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Microbiome in GI cancer

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Abstract: Neoplasms are one of the main causes of mortality worldwide. Hepatocellular carcinoma (HCC), oesophageal, gastric, and colorectal cancer represent malignancies with major incidence and impact of the gastrointestinal tract. Unfortunately, patients are often diagnosed with advanced stage disease and this is why our aim should be to implement screening and prevention strategies in order to reduce global cancer-related mortality. Human microbiota is defined as a mix of bacteria, eukaryotes, viruses, and archaea that live in our body; these microorganisms interact with immunological, metabolic, endocrinological, and neurological networks contributing to their modulation, through the production of active metabolites. Several studies have shown a correlation between human gastrointestinal (GI) cancers and dysbiosis defined by the qualitative/quantitative alterations of microbiota, but the exact mechanism through which microbiota is able to interfere with our networks and promotes carcinogenesis has not yet been well defined. Nevertheless, we know that H. pylori acts as a risk factor for gastric cancer, while hepatitis viruses C and B represent a trigger for HCC. Following these examples, many researchers hypothesized that gut microbiota may promote GI cancers, through different mechanisms, such as chronic inflammation, promotion of oxidative stress, alterations of immune response and disruption of body homeostasis then pushing cells towards a path of degeneration. In this review, we analysed studies published in 2019 exploring the role that the human microbiota plays in the genesis and progression of GI tract neoplasms. We also explore if and how microbiota interacts with anti-cancer drugs pharmacodynamic and pharmacokinetics during the drug resistance process.

Keywords: Cancer, Carcinoma, Microbiota, Dysbiosis, Gastrointestinal, Gastric, Oesophageal, Immune checkpoint in-hibitors.

INTRODUCTION

Gastrointestinal (GI) tract neoplasm mortality accounts nowadays for up to 40% of cancer related death worldwide[1]. Unfortunately, many patients present at an advanced disease stage at the time of diagnosis, making it difficult to initiate traditional therapies. Another problem is related to the occurrence of anti-cancer-drug resistance, which has become one of the most important challenges in the medical field. Pharmacological resistance is classified into primary and secondary resistance; the first is also called innate resistance and usually occurs 3-6 months after the beginning of therapy and is due to intrinsic conditions of cancer cells and microenvironment[2]. The second appears after a period of initial pharmacological response, usually after 18-36 months from the beginning of the therapy. For anticancer drugs to be effective, they need to pass through the tumour vascular system, interact with microenvironment, and finally reach the target cells at potentially lethal concentration. In this complex process the cancer microenvironment, including the microbiota, plays a crucial role. Several studies[3-5], in fact, reported how the microbiota could modulate cancer cell biology promoting inflammation, carcinogenesis, stimulating cancer cells growth, and drug resistance. Human microbiota is comprised of a vast number of microorganisms that live in our body; it includes bacteria, eukaryotes, viruses, and archaea. *Firmicutes* and *Bacteroidetes* are the most represented bacterial phyla followed by *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, and *Fusobacteria*.

Through dense bidirectional interactions with immunological, endocrine, metabolic, and neurological systems, the microbiota maintains homeostasis and ensures body equilibrium. Different body sites contain distinct microbial communities that promote various functions including nutrient absorption, metabolism modulation, and immune responses[6]. The GI tract harbours around 10^{14} microorganisms representing a significant microbial reservoir for microorganisms which are in direct contact with the host. It has been shown that intestinal dysbiosis (qualitative or quantitative alterations in the microbiota) influence our health and contribute to the occurrence of many diseases, such as asthma and allergic diseases[7], inflammatory bowel disease (IBD)[8,9], obesity[10,11], diabetes mellitus[12], neurodegenerative, and psychiatric disorders[13,14]. In the past years, researchers have focused their attention on defining the relationship between microbes and cancer. It is well-known that some specific microorganisms act as carcinogen, such as *H. pylori* in gastric cancer and hepatitis virus B and C for HCC[15,16] but what do we really know about the precise relationship between microbiota and cancer? In this review, we will illustrate the results of studies published in the last year exploring if and how microbiota could trigger tumorigenesis and regulates cancers biology. In addition, we want to analyse how it will be possible to overcome anti-cancer drug resistance through microbiota modulation in the next future.

