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Mini-review

Gastrointestinal cancers: Influence of gut microbiota, probiotics and prebiotics

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ABSTRACT

Cancers of the gastrointestinal (GI) tract continue to represent a major health problem, despite progress in therapy. Gut microbiota is a key element related to the genesis of GI cancers, countless papers addressing this burning issue across the world. We provide an updated knowledge of the involvement of gut microbiota in GI tumorigenesis, including its underlying mechanisms. We present also a comprehensive review of the evidence from animal and clinical studies using probiotics and/or prebiotics in the prevention and/or therapy of GI tumours, of GI cancer therapy-related toxicity and of post-operative complications. We summarize the anticarcinogenic mechanisms of these biotherapeutics from in vitro, animal and clinical interventions. More research is required to reveal the interactions of microflora with genetic, epigenetic and immunologic factors, diet and age, before any firm conclusion be drawn. Well-designed, randomized, double blind, placebo-controlled human studies using probiotics and/or prebiotics, with adequate follow-up are necessary in order to formulate directions for prevention and therapy.

1. Introduction

Cancers of the gastrointestinal (GI) tract continue to represent a major health problem, despite progress in therapy, accounting for 25% of all cancers and 9% of all causes of cancer death in the world [1]. In 2005, the worldwide burden of oesophageal cancer was estimated to be 500,000 new cases. Gastric cancer (GC) is the fourth most common cancer and the second cause of cancer-related death worldwide, accounting for nearly 1,000,000 new cases annually and over 850,000 deaths at the same time [2–4]. Overall GC incidence is constantly decreasing, possibly due to the fall in the H. pylori (HP) prevalence [5]. Neoplasms of the small intestine are rare throughout the world, global incidence ranging from 0.3 to 2.0 per 100,000 [6]. Colorectal cancer (CRC) is the third most frequent cancer worldwide (more than 1 million new cases/year) and the fourth most common cause of cancer death, with about 500,000 deaths annually [4].

The multi-steps mechanisms associated with GI cancer prevention and development are largely unknown, being the subject of much research. GI cancers are considered to be multifactorial diseases, the end result of complicated relationships between genetics, epigenetics, immunity, environment (including geographical area and socio-economic status), diet and lifestyle, all of which could interact with the GI microflora, altering its profiles and functions during the tumour genesis and growth [5,7].

2. Gut microbiota

2.1. Composition and beneficial activities

The normal intestinal microbiota represents a complex, dynamic, and diverse collection of microorganisms, which usually inhabit the GI tract [8,9]. Normally, between this flora and the human host a mutually beneficial long-term symbiotic relationship is established, where the host contributes essential nutrients necessary for the survival of the microbiota and the latter fulfils multiple roles for the host [9]. The development of sophisticated culture independent methods allowed the detection of the structures and functions of microbial communities, as well as their interactions with the habitats they occupy (Rev. in [9]). Human gut contains 10 times more bacteria (10^{14}) than eukaryotic cells in the entire human body. This gut flora has around 100 times as many genes in aggregate as there are in the human genome [10]. According to the metagenomic approach, humans are actually "superorganisms", whose genome is the sum of genes of their own genome and of the microbiome [11]. A complex metagenomic study showed that gut microflora comprises 1000–1500 species and each individual has at least 160 such species, which are also largely shared [10]. The most frequent phyla are represented by: *Firmicutes*, 30.6–83% *(Clostridium, Ruminococcus, Eubacterium, Dorea, Peptostreptococcus, Peptococcus, Lactobacillus – L)*; *Bacteroidetes*,

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8–48% (*Bacteroides*); *Actinobacteria,* 0.7–16.7% (*Bifidobacterium – BF)* and *Proteobacteria*, 0.1–26.6% (*Enterobacteriacee*) [9,12,13]. The content of bacteria increases from mouth (less than 200 species) to the colon (bacteria reaching 10^{10}–10^{12}/g of luminal content, with a predominance of anaerobes) [9]. The quantitative and qualitative variations along the length of the GI tract are due to host factors (pH, transit time, bile acids, digestive enzymes, mucus), non-host factors (nutrients, medication, environmental factors) and bacterial factors (adhesion capacity, enzymes, metabolic activity) [14].

Among the beneficial activities of the gut flora on human host, many are related to cancer protection (Rev. in [9]): control of the intestinal epithelial cell differentiation and proliferation; growth and development of the epithelial barrier [8]; apical tightening of the tight junctions; protection against pathogenic species; development/modulation of gut-associated lymphoid tissue (including host innate immune system, with the important roles of NOD-like receptors and Toll-like receptors – TLRs); fermentation of nondigestible carbohydrates to produce short-chain fatty acids – SCFA; biliary acids metabolism; xenobiotics and dietary carcinogens degradation [15]. The most important SCFA is butyrate, which regulates cell growth and differentiation (inhibiting transformed cell growth while encouraging reversion of cells from a neoplastic to a non-neoplastic phenotype), inhibits human colon carcinoma cell proliferation, and induces apoptosis in human colon carcinoma cells, colon adenoma, and colon cell lines [16,17]. Anticarcinogenic effects of butyrate include expression of differentiation markers (alkaline phosphatase) [18] and of the host's glutathione-S-transferases and other stress response genes, as well as suppression of cyclooxygenase-2 expression (Rev. in [19]). In addition, butyrate alters the epigenome through inhibition of histone deacetylases [20].

