MERAL Publications and Solutions Pvt. Ltd.

Original Article

Confrontation of the ambivalent roles of the intestinal microbiota in carcinogenesis: Oncogenic or anticancer agents?

Fatouma Mohamed Abdoul-Latif[1*], Ayoub Ainane[2], Omaima Saoudi[2], Houda Mohamed[1,3], Ali Merito Ali[1], Stefano Cacciatore[4], Tarik Ainane[2]

[1]Medicinal Research Institute, Center for Research and Study of Djibouti, BP 486, Djibouti. [2]Superior School of Technology, University of Sultan Moulay Slimane, BP 170, Khenifra 54000 Morocco. [3]Peltier Hospital of Djibouti, Djibouti City, Djibouti. [4]Bioinformatics Unit, International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town 7925, South Africa.

Correspondence: Fatouma Mohamed Abdoul-Latif, Medicinal Research Institute, Center for Research and Study of Djibouti, BP 486, Djibouti. fatoumaabdoulatif@gmail.com

Received: 23 November 2024; **Revised:** 12 February 2025; **Accepted:** 17 February 2025

ABSTRACT

The study of the contradictory roles of the gut microbiota in carcinogenesis reveals the complex interactions between intestinal microorganisms and tumor formation. This microbial ecosystem, composed of several bacterial species, plays an essential role in human biological balance. However, a disruption of this microbial community can potentially trigger the emergence of cancers, particularly colon cancer. This research aims to explore how certain intestinal bacteria, identified as oncogenic agents, participate in the initiation and progression of tumors through various processes, such as the induction of chronic inflammation, the production of genotoxic toxins, and the epigenetic regulation of genes. In parallel, the intestinal microbiota also has anticancer properties, where certain bacteria show an ability to trigger robust immune responses, positively modulate the tumor microenvironment, and increase the effectiveness of cancer therapies. A better understanding of these mechanisms could lead to innovative therapeutic approaches, where the protective properties of the microbiota would be integrated into personalized treatments, aimed at preventing and combating cancer while reducing the oncogenic risks associated with dysbiosis. This perspective opens new possibilities for precision medicine, where the microbiota could become both a therapeutic target and an essential tool in the fight against cancer diseases.

Keywords: Intestinal microbiota, Carcinogenesis, Dysbiosis, Oncogenic, Epigenetics, Bacterial therapy

Introduction

The gut microbiota, consisting of a complex community of billions of microorganisms, mainly residing in the gastrointestinal tract, is essential for maintaining homeostasis in humans [1]. This vast microbial ecosystem participates in key physiological functions such as nutrient digestion, vitamin synthesis, and the development and modulation of the immune system [2]. However, this microbiota is not only beneficial; it can also play a harmful role, notably by influencing carcinogenesis, i.e. the process of cancer formation and development. Some bacterial strains present in the gut microbiota can, in fact, promote the onset and progression of tumors, while others can play a protective role by preventing or limiting tumor development. This duality, where the microbiota acts as both an oncogenic and anticancer agent, is attracting increasing interest in oncological research [3].

At first glance, the relationship between the gut microbiota and cancer may seem unexpected. However, recent research has highlighted the basic role that these microorganisms play in modulating the immune system, thus influencing the development, progression, or regression of tumors [4]. On the one hand, some bacteria in the microbiota can promote

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Abdoul-Latif FM, Ainane A, Saoudi O, Mohamed H, Merito Ali A, Cacciatore S, et al. Confrontation of the ambivalent roles of the intestinal microbiota in carcinogenesis: oncogenic or anticancer agents? J Adv Pharm Educ Res. 2025;15(2):16-30. https://doi.org/10.51847/XocFRvwLrp

carcinogenesis through different mechanisms [5]. They can induce chronic inflammatory responses in the intestine, produce carcinogenic compounds, modify the expression of host genes, and disrupt immune responses, thus promoting the transformation of normal cells into cancer cells [6].