Microbiota in Oesophageal and Gastric cancer

Introduction of advanced molecular techniques, such as high-throughput DNA based pyrosequencing, metagenomics analysis and 16S rRNA sequencing, have made it possible to define a more complete picture of the gut microbiota. Through these techniques, it is possible to identify the presence of microorganisms even in some niches previously considered as sterile. Every day, many microbes are ingested primarily through the process of consuming food and liquid. Immediately after the oropharynx the oesophagus is the first organ of the GI tract that interacts with these microorganisms. It is possible to recognize two distinct groups of oesophageal microbial communities: type I and type II. Type I is associated with a normal oesophagus and is composed by Gram-positive bacteria, especially *Streptococcus species*. Conversely, in type II microbiota there is a prevalence of Gram-negative bacteria and it is associated with many oesophageal diseases, such as gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EOE), and Barrett's oesophagus (BE). Several studies showed how oesophageal dysbiosis, defined as a microbiota shift from type I to type II bacteria, is related to oesophagus pathologies. Liu et al[17] for the first time, linked a specific microbiota composition with oesophageal carcinoma prognosis. They demonstrated that dysbiosis with a shift to a higher abundance of *Prevotella* and *Streptococcus* was found in tissue samples from oesophageal carcinoma after surgery and inversely correlated with patient survival. Lv et al[18] analysed the mechanisms between dysbiosis and carcinogenesis. The microbiota alterations lead to persistent chronic inflammation that may promote genotoxins production that could cause genomic damage. Also, the microbiota interacts with the human host immune system and, through the activation of specific pathways (i.e., the LPS-TLR4-NF-κB pathway) may contribute to malignant transformation. However, they conclude that further studies are needed to better understand cancer's pathogenesis.

The stomach has been considered for long an almost sterile environment, until the discovery of *H. pylori*[19]. However, recent studies showed that our stomach is a complex ecosystem in which many microbial species are able to co-exist. The healthy adults' gastric microbiota is mainly comprised of *Prevotella, Streptococcus, Veillonella, Rothia, Pasteurellaceae, Fusobacterium, Actinomyces, Neisseria, Haemophilus* and *Porphyromonas*, which are equally represented in the different gastric regions. It is widely accepted that the gastric microbiota is modulated by several factors, including diet[20], use of antibiotics and probiotics, long-term use of proton pump inhibitors (PPIs)[21] or H2-antagonists and *H. pylori* infection[22]. Whether geographic origin may influence human gastric microbiota composition is still a matter of debate. The key point of the most recent research on microbiota and gastric cancer (GC) concerns the interactions between *H. pylori* and the other bacteria composing this complex ecosystem. The precise interaction between *H. pylori* and gastric microbiota is not fully understood; however,

most recent data suggest that while *H. pylori* colonization induces specific changes in gastric microbiota composition, gastric dysbiosis appears to influence both *H. pylori* pathogenicity/virulence and its capacity to colonize the stomach. It is very likely that a two-way interaction exists, in which *H. pylori* favors the growth of specific bacteria, while gastric dysbiosis may promote a favorable environment for *H. pylori* virulence and colonization. Defining specific steps in gastric microbiota carcinogenesis in the light of this complex interaction requires in-depth studies. In addition, the alterations of the microbiota phenotypes in the perioperative phase of patients with GC are a field of great interest. According to a recent study conducted by Liang et al[23] the relative abundances of *Akkermansia, Esherichia/Shigella, Lactobacillus*, and *Dialister* were significantly changed in the perioperative period. Remarkably, higher abundances of *Escherichia/Shigella*, *Veillonella*, and *Clostridium* XVIII and lower abundances of *Bacteroides* were observed in gut microbiota of overall patients affected by GC compared to healthy controls.

