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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

Implication of gut microbiome in immunotherapy for colorectal cancer

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Abstract

Colorectal cancer (CRC) constitutes the third most frequently reported malignancy in the male population and the second most common in women in the last two decades. Colon carcinogenesis is a complex, multifactorial event, resulting from genetic and epigenetic aberrations, the impact of environmental factors, as well as the disturbance of the gut microbial ecosystem. The relationship between the intestinal microbiome and carcinogenesis was relatively undervalued in the last decade. However, its remarkable effect on metabolic and immune functions on the host has been in the spotlight as of recent years. There is a strong relationship between gut microbiome dysbiosis, bowel pathogenicity and responsiveness to anti-cancer treatment; including immunotherapy. Modifications of bacteriome consistency are closely associated with the immunologic response to immunotherapeutic agents. This condition that implies the necessity of gut microbiome manipulation. Thus, creatingan optimal response for CRC patients to immunotherapeutic agents. In this paper, we will review the current literature

observing how gut microbiota influence the response of immunotherapy on CRC patients.

Key Words: Colorectal cancer; Gut microbiome; Immunotherapy; Checkpoint inhibitors; Tumor microenvironment

Core Tip: Colorectal cancer (CRC) constitutes the third most frequent malignancy. CRC is a complex, multistep process. The impact of environmental factors as well as the disturbance of the gut microbial ecosystem is associated with CRC development. There is a strong relationship between the gut microbiome and resistance to immunotherapy.

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INTRODUCTION

Colorectal cancer (CRC) constitutes the third most frequently reported malignancy in the male population and the second most common in women in the last several decades, based off GLOBACAN epidemiological data[1]. Colon carcinogenesis is a complex, multifactorial event composed of genetic and epigenetic aberrations, which additionally causes the disturbance of gut homeostasis resulting from gut microbiota modifications[2]. The microbiome constitutes a multiplex ecosystem of microorganisms located in the gastrointestinal tract of many species, including humans[3].

The relationship between the intestinal microbiome and disease development, including carcinogenesis, was relatively undervalued in the last decade. However, the interrelation of gut microbiota with the main functions of the host has recently been in the spotlight[4]. The digestive tract contains the largest amount of microbiota colonization among other anatomical regions, accounting for approximately 70% of the human microbiota make-up[5], including viral and bacterial microorganisms, archaea and fungi[6,7]. The proximal parts of the GI tract, including the stomach and small intestine, present few microbiota species whereas the distal part, the colon, presents the largest number of species (microorganisms) in the colonic substance[7]. The six main phyla of the gut microbiome (90% of the population) include[8]: Bacteroidetes, Actinobacteria, Firmicutes, Proteobacteria, Verrucomicrobia, and Euryachaeota[9]. Of all the genera found in the human gut, Bacteroides makes up the majority of the population (30%)[10], implying its significant effecton the human functional system. Additionally, many genera from the Firmicutes phylum compose a high amount of the intestinal substance, such as lactobacillus, Clostridium, Faecalibacterium, Eubacterium and Ruminococcus[11]. The application of metagenomics on fecal specimens has given the opportunity for microbiome quantification and analysis, and potentially its use as a potent diagnostic tool[12].

LITERATURE SEARCH

PubMed was searched to identify studies on gut microbiome, immunotherapy and CRC. PubMed and *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) were searched to identify studies on gut microbiome, immunotherapy and CRC. The literature review was completed on February 28, 2022. The following search terms were applied: "Colorectal cancer", "Immunotherapy", "Checkpoint inhibitors," "Tumor microenvironment," and "Gut microbiome". The reference lists of all related articles were screened for other potentially relevant studies. The search citation analysis is presented in the reference list. Finally, the authors similarly reviewed the reference lists of eligible articles to identify further eligible articles, books and other forms of publication. Publications that are written in any other language other than English were excluded. Publications of abstracts were also excluded.

