187]; - More often associated with left-sided CRC [163]; - Characterized by biofilms formation[38]; - Associated with unfavorable CRC prognosis[123]; - Potentiates oncogenesis in the distal colon in mice[188]	-Induction of stepwise cleavage of E-cadherin and stimulates cell proliferation[185]; - Synthesis of cytokines, incl. IL-17↑[26,123,163,188]; - Activation of the WNT/β-catenin pathway → c-Myc transcription and translation↑ → cell proliferation↑[189]; - STAT3 activation in the mucosal immune cells → mucosal permeability↑[163,186,188]; - NF-κB activation →Th17c↑[163]; - STAT3 and NF-κB activation→ COX-2 and MMP-9 expression↑[123,163]; - BRAF and KRAS mutations, expression of MLH1↓[123]; - APC mutations [187]
E. coli	
- Contains Colibactin and Cytotoxic necrotizing factor 1 (CNF1)[190]; - Can carry the pathogenicity island pks (pks + E. coli), which encodes a set of enzymes that synthesize Colibactin[191]; - Associated with inflammatory bowel disease and CRC[192]; - More frequently found in CRC biopsies than in healthy mucosa[191]; - More common in advanced stages of CRC [193,194]; - Potentiates induction of invasive cancer in mice[192]; – Differences in the frequency of pks + E. coli in patients with CRC, adenomas and in healthy people were not detected[195]	- Induction of DNA double-strand breaks[196]; - DNA alkylation[190]; - Decrease of tumor-infiltrating T lymphocytes (CD3+ and CD8 T cells) and increases colonic inflammation[197]; - Activation of angiogenesis[198] and epithelial-mesenchymal transition[199]; - Modulates activity Rho GTPases (signaling G-proteins of Ras subfamily), thereby affecting the actin cytoskeleton, that contributes to the disruption of cell adhesion (due to the reorganization of the expression of E-cadherin, β-catenin, zonula occludens-1 (ZO-1) and caveolin- 1), the reduction of phagocytosis and improve epithelial cell motility[200,201]; - Induction of cell proliferation[191]; - Depletion of host mismatch repair proteins *via* bacterially secreted EspF effector protein[142]
F. nucleatum	
- Contains adhesion protein FadA, Fap2 и RadD[96]; - Synthesis of toxic metabolites: Secondary bile acids, trimethylamine N-oxide, hydrogen sulfide, heme, nitrosamines, heterocyclic amines and polyaromatic hydrocarbons[96]; - Characterized by biofilms formation[38]; - Often detected in adenomas[38,202], tumor samples with high grade dysplasia [203], carcinoma tissue[44,202,204], distant CRC metastases[125]; - More frequently found in CRC biopsies than in healthy mucosa[205]; - Associated with proximal tumor localization[161,204,206,207], higher depth of invasion[206], higher clinical stage[206,207], low tumor differentiation[206,207], lymph node metastases and low survival rate[204]; - Promotes CRC induction in a traditional experimental model in mice[202]	- Associated with MLH1 methylation[206,207]; MSI-H[161,206-208]; CIMP-H [161,207]; BRAF mutation[206,207]; - FadA-dependent activation of the E-cadherin/β-catenin pathway → cell proliferation↑ and expression of E-cadherin↑[96]; - Activation of p38 MAPK and NF-κB signaling pathways → synthesis IL-6, IL-8 and IL-18↑[204]; - Inhibition of NK cell cytotoxicity by the Fap2 protein and an increase in the number of myeloid suppressor cells[96, 204,208]; - Regulates miR21 expression *via* the TLR4/MYD88/NFκB[96,202, 208,209]
Streptococcus gallolyticus (Sg)	
- More frequently found in CRC biopsies than in healthy mucosa[210,211]; - Circulation of Sg in the blood in patients with CRC is most likely associated with dysfunction of the epithelial barrier[212]; - In a mouse xenograft model of CRC, Sg promotes tumor growth[211]	- Induction of cell proliferation through WNT/β-catenin pathway[211] and modulation of extracellular matrix[213]; - Increase in expression of c-Myc and cyclin D1 proteins[211]; - Stimulation of proliferation of the intestinal epithelium by some Sg strains which is associated with their ability to adhere to the intestinal epithelium and the genetic characteristics of the host cells [211,214]
Enterococcus faecalis (Ef)	
- Contains superoxide[215]- Promotes CRC induction in Il10 $^{-/-}$ mice experimental model[215]	- Promotes chromosome instability[215]; - *Ef* polarize colon macrophages to produce endogenous mutagens → initiation CIN → expression of progenitor and tumor stem cell markers[216]; - Induces gene mutation and endogenous transformation through microbiome-induced bystander effects[217]; - Activation of the WNT/β-catenin pathway[217]; - Activation of transcription factors c-Myc, Klf4, Oct4 and Sox2[217]

APC: Adenomatous polyposis coli; BFT: *B. fragilis* toxin; BRAF: B-Raf proto-oncogene; CIMP: CpG island methylator phenotype; CIN: Initiate chromosomal instability; CNF: Cytotoxic necrotizing factor 1; COX2: Cyclooxygenase 2; FadA: Fatty acid desaturase A; KRAS: Kirsten ras; MAPK: Mitogen-activated protein kinase; MLH1: MutL homolog 1; MPP-9: Metalloproteinase-9; MSI: Microsatellite instability; MYD88: Myeloid differentiation primary response 88; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NK: Natural killer; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SMAD4: Small mothers against decapentaplegic 4; TLR: Toll-like receptor; TP53: Tumor protein 53; ZO-1: Zonula occludens-1.

