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REVIEW

Familial adenomatous polyposis and changes in the gut microbiota: New insights into colorectal cancer carcinogenesis

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Abstract

Patients with familial adenomatous polyposis (FAP), an autosomal dominant hereditary colorectal cancer syndrome, have a lifetime risk of developing cancer of nearly 100%. Recent studies have pointed out that the gut microbiota could play a crucial role in the development of colorectal adenomas and the consequent progression to colorectal cancer. Some gut bacteria, such as *Fusobacterium nucleatum*, *Escherichia coli*, *Clostridium difficile*, *Peptostreptococcus*, and enterotoxigenic *Bacteroides fragilis*, could be implicated in colorectal carcinogenesis through different mechanisms, including the maintenance of a chronic inflammatory state, production of bioactive tumorigenic metabolites, and DNA damage. Studies using the adenomatous polyposis coli$^{Min/+}$ mouse model, which resembles FAP in most respects, have shown that specific changes in the intestinal microbial community could influence a multistep progression, the intestinal "adenoma-carcinoma sequence", which involves mucosal barrier injury, low-grade inflammation, activation of the Wnt pathway. Therefore, modulation of gut microbiota might represent a novel therapeutic target for patients with FAP. Administration of probiotics, prebiotics, antibiotics, and nonsteroidal anti-inflammatory drugs could potentially prevent the progression of the adenoma-carcinoma sequence in FAP. The aim of this review was to summarize the best available knowledge on the role of gut microbiota in colorectal carcinogenesis in patients with FAP.

Key Words: Familial adenomatous polyposis; Microbiota; Colorectal cancer; Polyps; Carcinogenesis; Bacteria

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Core Tip: A number of studies have demonstrated that gut microbiota dysbiosis could be a key factor in colorectal carcinogenesis. The adenomatous polyposis coli (*APC*)$^{Min/+}$ mouse model has been extensively used to study the underlying mechanisms of colorectal carcinogenesis in familial adenomatous polyposis. Interventions aimed at improving dysbiosis by administration of probiotics, prebiotics, or antibiotics could decrease colorectal cancer development in *APC* mutation carriers.

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INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colorectal cancer (CRC) syndrome characterized by the development of numerous (*i.e.* tens to thousands) colorectal adenomas[1,2]. A mutation in the adenomatous polyposis coli (*APC*) gene, found on chromosome 5q21, is responsible for FAP[3]. The incidence of FAP is around 1/8300, and the onset is commonly in the second or third decade of life. The risk of CRC is nearly 100% by the time patients with FAP reach the age of 40-50 years[4,5]. Such patients have an increased risk of desmoid tumors and gastric, duodenal, biliary duct, and thyroid cancers[6]. Extraintestinal manifestations of FAP may include osteomas, dental abnormalities such as unerupted or supernumerary teeth, congenital absence of one or more teeth, odontomas, and dentigerous cysts; and congenital hypertrophy of the retinal pigment epithelium[7,8]. Prophylactic colectomy is generally performed by age 40 in patients with FAP, and is the gold standard treatment to reduce the risk of developing CRC[9]. Nonetheless, colectomy is associated with postoperative morbidity and does not reduce the risk of developing extraintestinal manifestations of FAP[10]. Endoscopic surveillance of patients with FAP and their family members has decreased the occurrence of CRC at the time of FAP diagnosis by 55% and has also increased overall survival[4,11].

Recent studies have shown that the gut microbiota could play an important role in the development of colorectal adenomas and the consequent progression to CRC[12]. Indeed, gut bacteria such as *Fusobacterium nucleatum*, *Escherichia coli*, *Clostridium difficile*, *Peptostreptococcus*, and enterotoxigenic *Bacteroides fragilis*, could be responsible for colorectal carcinogenesis through a number of mechanisms, including the maintenance of a chronic inflammatory state, production of bioactive tumorigenic metabolites, and DNA damage[13-15]. A number of studies investigated the interaction between gut microbiota and host genetics in patients with intestinal adenomatous polyps. A study by Liang *et al*[16] showed a close relationship between the presence of *APC* mutation and modification of the gut microbiota and serum metabolites. Low levels of *Faecalibacterium prausnitzii* and an abundance of *Fusobacterium mortiferum* had the potential to predict the development of CRC from adenomatous polyps. It has been also observed that mutation of the *APC* gene could modify colonic-microbial interactions before the development of polyposis in mouse models[17]. After *F. nucleatum* infection, *APC*$^{Min/+}$ mice, carrying an inactivated allele of the *APC* gene, had an increase of small intestinal and colonic adenoma formation and an acceleration of small intestinal adenocarcinoma development[18]. Thus, it has been hypothesized that interventions aimed at improving dysbiosis in *APC* mutation carriers, including administration of probiotics, prebiotics, or antibiotics, could decrease CRC development. The aim of this review was to summarize the best available knowledge on the role of gut microbiota on colorectal carcinogenesis in patients with FAP.

