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Proceeding Paper

Intestinal Microbiota in the Clinical Results of Cancer and Its Modulation as Auxiliary Therapy †

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Abstract: Dysbiosis has been related to the inflammation that precipitates tumorigenesis and to the mediation of the anticancer immune response. Results suggest that ecological imbalance and changes in microbial metabolites, such as short-chain fatty acids (SCFAs), influence tumor progression and metastasis. Regarding the clinical response to chemotherapy/immunotherapy, it has been demonstrated that *Escherichia coli* is one of the main strains related to the increased metabolism of chemotherapy drugs, such as gemcitabine, reducing their therapeutic efficacy. Therefore, it is proposed that, despite the harmful examples regarding tumor progression, the intestinal microbiota can also have a positive impact on anticancer therapy.

Keywords: microbiota; cancer; progression; biotherapy

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1. Introduction

The human intestine helps maintain the physiology and health of the host. Composed of approximately 10 to 100 trillion microorganisms, including bacteria, viruses, protozoa and fungi, the intestinal microbiota plays a fundamental role in homeostasis, including the development and regulation of adaptive and innate immunity. At the same time, it plays important roles in the pathogenesis of diseases from intestinal microbial dysfunction, known as dysbiosis [1,2].

This correlation occurs because there is an intimate association between the history of cancer and the human microbiota. In the late 1800s, after the establishment of the germ theory of infectious diseases, Wilhelm Busch and Friedrich Fehleisen independently reported a relationship between *Streptococcus pyogenes* infections and spontaneous tumor regressions in several patients. Currently, through greater appreciation of the number of microorganisms that colonize the human body, as well as knowledge of their metabolic diversity and their effects on the host's immunological activity, the idea is growing that they are capable of playing a broad role in diagnosis, pathogenesis and cancer treatment [3].

Therefore, the present study seeks to identify how the intestinal microbiota is related to tumorigenesis, as well as its participation in modulating the anticancer immune response, influencing both tumor progression and treatment efficacy.

2. Methodology

2.1. Characterization of the Research

The present study has a qualitative, descriptive and exploratory nature, carried out through a Narrative Literature Review, a traditional review method in which the selection of articles does not follow a systematic model and the author can include documents according to his bias, without explicit definition criteria [4]. Given this, the PICO strategy was used to develop the following guiding research question: "What is the influence of the intestinal microbiota on the clinical progression and therapy of cancer?".

2.2. Conducting the Investigation and Selection Criteria

The search was carried out during the month of June 2023, using the PubMed databases. The descriptors used were "Gastrointestinal Microbiome", "Neoplasms" and "Biological Treatment", associated with the Boolean operator "AND". Furthermore, the criteria used to select the sample were publications that explicitly mentioned, in their abstract and title, references about the interference of the intestinal microbiota in the clinical results of different types of neoplasms. Such publications should meet the following inclusion criteria: complete texts, published in Portuguese, English and Spanish, without time frames and with free access. Articles that were unavailable in full, duplicated and did not address the topic were excluded. Finally, data collection occurred through the individual analysis of each bibliography, correlating the findings to the proposed theme.

2.3. Presentation of Discoveries and Synthesis of Information

After reading the works in full, the research was developed into a descriptive and exploratory dissertation, organized based on the synthesis and critical analysis of 18 articles, with the aim of answering the guiding question of the investigation and enabling a state of the art on the subject. in question. We also sought to extract findings considered innovative regarding cancer biotherapeutics. It should be noted that there was no need to submit the study to the Research Ethics Committee (CEP), given the use of public data and the fact that the research was not carried out on human beings.

3. Gut Microbiota and Cancer Progression

Oncobiome is defined as the field of research that investigates the role of the microbiota in the development of human cancer. Initially focused on colorectal cancer, it has rapidly expanded to other malignant diseases, presenting hypotheses about dysbiosis and the mechanisms influencing the initiation and progression of neoplasms, which include the following: direct impact of bacterial toxins and/or metabolism, modulation of the immune response local and systemic and changes in microbial and host metabolism [5].

Under normal conditions, microorganisms in the gastrointestinal tract provide protection and maintain balance in the host by regulating basic metabolic processes. However, through molecular patterns associated with Toll-like receptors, intestinal dysbiosis increases the production of pro-inflammatory factors by cells of the intestinal mucosa, contributing to carcinogenesis [6]. In addition, dysbiosis resulting from the use of broad-spectrum antibiotics during anticancer treatments can also disrupt the tumor microenvironment and contribute to its progression [7].

In addition to dysbiosis, several microbial products influence neoplastic development and progression. Among them, butyrate, a product of short-chain fatty acids (SCFA), has antitumor characteristics, as it maintains epithelial integrity, inhibiting inflammation, invasion and proliferation. The significant reduction of SCFA in the plasma of patients with colorectal cancer (CRC) supports the close association between its decrease and the progression of cancer, from growth to metastasis [8].

Evidence also shows that, by analyzing the intestinal microbiome of patients with colorectal cancer (CRC), it is possible to recognize significant changes in specific microbial groups. According to [9], the number of operational units belonging to the genera *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus* and *Peptostreptococcus* was substantially higher in patients with CRC, while bacteria from the genus *Roseburia* and other butyrate-producing bacteria were less abundant. This finding confirms the microbiological imbalance among patients with neoplasms, which can induce inflammation and cause neoplastic progression.

4. Microbiological Influence on Pharmacological Therapy of Cancer

The implications of the microbiota for the treatment of cancer patients are multifaceted, as bacteria alter the effectiveness of medications through their metabolic processes and immune modulation mechanisms. According to [5], these changes can occur

due to a decrease/increase in drug efficacy and an increase in chemotherapy toxicity, which indirectly reduces drug effectiveness due to the need for changes in dosage. In this study, evidence suggests that *Escherichia coli* may act to decrease the effectiveness of gemcitabine in the treatment of pancreatic cancer by increasing the drug's metabolism through bacterial acetylation.

