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Microbes in Cancer

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A B S T R A C T

Cancer is the uncontrolled growth of abnormal cells anywhere in a body. There are different types of cancers involves uncontrolled cell division and metastasis forming neoplasm and mass of undifferentiated cells that is tumor is a group of cells that have undergone unregulated growth which will often form a mass of tissue, but may be distributed slowly. Recent studies indicate that, the gut micro biome has emerged as an important mediating factor of health and disease. Interactions between microbes and human cells play very important roles in human metabolism including digestion of biomolecules like carbohydrates, production of essential amino acids, beneficial fatty acid synthesis and vitamin compounds. During cancer progression, these metabolic interactions between microbes and human cells may shift from one that support health to another that threatens it, as microbes begin interacting with cancer cells rather than healthy human cells. Indeed, microbial dysbiosis (disruption to the gut microbiota homeostasis caused by an imbalance in the microflora, changes in their functional composition and metabolic activities, or a shift in their local distribution) has been found to contribute to gastrointestinal cancer development. The mechanisms of action and these microbes appear to be diverse, with some activating the immune system, others inducing cell death via apoptosis and others inhibiting the growth of new blood vessels thereby depriving tumors of resources. It is the need of the hour for researchers where Future work should investigate the metabolic and ecological interactions between tumor cells and microbes that underlie this effect in order to discover new microbes that can be used in cancer treatments.

Keywords

Angiogenesis, cancer, tumor cells, *Helicobacter pylori*

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Introduction

Cancer is the uncontrolled growth of abnormal cells anywhere in a body. There are over 200 types of cancers involves uncontrolled cell division and metastasis forming neoplasm and mass of undifferentiated cells that is tumor is a group of cells that have undergone unregulated growth which will often form a mass of tissue, but may be distributed slowly. All tumor cells show some of the common characteristics like continuous growth and division even given contrary signals, absence of programmed cell death, uncontrolled cell

division angiogenesis and formation of metastases.

What microorganism can cause cancer?

Human papilloma viruses (HPV; causing anogenital cancers), *Helicobacter pylori* (gastric cancers), and hepatitis B and C viruses are most known causes of cancer risk. Involvement of microbes in cancer has been known for over a century, and different types of parasites, bacteria and viruses have been associated with oncogenic processes. Among the bacteria, the first recognised was *Helicobacter pylori* which causes gastric cancer and might be related to extra-gastric cancer in humans.

Helicobacter hepaticus has been associated with causing liver cancers tested in animal models. Other bacteria such as, *Chlamydia psitacii*, *Borrelia burgdorferi* and *Streptococcus bovis* have been associated with ocular, skin and colorectal cancers formation respectively. Also, a commensal bacterium in the human intestine, *Bacteroides fragilis*, has been linked to cause very recently, colorectal cancer tested in animal models. (Masrour-Roudsari J, Ebrahimpour 2017)

Gut Micro flora

Human gastrointestinal microbiota, also known as gut flora or gut microbiota, are the microorganisms (generally bacteria and archaea), that live in the digestive tracts of humans. The human gastrointestinal metagenome is the aggregate of all the genomes of gut microbiota.

The gut is one niche where that human microbiota inhabits. In humans, the gut microbiota has the largest numbers of bacteria and the greatest number of species compared to other areas of the body. In humans, the gut flora is established at one to two years after birth, by which time the intestinal epithelium and the intestinal mucosal barrier that it secretes have co-developed in a way that is tolerant to, and even supportive of, the gut flora and which also provides a barrier to pathogenic organisms.

Recent studies indicate that, the gut micro biome has emerged as an important mediating factor of health and disease. We have approximately as many microbes in and on us as we have human cells (3.8×10^{13} microbial cells relative to 3.0×10^{13} human cells). The human gut houses the most diverse and metabolically varied proportion of these microbes when compared to any other body surface, serving as home to more than 1000 unique species

Interactions between microbes and human cells play very important roles in human metabolism including digestion of biomolecules like carbohydrates, production of essential amino acids, beneficial fatty acid synthesis and vitamin compounds. During cancer progression, these metabolic interactions between microbes and human cells may shift from one that support health to another that threatens it, as microbes begin interacting with cancer cells rather than healthy human cells. Indeed, microbial dysbiosis (disruption to the gut microbiota homeostasis caused by an imbalance in the microflora, changes in their functional composition and metabolic activities, or a shift in their local distribution) has been found to contribute to gastrointestinal cancer development.

