Colorectal Cancer

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Introduction to Colorectal Cancer

Colorectal cancer (CRC) is the most common gastrointestinal cancer. It is the second most common cancer in men and third most common in women by incidence. It represents the fourth most common cause of cancer mortality in both sexes worldwide [1]. It is mainly a disease of the western civilization with almost 60 % of the cases recorded in the developed countries. Nearly 90 % of CRCs are sporadic and caused by a complex interplay between genetic, host, and (most importantly) dietary factors. A "western" diet rich in red and processed meat and animal fat and of low fiber content is a well-recognized risk factor [2]. Recent research has further highlighted the key role of microbiota in mediating the dietary risk of colon cancer [3]. In addition, other environmental factors such as alcohol and smoking, inflammatory bowel disease, and obesity increase the CRC risk [4].

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Pathophysiology of Colorectal Cancer

CRC results from a stepwise accumulation of genetic defects and clonal proliferation of mutated colonic epithelial cells in an adenoma-carcinoma transformation sequence of normal colonic mucosa, a protuberant growth known as polyp or adenoma (Fig. 1), and ultimately adenocarcinoma [5]. Mutations of the adenomatous polyposis colon (APC) tumor suppressor gene are the most common (~80 %) genetic defects observed in sporadic CRC. The non-mutated protein product of the APC gene prevents the accumulation of β-catenin protein, its nuclear translocation, and inappropriate activation of gene transcription via the canonical Wnt pathway that promotes cell proliferation [6]. A plethora of carcinogens, e.g., present in tobacco smoke, reach the colonic mucosal epithelium and cause genetic mutations. Poor folate intake among heavy alcoholics and interference of its absorption by alcohol can result in genetic defects from impaired folate-mediated DNA synthesis, DNA methylation, and repair processes [7]. The proliferative influence of high levels of insulin-like growth factors (IGF-1 and IGF-2) on colonocytes during hyperinsulinemia and inflammation is believed to contribute to a higher CRC risk in obesity (see chapter "Metabolic syndrome") [8]. There is also a convincing evidence of a positive association between consumption of red and processed meat and CRC, whereas

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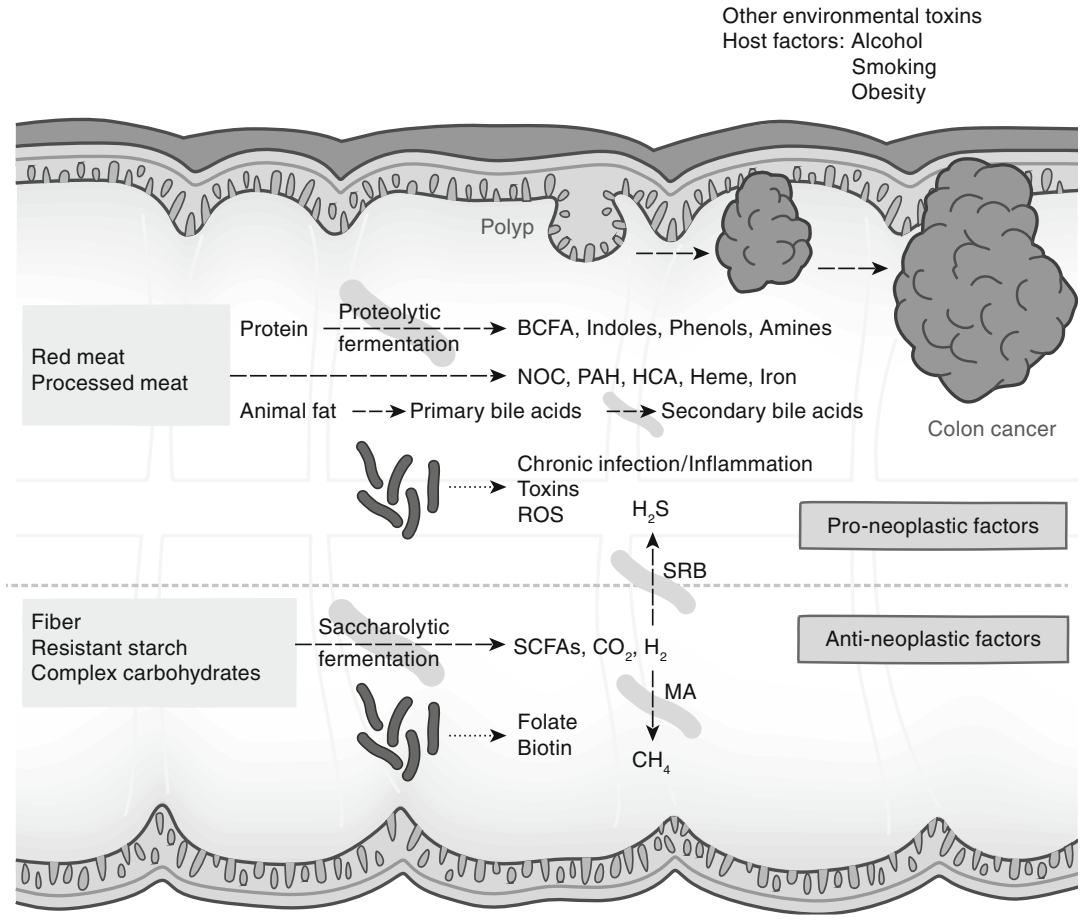