GENETIC FEATURES

The classic colorectal carcinogenesis model described by Fearon and Vogelstein[19] includes development of most CRCs from a minimum of five or more genetic

alterations, while adenomas require fewer alterations. It has been hypothesized that inactivating mutations of the *APC* gene could represent the initial step of the "adenoma-carcinoma sequence" (Figure 1). The *APC* gene is a fundamental component of the β-catenin and Wnt signaling pathways, modulating cell differentiation, adhesion, migration, and apoptosis[20]. Somatic mutations of the *APC* gene occur in around 80% of sporadic CRCs, whereas germline *APC* mutations are responsible for FAP, making this a key target to study the environmental and genetic modifiers of CRC[16,17]. Loss of *APC* gene function has been shown to produce a survival advantage by mimicking hypoxic conditions and stimulate the accumulation of β-catenin and abnormal cell proliferation, associated with development of adenomatous polyposis[21-24].

Mouse models of FAP

Laboratory mouse models have proven to be valuable in the study of CRC[25]. The Min (multiple intestinal neoplasia) is the first key CRC mouse model and is induced by treatment with ethylnitrosourea[26]. Adult $APC^{Min/+}$ mice develop multiple intestinal polyps and anemia and usually die at a young age because of intestinal blockage and bleeding from the larger polyps[27]. Other mouse models have also been reported, such as conditional *APC* mutant alleles[28]. The $APC^{Min/+}$ mouse model shares numerous phenotypic and genetic similarities with FAP. However, patients with FAP develop adenomas mainly in the colon, while adenomas in $APC^{Min/+}$ mice are mainly located in the small intestine and have benign characteristics. Also, desmoid tumors and epidermoid cysts are rarely seen in mouse models compared with patients with FAP[29]. Nonetheless, the $APC^{Min/+}$ mouse represents an outstanding experimental model for investigating genetic features and therapeutic responses of CRC in humans.

Bacterial genotoxicity

Interplay between the gut microbiota and genetic characteristics could be responsible for the genetic pattern of the adenoma-carcinoma sequence. It has been hypothesized that bacterial drivers could initiate the development of precancerous lesions and the subsequent accumulation of gene mutations[30,31]. Different gut bacteria, such as *E. coli*, *Enterococcus faecalis*, *Streptococcus gallolyticus* and *B. fragilis* have been shown to promote carcinogenesis through genotoxic effects[32]. Some *E. coli* strains, mainly B2 and D, strongly express virulence genes, such as those encoding toxins and effectors that could promote carcinogenesis (*e.g.*, colibactin, cytotoxic necrotizing factors, cytolethal distending toxins, and cycle-inhibiting factor)[33,34]. Colibactin could be responsible for DNA alkylation on adenine residues, thus favoring double-strand breaks[35]. A recent study showed that expression of colibactin-producing polyketide synthase (*pks*+) in *E. coli* could was associated with the occurrence of a specific mutational signature in human gut organoids. The same mutational signature was detected in 5876 human cancer genomes in two independent study cohorts, especially in CRC[36]. Also, *pks*+ *E. coli* could be responsible for aneuploidy and abnormal cellular division, an effect promoted by the mutagen colibactin[37]. Such effects of *pks*+ *E. coli* were mainly observed in $APC^{Min/+}$ mice that lacked the autophagy gene *Atg16 L1*, and consequently were not able to recruit the DNA repair protein RAD51, thus accumulating DNA double-strand breaks and developing tumors[38]. *Enterococcus faecalis* was shown to promote DNA damage by induction of inflammation and oxidative stress resulting from the release of reactive oxygen species and reactive nitrogen species[39]. Fragilysin (also known as BST), is a toxic virulence factor released by enterotoxigenic *B. fragilis* (ETBF) that can induce DNA damage *in vivo*[40]. Colonization by sulfidogenic bacteria, such as *F. nucleatum*, has been associated with genomic or chromosomal instability and CRC development associated with the genotoxic effects of hydrogen sulfide (H_2S)[41,42]. A prior state of dysbiosis could enhance these specific bacterial genotoxic effects[31].