THE FUNCTIONAL ROLE OF THE GUT MICROBIOME

Gut microbiota exhibits diverse functions in the human organism and are responsible for many metabolic processes and biosynthesis. Vitamin synthesis constitutes one of the key roles of gut microbiota, such as riboflavin, vitamin B1, biotin, vitamin K and cobalamin[13]. They also have a crucial role in non-digestible carbohydrate metabolism; to transform them into short-chain fatty acids (SCFAs), such as butyric acid, acetic acid and propionic[14], which are produced by the main phyla of bacteriome, this includes Bacteroidetes and Firmicutes[15]. Alteration of the above metabolic process leads to modification of the fatty acid production and overall metabolic imbalance[16]. Along with their involvement in vitamin and short fatty acids synthesis, they take part in bile acid production[17]. Neuromodulators are also produced by gut microbiota, with a significant implication for the gut-brain axis, which includes the peripheral and central nervous systems as well as the enteric nervous system [18]. Many neurological and psychiatric disorders are closely connected with the gut microbiome. This can occur because they are responsible for synthesizing many pro-inflammatory cytokines, amyloids and liposaccharides[18]. Based on metagenomics, genome disturbance and dysbiotic flora can cause a predisposition to develop a number of malignancies[19], including non-neoplastic disorders, such as atopy, functional intestinal disturbances, like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and metabolic syndrome[20,21].

There is a strong relationship between gut microbiome dysbiosis and bowel pathogenicity. In the case of the bowel, functional disorders such as IBS have many studies illustrating an altered consistency of the bacteriome, with both an increase or decrease in the quantity of many bacteria. It is specifically observed as an aberrant increase of *Ruminococcus, Firmicutes*, and *Clostridium spp*. with an abnormal decrease of *Ruminococcusalbus* and *callidus, Bacteroidesfragilis* and *bulgatus*[18]. Additionally, the overproduction of SCFAs that deregulate the secretion of serotonin from the enteroendocrine cells leads to increased bowel movements and fermentation. This causes the symptomatology associated with meteorism[22]. Patients who suffer from organic bowel diseases, such as IBD, Ulcerative colitis and Crohn's disease (CD) have been observed to have an altered microbiome. The modification of the gut microbiome is closely associated to dietary habits[23]. Patients with CD specifically demonstrate increased amounts of *Neisseria caeacorrodens*, *E. coli* and proteobacteria[24], while enhanced amounts of fungal species such as *Candida albicans*, *Cyberlindnera jadinii* and *Saccharomyces cerevisiae*can also be observed[25]. In addition, a decreased number of some bacterial taxa, such as Firmicutes, *Faecalibacterium prausnitzii*, Bacteroidetes and Roseburia, is observed[26]. Dietary habits that include a high amount of fruit and vegetable consumption can lower the risk for developing CD[27].

Intestinal epithelial cell sare closely interrelated with the immune system *via* the existence of goblet and Paneth cells and their products. Goblet cells are located in intestinal mucosa and have a crucial role in producing mucus. Paneth cells are located in the crypts of Lieberkühn, secreting various immunomodulatory peptides with antimicrobial qualities[28]. Moreover, bacterial metabolites also take place in immune responses *via* the production of SCFAs and are closely associated with innate immunity and antibody production[29].

Immunotherapy constitutes a significant therapeutic option, including immune checkpoint inhibitors, cancer vaccines and chimeric antigen receptor-T cells[30]. This treatment modality makes use of the immune responses to create an anti-neoplastic effect. The main therapeutic agents include the following monoclonal antibodies: (1) Anti-cytotoxic TT-lymphocyte antigen-4 (anti-CTLA-4); (2) Anti-programmed cell death 1 ligand 1 (anti-PD-L1); and (3) Anti-programmed cell death protein 1 (anti-PD-1)[28,31]. The principal advantage of immunotherapeutic agents includes their aimed action on malignant cells appears in Figure 1.