Furthermore, the study by [10] demonstrates that bacterial beta-glucuronidase can convert the chemotherapy drug irinotecan into a toxic metabolite, just as bacterial citadine deaminase has the ability to degrade gemcitabine. It was also observed that, by reducing the production of reactive oxygen species (ROS), the absence of *Lactobacillus* reduces the cytotoxicity of oxaliplatin. Similarly, the anticancer effect of cyclophosphamide is dependent on the participation of some bacterial species in activation, such as *Enterococcus hirae* [11]. Thus, it is noted that variation in the commensal microbiota can modify the effectiveness of conventional chemotherapy and directly impact treatment results.

Likewise, the enrichment of certain intestinal strains triggers anticancer effects. Lactobacilli and bifidobacteria play an important role in tumor suppression by inducing an increase in short-chain fatty acids (SFCAs), which act in apoptosis and inhibit tumor proliferation [9].

Another relationship observed was the direct influence of the microbiome on the response to immunotherapy. In mice, it was observed that the administration of *Bifidobacterium* associated with PDL-1 antibody treatment increases the effectiveness of the drug through the accumulation of CD8 T cells, driven by the activation of dendritic cells. *Lactobacillus rhamnosus GG* is also related to greater therapeutic efficacy of the PD-1 antibody (antibody against Programmed Cell Death Protein 1), as well as antibodies against the receptor that tumor cells use to escape immunological surveillance through the action of dendritic cells that produce IFN-γ, a cytokine related to the expression of the Programmed-Death Ligand 1 (PDL-1) [12].

In breast cancer, an accumulation of evidence points to the ability of the intestinal ecosystem to reduce systemic inflammation and modulate immune responses. This is justified given the potential of nicotiamide, produced by microbial components of the intestine, to reduce breast tumorigenesis in a manner dependent on T and NK cells [13]. Furthermore, studies by [14] reveal the direct involvement of the intestinal microbiota in the antitumor efficacy of transtuzumab, by demonstrating that the lower abundance of *Lachnospiraceae*, *Turicibacteriaceae*, *Bifidobacteriaceae* and *Prevotellaceae* is related to non-responsiveness to treatment due to the use of antibiotics, consequent reduction in the activation of dendritic cells and the release of IL12p70, a mechanism necessary for the effectiveness of the antineoplastic.

5. Available Biotherapeutics

There is growing evidence of how the intestinal microbiota impacts tumors. Recognized as safe and beneficial to the host's health, lactic acid-producing bacteria, such as *Lactobacillus*, *Lactococcus*, *Leuconostoc* or *Pediococcus*, are candidates for bacterial therapy against cancer, also serving as living vehicles that help deliver medications [15].

From this perspective, antimicrobial therapy corresponds to the approach and prevention of known microbial carcinogens through the use of probiotics (live or dead), prebiotics and dietary interventions capable of modifying the microbiome. The use of Fecal Microbiota Transplantation (FMT) also constitutes a way of modulating the intestinal microbiota [3].

Probiotics are live, non-pathogenic microorganisms, while prebiotics are indigestible food ingredients capable of promoting the growth of probiotics. Metabolic secretions (inactive probiotics) can also play an auxiliary role in therapy, such as bacterial lipopolysaccharides (LPS), which activate the Toll-like receptor 4 and trigger an immune response against tumor cells and short-chain fatty acids (SCFAs) produced by *Lactobacillus* extracts, which induce apoptosis of cancer cells. Other probiotic metabolites active in cancer therapy are inhibitory proteins, siderophores and ferrichrome [11,16].

It is still unclear whether factors such as dietary fiber intake can affect therapeutic responsiveness in cancer, but ref. [17] demonstrated in their work an association between higher fiber content and improved free survival in melanoma patients treated with immune checkpoint blockade (ICB). The benefit was more pronounced in patients with sufficient fiber intake and no probiotic use.

Regarding FMT, it is a biotherapeutic method that alters the microbiota by transplanting information present in the feces of healthy donors [9]. Most clinical experiences with FMT derive from the management of *Clostridium difficili* infections; however, recent studies demonstrate positive results with the use of this technique in various pathologies, including cancers. According to [18], in non-responsive patients, the association of fecal microbiota transplantation and immunotherapy increased the response to the PD-1 antibody in the treatment of refractory melanoma, overcoming resistance to immunotherapy. Furthermore, it reduced myeloid cells producing IL-8, an important pro-inflammatory cytokine associated with tumor progression in several cancers.

6. Conclusions

The interaction between environmental and genetic factors in the emergence and evolution of cancer is known. But, in addition to genetic determinants, additional oncogenic microorganisms act synergistically in tumorigenesis [19]. Among the risk factors, changes in eating habits to a Western standard stand out, especially due to a reduction in fiber intake, which can be fermented into SFCAs by intestinal bacteria, affecting the onset and progression of neoplastic disease. It is no coincidence that the colorectal region is the most affected, as it corresponds to the site of direct impact of changes in the microbiota [9].

Regarding neoplastic drugs, their relationship with the intestinal microbiota has been demonstrated, as it can affect the response of intestinal and extraintestinal organs to chemotherapy treatment. Therefore, maintaining an ideal microbial composition corresponds to an important condition in the prevention and progression of tumorigenic events, with the modulation of the microbiota constituting a great therapeutic promise. To achieve this, additional research into its mechanisms is necessary, given the complex interaction between host–drug–microbiota, which requires the construction of personalized approaches.

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