GUT MICROBIOTA AND CARCINOGENESIS

There is extensive evidence of an association between infectious agents and development of tumors[43]. It has also been demonstrated that specific mucosa-associated bacterial species could play a pivotal role in the pathogenesis of CRC[44-46]. Indeed, bacterial toxins and effector proteins have been shown to damage host cell DNA, and therefore affect crucial host cell signaling pathways that regulate cell differentiation, apoptosis, proliferation, and immune signaling[47-57] (Table 1).

Table 1 Studies of colorectal cancer-associated bacteria in the *APC*$^{Min/+}$ mouse model

Ref.	Bacterial strain	Mechanism of carcinogenesis
Kostic *et al*[18], 2013	*F. nucleatum*	Infiltration of CD11^{+} myeloid-derived immune cells
Tomkovich *et al*[49], 2017	*F. nucleatum* and *pks*+ *E. coli*	Mediated by inflammation, with colibactin-producing *E. coli* but not with *F. nucleatum* (FadA^{+} or Fap2^{+})
Yang *et al*[50], 2017	*F. nucleatum*	Regulation of miR-21 *via* TLR4/MYD88/NF-κB pathway
Wu *et al*[51], 2018	*F. nucleatum*	TLR4/p-PAK1/p-β-catenin S675 pathway
Chen *et al*[52], 2018	*F. nucleatum*	Induction of M2 macrophage polarization *via* TLR4. Activation of the IL-6/p-STAT3/c-MYC signaling pathway
Rubinstein *et al*[53], 2019	*F. nucleatum*	FadA adhesin upregulates Annexin A1 expression through E-cadherin
Dejea *et al*[54], 2018	Mono- or co-colonization of ETBF and *pks*+ *E. coli*	Upregulation of IL-17 and DNA damage
Chung *et al*[55], 2018	ETBF	Pathway involving activation of IL-17R, NF-κB, Stat3, and CXCL1
Goodwin *et al*[56], 2011	ETBF	Production of spermine oxidase, reactive oxygen species and DNA damage
He *et al*[57], 2019	*Campylobacter jejuni*	DNA damage due to cytolethal distending toxin
Li *et al*[15], 2019	Mixed strains from fecal samples of CRC patients after antibiotic cocktails	Wnt/β-catenin and cyclin D1 pathway

CRC: Colorectal cancer; *E. coli*: *Escherichia coli*; ETBF: Enterotoxigenic *Bacteroides fragilis*; *F. nucleatum*: *Fusobacterium nucleatum*; IL: Interleukin; NF-κB: Nuclear factor-kappa B; *pks*: Producing polyketide synthase; TLR: Toll-like receptor.