This therapeutic modality is currently selected as an anti-cancer treatment specifically in cases of tumors that are characterized by high microsatellite instability (MSI-H)[32]. Tumors that present MSI-H arise from a defective DNA mismatch repair (MMR) mechanism that leads to the accumulation of genetic mutations. This can be seen in the case of mutant MSH2, PMS2, MSH6 and MLH1. Or by epigenetic aberration, such as genome hyper-methylation[33]. There are many reports that gut microbiota influences the response to anti-cancer treatment including immunotherapy[34]. It is observed that a significant number of CRC patients that lacked a specific taxa in their bacteriome, presented a limited response to immunotherapy agents such as anti-PD1.This condition implies the use for more personalized anti-cancer treatments that can prove to be potent. In this paper, we review the current literature on how gut microbiota influences the response of CRC patients to immunotherapy[35].

THE ROLE OF MICROBIOME IN COLON CARCINOGENESIS

There are many studies about the implication of gut microbiota in immunotherapeutic agents including immune checkpoint inhibitors for melanoma. Fewer studies exist about its role in CRC treatment management.

Modifications in the gut microbiome and microbial metabolites have been involved in many pathological processes and diseases, including colon carcinogenesis[36]. Many intestinal bacterial

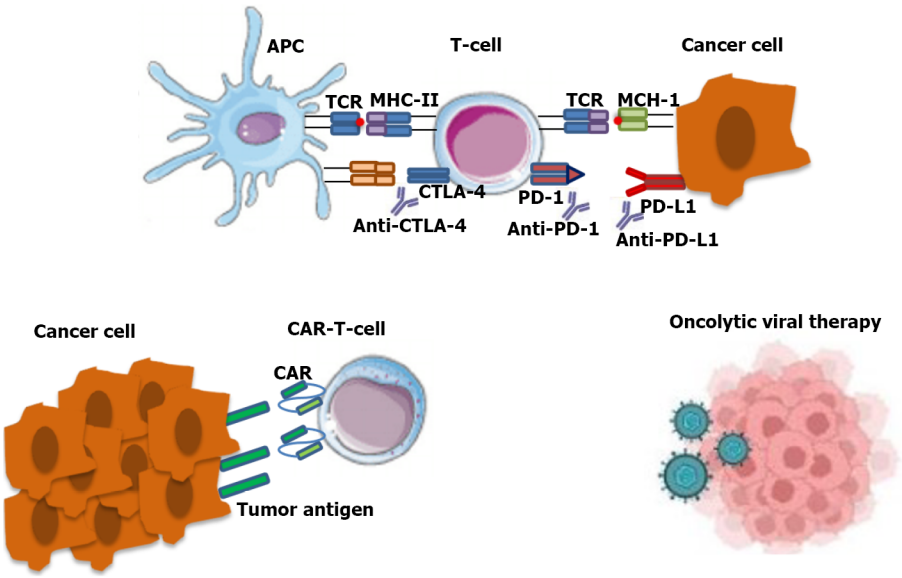

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Figure 1 Mechanism of action of both anti anti-cytotoxic TT-lymphocyte antigen-4 and anti-programmed cell death protein 1/programmed cell death 1 ligand 1 check point inhibitors. In the tumor microenvironment, antigen-presenting cells (APCs), such as dendritic cells processed specific tumor peptides (TAAs) and complexed them to major histocompatibility complex (MHC) molecules. Then, APC migrated to T cell-dependent areas of tumor presented TAA to naïve or quiescent T cells. Checkpoint inhibitor, such as anti-programmed cell death protein 1 (anti-PD-1)/anti-programmed cell death 1 ligand 1 (anti-PD-L1) and/oranti-cytotoxic TT-lymphocyte antigen-4 (anti-CTLA-4) on tumor cells, lead to re-activation of immune responses. The anti-PD-1 or anti-PD-L1 blocking by monoclonal antibodies (as nivolumab, pembrolizumab for PD-1 or atezolizumab for PD-L1) ipilimumab restore CD28 pro-activity signaling and restore effective anti-tumor T lymphocyte responses. The anti-CTLA-4 blocking by monoclonal antibodies as ipilimumab restore CD28 pro-activity signaling and result in effective anti-tumor T lymphocyte responses. The binding of PD-L1 to PD-1 and CTLA-4 to B7 keeps T cells from killing tumor cells in the body. Blocking the binding with an immune checkpoint inhibitor allows the T cells to kill tumor cells (upper panel).Chimeric antigen receptor (CAR) T cells are T cells that have been genetically engineered to produce an artificial T cell receptor for use in immunotherapy. CARs are receptor proteins that have been engineered to give T cells the new ability to target a specific protein (lower panel).