Interestingly, the gut microbiota in right-sided and left-sided CRC also differ significantly. *Prevotella*, *Selenomonas*, and *Peptostreptococcus* are the most abundant phyla in right-sided CRC, while *Clostridium perfringens*, *F. nucleatum*, *Escherichia/Shigella*, and *Leptotrichia* are found at a higher abundance in left-sided CRC[62,63]. A recent study by Keskin *et al*[64] reported an association of CRC with patient height [64]. Unfortunately, the authors did not compare the risk of cancer development in the right and left halves of the colon depending on the patient height, but it can be assumed that an increased risk of CRC may be associated with elongation of the intestine, which leads to a decrease in the concentration of antimicrobial peptides and an increase in bacterial density in the distal part of the intestine.

It is important to note that the study of gene markers of the intestinal microbiota in colorectal polyps and CRC has made it possible to develop effective predictive models that not only identify individuals at high risk of developing adenomas and CRC[65] but also predict the survival of patients with CRC

[66]. These studies open up new possibilities for screening for CRC but also for the prevention and treatment of this pathology.

GUT MICROBIOTA AND MECHANISMS OF COLON CANCER INITIATION

According to modern concepts, CRC is a progressive process involving a sequence of cellular mutations during the transition from adenoma to carcinoma[67,68]. Most cases of CRC (> 95%) are sporadic and develop from polypoid adenomas that can progress to intramucosal carcinoma (stage 0) and CRC[69]. The risk of developing CRC is associated with (1) The genetic predisposition to CRC, which determines the proliferation rate of colon epithelial cells and their susceptibility to cell death, as well as the features of their metabolism that affect the formation of a protective mucous layer; (2) The state of the colon mucosa local immunity; and (3) The intestinal microbiome, which, in turn, can influence the stability of the cell genome, metabolism and immune response[70]. At the same time, it should be taken into account that the influence of the microbiota on the development of CRC may be indirect. Thus, in a study by Wang *et al*[71], it was noted that in patients with H. pylori-associated atrophic gastritis or intestinal metaplasia, the risk of developing colorectal polyps and CRC was 2.19 and 3.05 times higher, respectively, than in patients without H. pylori infection. Multiple and adenomatous polyps were significantly more common in the group of infected patients than in the uninfected group[71].

Factors that determine the role of the microbiota in CRC carcinogenesis include: (1) Inflammation; (2) The impact of bacterial metabolites on the activation of signaling pathways associated with proliferation, apoptosis, epithelial-mesenchymal transformation and their genotoxicity; (3) Changes in intestinal stem cell function; and (4) Disorders of local and systemic immunity and others[72,73]. Let us consider them in more detail.

Gut microbiota and inflammation

The interaction of bacteria and other microorganisms with the intestinal epithelium is carried out through TLRs and nucleotide-binding oligomerization domain receptors. Enterocytes express TLR2, TLR3, TLR4, TLR5 and TLR9. Most TLRs are localized on the basolateral membrane, while TLR2, TLR3, and TLR9 are also expressed on the apical surface[74,75]. Basolateral TLR stimulation results in a signaling cascade, activation of nuclear factor-kappaB (NF-κB), and increased secretion of cytokines and chemokines, including tumor necrosis factor-α (TNF-α), IL-6, IL-12, IL-18, C-X-C motif chemokine ligand 8 (CXCL8), and C-C motif chemokine ligand 20 (CCL20). Cytokines activate immunocompetent cells, thereby promoting inflammation and proliferation of the intestinal epithelium[76]. It is believed that with an increase in the number of intestinal bacteria, hypersecretion of cytokines contributes to bacterial invasion into the dense layer of mucus. Bacterial invasion into the mucus layer and interaction with the epithelium may cause early stages of cellular transformation with a deficiency in DNA MMR as a consequence of increased epithelial proliferation[77].

Importantly, the composition and quantity of the intestinal microbiota are regulated by antimicrobial peptides produced by Paneth cells and IgA present in intestinal mucus[78]. On the one hand, mucus determines the distribution and organization of the microbiota in the intestine and protects epithelial cells and crypts against bacterial colonization. However, on the other hand, the presence of microbiota is absolutely necessary for the correct location of intestinal mucus[79]. Mice treated with antibiotics had a thinner layer of mucus, and it was permeable to bacteria. Moreover, epithelial stem cell replication was impaired, and antibiotic-treated mice were more susceptible to colitis induced by physical or chemical exposure[80,81].