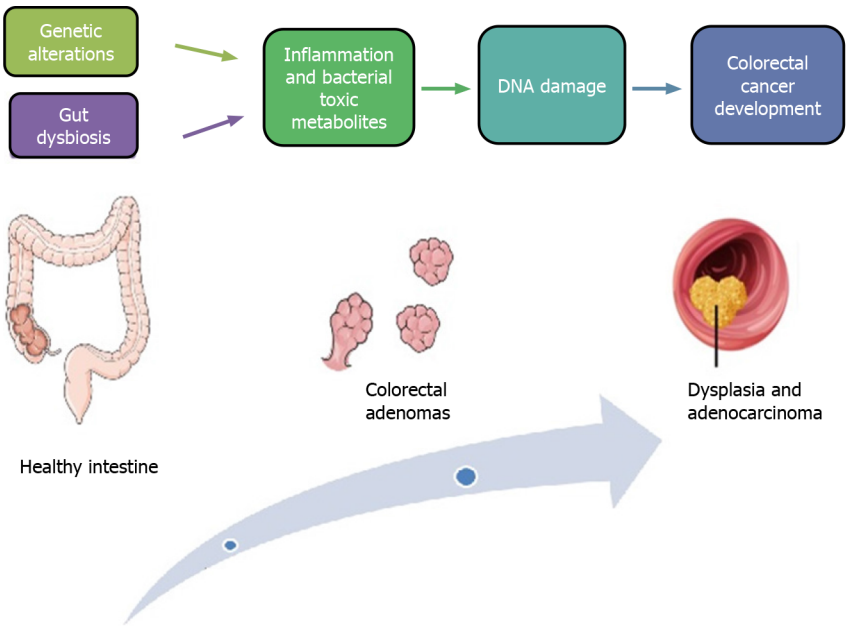

Figure 1 Pathway of the development of colorectal adenomas and the consequent progression to colorectal cancer.

Dysbiosis and bacterial toxins

Changes in the gut microbiota, can stimulate the c-Jun/JNK and STAT3 signaling pathways, thus promoting, in combination with anemia, tumor growth in *APC*$^{Min/+}$ mice[58]. A study carried out in *APC*$^{Min/+}$ mice by Son *et al*[17] reported that mutation of the *APC* gene modified colonic-microbial interactions prior to polyposis. Indeed, changes in the gut microbiota, characterized by an increased relative growth of *Bacteroidetes spp.* identified in association with intestinal tumors, has been shown to precede the development of microscopically evident intestinal tumors in 6-wk-old *APC*$^{Min/+}$ mice. A recent study by Dejea *et al*[54] detected colonic biofilms mainly composed of *E. coli* and *B. fragilis* in patients with FAP. Genes for colibactin (*clbB*) and *B. fragilis* toxin (*bft*) were highly expressed in the colonic mucosa of patients with FAP

compared with healthy subjects. Co-colonization with *E. coli* and ETBF led to an increase in interleukin-17 (IL-17) and DNA damage in colonic epithelium of tumor-prone mice, compared with mice with either bacterial strain alone. As ETBF and *pks*+ *E. coli* frequently colonize young children, it has been suggested that constant co-colonization in the colon mucosa from a young age could play a role in the pathogenesis of FAP[54]. The *B. fragilis* toxin (BFT) can bind to intestinal epithelial-cell receptors, promoting cell proliferation through cleavage of the tumor suppressor protein E-cadherin[55]. It has been shown that BFT can provoke acute and chronic colitis in C57BL/6 mice, and colon tumors in an $APC^{Min/+}$ mouse model[59-61]. Infections with enterotoxigenic strains of *B. fragilis*, compared with non-toxigenic strains, were more frequently observed in patients with CRCs. Enterotoxigenic strains were detected in only 10%-20% of healthy controls, but enterotoxigenic *B. fragilis* was found in stool samples from 40% of CRC patients[62]. A study by Tomkovich *et al*[49] carried out in germ-free, specific-pathogen-free, and gnotobiotic $APC^{Min/+}$;$IL10^{-/-}$ mice reported that colon carcinogenesis was associated with an inflammatory state. CRC did not develop in germ-free $APC^{Min/+}$;$IL\text{-}10^{-/-}$, and *pks*+ mice. *E. coli* promoted carcinogenesis in the $APC^{Min/+}$;$IL\text{-}10^{-/-}$ model in a colibactin-dependent way. An interesting study by Li *et al*[15] investigated the role of gut microbiota on adenoma progression in $APC^{Min/+}$ mice. Transplants of gut microbiota from CRC patients into $APC^{Min/+}$ mice enhanced the progression of adenoma, damaged the intestinal barrier, promoted chronic low-grade inflammation, and stimulated the Wnt signaling pathway. These results suggest that microbial targeted therapy could represent a novel FAP therapy.