products have been implicated in malignant states in the intestinal tract[37]. Several studies demonstrate the presence of an altered microbiome either in CRC patients' fecal specimens or in malignant tissues compared to healthy patients[38]. These alterations in the microbiome which take place in the initial steps of CRC development can be utilized as predictive biomarkers as well as microbial diagnostic gene markers. This can be utilized in patients with an increased risk of developing colon adenomas that can potentially lead to CRC[39].

Environmental factors have a high influence on the gut microbiome along with idiosyncratic factors [40] which subsequently induce carcinogenesis and CRC development *via* the overgrowth of particular microbial species in the flora[41]. The formulation of colonic microbial substances is closely related to modifiable factors such as eating behavior and style of living[42]. While there is a key role in the metabolism of nutrients[43], there is also a diversity of environmental risk factors that are associated with colorectal carcinogenesis such as obesity, tobacco use, alcohol consumption and prepared meat products[44].

Many studies demonstrate the implication of specific bacterial taxa in carcinogenesis, such as *Enterococcus faecalis, Helicobacter hepaticus*, *Bacteroides fragilis* and *Fusobacterium nucleatum*. The products of the previously mentioned microbes lead to genomic alterations[45]. While in the case of the *Fusobacterium nucleatum*, the carcinogenesis indirectly occurs *via* the perpetual secretion of pro-inflammatory cytokines [46]. This phenomenon implies the close interrelation of the microbiome with immune response and metabolic processes[47].

There is a notable reduction of genera from the Firmicutes phylum, which produce a significant metabolite, the alleged butyrate. An enhanced reproduction of specific phyla, such as *Bacteroides fragilis, Peptostreptococcus stomatis* as well as *Tarvi monas micra, Fusobacterium nucleatum*[48] and *Solobacterium moorei*[49]. Additionally, there are reports that show an increased amount of *Enterococcus*, *Escherichia coli*, *Klebsiella* and *Streptococcus,* as well as a decrease in *Rothia*[2].

There is considerable evidence that CRC development is closely associated with the presence of Fusobacteriaceae family members, such as *Fusobacterium nucleatum*, *necrophorum* and *mortiferum*[37] *via* a mechanism that was reportedly observed in mice[50].

Generally, dysbiosis which includes the modification of microbial taxa in the gut ecosystem leads either to a limited variety of microbiota or the overgrowth of microbes. This can further lead to the development of opportunistic infections[51], destruction of the intestinal epithelial barrier, bacterial translocation to the mesenteric lymph nodes or the circulatory system, ultimately leading to a local and

systemic inflammatory response[52].

Recruitment of T lymphocytes is observed in CRC malignant tissues[53] *via* the secretion of chemotactic cytokines. This is further related to an abundance in proteobacteria Ruminococcaceae, *B. fragilis* and *E.coli*. Alternatively, a high number of Fusobacteriais is associated with a dismal prognosis. In *in vitro* it has been observed to express an increased number of recruited T cells and inflammatory modulators [interleukin (IL)-6, IL-8, IL-1][54], an inhibitory effect on Natural killer cells, as well as tumor-infiltrating lymphocytes[55]. Although *Fusobacterium nucleatum* is normally associated with a worse prognosis, it constitutes a promoter for differentiation in regulatory T cells leading to a decrease in expression of scurfin or forkheadbox P3 which is correlated to prolonged survival[56].