2.2. Microbiota and GI cancers

Most studies have been focused on GC and (especially) CRC. The effects of microbiota on other segments of the GI tract (oesophagus, small bowel) are unclear and further studies are required.

Oesophageal adenocarcinoma (OAC) is a consequence of long-term gastroesophageal reflux disease (GERD), often through progression to Barrett's oesophagus (BO) (Rev. in [21]). A recent meta-analysis of 19 studies involving over 1700 cases and 5600 controls showed that there was an inverse relationship between the presence of HP in the stomach and OAC, this effect appearing to be essentially exclusively related to CagA-positive strains. The meta-analysis also revealed that there was no relationship of HP with *oesophageal squamous* cell carcinoma [21,22].

GC has been related mostly to HP, considered a type I carcinogen agent for adenocarcinoma (AC) and mucosa-associated lymphoid tissue (MALT)-lymphoma. The development of HP-related AC follows Correa's hypothesis [3]. HP eradication could lead to prevention of GC in 70–80% of cases [23]. Studies on HP-infected patients with gastric MALT-lymphoma have shown that, after successful eradication, patients heal completely [5].

Small intestine cancers have been related to chronic inflammation and immune dysfunction (especially Crohn's disease and celiac disease) and also to polyposis syndromes. Given the contrasting incidence of AC in the small and large bowel, other factors may be also involved: differences in microbial density and taxonomy of anaerobic microorganisms in the fecal stream, enterohepatic metabolism of bile acids and rate of intestinal transit (Rev. in [6,24]).

Sporadic *CRC* represents 85–90% of all CRC and will be addressed in this topic. There is mounting evidence that colonic microbiota is involved in tumorigenesis, its structure and characteristics being significantly altered in CRC, precancerous lesions, and high-risk population compared with healthy controls (HC) and low-risk population [7]. However, it cannot be always clearly ascertained whether these modifications are causally related to tumour development or are a consequence of tumour-induced changes [9,25]. The cytotoxicity/genotoxicity of the microflora in CRC was demonstrated by using fecal extracts from HC ("fecal water" – FW) [26]. FW cytotoxicity determines mucosal cell proliferation [27], possibly through secondary bile acids [28] and produces DNA damage (genotoxicity) [29], proving that carcinogens exist in the colonic lumen. Genotoxicity has been significantly associated with FW from people on a diet high in fat and meat, but low in fibers (considered to be of high-risk for CRC), as compared to a diet low in fat and meat [26]. Another strong argument supporting the involvement of gut microflora in CRC genesis comes from animal studies: under germ-free (GF) conditions, colitis and tumour formation are significantly reduced or do not appear, compared with monoassociated and conventional animals [30,31]. In addition, tumour free GF rats exhibit increased natural killer cells, cytotoxic T lymphocytes, and B cells in peripheral blood, indicative of a better anticancer immune response. Azoxymethane-treated interleukin (IL)-10-/- mice develop colitis-associated CRC in the presence of *Bacteroides vulgatus*, whereas GF mice do not [32].

Microbiota could contribute to CRC via altered composition of the components (dysbiosis) [33], harmful properties of some bacteria, shift in local distribution of communities, and change in bacterial metabolic activity [9,34]. Many factors can alter the GI ecosystem, including antibiotics, psychological and physical stress, radiation, modified peristalsis, diet, etc. [35].

2.2.1. Gut bacteria/dysbiosis associated with GI cancer

Most studies (in addition to the above-mentioned papers) have been performed in CRC.

Until recently, there has been no research on the diversity of oesophageal microbiota in patients suffering from *oesophageal squamous* or *adenocarcinoma* [36]. A more recent study compared the oesophageal microbiota of patients with GERD, BO, *OAC* and controls. There was a significant decrease in bacterial counts in the GERD and BO groups for all genera except Campylobacter, which colonised GERD and Barrett's patients in increasing numbers. Campylobacter concisus was the dominant species. However, this relationship was not seen in the cancer group. Significant increases in IL-18 were seen in GERD and BO colonised by Campylobacter [37]. The role of IL-18 in OAC has not been investigated yet; however, a correlation between the serum IL-18 levels and stage of disease in *squamous carcinoma* was found earlier [38].

In a recent study, gastric microbiota from patients with *GC* revealed a complex bacterial community that was not significantly different from controls. A relatively low abundance of HP was found, GC microbiota being dominated by different species of the genera *Streptococcus, L, Veillonella* and *Prevotella*, whose role in development of GC remains to be determined [39,40].

There are suggestions that infections with HP and Campylobacter jejuni are related to the risk of developing *lymphoma of the small intestine*, especially immunoproliferative small intestinal disease (Rev. in [6,24]). It has been proposed that the small intestinal bacterial overgrowth might increase the risk of *small bowel adenocarcinoma* development, since intestinal anaerobic bacteria possess enzymes (β-glucuronidase, b-glucosidase, sulfatase, reductases, and decarboxylases), which act on various substrates (bile acids, fatty acids, etc.) and might produce carcinogenetic agents [41]. However, research on this area is scarce and the evidence is too limited; further studies are necessary to clarify the role of the microbiota in the genesis of small bowel cancer.

Bacteria associated with *animal-CRC* are listed in Table 1. In mice, *Mitsuokella multiacida, Clostridium butyricum or BF longum* have been associated with higher incidence of colonic adenoma (68% in each case), as compared with *L acidophilus* (30%) [42].