Currently, microbes are believed to contribute in cancer causing risk by modifying DNA in human somatic cells thereby altering cell cycle controls, accelerating cell proliferation, and disrupting normal programs for controlled cell death that protect the body from aberrant cells. Microbes have been linked to cause

approximately 10–20% of human cancers. To date, ten microorganisms have been designated as carcinogens by the International Agency for Cancer Research, one of which is Helicobacter pylori for its association with stomach cancer. Microbes and cancer cells evolve in the ecology of the body and in the tumor microenvironment.

Tumor microenvironments can include microbes that reside in or near the tumor. Microbes can alter the microenvironment by producing factors that influence cancer cells. For example, certain strains of E. coli produce colibactin toxin that is more commonly found in the mucosa of individuals with colorectal cancer than healthy controls. Colibactin induces cells in the microenvironment to produce growth factors which may promote tumor growth. Another way that microbes can influence the microenvironment is through producing bacterial biofilms which have been associated with higher cell proliferation rates and increased risk of colorectal cancer (Corrie M. Whisner & Athena Aktipis 2019)

Excess Energy Can Feed Both Cancer Cells and Harmful Microbes

Microbial community structure (diversity and abundance of specific taxa) and function is rapidly influenced by acute. And long-term dietary changes, Thereby highlighting the importance of dietary inputs for gut microbial community growth and maintenance. Our ancestors relied on their gut microbes to break down plant fiber so that their bodies could obtain adequate amounts of energy and nutrients. Gut microbiota express enzymes that carry out diverse reactions, including fermentation, hydrolysis, denitrification, sulfate reduction, and aromatic fission, to process compounds that persist in the gastrointestinal tract and are not metabolized by human enzymes. Specific microbes can convert glucosinolates from cruciferous vegetables into isothiocyanates which have anticancer properties. E.g. *Eubacterium hallii*, and *Phascolarctobacterium faecium.*

Cancer Cells and Microbes May Protect One Another from the Immune System

Chronic inflammation as a result of bacterial infections with *H. pylori, Campylobacter jejuni*, and *Chlamydia psittaci* can result in lymphomas that are mediated by overactive adaptive and innate immune signaling. Enterotoxigenic B. fragilis has been linked to colon cancer in mice via inflammatory pathways that involve Stat3 signaling and increases in IL-17-secreting CD4+ T cells. Microbes also interfere with the ability of the immune system to detect them through a variety of different mechanisms, including interfering with natural killer cell activity, which could have an impact on the ability of the body to detect and respond to cancer cells. (Corrie M. Whisner & C. Athena Aktipis 2019)

Microbes Can Induce Host Cell Proliferation Which Can Expand Microbes' Ecological Niche

Many microbes can use host cells to expand their ecological niches through inducing proliferation of the cells upon which they rely.

For example, viruses replicate themselves after entering the nucleus, integrating with host cell DNA and inducing cell proliferation. This is the mechanism underlying virally initiated cancers such as HPV. Bacteria can also expand their ecological niches through inducing cell proliferation. Fusobacteria does this by entering the cell and inducing proliferation which expands the ecological niche for the microbes. This also has the effect of promoting colorectal cancer.

Microbes that bind to epithelial surfaces then increase the proliferation rates of the cells they are attached to like H. pylori does to gastric

cells. In these situations, harmful microbes and cancer cells may have aligned fitness interests. Such fitness interdependence can arise anytime entities can benefit from one another's success, as is the case when microbes benefit from the expansion of the cancer cell population because this increases the ecological niche for microbes. (Alberts B, Johnson A, Lewis J, *et al.,* Molecular Biology of the Cell.)

Opportunities and Challenges in Treating Cancer Given Interactions with the Microbiome

Can We Jump for the Start of the Immune System to Break up Microbe-Cancer Cell Cooperation?