The oncogenic role of the intestinal microbiota is largely based on its ability to induce chronic inflammation, a pathological state that can damage the DNA of intestinal cells and promote their mutation. These genetic mutations, often considered precursors to tumor development, occur when a persistent inflammatory environment activates pro-inflammatory signaling pathways. This inflammatory context increases the risk of cancer because it creates a breeding ground for the proliferation of abnormal cells. Furthermore, some toxins produced by gut bacteria can directly alter DNA, causing double-strand breaks that facilitate the onset of oncogenic mutations. This toxin production, combined with chronic inflammation, creates a microenvironment conducive to tumor cell growth and progression [7].

In addition, the gut microbiota can influence carcinogenesis by modulating host cell gene expression through epigenetic mechanisms. For example, it can regulate DNA methylation, a key epigenetic process that controls gene expression. Abnormal regulation of DNA methylation can lead to the suppression of cancer-protective genes, such as tumor suppressor genes, thereby increasing the risk of tumor development. In addition, epigenetic modulation can also lead to the increased expression of pro-inflammatory cytokines, which not only stimulate cell proliferation but also promote tumor vascularization, facilitating their development and dissemination [8].

On the other hand, despite these potential oncogenic effects, the gut microbiota also has notable anticancer properties. Some bacteria play a protective role by enhancing host immune responses, which is essential for the detection and elimination of tumor cells. By activating key signaling pathways within the innate immune response, the microbiota can increase the efficacy of immune therapies, allowing the immune system to better target and eliminate cancer cells. This improvement in immune defenses can limit tumor progression and reduce the risk of relapse after treatment [4].

In addition, the gut microbiota can stimulate effector and memory T-cell responses, which are essential for the continued destruction of cancer cells and for the prevention of recurrence [9]. These T-cell immune responses are enhanced by the ability of the microbiota to reduce populations of immunosuppressive cells, such as regulatory T cells (Tregs) and marrow-derived suppressor cells (MDSCs). By reducing the influence of these cells that usually inhibit antitumor immune responses, the microbiota promotes a more effective and sustained immune response against tumors [10].

Furthermore, the microbiota also protects against cancer by producing metabolites with anticancer properties. These metabolites, such as short-chain fatty acids like butyrate, are able to induce apoptosis, or programmed cell death, of cancer cells, which prevents their proliferation [11]. The ability of these metabolites to induce apoptosis has been demonstrated in various animal models, where their presence not only reduced the incidence of cancer but also prolonged the survival of subjects with tumors. These observations suggest that the production of metabolites by the microbiota could be exploited for the development of new anticancer therapeutic strategies [12].

This study aims to analyze the ambivalent roles of the gut microbiota in carcinogenesis, highlighting its ability to both promote and inhibit tumor development. By examining the complex interactions between gut bacteria and the tumorigenesis process, this review explores how certain bacterial strains can modulate the formation and progression of neoplasms, notably by inducing chronic inflammation and producing genotoxic molecules. At the same time, it focuses on the anticancer properties of other bacteria, capable of regulating the tumor microenvironment favorably, optimizing host immune responses, and inspiring innovative therapeutic strategies.

Gut microbiota

Overview

The gut microbiota is one of the most studied areas in biology and medicine, largely thanks to international initiatives such as MetaHIT and the Human Microbiome Project, which aim to better characterize and understand this microcosm. This microbiota, weighing between one and five kilograms in adult humans, is composed of approximately 10^{14} microorganisms, which is ten times greater than the number of human cells in our body. Although bacteria make up the majority, the microbiota also includes archaea, viruses, and eukarya, making it an incredibly diverse ecosystem [13].

