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The role of microbiota in cancer patients

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Abstract
The human microbiota, a diverse community of microorganisms inhabiting various regions of the body, has emerged as a crucial player in maintaining health and influencing disease development. This complex ecosystem, known as the microbiome, comprises bacteria, archaea, fungi, protozoa, and viruses, with its composition influenced by factors such as birth mode, lifestyle, diet, genetics, and antibiotic use. Notably, the gut microbiota, constituting over 90% of the human microbiota, plays a pivotal role in preventing pathogen colonization, preserving intestinal mucosal barriers, and shaping the immune system.
This article explores the multifaceted relationship between microbiota and cancer. Differences in microbiota composition are observed in patients with various cancer types, raising questions about their roles in cancer development. Certain microorganisms are present in the tumor microenvironment, potentially influencing cancer progression through interactions with cancer cells. Moreover, the microbiota can affect the effectiveness of cancer therapies, introducing the possibility of personalized interventions.
Keywords: microbiota, tumor microbiome

Human microbiota

The human microbiota represents a complex community of all microorganisms that inhabit various regions of the human body (skin, mucous membranes of the digestive, respiratory, and urogenital tracts, and the conjunctiva of the eye). This diverse aggregate of microorganisms has significant importance both in maintaining human health and in the development of certain diseases. The symbiosis between the human body and the microbiota represents a "superorganism" called the holobiont (1). The term "microbiome" was first introduced by Nobel laureate Joshua Lederberg in 2001 to emphasize the importance of this complex ecological community (2). The term "human microbiome" refers to the collection of all microorganisms that constitute the microbiota, their genes, gene functional products, and metabolites (3,4).
The microbiota of healthy individuals comprises saprophytic and opportunistic pathogenic bacteria, archaea, fungi, protozoa, and viruses (mostly bacterial viruses – bacteriophages) (5).
Contemporary research on the microbiota involves analysing the prevalence of specific genera and species (including both quantitative and qualitative analysis), as well as their gene expression at the RNA level. However, research was hindered by the fact that conventional microbiological methods for culturing samples were not applicable, because certain microbiota bacteria cannot be cultivated *in vitro* conditions. New research technologies (meta-transcriptomics, metagenomics, metabolomics, and bioinformatics tools) have significantly contributed to shedding light on the importance of the microbiota (6).
Today, it is known that microorganisms forming the microbiota form organised communities within the region they inhabit, and that they communicate among themselves by producing various signalling molecules. These interactions contribute to the stability of the ecological community and better defence against competitive (pathogenic) microorganisms (1,7).
Numerous factors influence the composition of the microbiota, including the mode of delivery (natural childbirth or C-section), lifestyle, geographic location, dietary habits, genetic factors, and the use of antibiotics (8, 9).

The formation of microbiota

When does the formation of the microbiota begin? The long-held belief was that colonisation of the human body

begins immediately after birth. However, in recent years, research results have become available indicating that microorganism colonisation starts in utero (the prenatal colonisation phase). Some studies suggest the existence of microbial communities in the placenta and amniotic fluid, with their origins traced back to the mother's oral cavity (10). The next phase of microbiota development occurs in the birth stage. The newborn's organism becomes colonised during the delivery itself. The mode of delivery is one of the factors influencing the composition and prevalence of microbiota species in the newborn.

The oral mucosa, conjunctiva, and skin of newborns delivered vaginally will exhibit a higher prevalence of lactobacilli compared to infants born via Cesarean section, who will be colonised by streptococci living on the mother's skin. Diet plays a significant role in shaping the gut microbial communities during the first year of life. The gut microbiota of formula-fed infants tends to be enriched in species predominant in adults, such as *Roseburia, Clostridium,* and *Anaerostipes*. In contrast, *Bifidobacterium* and *Lactobacillus* dominate the gut microbiota of breastfed infants during their first year (11,12). The first two years of life are considered the most crucial for microbiota formation. In childhood and adolescence, the microbiota changes to a lesser extent. In adulthood, the microbiota is characterized by significantly lower plasticity (13).

The impact of microbiota in health and disease

It is clear that the interaction between microorganisms that make up the microbiota and the human organism persists throughout an individual's entire life. This interaction is an important component in maintaining human health. Researchers worldwide have paid the greatest attention to the microbiota of the gastrointestinal tract (GIT), as it constitutes more than 90% of the human microbiota.