Inflammation

Commensal and pathogenic bacteria were found to promote CRC development after colonizing normal colonic mucosa and promoting sustained local inflammation, and by releasing genotoxic compounds against colonic epithelial cells to induce their tumorigenic transformation[63]. Conversely, a balanced population of microbiota prevented development of CRC by producing bacterial metabolites that reduced inflammation[64]. Chronic inflammation is associated with the development of various tumors, including CRC. Inflammation of the colonic mucosa may enhance carcinogenic mutagenesis, thus favoring CRC initiation[65]. Also, a chronic inflammatory state is characterized by loss of IL-10-secreting regulatory T cells (Tregs) and stimulation of Th17cells producing IL-17A, which supports IL-17A-dependent tumor growth, and promotes colonic carcinogenesis in the $APC^{Min/+}$ mouse model, which resembles FAP in most respects[66]. An association between *F. nucleatum* infection and increased expression of the nuclear factor-kappa beta (NF-κB) pro-inflammatory profile in mouse intestinal cancers has been observed, consistent with the development of human CRC[18]. FadA, a *Fusobacterium*-specific adhesion molecule, can facilitate *F. nucleatum* adherence to host cells[67], and *F. nucleatum* colonization was found to recruit tumor-infiltrating myeloid cells and stimulate the Wnt/β-catenin pathway, leading to NF-κB activation and cancer cell proliferation[68]. Chronic inflammation in $APC^{Min/+}$;$IL\text{-}10^{-/-}$ mice was shown to modify the gut microbiota composition and selectively favor the growth of *Enterobacteriaceae*. Chronic inflammation also supported the selection of pathogenic strains of *E. coli* and was essential for the cancer-promoting effects of those bacteria[69]. Colonization of $APC^{Min/+}$ mice with ETBF led to the activation of a pro-tumorigenic multistep inflammatory cascade involving IL-17R, NF-κB, and Stat3 signaling in colonic epithelial cells. Indeed, BFT could stimulate a protumorigenic signal in colon mucosal epithelial cells that led to a Th17 response that in turn activated NFκB and myeloid cell-dependent carcinogenesis in the distal colon [55]. Grivennikov *et al*[70] reported that the loss of intestinal barrier function in $APC^{Min/+}$ mice induced by CRC-initiating genetic alterations led to adenoma invasion by microbial metabolites that stimulated inflammation and, in turn, cancer growth. It is noteworthy that even colonization of commensal bacteria can promote CRC. Indeed, infection of germ-free $APC^{Min/+}$;$IL\text{-}10^{-/-}$ mice with commensals of specific-pathogen free mice enhanced the tumor load[49]. Commensal bacteria and their constituents have been shown to stimulate Toll-like receptors on tumor-infiltrating myeloid cells and MyD88-mediated production of inflammatory cytokines, such as IL-23. Therefore, IL-23 supported CRC development by activating the release of other cytokines, such as IL-6, IL-17A, and IL-22[71].

Short-chain fatty acids and bacterial metabolites

A number of studies demonstrated that the gut microbiota was responsible for the production of various bioactive food elements and micronutrients, such as essential vitamins, and the fermentation of dietary fibers and complex carbohydrates, producing short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate

[72-74]. The role of butyrate in colorectal carcinogenesis is controversial[75]. In fact, in *APC*$^{Min/+}$; Msh2$^{-/-}$ mice that were also deficient for the DNA mismatch repair gene MutS homolog 2, Belcheva *et al*[76] found that microbial metabolism of carbohydrates into SCFAs, such as butyrate, enhanced the proliferation of tumor-initiated epithelial cells, thus promoting carcinogenesis. In their study, the growth of SCFA-producing bacteria, such as *Clostridiaceae*, *Ruminococcaceae*, and *Lachnospiraceae*, was inhibited by antibiotic therapy or a low-carbohydrate diet, and in turn the number of polyps detected in *APC*$^{Min/+}$; Msh2$^{-/-}$ mice was also reduced. On the other hand, many studies have described antineoplastic effects SCFAs, such as the suppression of inflammation, stimulation of apoptosis, and inhibition of cancer cell progression[77]. Nonetheless, further investigation is needed for clarifying the role of butyrate in CRC protection or promotion. Other bacterial metabolites, such as H_2S, secondary bile acids, and nitric oxide, have been shown to contribute to progression of adenomatous colon polyps to CRC by affecting host metabolism and immunity[78].