Among bacteria, anaerobes dominate, mainly belonging to three major phylogenetic groups: Firmicutes, Bacteroidetes, and Actinobacteria [14-16]. However, the exact composition of the gut microbiota varies significantly between individuals and also changes throughout life. Enterotypes are used to describe these different dominant microbial configurations. The first microbial colonization occurs at birth, and the mode of delivery plays a crucial role in this initial process. During a vaginal birth, the newborn is first colonized by microorganisms from the maternal genital tract, leading to a stabilization of the microbiota around the age of three years. In contrast, a cesarean birth leads to initial colonization by skin germs, which can delay the establishment of the microbiota and has been associated with a higher incidence of chronic inflammatory pathologies, including allergies [17].

Diet is another key factor that modifies the composition of the microbiota. A diet rich in meat and saturated fatty acids favors the growth of Bacteroidetes and the genus Ruminococcus, while a diet rich in fiber and simple sugars favors the genus Prevotella [18]. These variations show how sensitive the microbiota is to environmental influences and how it can be modulated by dietary choices.

Recent research has also revealed that the gut microbiota could be considered a true microbial "identity card". Approximately 57 species of bacteria are common to 90% of the population, defining what is called the "core genome" of the human microbiota **(Table 1)** [19, 20]. However, despite these

commonalities, each individual has a unique microbiota. This uniqueness is influenced by many factors, including geography, with marked differences observed between the microbiotas of people living in remote areas. The greater the geographical distance, the more pronounced the differences between enterotypes will be, although important similarities may still exist [21].

The evolution of the microbiota throughout life is also influenced by age and nutritional status. The Firmicutes group, a minority in children, becomes the majority in healthy adults, representing approximately 45% of the microbiota. Conversely, Proteobacteria, which are decreased in healthy subjects, persist at high levels in malnourished or obese individuals, indicating a potential link between microbiota composition and various pathophysiological states. These observations highlight the importance of the gut microbiota in human health and the need to better understand the factors that influence its composition throughout life [22].

Table 1. Main bacterial species of the human microbiota.

Phylum	Class	Family	Species
Firmicutes	Clostridia	Ruminococcaceae	*Faecalibacterium prausnitzii, Ruminococcus bromii, Ruminococcus obeum, Ruminococcus gnavus, Ruminococcus torques*
		Lachnospiraceae	*Roseburia intestinalis, Eubacterium rectale, Eubacterium hallii, Blautia obeum, Blautia wexlerae, Anaerostipes hadrus, Butyrivibrio crossotus*
		Peptostreptococcaceae	*Peptostreptococcus anaerobius*
		Clostridiaceae	*Clostridium leptum, Clostridium coccoides, Clostridium symbiosum, Clostridium clostridioforme*
		Veillonellaceae	*Veillonella parvula*
		Eubacteriaceae	*Eubacterium rectale, Eubacterium hallii*
		Oscillospiraceae	*Oscillospira guilliermondii*
		Turicibacteraceae	*Turicibacter sanguinis*
	Bacilli	Lactobacillaceae	*Lactobacillus rhamnosus, Lactobacillus gasseri, Lactobacillus casei*
		Enterococcaceae	*Enterococcus faecalis, Enterococcus faecium*
Bacteroidetes	Bacteroidia	Bacteroidaceae	*Bacteroides fragilis, Bacteroides vulgatus, Bacteroides thetaiotaomicron, Bacteroides ovatus, Bacteroides caccae*
		Prevotellaceae	*Prevotella copri*
		Rikenellaceae	*Alistipes putredinis*
		Porphyromonadaceae	*Parabacteroides distasonis, Parabacteroides merdae, Parabacteroides johnsonii*
		Odoribacteraceae	*Odoribacter splanchnicus*
		Barnesiellaceae	*Barnesiella intestinihominis*
Actinobacteria	Actinobacteria	Bifidobacteriaceae	*Bifidobacterium longum, Bifidobacterium adolescentis, Bifidobacterium bifidum, Bifidobacterium breve*
		Coriobacteriaceae	*Collinsella aerofaciens*
Proteobacteria	Gammaproteobacteria	Enterobacteriaceae	*Escherichia coli*
		Desulfovibrionaceae	*Desulfovibrio piger*
		Sutterellaceae	*Sutterella wadsworthensis*
	Deltaproteobacteria	Bilophilaeaceae	*Bilophila wadsworthia*
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiaceae	*Akkermansia muciniphila*
Euryarchaeota	Methanobacteria	Methanobacteriaceae	Methanobrevibacter smithii