When the immune system is functioning properly, it limits the growth and proliferation of harmful microbes and cancer cells.

Microbes and cancer cells may cooperate to create an ecological niche that allows them to proliferate outside of normal immune control. So immune therapies targeted at disrupting microbe cancer cell interactions may have potential for treatment.

Gut microbiota biology in cancer therapies and its predictive potentials

Bacteria can work carrier for cancer therapeutic agents. Apart from their direct anti-cancer effect, tumor targeting bacteria can also be used as carriers for cancer therapeutic agents in cancer treatments.

Recent studies have revealed that bacteria are capable of targeting both primary tumors and metastasis. Successful treatment of cancer remains a challenge, due to the unique pathophysiology of solid tumors, and the predictable emergence of resistance. Traditional methods for cancer therapy including radiotherapy, chemotherapy, and immunotherapy all have their own limitations. A novel approach is bacteriotherapy, either used alone, or in combination with conventional methods, has shown a positive effect on regression of tumors and inhibition of metastasis. Bacteria-assisted tumor-targeted therapy used as therapeutic/gene/drug delivery vehicles has great promise in the treatment of tumors.

Oncolytic Virus Therapy: Using tumour targeting viruses to treat Cancer

Most oncolytic virus therapies have been tested in patients with melanoma or brain tumors, and most treatments have been given as injections into tumors.

One of the studies found that an oncolytic virus delivered intravenously could cross the blood–brain barrier and enter brain tumors, killing tumor cells. The treatment uses a type of virus known as a reovirus, which causes mild symptoms of a cold or stomach bug in children.

In the second study, researchers have tested the Maraba virus, which was originally isolated from a species of sand fly in Brazil, as a way to sensitize tumors to immunotherapy in a mouse model of triple-negative breast cancer. In above both studies, the researchers found that giving oncolytic virus therapy prior to surgery may alter the body's immune response and enhance the effects of subsequent treatment with a checkpoint inhibitor. (Hemminki *et al.,* Journal of Hematology & Oncology (2020)

The potential of fungal metabolites to provide a marketed cancer drug is discussed

It was also noted that a significant number of fungal metabolites have been successfully tested in a wide variety of mouse cancer models.

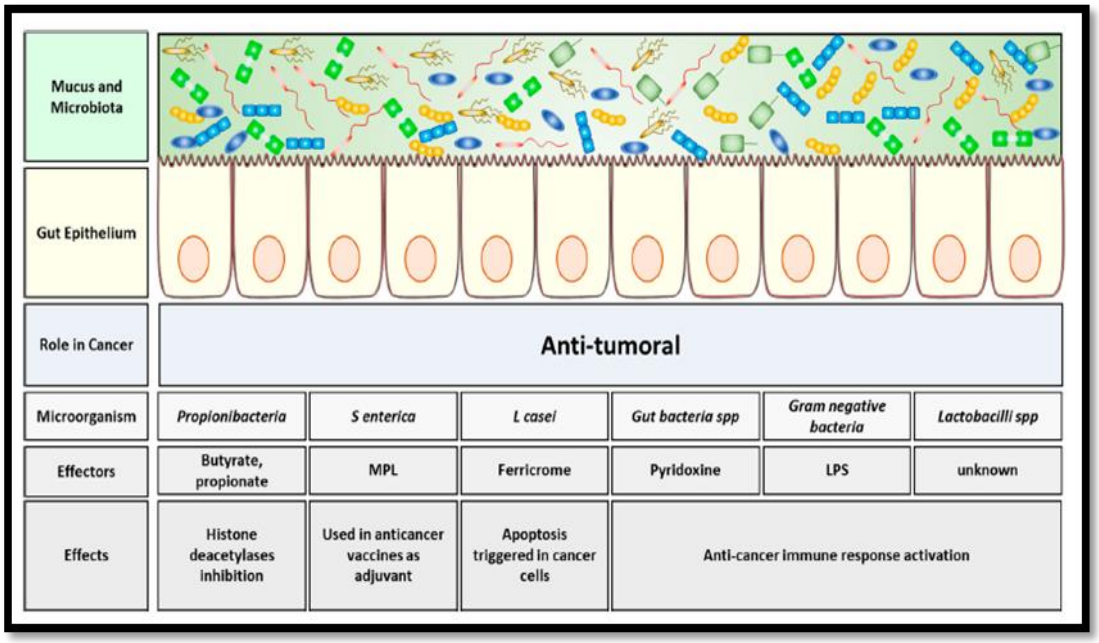
Table.1 A representative list of microorganisms used/planned to be used in anticancer therapy