Fig. 1 Dietary factors and microbiotal metabolites mediating the risk of colorectal cancer. The balance between health-promoting and proinflammatory metabolites determines the risk of colorectal cancer (*CRC*). Their production is dependent on both food compositions and (food metabolizing) microbiota. High fiber and resistant starch diet promote saccharolytic bacterial fermentation and enhance production of anti-inflammatory short-chain fatty acids (*SCFAs*), whereas high dietary red meat and fat promote production of proinflammatory proteolytic bacterial fermentation end products and carcinogenic secondary bile acids. *MA* methanogenic archaea, *SRB* sulfate-reducing bacteria, *BCFA* branched-chain fatty acids, *NOC* N-Nitroso compounds, *PAH* polyaromatic hydrocarbons, *HCA* heterocyclic amines, *ROS* reactive oxygen species

dietary fibers appear to be protective (Fig. 1) [9]. Evidence supporting the cancer-protective effect of dietary components such as vitamin D, folate, fish, fruits, vegetables, and selenium is suggestive but limited. Interestingly, colonic microbiota (see chapter "Overview" under the part "Gastrointestinal tract") seem to play a crucial role in mediating the influence of diet on CRC (see below).

Pathophysiologic Role of the Colonic Microbiota and Its Metabolites

Beside its role in regulation of fluid conservation, electrolyte balance, and terminal conduit of undigested human excreta, the colon is inhabited by approximately 100 trillion microbes belonging to a diverse group of microorganisms, termed

microbiome, which holds a rich repertoire of metabolic functions [10]. In a symbiotic relationship, the microbiota are dependent on undigested food residues and in turn produces essential metabolites (see below).

The microbiota include ~800 different bacterial species with over 7,000 strains. Recent advances in molecular identification and characterization techniques have led to a better understanding of the microbiotal composition and appreciation of their metabolic potential [10]. Interestingly, microbial analyses revealed fundamentally different microbiomes among people of different origins, which even allow categorization into human fecal enterotype categories [11].

While ~90 % of protein and carbohydrate are digested and absorbed along the small intestine, residual food is metabolized by the colonic microbiota through fermentation, producing protective and vital metabolites, such as short-chain fatty acids (SCFAs), or vitamins such as folate and biotin that are essential for DNA synthesis and repair. However, the microbiota can also produce toxins and detrimental metabolites such as hydrogen sulfide (H_2S), reactive oxygen species (ROS), and secondary bile acids (BAs) promoting inflammation and neoplastic progression (see below).

Chronic inflammation is triggered and perpetuated by some microbiota through signaling pathways such as induction of Toll-like receptors, upregulation of cyclooxygenase-2 (COX-2), and activation of mitogen-activated protein kinases (MAPKs) that promote proinflammatory cytokine release, cell proliferation, genetic mutation, and neoplastic transformation [12]. It is the fine balance between the beneficial and harmful microbiota and their metabolites that determines the state of health versus disease (Fig. 1). A disturbed microbial composition and function result in a state of dysbiosis, a key predecessor of diseases such as diabetes (see chapter "Diabetes mellitus"), obesity (see chapter Metabolic syndrome), inflammatory bowel disease, and CRC.