Physiological roles

The gut microbiota performs several physiological functions that are essential for human health. One of its most important contributions concerns the regulation of angiogenesis, muscle development, and energy production. Gut bacteria release hundreds of enzymes that facilitate the digestion of plant-derived sugars, such as pectins and arabinose, allowing the body to maximize energy extraction from these compounds. In turn, the fermentation of these sugars by the bacteria feeds themselves, creating a cycle of mutualism that benefits the host [23].

In addition to digestion, the bacteria of the microbiota are also able to synthesize vitamins, amino acids, and short-chain fatty acids (SCFAs), which play an important role in the host metabolism. These SCFAs, such as butyrate and propionate, do not only provide energy; They are also involved in the regulation of inflammation and modulation of the immune response, thus providing protection against various inflammatory pathologies and potentially against the development of cancer [24].

The gut microbiota is also essential for the development of the enteric nervous system, which is one of the oldest nervous

systems that has emerged during evolution. This system, often called the "second brain", works closely with the central nervous system to regulate intestinal motility and other gastrointestinal functions. In addition, gut bacteria participate in the regulation of certain genetic processes, influencing key aspects such as immune responses, bacterial proliferation, and inflammation. For example, disturbances in the composition of the microbiota have been associated with genetic alterations in animal models of inflammatory bowel disease (IBD), highlighting the link between the microbiota and gene regulation [25].

The role of the microbiota as a barrier against pathogens and its importance in maintaining the immune system is also important. Studies on germ-free mice, devoid of microbiota, have shown significant deficiencies in their immune systems. These mice have smaller Payer's plaques (lymphoid structures in the intestine), a decrease in the number of plasma cells, IgA, and intraepithelial lymphocytes. These immune deficiencies can be corrected by recolonization of microbiota from healthy mice, illustrating the importance of the microbiota in the maturation and optimal functioning of the immune system [26].

However, although the microbiota is necessary for adequate maturation of the immune system, it is not sufficient on its own to guarantee complete protection against pathogens. Firmicutes, a dominant bacterial group, are distributed differently depending on the health status and are associated with variable protection against infections. The first microbial colonization, which occurs at birth, is particularly basic to stimulate an optimal immune response, especially if this colonization is by commensal bacteria capable of synthesizing SCFAs such as butyrate and propionate. These SCFAs promote the differentiation of regulatory T cells (LTreg) via acetylation of the FoxP3 locus, thereby reducing inflammation by inhibiting the NFKb pathway. In addition, they play a role in controlling the Th17 cell pool, which could provide protection against cancerization by modulating inflammatory responses. These observations highlight the importance of the gut microbiota not only in maintaining daily health but also in preventing chronic diseases and cancer [27].

Intestinal bacteria and their involvement in carcinogenesis

Dysbiosis and disruptions of the gut microbiota

The gut microbiota, a complex and dynamic ecosystem, can undergo significant disruptions, often referred to as dysbiosis, in response to various environmental factors. Among these factors, diet plays a key role, as does exposure to irritants to the intestinal mucosa such as alcohol, tobacco, airborne microparticles, pesticides, and heavy metals. Overuse or inappropriate use of antibiotics is also a major cause of dysbiosis, leading to imbalances that can have adverse health consequences [28].

Dysbiosis has been closely associated with several chronic diseases, including allergies, diabetes, obesity, autism, and inflammatory bowel diseases (IBD) such as Crohn's disease and irritable bowel syndrome. These pathologies are often characterized by chronic inflammation, a biological process that is recognized as a crucial preliminary step in the development of cancer, particularly in the context of carcinogenesis [29].