Gut microbiota metabolites and proliferative activity of the intestinal epithelium

Bacterial metabolites play a key role in maintaining intestinal homeostasis. As noted above, the synthesis of intestinal mucins is regulated by the gut microbiota. However, intestinal mucus not only protects epithelial cells from bacterial invasion but also serves as a bacterial breeding ground. These bacteria include *Akkermansia muciniphila*, *Bacteroides thetaiotaomicron*, *Bifidobacterium bifidum*, *B. fragilis*, *Ruminococcus gnavus* and *Ruminococcus torques*. These species generate short-chain fatty acids (SCFAs) during fermentation using glycans as an energy source[80,82]. SCFAs are carboxylic acids resulting from bacterial anaerobic fermentation predominantly of dietary fibers in the intestine, where acetate and propionate are produced by *Bacteroidetes* (gram-negative bacteria) and butyrate is produced by *Firmicutes* (gram-positive bacteria) in human intestines[83]. It is assumed that the effect of butyrate on intestinal epithelial cells (IECs) and on tumor cells is different[84]. Butyrate, the main source of energy in normal IECs, maintains low levels of Wnt signaling and normal proliferative activity[84,85]. In germ-free mice and in specific pathogen-free (SPF) mice treated with antibiotics selective for gram-positive bacteria, a decrease in proliferative activity in IECs was noted. Oral administration of chloroform-treated SPF mouse feces to sterile mice or oral administration of SCFAs restored the proliferative activity of IECs[86].

At the same time, in intestinal stem cells (ISCs) and tumor cells, Wnt hyperactivation by butyrate leads to increased transcription of proteins involved in apoptosis of colon cancer cells and a decrease in cell proliferative activity[87]. It is believed that hyperactivation of Wnt signaling in tumor cells raises Wnt activity levels to the range leading to apoptosis, while stimulation of normal colon cells with BAs likely results in moderate levels of Wnt activity that promote proliferation[85,88].

The following antitumor effects of butyrate have been described: Butyrate suppresses miR-92a expression *via* c-Myc, which reduces colon cancer cell proliferation and stimulates apoptosis[89]; butyrate reduces the phosphorylation of AKT serine/threonine kinase 1 (Akt1) and extracellular signal–regulated kinases ½ by blocking histone deacetylase 3 (HDAC3) activity with subsequent cell motility inhibition and inhibiting any subsequent cell movement, which impedes CRC cell metastasis and invasion[90]; and butyrate activates miR-203, which inhibits CRC cell proliferation, colony formation and invasion and promotes apoptosis of CRC cells[91].

An interesting hypothesis has been proposed to explain the antitumor effect of butyrate by the fact that colon cancer cells prefer glucose to butyrate as an energy source owing to the Warburg effect pathway. As a result, colon cancer cells accumulate large amounts of butyrate, which acts as an HDAC inhibitor, disrupting gene transcription[92]. Butyrate can enter the nucleus directly, inhibit HDAC1 and cause a decrease in the levels of short chain acyl-CoA dehydrogenase (SCAD), which is the primary process in the catalysis of mitochondrial butyrate oxidation[93]. This reduces the autoxidation of butyrate in CRC cells and allows butyrate to accumulate in carcinoma cells, thereby inhibiting the development of CRC by inhibiting CRC cell proliferation and activating apoptosis.

At the same time, a number of studies have shown the pro-oncogenic effect of butyrate. In an experimental model of Lynch syndrome, its ability to induce the formation of reactive oxygen species (ROS) and promote the accumulation of 8-oxo-7,8-dihydro-2'-deoxyguanosine damage in MMR-deficient cells was noted. In an experiment on mice, DNA damage, polyp formation, and tumorigenesis were reduced by treatment with the antioxidant Vit C or N-acetylcysteine[94,95]. These data may be important, as 5% of patients with Lynch syndrome and approximately 15% of patients with sporadic CRC carry mutations or epigenetically silenced MMR genes[94].

Gut microbiota metabolites and genotoxicity

It should be noted that a number of bacterial metabolites have direct procarcinogenic effects. These include secondary BAs, trimethylamine N-oxide, hydrogen sulfide, polyamines and others[96-99]. It is known that high concentrations of secondary BAs, caused, in particular, by the Western diet, promote inflammation, activation of Wnt and NF-κB signaling pathways, oxidative DNA damage, and disruption of mitotic activity, which ultimately leads to hyperproliferation and invasiveness of colon cells[68,85,100]. Secondary BAs can cause destruction of cell membranes and local disorders of the intestinal epithelium that stimulate the repair mechanisms, which is involved in the excessive proliferation of undifferentiated cells. Hydrophobic BAs can also contribute to increased ROS and reactive nitrogen species that cause oxidative stress, DNA and protein damage and disruption of base excision repair pathways[93,100,101]. In addition, secondary BAs promote epidermal growth factor receptor (EGFR) activation through phospholipid acid aggregation, which induces EGFR dimerization/oligomerization and stimulates EGFR-mitogen-activated protein kinase signaling and cell proliferation [93,102].

The genotoxicity of microbial metabolites may be associated with the biotransformation of a number of xenobiotics, such as heterocyclic amines (HCAs). HCAs are formed as a result of the thermal processing of foods, including oils, grains and vegetables, and processed meats[103]. The intestinal microbiota can metabolize them into molecules with increased mutagenic activity, which have pronounced genotoxic and mutagenic properties. HCAs can promote the development of malignant neoplasms of the intestine, liver, lung, breast, and other tumors[104]. Their carcinogenicity is associated with mutations in proto-oncogenes and tumor suppressor genes, including KRAS, HARAS, adenomatous polyposis coli (APC), β-catenin, and tumor protein 53 (TP53)[105]. However, the intestinal microbiota can metabolize food-derived HCAs, facilitating their excretion with feces or conversion into less toxic compounds[103]. These processes involve bacterial enzymes produced by some lactic acid bacteria and probiotics. A decrease in the number of taxa with their activity was noted in patients with CRC[106].