Indeed, diet is the cause of over 90 % of gastrointestinal cancers, the risk differing significantly based on dietary habits [13]. Whereas native Africans consume a diet rich in indigestible fiber and resistant starch and low in animal products, African Americans consume more animal protein, red meat, and saturated fat and lower amounts of complex carbohydrates, resulting in a ten times higher CRC incidence [14].

Indigestible fiber, resistant starch, and complex carbohydrates undergo saccharolytic fermentation predominantly in the proximal colon yielding SCFAs (acetate, propionate, and butyrate), ethanol, and gases such as carbon dioxide (CO_2) and hydrogen (H_2; Fig. 1) [15]. Acetate and propionate are the major (~85 %) fraction of SCFAs but are absorbed mostly into the systemic circulation, with acetate being taken up by the liver for cholesterol synthesis and propionate participating in gluconeogenesis [16]. Butyrate, on the other hand, is the most important pluripotent SCFA that exerts its principal actions locally in the colon serving as the chief energy source for the colonocytes, regulator of the epithelial growth and differentiation, and anti-inflammatory and antineoplastic factor [17]. It causes hyperacetylation of histones by inhibiting histone deacetylase and modulates transcription factors to regulate gene expression and cell function [18]. Its actions are also mediated by signaling pathways involving upregulation of peroxisome proliferator-activated receptor-γ (PPARγ), suppression of nuclear factor-κB (NF-κB) activation, and G-protein-coupled receptor signaling [16]. Finally, butyrate plays a critical role in reinforcing the gut mucosal defense barrier by enhancing mucin gene expression and induction of trefoil factors (i.e., secretory proteins with a short trefoil motif involved in mucosal stabilization, protection, and regeneration), antimicrobial peptides, and transglutaminase activity (that cross-links and stabilizes proteins) [19].

On the contrary, undigested protein residues reaching the distal colon undergo proteolytic fermentation by bacteria producing branched-chain fatty acids and inflammatory nitrogenous metabolites such as phenolic and indolic compounds that have been shown to cause colonocyte DNA

damage in experimental models (Fig. 1) [20]. High consumption of red meat promotes proteolytic fermentation by providing large amounts of undigested protein residues. Red meat is also responsible for increasing CRC risk in several other ways. Hydrogen (H_2), produced during fermentation, is generally excreted in the breath (directly or as methane). However, it can also be converted to hydrogen sulfide (H_2S) by sulfide-reducing bacteria using methionine and cysteine from animal protein [21]. H_2S induces mucosal hyperproliferation and free radical-mediated genotoxicity, effects that can be reversed by butyrate [22]. Aromatic amino acids, which are abundant in red meat, undergo bacterial decarboxylation and N-nitrosation resulting in formation of N-nitroso compounds (NOC) [23]. In a rat model, dietary heme was shown to promote colonocyte proliferation by causing epithelial injury, inhibition of apoptosis, and crypt cell hyperplasia, the precursors of carcinogenesis [24]. In addition, meat processing and cooking practices that expose meat to very high temperatures also result in formation of several mutagens (such as NOC, polycyclic aromatic hydrocarbons, and heterocyclic amines) that cause DNA base alkylation and formation of base adducts, biomarkers of chemical carcinogenesis [23, 25].

Finally, high dietary fat increases BA synthesis and consequently BA transition to the colon allowing bacterial conversion to secondary BAs (such as deoxycholic acid and lithocholic acid), which have strong inflammatory properties and cause oxidative DNA damage and genomic instability of the colonocytes [26]. High-fat diet also stimulates delivery of sulfur-rich taurine conjugates to the colon promoting certain detrimental bacterial strains and inducing colitis by proinflammatory T_h1-mediated immune responses and bacterial by-products such as H_2S and secondary BAs [27].

Treatment and Influence on Metabolism

Prevention

In general, adopting a healthy lifestyle with increased physical activity, limited consumption of alcohol, avoidance of tobacco use, and, most importantly, dietary modifications (see below) can mitigate CRC risk.

