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EDITORIAL: ONCOBIOME AND PERSONALIZED CANCER MEDICINE: MYTH OR REALITY?

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The human body is a complex ecosystem inhabited and influenced by an abundance of microorganisms that include bacteria, viruses, fungi, archaea, and protozoa, which collectively make up the commensal microbiota.

Thanks to the development and application of next-generation sequencing methods it has become quite evident that several specific microbiotas have developed in different areas of the healthy human body – nose, mouth, respiratory tract, skin, and urogenital tract[1].

In adult humans, the largest percentage of commensal bacteria resides in the gastrointestinal tract and consists of several phyla – mainly Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia, with Firmicutes and Bacteroidetes making up about 90% of the gut microbiota[2].

Many studies show that the gut microbiota has co-evolved to exist in a mutually beneficial symbiotic state with its host and thanks to its complex genome, encodes an amplitude – surpassing even that of the human genome – of functional genes, which influence many physiological processes like development, metabolism, and immunological functions[3].

Several studies have also shown that various environmental and host-related factors such as maternal microbiota composition, birth patterns, breastfeeding, drug exposure, diet and genetic factors can alter the microbial ecosystem to such an extent as to have an impact on its resistance and resilience, which in turn has consequences on the immune and anti-inflammatory responses that are responsible for autoimmune, neurodegenerative, inflammatory bowel and oncological diseases[4].

There is evidence to support the idea that gut microbiota dysbiosis can trigger inflammatory signaling pathways that affect the intestinal and extra-intestinal immune function and contribute to carcinogenesis and cancer progression.

Carcinogenesis is an inflammatory process in which the microbiota appears to be involved both through direct and indirect mechanisms, in particular through immune pathways.

Functional studies of these immunological pathways have been conducted on humans and mouse cancer models, such as colorectal cancer (CRC).

Several studies have compared the gut microbiota of the intraluminal surface and mucosa of healthy patients with those suffering from CRC. These studies have demonstrated a state of dysbiosis of the gut microbiota with the reduction in the profusion of taxa that have a protective function (i.e., Roseburia) and an increase in taxa with detrimental effects (i.e., Escherichia, Klebsiella, and Fusobacterium) both in the feces and in the mucous membranes[5].

These studies demonstrate the relationship between microbial dysbiosis and CRC, even if the causal relationship between bacteria and the onset and progression of cancer is not yet fully understood.

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Recently some studies have shown a correlation between colorectal cancer and a specific bacterium – Fusobacterium nucleatum[6], a gram-negative, non-spore-forming, oral anaerobe and one of the many species present in the oral cavity of a healthy subject, especially those with periodontal disease[7].

Genomic studies have shown that F. nucleatum is prevalent in CRC and plays a role in the development of CRC. In particular, the evidence demonstrates that fusobacteria from the oral cavity can translocate to the colon by descending through the digestive tract, or by using the hematogenous pathway during frequent episodes of transient bacteremia caused by chewing, daily hygiene activities or dental procedures[8].

The extensive evidence linking this bacterium to CRC indicates that it promotes tumor progression by generating a proinflammatory tumor that stimulates the microenvironment and accelerates the proliferation of colon cancer cells. Additionally, F. nucleatum plays a role in metastasis and disease outcome. In fact, the presence of a large number of this bacterium is inversely related to the patient's overall survival rate[9].

The study of the relationship between the microbiota and its quantitative and qualitative variations associated with those of its genome and their effects on carcinogenesis have made it possible to advance the hypothesis of the involvement of specific microbial products.

One of the important discoveries in recent years is the fact that the gut microbiota produces various metabolites that can contribute to carcinogenesis, not only in the immediate area, but also by being absorbed into the systemic circulation from the gut, through which they can travel to distant parts of the body and impact carcinogenesis or progression of cancer in areas far from the gut, like breast cancer.

It has been hypothesized that the gut microbiota may promote carcinogenesis through its influence on estrogen metabolism, particularly through its ability to alter circulating estrogen levels. Estrobolome is, in fact, a specific aggregate of intestinal bacterial genes that regulate estrogen levels through the secretion of β-glucuronidase, an enzyme that deconjugates estrogens in their active forms. An alteration of estrobolome and its regulatory functions can increase the risk of breast cancer[10].

Another extremely interesting aspect regarding oncobiomics research is the growing evidence of a bidirectional relationship between the gut microbiota and anticancer therapies.

Antineoplastic drugs can, in fact, act on the composition of the gut microbiota and alter its bacterial biodiversity, which contributes to the onset of a dysbiosis condition of the gut.

Pharmacomicrobiomics studies have demonstrated that the gut microbiota, in turn, appears to significantly influence the metabolism of individual chemotherapeutic and immunotherapeutic drugs, modifying both their efficacy and toxicity[11]. Particular attention has recently been paid to the correlation between the microbiome and immunotherapy. Despite the remarkable clinical success of immunotherapy in a wide variety of cancers, only a subgroup of patients responds optimally to treatment. Recent evidence shows that the gut microbiota is involved in the response to cancer immunotherapy[12]. In particular, the gut microbiota is implicated in the modulation of immune checkpoint blocking responses in different types of cancer[13]. Gut microbiota sequencing techniques have demonstrated that cancer patients who responded to programmed cell death protein 1 (PD1) therapy were shown to harbor a more diverse gut microbiota than non-responders. In fact, greater alpha diversity, and relative abundance of Ruminococcus/Faecalibacterium have been observed in responsive patients. It has been proposed that this favorable gut microbiota response may contribute to a better systemic and antitumoral immune response in patients with melanoma.

In contrast, non-responders have a low diversity and higher relative profusion of Bacteroidales. They also have a reduction in specific bacterial taxa like Akkermansia, Faecalibacterium, and Bifidobacterium. This microbiota composition in the non-responders correlates with poorer anticancer immune responses.

Data from the first human clinical trials to investigate the role of fecal microbiota transplant (FMT) in influencing the way patients with metastatic melanoma respond to anti-PD-1 immunotherapy have recently been published. These studies have shown, in a subgroup of patients, that FMT increases the abundance of certain bacterial taxa and causes a greater response to immunotherapy treatment. These observations, although preliminary, suggest that studying the composition of the gut microbiota could provide the opportunity to identify patients who are most likely to respond to treatment with immunotherapy drugs[14]. Some studies even speculate that specific bacteria could be used as gut microbiota biomodulators to increase the effectiveness of checkpoint inhibitors.

There is still much to discover about the relationship between the gut microbiota and cancer and between the microbiome and anticancer therapies. Current knowledge should be complemented with extensive microbiome studies to better understand the new mechanisms that link microbes, cancer, and anticancer therapies. Understanding the relationship between variations in the gut bacterial genome and its effect on the response to cancer treatments, especially immunotherapies, could represent an important step towards maximizing drug efficacy and improving the toxicity profile.

It would, therefore, be desirable to conduct research with a multidisciplinary approach based on the study of the biology of systems – research which combines microbial ecology, tumor biology, metabolomics and pharmacomicrobiomics with the aim of producing a medicine for specific, targeted oncological therapies. "The right therapeutic drug for the right patient".

Conflict of Interest:

The Author declares that he has no conflict of interests.

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