Chronic intestinal inflammation, in particular, represents a set of conditions that can progress to malignant tumors after several years. Although the causes of these inflammations are often multifactorial and poorly understood, the close relationship between immunity, microbiota, and cancer development is evident. Studies have shown that patients with these pathologies often have significant differences in the composition and diversity of their intestinal microbiota. This observation has led to the hypothesis that restoring the microbial balance could prevent the progression of these diseases to cancerous states. Treatments such as fecal microbiota transplantation, where bacteria from a healthy donor are transplanted into a patient, have shown promising results, particularly in the treatment of Crohn's disease [30].

Pro-oncogenic mechanisms of intestinal bacteria

The intestinal microbiota, although generally beneficial, can play a pro-oncogenic role when imbalanced. Pro-oncogenic bacteria contribute to cancer development through various pathogenic mechanisms. One of the key mechanisms is the stimulation of cell proliferation. Some bacteria in the microbiota can activate signaling pathways that increase host cell viability, thereby promoting uncontrolled tumor cell growth [31].

In addition, these bacteria can exacerbate the production of reactive oxygen species (ROS), causing DNA damage and genomic instability, conditions favorable to carcinogenesis. They can also modulate the expression of tumor suppressor genes, decreasing them while increasing the expression of oncogenic genes, which creates an environment conducive to tumor progression [32].

Furthermore, some bacteria can recruit immune suppressor cells into tumors, thereby thwarting antitumor immune responses and allowing tumors to grow. Activation of inflammasomes by these bacteria creates an inflammatory microenvironment that promotes cancer progression. Lastly, these bacteria can lessen the efficacy of anticancer therapies like chemotherapy and immunotherapy by interfering with immune responses and causing alterations in cells [33].

Bacterial strains associated with carcinogenesis

The gut microbiota, a complex community of microorganisms inhabiting the gastrointestinal tract, is essential for the preservation of human health. However, imbalances within this microbial community, referred to as dysbiosis, can cause various disorders, including the development of cancers [34]. Among the many microorganisms present in the intestine, certain bacterial strains have been recognized for their pro-oncogenic role, and

also they participate in the initiation and progression of tumors **(Table 2)**.

Fusobacterium nucleatum is one of the most studied bacteria for its involvement in colorectal cancer. It stands out for its ability to disrupt adaptive immunity by inhibiting antitumor T-cell responses, allowing cancer cells to proliferate undetected by the immune system. F. nucleatum also activates inflammatory signaling pathways, such as NLRP3, and interacts with the TIGIT receptor, inhibiting the cytotoxic function of NK cells. In addition, it influences tumor cell glycolysis via the ANGPTL4 protein, enhancing tumor aggressiveness [35].

Bacteroides fragilis is another intestinal bacterium strongly associated with colorectal cancer. It promotes cancer cell proliferation by activating the RHEB/mTOR pathway, which is essential for tumor cell growth and survival. B. fragilis also produces the toxin BFT, which causes DNA damage and induces chronic inflammation, two processes closely linked to carcinogenesis. This bacterium is also involved in intestinal mucosal hyperplasia, a precursor state of cancer, and the production of ROS, exacerbating oxidative damage and increasing the risk of cancer [36].

Escherichia coli, although generally harmless in the intestine, becomes pathogenic when it produces colibactins, molecules capable of causing DNA breaks, a key event in the malignant transformation of cells. E. coli also promotes epithelial-mesenchymal transition (EMT), a process by which epithelial cells acquire migratory and invasive properties, facilitating metastasis [37].

Clostridium difficile, mainly known for its severe intestinal infections, is also involved in carcinogenesis. This bacterium produces the toxin TcdB, which disrupts cellular signaling pathways, leading to cytoskeletal alterations, apoptosis, and chronic inflammation. These processes create an environment conducive to tumor growth and colorectal cancer development [38].