CURRENT CLINICAL TRIALS

A growing number of clinical trials have reported an association between gut bacteria and their metabolites and progression of CRC through various mechanisms[79,80]. However, the role of the gut microbiota in the progression and development of CRC is intricate and still not entirely understood, especially in patients with FAP. Currently, only a few clinical trials are recruiting subjects with FAP to determine whether modifying the gut microbiota might influence CRC development[81]. The Memorial Sloan Kettering Cancer Center in New York (United States), is conducting a clinical trial (Clinicaltrials.gov ID: NCT02371135) enrolling patients with Lynch syndrome or other hereditary colonic polyposis syndromes, in order to assess the role of the gut bacteria in CRC development. Investigators collect fecal samples, colon biopsies, and questionnaire responses on diet and lifestyle[82]. A phase 2, randomized, double-blind, placebo-controlled study sponsored by the Tel Aviv Sourasky Medical Center (Israel) is evaluating the efficacy of curcumin supplementation on polyp number and size in patients with FAP (Clinicaltrials.gov ID: NCT03061591)[83].

POTENTIAL THERAPEUTIC APPROACHES AND FUTURE DIRECTIONS

It has been suggested that interventions directed at improving gut dysbiosis in *APC* $^{Min/+}$ mice, for instance through probiotics, prebiotics, some antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), can inhibit the progression of the adenoma-carcinoma sequence, thus reducing the development of CRC[84-86].

Fap-related pouch

The ileoanal pouch is the surgical procedure of choice for patients with the classical phenotype of FAP[87]. Many studies have shown that the gut microbiota play a key role in the development of pouchitis, as supported by clinical evidence of the benefits of antibiotic therapy[88,89]. Metronidazole, ciprofloxacin, or a combination of both, is usually the initial approach, and it is often effective in chronic pouchitis[90]. A meta-analysis of 21 studies showed that antibiotics induced a significant remission rate (74%) in patients with chronic pouchitis (95% confidence interval: 56-93; $P < 0.001$), whereas the remission rate after administration of biologics was 53% (95% confidence interval: 30-76; $P < 0.001$). Conversely, steroids, bismuth, tacrolimus, and an elemental diet did not result in a significant remission, which was achieved by fecal microbiota transplantation[88]. Probiotics have been shown to be effective in the prevention of pouchitis[91]. Indeed, Shen *et al*[92] showed that administration of a probiotic treatment (*Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Bifidobacterium bifidus*) prevented pouchitis, decreased the Modified Pouch Disease Activity Index score, and reduced fecal pyruvate kinase and calprotectin in FAP patients after restorative proctocolectomy[93].

Probiotics and prebiotics

Gut microbiota composition and function are considerably modulated by diet[14]. An association between the intake of nondigestible fibers, such as prebiotics, and an abundance of beneficial bacteria in the gut, including *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, *Ruminococcaceae*, and *Roseburia* has been widely reported. Indeed

administration of both probiotics and prebiotics has shown beneficial effects in prevention and reduction of the prevalence of adenomatous colon polyps[94,95]. A metagenomic study by Ni *et al*[96] reported a preventive effect of *Lactobacillus rhamnosus* GG (LGG) on polyp formation in *APC*$^{Min/+}$ mice. The results showed that LGG had beneficial effects and reduced polyp development in mice by preserving gut microbial functionality. A study by Urbanska *et al*[97] reported similar results using an orally delivered probiotic formulation that reduced overall intestinal inflammation and the number of polyps in the small intestine of *APC*$^{Min/+}$ mice after administration of microencapsulated live *Lactobacillus acidophilus* cells.

Antibiotics

There is evidence that antibiotic treatment can modify the gut microbiota physiological processes and functions[98]. Some studies showed that shifts in the composition of the intestinal community caused by antibiotics were associated with development of polyps and progression to CRC. Other studies reported a possible protective effect on carcinogenesis[99-101]. A nested case-control study by Dik *et al*[102] reported a significant dose-dependent association between administration of penicillin and quinolone antibiotics and increased risk of CRC development. Another nested case-control study by Boursi *et al*[103] carried out in a large population-based database in the United Kingdom, showed similar results, and concluded that past exposure to several courses of penicillin was associated with a slight increase in CRC risk. A recent study found that long-term treatment of *APC*$^{Min/+}$ mice with an antibiotic cocktail composed of vancomycin, neomycin, and streptomycin resulted in gut inflammation with polyposis and cancer progression, perhaps caused by specific changes of the gut microbiota and thinning of the protective mucus layer[104]. On the contrary, Belcheva *et al*[76] observed a decreased number of polyps in both the small and large intestine of C57BL/6 *APC*$^{Min/+}$; Msh2$^{-/-}$ mice treated with ampicillin, metronidazole, neomycin, and vancomycin. The gut microbiota in *APC*$^{Min/+}$; Msh2$^{-/-}$ mice might affect the development of CRC at an early stage, thus acting as a tumor initiator. These contrasting results suggest that the changes of gut bacteria caused by antibiotic treatment can be either detrimental or beneficial in a context-dependent way[105]. Further studies are needed to investigate the role of specific antibiotics in modulating the microbiota response and the relationship with colorectal carcinogenesis.