Microbiota in Colorectal cancer

Colorectal cancer (CRC) represent the third most common tumor in males and the second in females worldwide. Genetic alterations are implicated in the minority of CRC cases constituting only 5%, such as familial adenomatous polyposis (FAP), Lynch syndrome (non-polyposis hereditary colorectal carcinoma [HNPCC]), hereditary breast, and ovarian cancer syndrome[24,25]. The majority of CRC are classified as sporadic. It is possible to identify some conditions that predispose to malignancy and require a closer surveillance as personal or family history of sporadic CRCs or adenomatous polyps, IBD and patients that underwent abdominopelvic radiation for other malignancies[26]. Even though the global incidence of CRC is increasing there is a decrease of global cancer mortality thanks to prevention strategies (fecal occult blood test and screening colonoscopy)[27]. It is known that CRC pathogenesis progresses through several steps, which include hyperplasia, low/high-grade dysplasia, and neoplasia. The intestinal microenvironment, which includes its resident gut microbiota, contributes to determining an inflammatory state that pushes normal intestinal epithelial cells to neoplastic degeneration[28]. Any change of the GI eubiotic status, possibly induced by diet, inflammatory disease or antibiotic therapy may then activate the dysplasia-cancer sequence of events. Several theories[29] have been proposed to correlate CRC with gut microbiota alteration, although the complexity of this topic is still far from drawing any conclusive statement. Some years ago, an interesting study[30] introduced the dynamic "bacterial driver-passenger" model. According to this model, there are specific bacterial populations (drivers), presenting pro-carcinogenic characteristics which are able to promote the progression of the disease through DNA impairment in the intestinal epithelial cells. Most recent studies highlight the role of microbially-induced chronic inflammation, specifically chronic unchecked activation of the immune system, thereby creating a proinflammatory activation, which may favor the development and progression of CRC. Tumorigenesis could then progress by preventing apoptosis, generating mutations or triggering angiogenesis, and cell proliferation[31]. As a result, an up-regulation of IL-17C from CD3 cells, an up-regulation of TLRs (TLR2), a down-regulation of their inhibitors (TOLLIP) and the deficiency in TGF-β signaling pathways were recently described in CRC cases. Zhang et al[32] used high throughput sequencing of fecal samples to define microbiota composition in 130 CRC patients and showed that plasma C-reactive protein (CRP) and soluble tumor necrosis factor II (sTNFR-II) increased as the adenoma-carcinoma sequence progressed. Finally, the intestinal microbiota may be responsible for the production of toxic or specific genotoxic microbial metabolites able to influence the occurrence of CRC. To sum up, colonic microbiota plays a major role in CRC pathogenesis, but also cancer alters colonic microbiota, meaning that there is a bidirectional relation between them. Some studies also showed a significant relationship between effectiveness of CRC therapy and microbiota composition, considering the double role of microbiota by either enhancing or reducing the efficacy of CRC treatment. However, available evidence[33] is still not sufficient and new hypotheses are generated day by day. Future studies will probably allow to better identify the characteristics of the microbiota alterations, according to the molecular subtypes of CRC.

DISCUSSION

Several studies[34] have confirmed connections between gut microbiota changes and occurrence of GI tumours. As we know there are increasingly and innovative therapeutic strategies against cancer, but the "classic" ones remain surgery, chemotherapy, and radiotherapy. However, new therapeutic strategies could be used in patients with advanced tumours that do not respond to conventional therapies. Immunotherapeutic agents represents a good weapon to fight tumours; immune checkpoint inhibitors (ICIs) which target the programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) axis have changed the therapeutic landscape in epithelial tumours, including melanoma, non-small cell lung cancer, and renal cancer[35-37]. Primary resistance to ICIs is common and remains unpredictable with a significant body of evidence accumulating to highlight the microbiota as a major influence on resistance. Antibiotic-induced dysbiosis was recently associated with worse clinical response from immune checkpoint inhibitors in patients with cancer[38,39]. Moreover, preliminary studies also showed that patients with advanced renal cell carcinoma (aRCC), whose gut microbiota shows a higher richness and increased specific genera and species (e.g., *Akkermansia muciniphila, Enteroccoccus hirae*, or *Alistipes*), are more likely to respond to treatment with ICIs and to experience longer progression-free survival compared to other patients. In addition, germ-free mice that received fecal transplant from patients with aRCC responding to anti PD-1 therapy had significantly reduced tumor growth when subsequently challenged with renal cancer cells compared to those receiving fecal transplant from non-responder patients[40].

Different options are available to therapeutically modulate the gut microbiota[41], they include diet, antibiotics, prebiotics and probiotics, and faecal microbiota transplantation (FMT)[42-44]. Based on its success in treating various conditions, there is a strong rationale to design studies to test whether FMT may be also applicable to prevent CRC. Similarly, there is also a rational to test the effect of FMT in cancer patients undergoing immunomodulatory therapy to enhance their final response to the therapy.

CONCLUSIONS

The gut microbiota assessment and modulation, through modification of the diet or the use of pre- and probiotics and FMT could represent in the next future a way to prevent and treat GI neoplastic diseases[45-48].

Author Contributions

All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict of Interest

No potential conflicts of interest. No financial support.

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