Gut microbiota and Paneth cells

Paneth cells are the source of secreted proteins, such as Wnt3, EGF, and Notch ligand Delta-like (Dll) 4 and Dll1, which are crucial for stem cell support[107-110]. They are in direct contact with crypt base columnar cells expressing leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5), known as a stem cell marker for colon cancer and gastric cancer. Due to their proximity to LGR5+, Paneth cells affect the function of ISCs by activating the canonical Wnt/β-catenin signaling pathway and producing Wnt3, which binds to Frizzled receptors to improve the function of Lgr5 stem cells[109,111]. There is an assumption that the development of adenomas and CRC is preceded by the appearance of metaplastic Paneth cells as a protective antibacterial and inflammatory reaction caused by altered microbial activity [78,110]. In epithelial injury followed by inflammation, when rapid barrier repair is needed, Paneth cells are able to acquire stem cell characteristics through dedifferentiation upon Notch and stem cell factor/c-

kit signaling, thereby promoting epithelial repair[109,112,113]. In addition to Paneth cells, other differentiated IECs can also acquire stem cell properties under certain conditions and participate in the repair of epithelial damage[113]. When studying tissue samples of polyps, normal tissues and CRC, it was found that some polyps and CRC cells demonstrate a stem-like phenotype. Advanced polyps contain an increased number of stem-like cells, regulatory T cells and a subtype of precancerous fibroblasts[114].

Gut microbiota and immunity

The intestine is an important immune organ that not only protects against external pathogens but also participates in the formation of immune tolerance to food substrates and the normal intestinal microbiome. At the same time, the intestinal microbiome is directly involved in the formation of local and systemic immunity by activating the synthesis of IgA and interferons and activating immune cells [115]. Thus, germ-free animals are more susceptible to viral and bacterial infections and have reduced digestive enzyme activity, cytokine production and serum immunoglobulin levels, smaller Peyer's patches and fewer intraepithelial lymphocytes[116].

A number of experimental studies have demonstrated an association between the gut immune system, gut microbiota, and CRC risk[117-119]. Hurtado *et al*[117] showed that the induction of experimental CRC is associated with increased synthesis of the proinflammatory cytokine IL17A by immune cells, for activation of which specific microbes are needed, such as *B. fragilis*[117]. Activation of IL17A receptors leads to activation of the NF-κB transcriptional pathway and induction of IL6 production by epithelial cells, which, in turn, activates STAT3 in epithelial cells, promoting their survival and proliferation[118]. At the same time, it should be noted that the role of Th17, IL17 and regulatory T cells (Tregs) in CRC is ambiguous and can be associated with both oncogenic and antitumor activity, as evidenced by the data of experimental and clinical studies[117,119]. The interaction between the intestinal immune system, microbiota, and CRC is complex and multipolar and depends on the stage of the tumor process, the tumor microenvironment, the ratio of bacteria in the intestine with oncogenic and antitumor properties, diet, and other factors[119-121]. This issue still requires detailed study, especially given that modulation of the immune system by the gut microbiome can directly influence the outcome of CRC treatment[122].

GUT MICROBIOTA AND PROGRESSION OF CRC

A growing body of research suggests that the gut microbiome can influence not only the initiation but also the progression of CRC[72]. It has been established that high infection of the tumor tissue with "pro-oncogenic" bacteria, for example, *P. micra*, *F. nucleatum* and *B. fragilis*, is associated with more advanced stages of CRC and with a decrease in patient survival[44,123,124]. Some authors have noted positive correlations between the number of *F. nucleatum* in the tumor and the presence of metastases in regional lymph nodes[44]. Furthermore, pro-oncogenic bacteria, such as *F. nucleatum*, have been found not only in primary colorectal tumors but also in metastatic lesions of the liver[125] and lungs[126].

The influence of the intestinal microbiome on the progression of CRC can be carried out by various mechanisms, for example, by modulating the tumor microenvironment and initiating the processes of inflammation, angiogenesis, epithelial-mesenchymal transition (EMT) and immunological tolerance that promote cancer metastasis[33,127,128]. For example, it has been found that a high abundance of *F. nucleatum* in tumor tissue is associated with increased expression of TNF-α, β-catenin and NF-κB, while high B. fragilis level is positively related with COX-2, metalloproteinase-9, NF-κB, and the presence of Kirsten ras (KRAS) and B-Raf proto-oncogene (BRAF) mutations[123]. In an experiment, *F. nucleatum* infection promoted increased tumor cell migration and translation of factors associated with EMT, which promoted CRC metastases to the lungs and liver[126,129]. *F. nucleatum*-infected cells have been shown to secrete specific exosomes that increase the ability of tumor cells to migrate *in vitro* and promote tumor metastasis *in vivo*[130]. *F. nucleatum* may also promote immune evasion by binding the Fap2 protein to the immunosuppressive T-cell immunoglobulin and ITIM domain receptor, which inhibits T-cell activation and induces the death of human natural killer cells[131,132]. In addition, the gut microbiome may influence macrophage polarization and the formation of neutrophil extracellular traps, which may promote tumor metastasis through local invasion, increase vascular permeability, and facilitate immune escape and colonization[133,134].