The GIT microbiota plays a significant role in preventing the colonization of pathogenic microorganisms, preserving the mucosal barrier of the intestines, and participating in the maturation of the immune system. In the GIT, immune tolerance is established towards a large number of commensal microorganisms that constitute the microbiota, whose composition undergoes significant changes during the first three years of life. At the same time, the GIT maintains an immune response against pathogenic microorganisms and also responds to opportunistic microorganisms should they enter sterile regions of the body. Here a dense mucus layer plays an important role in the maturation of the immune system by separating microorganisms from the microbiota and the intestinal epithelium. This mucosal barrier is not only mechanical but also induces the development of a tolerogenic phenotype in immune cells (14,15,16).

Generally, the diversity of the GIT microbiota is considered a good indicator of 'healthy' intestines. Reduced diversity of GIT microbiota (dysbiosis characterized by a lower diversity) has been observed in various conditions, such as psoriatic arthritis (17), celiac disease (18), inflammatory bowel disease (19), andeczema (20), among others.

Today, there is significant interest among research groups worldwide in understanding the role of altered gut microbiota. In fact, the question arises as to how significant dysbiosis is in the pathogenesis of various diseases (carcinomas, diabetes, inflammatory bowel diseases, cardiovascular diseases, mental illnesses, allergies, etc.) and whether the composition of the microbiota can have predictive significance.

The microbiota and cancer

The association between microorganisms and cancer can be viewed from different perspectives: 1) which microorganisms can lead to malignant transformations of human cells, 2) whether dysbiosis plays a role in carcinogenesis, 3) whether human microbiota can have a protective function in cancer, 4) how human microbiota affects the success of therapy in oncology patients, and 5) what is the significance of the tumour microbiome.

While the development of cancer cells is generally associated with genetic predisposition and environmental factors, it is important not to overlook the fact that microorganisms can be linked to changes in cell biology and the onset of malignancy (21). Of a multitude of microorganisms inhabiting the Earth, ten have been shown to be associated with alterations in cell biology and are linked to the malignant transformation of human cells (*Helicobacter pylori, Clonorchis sinensis, Opisthorchis viverrini, Schistosoma haematobium*, hepatitis B virus, hepatitis C virus, human papillomavirus, Epstein-Barr virus, Merkel cell virus, and Kaposi sarcoma-associated herpesvirus). This group of oncogenic microorganisms is associated with the development of epithelial cancers (gastric cancer, liver cancer, urinary bladder cancer, cholangiocarcinoma, cervical cancer, as well as other anogenital cancers, lymphoma, skin cancer and Kaposi sarcoma) (5, 22).

Microbial metabolites can also be associated with carcinogenesis. One of the more extensively studied microbial oncometabolitesis colibactin, which is produced by *Escherichia coli*, found in the human colon. Colibactin is a cytotoxin known to be directly associated with the development of colorectal cancer (23). The mechanism through which colibactin damages DNA involves the alkylation of adenine residues on various DNA strands and the formation of DNA interstrand links (24).

In animal models, it has been demonstrated that enterotoxigenic *Bacteroides fragilis* can induce carcinogenesis of colonic epithelial cells through reactive oxygen radicals that damage DNA (25).

When we examine the composition of the microbiota in oncological patients, we can observe differences compared to healthy controls. One clinical study demonstrated variations in the composition of the gut microbiota between a group of patients with benign breast tumours and a group of patients with malignant breast tumours. In the group with

benign tumours, a higher percentage of the genera *Clostridium, Faecalibacterium, Lachnospira, Erysipelotrichaceae, Romboutsia, Fusicatenibacter, Xylophilus,* and *Arcanobacterium* was observed. Differences in the prevalence of certain genera were also noticed among different types of breast cancer (Table 1). It was found that the percentage of the genus *Citrobacter* was statistically significantly higher in the group with malignant breast tumours (26). This could be significant, as precursor studies in animal models (27) have shown that *Citrobacter rodentium* promotes colon tumour growth. In one clinical study, Goedert et al. (28) demonstrated that the genera *Dorea* and *Lachnospiraceae* were present in a lower percentage in the gut microbiota of the postmenopausal breast cancer patients compared to healthy controls. Clinical studies that have monitored changes in the GIT microbiota in patients with colorectal cancer show that there is a lower percentage of commensal microorganisms in the intestines of these patients, which can affect the gut mucosal immune response. The most frequently isolated pathogen in these patients is enterotoxigenic *Bacteroides fragilis*. It is still not entirely clear whether dysbiosis results from the development of cancer or if it predates carcinogenesis in the colon (29, 5).
In this group of patients, it has been shown that there is a polymicrobial biofilm in the intestines dominated by the genera *Sporobacter, Peptostreptococcaceae,* and *Ceilonellaceae.* Hence, research is underway to determine whether such organization of microorganisms could potentially affect the proliferation of epithelial cells and cancer progression via polyamine metabolism (30).