IMMUNOTHERAPY IN CRC

The therapeutic management of CRC is considered quite challenging due to the complex molecular basis including genetic and epigenetic alterations[57]. In recent years, immunotherapeutic agents are utilized for tumors that present high MSI-H which results from a defective DNA MMR or epigenetic modification[33]. An epigenetic aberration is genome hyper-methylation in addition tomutant genes such as PMS2, MLH1 as well as MSH2 and MSH6[58]. In the case of MSI-H colorectal tumors, there is evident methylation of CpG islands in the promoter of the BRAF proto-oncogene[59]. It is observed that patients with BRAF and RAS genetic mutations present resistance to immunotherapeutic treatments with a limited enhancement of survival[60]. It can occur in cases of epidermal growth factor receptor inhibitors, like cetuximab, as well as Panitumumab[61]. In comparison with MSI tumors, the microsatellite stable tumors present a more aggressive phenotype and poor prognosis[62]. Immunotherapeutic agents, such as pembrolizumab are commonly used in cases of chemo-resistant advanced colorectal malignant tumors despite the existence or lack of either MMR or MSI-H based off the KEYNOTE 028 clinical trial[63]. For tumors with MMR phenotype, the utilization of nivolumab alone or with ipilimumab is highly recommended[47]. The administration of cancer vaccines in CRC is still under study and it is limited solely to cases of end-stage CRC[64]. Talimogene laherparepvec vaccine uses Herpes virus type-1 as a vector which targets the *GM-CSF* gene. The combination of systemic use of atezolizumab (anti-PD-L1 immunotherapeutic agent) with the above vaccine is currently under assessment for tumors with microsatellite stability[63] or as a monotherapy in secondary liver cancer [65].

Tumor microenvironment and microbiome in CRC

Tumor microenvironment (TME) includes multiple types of cells, such as fibroblasts, immune cells, endothelial and stromal cells[66]. TME demonstrates a significant role in immune responses, particularly in CRC, and constitutes as a therapeutic target for many anti-cancer agents[67]. The stroma around the tumor has a key role in resistance to chemotherapy due to the fact that it includes a heterogeneous population of cells with various levels of differentiation. This contributes to invasive tumor behavior and dissemination. This is shown in the case of tumor-associated macrophages and cancer-associated fibroblasts. Both of these are related to a dismal prognosis and neoangiogenesis[68,69], as well as Myeloid-derived suppressor cells which are also implicated in tumor progression and invasion. Their effect is under the regulation of tumoral products like chemokine (C-C motif) ligand 2 and 5 (CCL2 and CCL5)[70].

It was previously stated that the gut microbiota exhibited various effects on the differentiation mechanism and tumor development. While they influence the tumor response to immunotherapeutics [71], the existence of intra-tumoral bacteria is reported in many solid tumors, especially in breast cancer. It was demonstrated that the microbiome is particular for each kind of malignant tumor presenting distinct metabolic functions[72]. Based on data that was collected by whole-transcriptome analysis, there is a distinct microbiome correlated with different malignant tumors, implying a specific microbial profile for each type of cancer[73]. Additionally, TME has a crucial role in the existence and multiplication of intra-tumoral bacteria[74]. Many studies illustrate the close relationship between immunotherapy and gut microbiota, and their implication in the anti-tumor mechanism such as immune-checkpoint inhibitors[72].

THE IMPLICATION OF GUT MICROBIOME IN IMMUNOTHERAPY

Resistance to immunotherapy is difficult to overcome in clinical practice[31]. Manipulation of gut microbiota constitutes a promising method for reducing the resistance to therapeutic agents. This is implied by the notable effect of intestinal microbial products on the malignant tumor where they could also be considered cancer-driving molecules[75].

Experimental studies on mice have shown that bacteria have a crucial role in the anti-cancer immune response. While the response was limited in the case of germ-free mice[28], it was primarily reported that intestinal microbiota have a significant role in the response especially to immune checkpoint

inhibitors. However, the previous observation was also demonstrated in humans when an immune checkpoint blockade was applied[28]. In mouse-model studies, fecal microbial transplantation (FMT) from mice that presented immune-responsive microbiota, to germ-free mice, provided a better anti-neoplastic response and tumor growth management. This result is associated with an increased amount of cytotoxic T lymphocytes (CD8+) in TME[76]. Whereas the transfer of fecal samples, including microbiota prone for carcinogenesis, provides the opposite results to physiological mice[77]. However, the correlation of the anti-tumor response with external factors must be taken into consideration.