A number of authors drew attention to the similarity of the mechanisms of tumor and bacterial metastasis (dissemination), which, in their opinion, indicates a possible role of bacterial translocation in the progression of CRC[135,136]. Translocation is the process of penetration of bacteria into the intestinal epithelium and beyond into the lymphatic vessels and nodes, blood vessels and distant organs. Translocation mechanisms may be associated with a violation of the composition and amount of mucus, remodeling of tight junctions, invasive bacterial properties, local and systemic inflammation, alcohol, infection, dysbacteriosis, drug treatment, and other factors[137]. In particular, it was found that *E. coli*, depending on the virulence regulator VirF, destroys the intestinal vascular barrier that controls the spread of bacteria along the gut-liver axis. When it is disturbed, bacteria disseminate to the liver, stimulate the formation of a premetastatic niche, and promote the recruitment of metastatic cells.

Elevated levels of vesicle-associated protein-1 (PV-1), a marker of disruption of the intestinal vascular barrier, are associated with dissemination of hepatic bacteria and metachronous distant metastases[136].

It should be noted that the assessment of the microbiome role in the progression of CRC is important, as it determines the feasibility of using antibiotic therapy in patients with CRC. A number of experimental studies have shown that the use of antibiotic therapy against F. nucleatum contributed to a decrease in tumor cell proliferation and overall tumor growth[125]. Depletion of intratumoral bacteria in experimental breast cancer significantly reduced lung metastasis without affecting primary tumor growth[127]. Moreover, some researchers have noted the positive effect of antibiotic therapy in the treatment of malignant neoplasms, including CRC[138].

GUT MICROBIOTA AND GENETIC HETEROGENEITY IN CRC

Microbiome and genetic and epigenetic changes in CRC

In 1990, Fearon and Vogelstein offered a multistage genetic model for the formation of CRC[69]. According to this model, the formation of CRC occurs due to the accumulation of several genetic and epigenetic changes in key tumor suppressor genes and the activation of oncogenes[69,139]. The first mutations in CRC most often affect the APC gene. These mutations confer a selective growth advantage on normal IECs and result in slow-growing intestinal adenomas. The appearance of the 2nd mutation over time, for example, in the KRAS gene, increases the growth rate of adenomas. Accelerated proliferation of epithelial cells contributes to the accumulation of new mutations in genes such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), small mothers against decapentaplegic 4 (SMAD4) and TP53, which ultimately leads to the emergence of a malignant tumor with invasive and metastatic properties. These mutations give epithelial cells certain advantages over other cells and are called "driver" mutations[140].

The authors proposed two main pathways of CRC formation. The first pathway accounts for 85% of all CRCs and involves inhibition of Testis-Specific GTPase expression and APC. The second pathway is associated with mutational inactivation of proteins involved in MMR, namely, the mutS homolog 2 (MSH2), mutL homolog 1 (MLH1), and post meiotic segregation 2 (PMS2) genes. This pathway is seen in 15% of all sporadic cases of CRC[69,139,141].

Currently, CRC is considered a heterogeneous group of tumors with different mechanisms of carcinogenesis and macro- and microscopic characteristics, as well as with different 5-year survival prognoses. A growing body of evidence points to an important role of the gut microbiome in the development of genetic and epigenetic changes in CRC[142-145]. It is believed that there are two main mechanisms by which the microbiome influences the genome or epigenome of the intestinal epithelium in CRC: the ability of intestinal microbes to induce a pro-carcinogenic inflammatory response and the production of secondary metabolites by intestinal microbes[146-149]. In addition, a number of microbial toxins, such as cytolethal distending toxin (CDT), colibactin and *B. fragilis* toxin, can directly cause DNA damage and trigger mutations[150].

Of particular interest is the role of the gut microbiota in hereditary syndromes. A number of studies have noted an increase in the number of *Bacteroides*, *Parabacteroides distasonis*, *Faecalibacterium prausnitzii*, *Ruminococcus bromii*, the *Pseudomonadaceae family*, *E. coli*, *Klebsiella species*, *Porphyromonas* and *Methanobrevibacter* in Lynch syndrome[151] and *B. fragilis* and *E. coli* in familial adenomatosis[35]. It is known that Lynch syndrome, which is characterized by a high risk of developing CRC and other forms of malignant tumors, is associated with a mutation of the MSH2 gene, which encodes a protein of the same name and plays an important role in DNA repair. The MSH2 protein is involved in the elimination of errors that occur during DNA replication in the process of preparing a cell for division. In Msh2-Lynch mice, there was an increase in the expression of genes associated with immunity, activation of K-Ras and genes responsible for the epithelial-mesenchymal transition and an increase in the number of Lyz1 and Wnt3 transcripts, which indicates increased proliferation of stem cells due to Wnt production by Paneth cells and activation of inflammatory pathways. In experimental Lynch syndrome, in MSH2-Lynch mice with MSH2-deficient intestinal epithelial crypts, the use of the methylating drug temozolomide resulted in a fivefold increase in the number of MSH2-deficient crypts and caused tumors in all experimental animals. Transfer of Msh2-Lynch mice from a normal room to a specific SPF room resulted in an almost complete loss of the intestinal tumor phenotype and increased survival of the experimental animals. SPF mice showed a decrease or absence of *Lactobacillus* and *Epsilonproteobacteria taxa* in the feces[77]. In addition, transplantation of cryopreserved conventional feces into SPF mice did not restore the tumor phenotype but increased the rate of epithelial renewal and accelerated the development of microsatellite instability (MSI). A number of authors have also demonstrated that depletion of the gut microbiota by antibiotics reduced the development of colitis and cancer formation in experimental animals[152].