Dietary Modifications for Minimizing Risk of Colorectal Cancer

In light of the decisive influence of diet on CRC risk, it is prudent to consume a balanced diet that can modulate the microbial composition to produce beneficial metabolites such as butyrate. Enhancing butyrate production can mitigate the mutagenic effects of secondary BAs, proliferative effects of H_2S, and DNA damage induced by red meat [28]. Chlorophyll (present in green leafy vegetables) has been shown to ameliorate the toxic effects of heme [29]. Increasing our dietary fiber, resistant starch, and complex carbohydrate content and moderating red meat and animal fat portions seem to be a simple step for promoting colonic mucosal health. This diet is well tolerated even if patients are used to a more traditional diet. Reduction of red meat does not disturb general metabolism. Our demand for dietary protein, important for our structural and metabolic needs, can quite easily be met by consumption of other protein-rich diets such as white meat, fish, and legumes.

Cancer Screening and Chemoprevention

The adenoma-carcinoma sequence usually takes 7–10 years offering an adequate window period to screen and intervene. At least 60 % of deaths from CRC can be prevented by early detection of precancerous polyps through diligent screening of people who are 50 years or older (or earlier in case of higher risk) using high-sensitivity fecal occult blood testing (meaning detection of blood in the stool), flexible sigmoidoscopy (i.e., an investigation of the rectum and last third of the colon by insertion of a camera mounted on a flexible scope into the anus and its guidance through the rectum into the colon), and/or colonoscopy (or coloscopy, i.e., an endoscopic examination of the large bowel with a flexible tube inserted via

the anus) with the latter allowing the removal of polyps (surgical prevention) [30]. Several pharmacological agents such as aspirin and other nonsteroidal anti-inflammatory agents (NSAIDs), statins, calcium, vitamin D, selenium, and postmenopausal hormone replacement therapy potentially reduce the incidence or recurrence of adenoma (chemoprevention) [4]. Significant associated risks (e.g., gastrointestinal bleeding with NSAIDs) render chemoprevention less attractive for the general population, yet it can be considered when the potential benefits outweigh the risks especially in those with high CRC risk.

Treatment of Colorectal Cancer

Surgery, chemotherapy (including targeted monoclonal antibody therapies), and/or radiotherapy are the common therapeutic modalities, utilized either alone or in combination. Tumor location and stage at diagnosis (local extent, spread to lymph nodes, or distant metastasis) determine the treatment strategy [31]. Surgery is the cornerstone of CRC treatment, and resection can be curative when the tumor is localized to the colon or rectum and sometimes even when isolated metastatic foci in the liver or lung are amenable to resection. Systemic chemotherapy is used in combination with surgery either postoperatively (adjuvant therapy) when regional lymph nodes are involved or preoperatively (neoadjuvant chemoradiotherapy; see also chapter "Breast cancer") to shrink metastatic foci before resection. Chemotherapy alone is used to prolong survival and for palliation in non-resectable advanced or metastatic CRC patients. 5-Fluorouracil (5-FU) in combination with leucovorin, capecitabine, oxaliplatin, and irinotecan and monoclonal antibody therapy targeting vascular endothelial growth factor-A (bevacizumab; see also chapter "Age-related macular degeneration") or epidermal growth factor receptor (cetuximab, panitumumab) are the traditional chemo-immunotherapeutic agents. Better screening and treatment options have helped to improve the 5-year survival rates for CRC to 90 % (local cancer), 70 % (regional spread), and 12 % (distant metastasis) based on the staging at diagnosis [32].

Perspectives

Our ability to manipulate microbiota and their metabolic profiles in order to minimize CRC risk through administration of probiotics needs to be validated further through rigorous research. Moreover, better understanding of the molecular characteristics of CRC and their variations that can affect prognosis and response to treatment and development of novel-targeted antibody therapies in the present era of "personalized medicine" could enhance therapeutic success rates immensely. Advances in minimally invasive surgical techniques can help to improve tumor resectability and minimize surgical complications.

With the pandemic of obesity, the incidence rate of CRC is expected to rise. However, a preemptive strategy of addressing and mitigating the risk factors complemented by a diligent screening strategy can help to decrease the incidence of CRC.

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