Microorganism	Strain/antigen	Cancer	Type of treatment	Deployment
Mycobacterium bovis	Atenuated strain Calmette-Guérin	Superficial bladder cancer	Complementary therapy	Commonly used
Streptococcus pyogenes	OK-432	Lymphangioma	Alternative therapy for surgical treatment	Commonly used
Clostridium novyi	Strain NT	Solid tumors	No data	Clinical trials
Salmonella enterica serovar Typhimurium	Strain VNP20009	Melanoma	No data	Clinical trials
Magnetococcus marinus	MC1	Solid tumors and some metabolic tumors	Additional therapy supporting chemotherapy	Experimental research (animal studies)
Toxoplasma gondii	*CPS*/TLA	Pancreas, lung and ovarian cancer, and melanoma	No data	Experimental research
Plasmodium falciparum	rVAR2-DT	Melanoma expressing CS	No data	Experimental research

Table.2 Shows some examples of fungal metabolites that have progressed to various stages of cancer clinical trials.

Fungal metabolites	Fungal Source	Cellular Activity
Anguidine	**Fusarium sps. *F. roseum, F. sambucinum***	**Irreversibly blocks protein synthesis by inhibiting the protein chain initiation through degradation of polyribosomes**
Aphidicolin	***Cephalosporium aphidicola, Nigrospora sphaerica***	**specific inhibitor of DNA polymerases α and δ.**
Rhizoxin	***Rhizopus chinensis***	**Bind to tubulin at the vinca site and inhibit microtubule assembly. It was shown to possess cytotoxicity against a variety of human tumour cell lines and xenograft models**
Fumagillin	***Aspergillus fumigatus strain H-3***	**Disrupt tumor vasculature by targeting the enzyme methionine aminopeptidase**
Phenylahistin	***Aspergillus ustus***	**Have potent vascular disrupting properties through binding to the colchicine site on beta-tubulin**

Fig.1 Anti-tumoral effects of the gut microbiota. Probiotics and other gut resident bacteria that are able to secrete molecules, capable, in turn, to fight tumor growth and prevent tumorigenesis through several mechanisms. Schematic of the intestinal layers, from top to bottom: mucus and microbiota, gut epithelium. Into the grey boxes are illustrated, from top to bottom, the microorganism species implicated in the anti-cancer process, the molecules produced and the corresponding effects induced within the host.



Abbreviations: MPL, monophosphoryl lipid A; LPS, lipopolysaccharide.
(Silvia Vivarelli , Stefania Stefani 2018 Cancers)

These include triornicin, cytochalasin E, cotylenin A, myriocin, palmarumycin CP1, galiellalactone, epoxyquinol B, gliocladicillins A and B, apicidin, chaetocin and destruxin B. Also of importance is that recent patents, for the use of the metabolites and/or their analogues/derivatives in oncology, have been filed for cotylenin A, myriocin, palmarumycin CP1, apicidin and chaetocin and there is thus the possibility that these compounds will advance to clinical trials (Alexander Kornienkol, Antonio Evidente 2015).

Can Specific Microbes Be Used to Control Cancer Cell Populations as a Part of Treatment?

Microorganisms, such as Mycobacterium bovis and BCG, have been used in cancer treatment for more than 100 years, including the successful treatment of bladder cancer. Additionally, many microbial products are being used in cancer treatment, including redox proteins like azurin.

The mechanisms of action and these microbes appear to be diverse, with some activating the immune system, others inducing cell death via apoptosis and others inhibiting the growth of new blood vessels thereby depriving tumors of resources.

It is the need of the hour for researchers where Future work should investigate the metabolic and ecological interactions between tumor cells and microbes that underlie this effect in order to discover new microbes that can be used in cancer treatments.

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