Main ways of developing sporadic CRC

Analysis of genetic and epigenetic changes in CRC made it possible to identify the main mechanisms of development of sporadic CRC and offer molecular genetic classifications of CRC[153-156]. Thus, at present, it is customary to consider three main ways of developing sporadic CRC (Table 2). Of particular

Table 2 The main pathways for the development of sporadic CRC and their relationship to gut dysbiosis

Pathway	Clinical features	Genetic and epigenetic disorders
The chromosomal instability (CIN) – 38%-85%[157,158]	- Associated with traditional adenomas[158]; - Associated with *Fusobacterium, Escherichia/Shigella u Leptotrichia*[63]; - CIN-H tumors are more frequently located on the left colon (87%), are associated with lymphocytic infiltration (82%), are more common in older patients (73%) and are associated with worse prognosis[157]	- Alteration in chromosome number or structure, loss of heterozygosity and aneuploidy[158]; - Mutations in the APC gene, a negative regulator of β-catenin-dependent Wnt signaling pathway (in 70%-80% of cases)[158]; - Mutations in TP53, KRAS, and PIK3CA genes and tumor suppressor genes SMAD2, SMAD4, and DCC[157,158]; - 20%-60% of tumors are CIN-H[158]
The CpG island methylator phenotype (CIMP) – 15%-30%Three groups based on the degree of gene methylation: High CIMP (CIMP -H); low CIMP (CIMP -L) and negative (CIMP-)[157,158]	- Associated with sessile serrated polyps[158,161,218]; - Associated with *F. nucleatum*[161,208], and *E. faecalis*[219]; - Data on the clinical features of CIMP-H tumors are controversial:- CIMP-H tumors are more frequently located in the left colon (67%) and are more common in men (68%) and in older patients (73%)[157,158]; - CIMP-H tumors are more common in females (68%) and in older patients (73%) and are associated with smoking, alcohol consumption, overweight, Western diet, right colon cancer, tumor lymphocytic infiltration, and poor differentiation[159,220,221]; - CIMP-H tumors are associated with worse prognosis[157,158,198,221,222];- CIMP-H tumors with MSI-H and BRAF mutations are more common in the proximal colon, whereas CIMP-L tumors with KRAS mutations are more common in the distal colon[158,159]	- Data on the presence of mutations in BRAF, PIK3CA, KRAS and TP53 genes are contradictory:- KRAS mutation in 27% tumors, PI3KCA mutation in 27%, and BRAF mutation in 7% tumors[157]; - Mutations in BRAF and PIK3CA genes and absence of mutations in KRAS and TP53 genes[154,159,161]; - Methylation of the MINT1, MINT2, MINT31, p14, p16 and MLH1 genes[154,159,161]; - 25% to 60% of tumors are MSI-H[157-159]
The microsatellite instability (MSI) – 15%-20%Three groups based on the number of microsatellites associated: High MSI (MSI-H); low MSI (MSI-L), and microsatellite stable (MSS)[158]	- 20% of cases are hereditary[158]; - Associated with *F. nucleatum*[124,161,208], *E. faecalis*[219] and *P. micra*[124]; - MSI-H are more frequently located on the right colon (86,7%), are more common in older patients(80%), and have a good prognosis at an early stage[157,158]	- High frequency of replication errors in MLH1 and MSH3 mismatch repair (MMR) genes[158]; - Hereditary CRC is associated with germline mutations in MMR genes: MLH1, MSH2, MSH6, and PMS2[158]; - 20%- 70% of tumors are CIMP-H[157,158]; - Often BRAF mutation (40%)[158]; - Mutations in the ACVR2A, TGFBR, MSH3, and MSH6 genes, as well as in the RNF43, RNF213, and ZNRF3 Wnt regulatory pathways[158]; - APC, TP53 and KRAS mutations are rare[158]

APC: Adenomatous polyposis coli; CIMP: CpG island methylator phenotype; CIN: Chromosomal instability; KRAS: Kirsten ras; MMR: Mismatch repair; MSI: Microsatellite instability; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SMAD4: Small mothers against decapentaplegic 4; TP53: Tumor protein 53.

interest is their association with the gut microbiota[153].

Wielandt *et al*[157] defined a fourth pathway for the development of sporadic CRC: tumors with low or negative MSI-, chromosomal instability (CIN)- and CpG island methylator phenotype (CIMP)- status (30%) that are left-sided, 39% have KRAS mutations and are associated with better survival[157]. At the same time, attention was drawn to significant differences in the assessment of the clinical characteristics of MSI, CIN and CIMP subtypes of CRC, the frequency of BRAF, KRAS, PIK3CA, TP53 and other gene mutations within these subtypes, and the frequency of genetic subtype combinations among themselves. For example, Parmar *et al*[158] showed that CIMP-H tumors are more frequently located on the left colon and are more common in men, while Advani *et al*[159] determined that these tumors are more common in women and are associated with right colon cancer. We believe that these contradictions are associated with a large number of possible genetic subvariants of CRC, and in this connection within one subtype, variants with opposite characteristics are possible.