Peptostreptococcus anaerobius is a bacterium recently identified as being associated with colorectal cancer. It interacts with integrin α2/β1, overexpressed on colon cancer cells, stimulating their proliferation and migration. This interaction promotes tumor progression, supported by a local inflammatory environment conducive to cancer cell growth [39].

Hungatella hathewayi contributes to carcinogenesis through its ability to regulate DNA methylation, an important epigenetic process in the regulation of gene expression. By promoting the methylation of tumor suppressor genes, this bacterium facilitates the growth and proliferation of cancer cells, particularly in colorectal cancer [40].

Eubacterium, a commensal bacterial genus, is involved in chronic inflammation through activation of the transcription factor NF-κB. This activation supported by Eubacterium endotoxins creates a microenvironment favorable to tumor cell proliferation and colorectal cancer progression [41].

Streptococcus gallolyticus is closely linked to colorectal cancer by its ability to induce the expression of pro-inflammatory cytokines such as IL-1 and COX-2, as well as the chemokine IL-8, which promotes tumor growth and tumor vascularization. This bacterium also impairs the immune response, allowing uncontrolled proliferation of cancer cells [42].

Campylobacter jejuni, mainly associated with gastrointestinal infections, is also implicated in colorectal cancer. This bacterium produces a cytolytic distensive toxin (CDT) that causes DNA damage, inducing genomic instability, a key precursor to carcinogenesis. Furthermore, *C. jejuni* exacerbates chronic inflammation, creating an environment favorable to tumor development [43].

Table 2. Mechanisms and effects of some bacterial strains in carcinogenesis.

Bacteria	Type of Cancer	Mechanism	Effect
Fusobacterium nucleatum	Colorectal cancer	Inhibits anti-tumor T cells; activates NLRP3; interacts with TIGIT; influences glycolysis via ANGPTL4.	Promotes tumor cell proliferation; inhibits NK cell cytotoxicity; increases tumor aggressiveness.
Bacteroides fragilis	Colorectal cancer	Activates RHEB/mTOR pathway; produces BFT toxin; induces chronic inflammation; generates ROS.	Promotes cell proliferation; induces intestinal hyperplasia; increases cancer risk.
Escherichia coli	Colorectal cancer	Produces colibactins causing DNA breaks; promotes EMT.	Triggers malignant transformation; facilitates metastasis.
Clostridium difficile	Colorectal cancer	Produces TcdB toxin disrupting cell signaling; causes cytoskeletal alterations and inflammation.	Creates an environment conducive to tumor growth.
Peptostreptococcus anaerobius	Colorectal cancer	Interacts with α2/β1 integrin on colon cancer cells.	Stimulates tumor cell proliferation and migration.
Hungatella hathewayi	Colorectal cancer	Regulates DNA methylation.	Facilitates tumor cell growth and proliferation.
Eubacterium	Colorectal cancer	Activates NF-κB via endotoxins.	Promotes a tumor-friendly microenvironment.
Streptococcus gallolyticus	Colorectal cancer	Induces pro-inflammatory cytokines (IL-1, COX-2, IL-8); alters immune response.	Enhances tumor growth, vascularization, and cancer cell proliferation.
Campylobacter jejuni	Colorectal cancer	Produces CDT toxin causing DNA damage; exacerbates chronic inflammation.	Induces genomic instability; promotes tumor development.

Anti-oncogenic role of microbiota in tumor regression

The tumor microenvironment (TME) plays a central role in tumor development and progression. This microenvironment consists of tumor cells surrounded by blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, various signaling molecules, and the extracellular matrix. The rapid proliferation of tumor cells leads to the formation of immature vascular structures, thus creating a hypoxic microenvironment. This condition, coupled with high interstitial pressure and fibroblast density, limits the efficacy of antitumor drugs. However, some specific anaerobic bacteria can invade and colonize this hypoxic microenvironment, playing an anti-oncogenic role by promoting tumor regression [44].

