Microbiota on Clinical Outcomes and Chemotherapy Resistance

Subjects: Oncology

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The dual role of the gut microbiota in the preservation of host health and in the development of different pathologies, cancer among them. Our gut microbiota is capable of producing metabolites that protect host homeostasis but can also produce molecules with deleterious effects, which, in turn, may trigger inflammation and carcinogenesis, and even affect immunotherapy.

microbiota cancer immune

1. Importance of Gut Microbiota in Cancer Therapies

The common goal of the different cancer therapies is to effectively eliminate cancer cells in order to eradicate the disease in the patient and prevent a future recurrence. Despite the great advances in cancer treatments, almost all are also toxic for non-cancerous cells, which leads to the appearance of different side effects of varying severity, some of them even affecting the survival of patients. Gut microbiota and cancer therapies are closely related [1]. Treatments, such as radiotherapy, chemotherapy, and immunotherapy, can modify the microbiota of patients and, at the same time, the composition of the microbiota can influence efficacy and development of side effects of such therapies [2].

The gut microbiota can modulate the progression of cancer pathogenesis through its ability to synthesize different antitumor compounds, as well as to regulate the immune response and host inflammatory pathways. These combined mechanisms may explain the strong influence of the microbiota with the efficacy of different therapies.

2. Intestinal Microbiota and Chemotherapy

The gut microbiota can modulate the metabolism of different drugs used in chemotherapy, thus affecting both the response of cancer cells to this treatment and the susceptibility of healthy cells.

2.1. Gemcitabine

Gemcitabine (2′-2′-difluoro-deoxycytidine) is a pyrimidine antagonist, which therefore competes with deoxycytidine (a component of deoxyribonucleic acids derived from cytosine) during DNA synthesis. The antitumor activity of gemcitabine, used in the treatment of different types of cancer, is based on its intracellular activation and subsequent degradation, through its transformation into the inactive metabolite difluoro-deoxy-uridine by cytidine

deaminase (CDD) [3]. Studies in mice have concluded that gemcitabine resistance may be due to enhanced metabolic degradation of the drug into difluoro-deoxy-uridine due to the expression of a long isoform of the bacterial enzyme cytidine deaminase (CDDL), which is mainly observed in Gammaproteobacteria [4] On the other hand, the combined action of the antibiotic ciprofloxacin, together with gemcitabine, seems to increase the antitumor activity of the drug through the inhibition of bacterial growth caused by the antibiotic, demonstrating that modulation of the intestinal microbiota can influence the activity of gemcitabine in mice [5].

2.2. Cyclophosphamide

Cyclophosphamide is an alkylating agent used in different types of cancer, which acts by stimulating the immune response against cancer. Studies in mice have shown that when cyclophosphamide is administered together with gram-positive bacteria antibiotics, there is an inhibition of the immune response elicited by cyclophosphamide, and therefore of the anticancer effect of the drug, which is restored by oral administration of Gram-positive bacteria, such as *Lactobacillus johonsoni* and *Enterobacter Hirae* [6][7].

2.3. Irinotecan

Irinotecan (CPT-11) is an inhibitor of DNA replication through its anti-topoisomerase I action. This drug, used in different types of cancer, has an active form (SN-38) and an inactive form (SN-38-G) that are excreted into the intestine. When SN-38G is excreted into the intestinal lumen, it is converted back to SN-38 by the bacterial ß-glucuronidase of *E. coli*, a process that can cause enteric injury and, therefore, diarrhea, this being one of the main side effects of the drug. In mice, it has been shown that administration of this drug with a bacterial ß-glucuronidase inhibitor can prevent gastrointestinal toxicity [8].

2.4. Cisplatin

Cisplatin is an effective anticancer agent and is used in many advanced cancers. It has antibiotic effects on Gram-negative and Gram-positive bacteria and can cause intestinal dysbiosis [9][10]. In addition, cisplatin can also cause loss of intestinal mucosal integrity by binding to the DNA of epithelial cells, impairing their replication, which could lead to serious infections of different parasites [11]. Cisplatin also has other side effects in which the microbiota is involved, such as ototoxicity, mucositis, and weight loss. It has been determined that the administration of D-methionine, together with cisplatin treatment, protects against drug toxicity through, not only its antioxidant and anti-inflammatory properties, but also by promoting the growth of beneficial bacteria, such as *Lachnospiraceae* and *Lactobacillus*, thus regulating the imbalance of the intestinal microbiota [12]. On the other hand, the intestinal microbiota also seems to affect the efficacy of cisplatin. In mice with lung tumors, it has been shown that, when administering this drug with anti-Gram positive antibiotics, the efficacy of the treatment is reduced, as mice survive less and develop larger tumors than mice in which cisplatin is combined with probiotics, such as *Lactobacillus* [10].

2.5. 5-fluorouracil

5-fluorouracil (5-FU) is a thymidylate synthase inhibitor used for the treatment of gastrointestinal tumors. Its usefulness is limited due to the acquisition of resistance and the gastrointestinal toxicity effects it causes, one of the most relevant side effects of 5-FU being intestinal mucositis. 5-FU can cause intestinal dysbiosis even with a single dose; different studies have reported a drastic change in the microbiota, decreasing species such as *Bifidobacterium* and *Lactobacillus* and increasing others, such as *Escherichia*, *Clostridium,* and *Enterococcus*. Regarding drug efficacy, it has been shown, in mice, that combined administration with an antibiotic cocktail decreases antitumor efficacy, while probiotic supplementation seems to increase it significantly [13].

Figure 1 summarizes the impact of gut microbiota in several common drugs used in chemotherapy.