Notably, the listed pathways are also characteristic of CRC predecessors. In particular, it has been established that tumors derived from sessile serrated polyps are more often located on the right side of the colon and are associated with BRAF mutation, MSI-H and CIMP-H. They have been associated with human intestinal spirochetosis[160] and an increase in the relative abundance of *F. nucleatum*[161].

Molecular pathological classifications of CRC

Currently, two main molecular pathological classifications of CRC have been proposed[155,156]. The first classification based on complex molecular analysis (array and sequencing technologies) distinguishes two groups of CRCs. The first group includes hypermutated tumors (approximately 16%)[155]. They are characterized by microsatellite instability (MSI) due to defective MMR (approximately 13%) or exonuclease domain mutations (approximately 3%). The second group consists of nonhypermutated tumors (approximately 84%) and microsatellite-stable (MSS) cancers with Wnt pathway dysregulation and frequent gene mutations, including APC, KRAS, PIK3CA, SMAD4, and TP53[155]. The second classification proposed by Guinney *et al*[156] includes 4 consensus molecular subtypes (CMSs)[156].

CMS1 (17% of cases) is associated with a high frequency of CIMP-H and MSI-H; mutations in BRAF (48%), KRAS (29%), and APC (42%); activation of the JAK/STAT pathway; impaired MMR system; serrated polyps; diffuse immune infiltration; and diagnosis of CRC on stage I-III with good prognosis

and worse survival after relapse.

CMS2 (47% cases) is associated with CIMP- and MSS; mutations in BRAF (62%), KRAS (34%), APC (80%); Wnt & Myc activation; epithelial signature; tubular adenoma; diagnosis of CRC on Stage II (39%) and good prognosis and good survival after relapse.

CMS3 (13% of cases) is associated with CIMP- and MSS; mutations in BRAF (30%), KRAS (83%), and APC (91%); epithelial signature; metabolic dysregulation; tubulovillous adenoma with serrated features; and intermediate prediction.

CMS4 (23% cases) is associated with CIMP- and MSS; mutations in BRAF (60%), KRAS (37%), APC (77%); stromal signature; EMT; TGF-b activation angiogenesis; serrated polyps; diagnosis of CRC on Stage III-IY with poor prognosis and worse survival after relapse.

Approximately 80%-90% of CRCs fall into one of the four major transcriptional subgroups, and the remaining CRCs are heterogeneous cases exhibiting "mixed or indeterminate" gene expression patterns with varying features of these subtypes[153,156,158,162].

At present, a link between the microbiota and CMS has only been established for the CMS1 subtype, which was associated with an increase in the relative abundance of Fusobacteria and Bacteroidetes and a decrease in *Firmicutes* and *Proteobacteria*[163]. In particular, increases in the abundance of *F. nucleatum*, *Porphyromonas gingivalis*, *Tannerrella forsythia*, *Treponema denticola*, *P. micra* and *Peptostreptococcus stomatis* were noted[163,164]. For other molecular subtypes, this question remains open.

GUT MICROBIOTA AND CRC TREATMENT

Numerous studies suggest that the gut microbiome may influence the efficacy of CRC drug therapy, namely, the efficacy of hematopoietic cell transplantation, chemotherapy, and immunotherapy[122,165-167]. The influence of the intestinal microbiota on the immunotherapy of solid tumors has been studied the most. It has been established that the intestinal microbiota is able to influence the expression of immune checkpoints, both reducing and increasing the effectiveness of immunotherapy[166,167]. Thus, patients with increased levels of *Firmicutes* and *Verrucomicrobia* almost always had a better response to immune checkpoint inhibitor therapy, while in patients with increased levels of *Proteobacteria*, the treatment was ineffective[167]. Moreover, the targeted use of prebiotics and probiotics has contributed to improving the effectiveness of immunotherapy due to the immunomodulatory effect, in particular, by increasing the production of butyrate[168], inhibiting inflammation and reducing oxidative stress[169], and activating CD8+ T- cells[170].

At the same time, the intestinal microbiome can influence the development of resistance to immunotherapy, which is observed in 60%-70% of cases. It has been established that resistance to immunotherapy may be associated with low antigenicity of tumor cells, impaired priming of antigen-specific naive lymphocytes, including as a result of pretreatment with chemotherapy or radiation therapy, functional depletion of tumor-infiltrating lymphocytes, and other factors[122]. Routy *et al*[122] showed that the clinical response to immune checkpoint inhibitor therapy is positively correlated with the relative abundance of the mucin-degrading bacterium *Akkermansia muciniphila* (*A. muciniphila*)[122]. Subsequent studies have shown that *A. muciniphila* improves metabolic functions and immune responses in the host and has the potential to treat inflammatory bowel disease, obesity, and type 2 diabetes[171], diseases associated with the risk of CRC. The important role of *A. muciniphila* in reducing intestinal barrier permeability and the synthesis of intestinal peptide hormones, increasing the level of Tregs in the general population of CD4 T cells and reducing the levels of IL-6 and IL-1β expression was noted[172]. In an experiment, administration of A. muciniphila to mice for 4 wk accelerated the proliferation of LGR5+ ISCs, promoted the differentiation of Paneth and goblet cells in the small intestine and colon, and reduced intestinal damage caused by radiation and methotrexate[173]. The authors suggest that *A. muciniphila* may be one of the key components that maintains a healthy bacterial community by increasing the availability of mucin sugars[174].