Diet and anti-inflammatory drugs

A number of epidemiological studies have shown an association between diet, inflammation, and cancer, including CRC[106-109]. So far, there is a lack of preventive dietary recommendations for FAP patients. A nonrandomized prospective pilot study carried out on FAP patients showed that a low-inflammatory diet based on the Mediterranean diet pattern decreased gastrointestinal markers of inflammation, such as C-reactive protein and pro-inflammatory cytokines, through a modulation of the gut microbiota composition[110]. Combination treatment with curcumin and quercetin has been reported to reduce the development of adenomas in FAP. This beneficial effect might be a result of their antioxidative, anti-inflammatory, and antiproliferative properties and the maintenance of a diverse gut microbial community[111-113]. Black raspberry powder supplementation in FAP patients significantly decreased the burden of rectal polyps and reduced staining of the mucosal proliferation marker Ki-67, compared with placebo[114]. The results could have a response to beneficial effects of the anthocyanin and fiber content of the raspberries on the diversity and composition of the gut microbiota[115,116]. Administration of berberine, an alkaloid that can be isolated from many plants including barberry (*Berberis vulgaris*), significantly reduced the development of CRC and restored the gut microbiota community in *APC*$^{Min/+}$ mice fed a high fat diet[117].

There is evidence that the combination of anti-inflammatory drugs and regular endoscopic surveillance can decrease the risk of new adenomas in the rectal stump of FAP patients[118-120]. Administration of NSAIDs and omega-3 essential fatty acids reduced recurrence[121]. Even though long-term therapy with NSAIDs has been shown to increase gastrointestinal and cardiological risk, the use of omega-3 supplements can be expensive for patients[122,123]. NSAIDs may modify the composition and diversity of gut microbiota by inhibiting or facilitating bacterial growth, inducing bacterial cell death, or affecting bacterial metabolism[123]. The bacterial composition of the gut has been shown to change with the type of NSAID administered[124]. Specific shifts in the microbiota such as an increase in *Coriobacteriaceae* or reduction in *Bifidobacteriaceae* and *Lactobacillaceae* after chronic oral treatment with celecoxib, have been associated with a decrease of polyp burden in *APC*$^{Min/+}$ mice[125]. *APC*$^{Min/+}$ mice treated with aspirin showed a decrease in CRC number and load that depended on the

presence of gut microbes. Of interest, *Lysinibacillus sphaericus* in the gut degraded aspirin, thereby reducing its chemopreventive effects in mice. Stool samples from mice treated with aspirin had increased populations of beneficial bacteria such as *Lactobacillus and Bifidobacterium*, and decreased populations of pathogenic bacteria such as *Alistipes finegoldii* and *B. fragilis*[126].

CONCLUSION

The *APC*$^{Min/+}$ mouse model has been widely used to study the underlying mechanisms of colorectal carcinogenesis in FAP. Several studies demonstrated that gut microbiota dysbiosis as a key factor in colorectal carcinogenesis. Indeed, the intestinal microbial community played an important role in the multistep process of the intestinal adenoma-carcinoma sequence, and changes in the gut microbiota were found to be responsible for mucosal barrier injury, low-grade inflammation, activation of the Wnt pathway, and subsequent progression of adenomas. Recent evidence suggests that the modulation of gut microbiota could be a novel therapeutic target in FAP patients. Administration of probiotics, prebiotics, antibiotics, and NSAIDs can prevent the progression of the adenoma-carcinoma sequence in FAP. However, further study of the role of the gut microbiota in the malignant transformation of colorectal adenoma and how microbe-targeted therapies might be useful in preventing CRC development in FAP is needed.

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