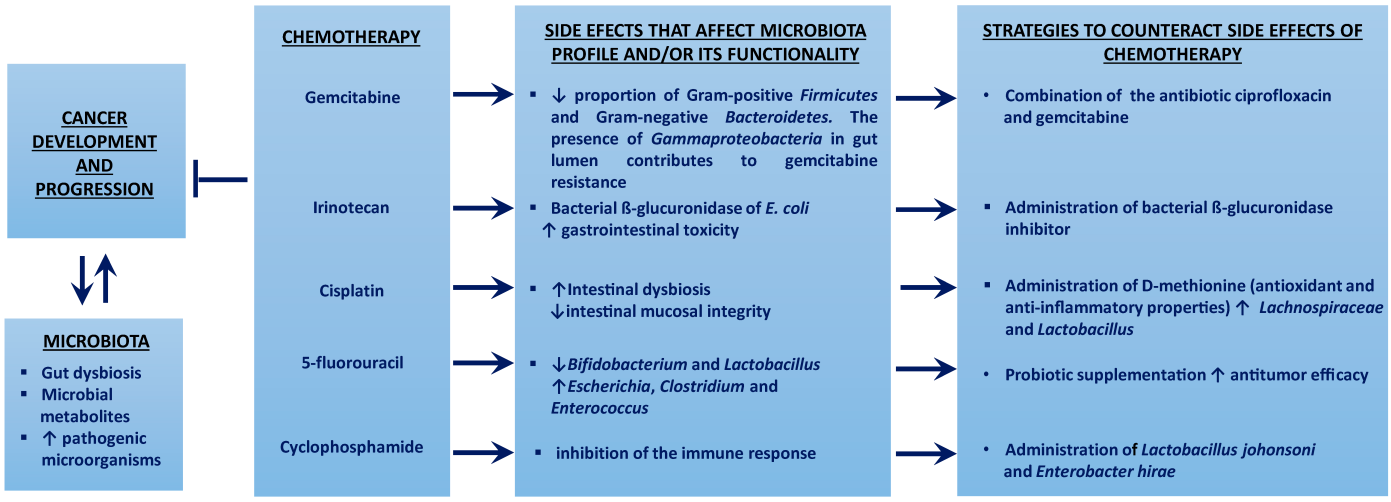

Figure 1. The gut microbiota affects cancer pathogenesis and the metabolism of chemotherapy drugs, conditioning both the response of cancer cells and the susceptibility of healthy cells. ↑ means increment; ↓ means decrease; ⊢ means inhibition.

3. Gut Microbiota and Immunotherapy

Immunotherapy is based on immune checkpoint inhibitor (ICI) molecules, which act by blocking certain immune regulatory pathways in order to enhance the antitumor immune response. ICIs are monoclonal antibodies that target receptor molecules on the surface of T lymphocytes, such as cytotoxic lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1), or PD-1 ligands (PD-L1 or PD-L2). The mechanisms of each of these antibodies are different [14].

Because they dysregulate the immune system, ICIs cause a wide spectrum of side effects that can affect any organ. These side effects are known as immune-related adverse events (irAEs), which will differ according to the therapy used. In general, the ICI with the highest incidence and severity of irAEs are antibodies to CTLA-4, followed by those to PD1, with antibodies to PD-L1 having the least effect. In particular, intestinal side effects, such as diarrhea or colitis, are more frequently observed with anti-CTLA-4 antibodies, while dysthyroidism or pulmonary toxicity are more frequent with anti-PD-1/PD-L1 [14]. Because of this, there are a significant number of patients to

whom such therapy can be applied only for a limited time due to the occurrence of strong side effects. However, oral administration of certain probiotics, such as *Bacterioides fragilis* and *Burkholderia cepacia*, has been linked to improvement of these immunotherapy-associated side effects [15].

In terms of efficacy, ICIs have demonstrated their usefulness in different solid tumors, as well as in hematologic malignancies. Although ICIs achieve a durable response and prolonged survival, a non-negligible percentage of patients do not obtain any benefit (primary resistance) or eventually progress (secondary resistance), and there is accumulated evidence that in some patients ICIs can even favor tumor growth (hyperprogression) [14]. Because of this, different studies have been carried out to identify predictive factors for the efficacy of this type of treatment, as well as strategies to avoid resistance to it, with some of these studies showing that the composition of the intestinal microbiota modulates the activity, efficacy, and toxicity of ICIs.

3.1. Anti-CTL-4

In patients treated with anti-CTLA4 antibodies, side effects are greater in those with a gut microbiota abundant in different *Firmicutes* species, such as *Faecalibacterium*, and a decreased abundance of *Bacterioides* [16][17]. In terms of treatment efficacy, in patients with metastatic melanoma, it was found that those whose gut microbiota was enriched in *Faecalibacterium* and other *Firmicutes* had longer progression-free survival and overall survival than those with microbiota rich in *Bacteroides* [16].

3.2. Anti-PD-L1

The efficacy of the antibody targeting PD-L1 in the treatment of melanoma in mice is improved in the presence of a gut microbiota enriched in *Bifidobacterium* species. Additionally, oral administration to patients of a cocktail of bacteria of this species combined with the anti-PD-L1 antibody specifically increases the T-cell response and blocks melanoma growth, whereas, when the treatment is combined with antibiotics, the survival rate is lower [18].

3.3. Anti-PD1

As was the case with anti-PD-L1 therapy, when combining anti-PD1 with antibiotics, the survival rate in patients is lower. In these patients, the responders to anti-PD1 treatment had a gut microbiota enriched in the *Akkermansia* and *Alistipes* genera [15]. Likewise, when analyzing the intestinal microbiota of patients with metastatic melanoma subjected to anti-PD-1 immunotherapy, a greater diversity and abundance of Faecalibacterium was observed in those with greater response to treatment and SSP, and a lower diversity and abundance of Bacteroilades in non-responders with lower SSP was observed [14].

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