Tumormicrobiome

Research by Kovacs et al. (31) underscores the significance of the fact that members of the human microbiota are often in direct contact with cancer cells, forming part of the tumour microenvironment. Recently, the concept of the tumour microbiome has been introduced: although it is not yet precisely defined, it encompasses all microorganisms within the tumour tissue, on the surface of cancer cells, or inside them. Currently, it is not known whether these microorganisms constitute a permanent niche or represent a transient colonization of the tumour (32,33). The most extensively researched direct interactions between microorganisms from the tumour microenvironment and cancer cells include autophagy mediated by intracellular microorganisms and the inflammation caused by extracellular microorganisms. It has been demonstrated that *Fusobacteriumnucleatum* alters the process of autophagy in colon cancer cells, leading to their chemoresistance and migration (34). It is well-known that chronic inflammation increases the risk of malignancy. The presence of inflammatory cells in the tumour tissue microenvironment promotes the proliferation and migration of cancer cells (35).

Table 1. Genera of microorganisms highly prevalent in the gut microbiota of patients with different forms of breast cancer

PR positive vs. PR negative breast cancer	PR negative vs. PR positive breast cancer	ER positive vs. ER negative breast cancer	ER negative vs. ER positive breast cancer
Prevotellaceae *Tyzzerella*	*Barnesiellaceae* *Lactobacilliaceae* *Lactobacillus* *Prevotellaceae* *Cloacibacillus* *Acinetobacter* *Hydrogenophilus* *Rhodobacteriae* *Hydrogenophilaceae*	*Megasphaera* *Roseburia* *Prevotellaceae*	*Bacteroides* *Bacteroidaceae* *Puniceicocceae* *Opitutales* *Hydrogenophilus* *Hydrogenophilaceae*
Ki-67 low vs. Ki-67 high expression	**Ki-67 high vs. Ki-67 low expression**	**Her2-positive vs. Her2-negative breast cancer**	**Her2-negative vs. Her2-positive breast cancer**
Lactobacillus *Clostridium* *Clostridiaceae* *Megasphaera* *Proteus* *Burkholderiaceae*	*Ruminiclostridium* *Tenericetes* *Mollicutes* *Ruminococcaceae_UCG* *Izimaplasmatales* *Sporobacter* *Syntrophomonadaceae*	*Megasphaera* *Barnesiellacea* *Alloprevotella* *Lachnospiraceae* *Moraxellaceae* *Acinetobacter* *Enorma* *Flavonifractor* *Burkholderiaceae*	*Enterococcus* *Peptostreptococcus*

PR- progesterone receptor, ER- oestrogen receptor, Her2 – human epiderma growth factor receptor 2
Yang P, Wang Z, Peng Q, Lian W, Chen D. Comparison of the Gut Microbiota in Patients with Benign and Malignant Breast Tumors: A Pilot Study

The microbiota and anti-cancer therapy

Perhaps one of the greatest potentials of the GIT microbiota lies in the fact that microorganisms can metabolize not only various host products but also drugs (36, 37). Several studies have indicated a correlation between the effectiveness of

anti-programmed cell death protein-1 (PD-1) treatment for malignant melanoma and the makeup of the GIT microbiota. Based on meta and bioinformatic analyses, it has been determined that a positive response to therapy is associated with the presence of the bacteria from the *Lachnospiraceae* and *Ruminococcaceae* families (phylum *Firmicutes*) and the *Actinobacteria* phylum. The presence of Gram-negative bacteria is linked to unfavourable treatment outcomes (38, 39, 40).

Conclusion

In conclusion, while the exact mechanisms underlying the microbiota-cancer connection are still evolving, it is clear that microbiota composition holds predictive and therapeutic potential in oncology. It is also worth noting that cancer therapy itself, as well as frequent antibiotic usage, can also lead to dysbiosis, which may further impact treatment efficacy in specific cases. The fact that the composition of the microbiota can influence a favourable treatment outcome opens the possibility of the application of faecal transplantation, or of selectively enriching the GIT microbiota with specific microorganisms. Understanding this intricate relationship may pave the way for innovative approaches in cancer prevention, treatment, and management.

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