Invasion of anaerobic bacteria in hypoxic TME

Anaerobic bacteria possess a unique ability to colonize hypoxic areas of tumors. These regions are often resistant to conventional therapies due to poor drug penetration. However, some bacterial strains not only manage to survive in these harsh conditions but also exert antitumor effects by directly killing cancer cells or by inducing innate and adaptive immune responses against infected tumor cells [45].

Salmonella typhimurium has shown an ability to specifically target tumors and colonize hypoxic microenvironments, contributing to tumor regression. Similarly, bacteria such as Listeria monocytogenes and Clostridium novyi-NT (a strain of Clostridium modified to eliminate the α-toxin gene) have been studied for their ability to directly attack tumor cells and induce immune responses favorable to tumor regression [46].

Stimulation of innate and adaptive immune responses

Some bacteria have the ability to induce innate and adaptive immune responses that play a basic role in tumor regression.

Salmonella typhimurium is able to stimulate a potent immune response against tumor cells by triggering the production of pro-inflammatory cytokines such as interleukin-1β. This cytokine promotes the activation of M1 macrophages, which are associated with antitumor responses while reducing the population of M2 macrophages, which generally support tumor progression [47].

Similarly, *Listeria monocytogenes* is known to induce long-lasting effector and memory T-cell responses, essential for the continued destruction of cancer cells and the prevention of relapse. These bacteria can also reduce the populations of regulatory T cells (Treg) and marrow-derived suppressor cells (MDSC), which normally inhibit antitumor immune responses [48].

Regulation of systemic anti-tumor immunity

Bacteria that possess low cytotoxicity toward tumor cells, such as *Bifidobacterium infantis*, play a key role in regulating systemic anti-tumor immunity. These bacteria can modulate the tumor environment by increasing the efficacy of immune therapies. For example, *B. infantis* has been shown to facilitate immunotherapies based on CD47 blockade by activating the STING signaling pathway, which is essential for the innate immune response. Studies have also shown that *Bifidobacterium bifidum* can increase the biosynthesis of immune-stimulating molecules and metabolites, leading to better recognition and destruction of tumor cells by the immune system [49].

Bacterial therapies

Some bacteria have the ability to thrive in oxygen-deficient environments, such as solid tumors, which are often characterized by hypoxic or anoxic conditions. This metabolic adaptation allows these bacteria to circumvent the complexities of tumor and immune biology. Unlike passive systemic treatments, these bacteria, considered "biologically active agents," are particularly effective at targeting and colonizing tumor tissues. Their specific metabolism, their ability to move in a directed manner, and their sensitivity to the tumor environment give them increased selectivity for cancer tissues, potentially offering safer and more targeted treatments [50].

The development of new therapeutic approaches in oncology is based on the need to accurately select and detect tumors. The distinct physiological properties of some bacteria, which can be genetically modified, if necessary, perfectly meet these requirements and they can localize and multiply in tumor tissues when administered intravenously in animal models. These bacteria can then exert direct toxicity on tumor cells by synthesizing and releasing cytotoxic molecules on-site while creating nutritional competition within the tumor [51].

Research using mice as test subjects has produced encouraging outcomes, including tumor remissions and minimal damage in certain cases. However, despite demonstrating good tolerance, clinical trials have shown inconsistent efficacy, and increasing doses to improve efficacy has resulted in significant toxicity. Despite these challenges, therapies based on the use of bacteria continue to be explored with encouraging results in preclinical and clinical studies [52].

Clostridium novyi-NT

Clostridium novyi-NT has emerged as a promising candidate for cancer therapy, particularly after preliminary findings revealed its potential to target and destroy tumor cells. This strain is a modified version of *Clostridium novyi*, a strictly anaerobic bacterium known for its ability to thrive in oxygen-deficient environments, such as hypoxic solid tumors. Its ability to selectively colonize these environments and induce tumor cell lysis makes it a subject of interest for anticancer therapies **(Figure 1)** [53].