Alterations in the consistency of bacteriome were reported in cases of patients with an active response to PD-1 inhibitors. More specifically, these patients presented a higher amount of *Enterococcus faecium*, *Bifidobacterium longum* and *Collinsella aerofaciens*. Fecal specimens that presented the above microbial taxa were characterized as "responder" stool samples and were transferred *via* FMT to germ-free mice. Subsequently, the germ-free mice started to express the stool phenotype of the responders[28].

Based on various human and animal-model cohort studies, intestinal microbiota could not only have been beneficial but also toxic effects on immune checkpoint inhibition[78]. Reduced toxicity was observed in specimens where Bacteroidetes genera were in abundance. Although they relate to unresponsiveness to immune checkpoint inhibitors (ICIs), in contrast to Firmicutes, and especially in the case of Ruminococcaceae, they were not only responsive to ICIs but also presented toxic effects. In cases of overgrown *Faecalibacterium prausnitzii*, patients had an increased risk of presenting colitis related with CTLA-4 inhibitors[79,80].

Manipulation of intestinal microbiota for immunotherapy-response improvement

Based on all the characteristics of the intestinal microbiota, they can either promote the anti-neoplastic response or induce inflammation and carcinogenesis[81]. A reduced anti-cancer response in the host was observed in germ-free mice or with antibiotic administration (broad-spectrum)[28,35]. In cases with urinary tract malignancies and lung cancer, antibiotics had a harmful effect on anti-PD1/PD-L1 treatment[35] in comparison to cyclophosphamide which presented a promoting effect on the overgrowth of *Barnesiella intestine hominis* in the intestinal tract and a stimulatory effect on anti-cancer immune response[82].

However, the manipulation of microbiota and utilization of antibiotics for the killing of bacteria is detrimental to the response to immunotherapeutic agents. This method includes the risk of killing favorable bacterial species. To avoid the non-elective effect of antibiotics, bacteriophage therapy is administered which permits a selective elimination of unfavorable bacteria[83].

Lastly, environmental and lifestyle habits could potentially alter the gut microbiome. These include physical exercise, proper dietary habits, sleep patterns, as well as *via* the utilization of FMT[84]. Bacterio-therapy or FMT includes the transferring of beneficial bacterial species such as Bacteroides, Bifidobacteria, *E. hirae* and *Akkermansia mucini philia*[85].

CONCLUSION

The relationship between the intestinal microbiome and disease development, such as carcinogenesis, was underestimated in the last decades. Nevertheless, the crucial role of intestinal microbiota has been in the spotlight as of recent years. Not only for their significant influence on the main metabolic functions of the host but also on the immune and anti-tumor responses. Immunotherapeutic agents are commonly used specifically for cases with chemo-resistant advanced colorectal malignant tumors. The implication of gut microbiota in the anti-cancer immune response is still under research. However, there are many reports supporting that the lack of specific bacterial taxa in CRC patients leads to a limited response to immunotherapy or complete unresponsiveness with the presence of specific phyla that could promote the anti-cancer response. Based on various human and animal-model cohort studies, intestinal microbiota could not only have beneficial effects on immune checkpoint inhibition but also have detrimental effects. The aforementioned phenomenon illustrates the necessity for the manipulation of intestinal microbiota. Specifically for the highest anti-neoplastic immune response, either *via* bacteriophage therapy or lifestyle habits modifications as well as FMT. Further research regarding the implication of gut microbiome on immunotherapy responses is needed for the identification of additional druggable targets, along with the manipulation of intestinal microbiota to achieve an optimal therapeutic response personalized for each patient.

FOOTNOTES

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