The gut microbiota can also influence the efficacy of chemotherapy by inducing CRC chemoresistance [175]. The mechanisms of development of chemoresistance under the influence of microbiota may be associated with a violation of autophagy mechanisms[166] or a change in the metabolism of chemotherapeutic drugs, for example, gemcitabine[176].

Discussions continue in the scientific world about the effect of antibiotic therapy on the effectiveness of therapy for malignant neoplasms, including CRC. A number of meta-analyses have shown that antibiotic therapy can reduce the survival of patients with malignant neoplasms[177], while other authors have shown that antibiotics can inhibit tumor growth or metastases and improve treatment outcomes[125,127,138,178-180]. Thus, the depletion of intratumoral bacteria in experimental breast cancer significantly reduced lung metastasis without affecting the growth of the primary tumor[127]. At the same time, Routy *et al*[122] demonstrated that dysbiosis associated with malignant disease or antibiotic use can influence primary resistance to programmed cell death protein 1 (PD-1) blockade in mice with tumors and cancer patients. In mice with experimental MCA-205 sarcoma and RET melanoma, treatment with broad-spectrum antibiotics significantly compromised the antitumor effects and survival of mice treated with PD-1 mAb alone or in combination with cytotoxic T lymphocyte-

associated antigen-4 mAb. Moreover, the authors demonstrate that in patients with non-small cell lung cancer, renal cell carcinoma, or urothelial carcinoma, the use of antibiotics before or 1 mo after the first mAb administration resulted in a significant reduction in progression-free survival and overall survival. The authors believe that the deterioration of the immunotherapy effect is due to a decrease in the number and species diversity of the intestinal microflora. Oral administration of *A. muciniphila* to experimental animals resulted in increased expression of CD4+ T cells expressing the small intestine–associated chemokine receptor CCR9 and/or the Th1-associated chemokine receptor CXCR3 in mesenteric lymph nodes and tumor-draining lymph nodes[122].

Despite the impressive results obtained in this study, some heterogeneity of patient groups in terms of nosology, the prevalence of the tumor process, the number of A. muciniphila, and antibacterial therapy regimens is embarrassing. In particular, in the group of patients with renal cell carcinoma treated with antibacterial therapy, there were significantly more patients with liver metastases than in the group of patients who did not receive antibacterial therapy. Moreover, regardless of whether patients received antibacterial therapy or not, *A. muciniphila* and *E. hirae* were the commensals most significantly associated with a favorable clinical outcome. This raises a reasonable question: Are the best survival rates associated with the absence of antibacterial therapy or are they due to the noted differences?

We believe that further study of the feasibility of using targeted antibacterial therapy and probiotics in patients with CRC is relevant. It seems logical that if certain types of bacteria can be associated not only with the initiation but also with the progression of cancer, then the elimination of pathogenic bacteria can improve long-term treatment outcomes. A number of researchers have demonstrated the effect of antibacterial therapy in the treatment of malignant neoplasms[179-182].

In connection with the above, it can be stated that the effect of antibacterial therapy on the effect of immunotherapy and the survival of patients with malignant neoplasms is insufficiently unexplored. Contradictions in the results obtained require a detailed study with stratification of patients depending on the type and stage of cancer, the type of antibiotics used and the characteristics of the patient microbiome, as well as the nature of changes in the microflora as a result of treatment. Considering the literature data, macrolides (azithromycin, clarithromycin), doxycycline and salinomycin seem to be the most promising groups of antibacterial drugs[138,179-182]. At the same time, the sensitivity of "pro-oncogenic" strains to antibacterial drugs requires a detailed study, since under modern conditions, polyresistance to antibacterial drugs is not so rare[183,184].

CONCLUSION

Thus, the results of numerous studies confirm the important role of the gut microbiome in the development of intestinal polyps and CRC. The microbiota and its metabolites affect the severity of inflammatory changes in the intestine and activation of signaling pathways associated with proliferation, apoptosis, and epithelial-mesenchymal transformation and may contribute to the accumulation of genetic mutations. In addition, intestinal bacteria can affect the effectiveness of immunotherapy and chemotherapy and the survival of CRC patients, as they are associated with the formation of immunological tolerance, priming of tumor antigens, and the qualitative and quantitative characteristics of immune cells infiltrating the tumor. Changing the microbiome aimed at eliminating pro-oncogenic bacteria and microorganisms and saturating it with a population of microorganisms responsible for correcting immune defense may be one of the promising directions not only in the prevention but also in the treatment of sporadic CRC. In this regard, further study is required to determine the role of specific bacteria in the progression of CRC and their influence on the effectiveness of antitumor therapy. Considering that CRC is a heterogeneous disease with different mechanisms of carcinogenesis, macro- and microscopic characteristics, as well as an unclear prognosis, further study of the connection between the intestinal microbiota and molecular genetic subtypes of CRC is of great interest. The results of these studies may contribute to the development of new approaches to the diagnosis, treatment and prevention of CRC.

FOOTNOTES

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