Initially, studies focused on *Clostridium histolyticum M-55*, an avirulent strain tested in animal models for colon tumors and melanoma, but clinical results were disappointing. Subsequently, a selection process identified *Clostridium novyi* as the most effective strain for colonizing tumors and inducing carcinolytic effects, despite its sensitivity to oxygen toxicity. This strain initially produced a lethal α-toxin, which led to the development of the *Clostridium novyi-NT* (Non-Toxigenic) strain via heat treatment to destroy the toxin-producing system [54].

Clostridium novyi-NT has a unique advantage as targeted therapy, as its strict requirement for an anaerobic environment makes it specific to hypoxic tumors, minimizing the risk of toxicity in normoxic tissues. Preclinical studies have shown that injection of spores of this strain into tumor-bearing mouse models resulted in a significant reduction in tumor mass. The bacteria act by producing enzymes such as proteases and lipases that degrade tumor tissues while triggering an inflammatory and immune response that enhances the anticancer effect [55].

One of the main mechanisms of action of *Clostridium novyi-NT* is the induction of local inflammation and stimulation of the immune system, in particular by the production of cytokines such as IL-6, which promote the differentiation of TH17 cells and the activation of CD8+ T lymphocytes, thus enhancing the antitumor immune response. These properties make *Clostridium novyi-NT* a potential tool for combination therapies, including the use of antiangiogenic agents, radiotherapies, and DNA poisons to maximize efficacy while minimizing toxicity [56].

Clinical trials in animal models have shown that the use of *Clostridium novyi-NT* alone, or in combination with other treatments, can induce significant tumor regression, even in large tumors. Furthermore, these studies revealed that the immune response induced by *Clostridium novyi-NT* could provide long-term protection against relapse, with results showing sustained efficacy up to 11 months after initial treatment [57].

However, the therapy is not without risks. Toxicity studies indicated that high doses could lead to reversible side effects, such as hepatomegaly and splenomegaly. The studies also revealed that *Clostridium novyi-NT* only germinates in hypoxic tumor environments, thus limiting the risks of systemic infection. The addition of antibiotics reduced some side effects, although this also decreased antitumor efficacy. Simple hydration has been suggested as an effective method to mitigate toxicity without compromising therapeutic efficacy [58].

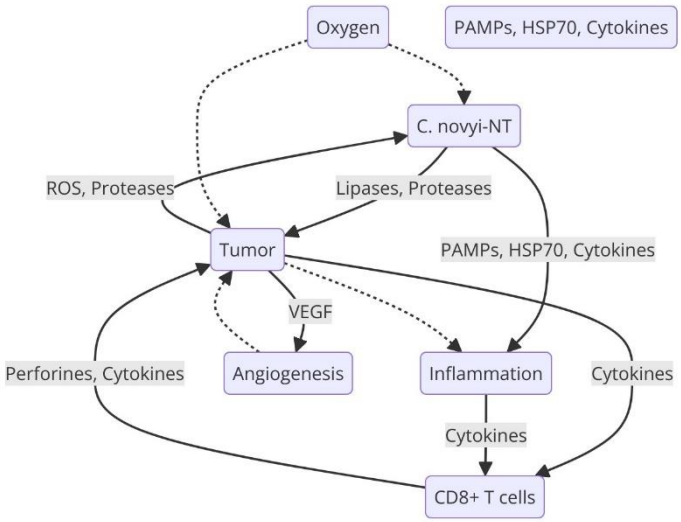

Figure 1. Mechanism of action of C. novyi-NT. (Spores localize in anoxic areas of the tumor where they germinate and cause tumor cell lysis)

Salmonella typhimurium

Salmonella Typhimurium is an enterobacteria, a Gram-negative bacillus often found in the intestinal lumen of mammals. This microorganism has several characteristics that make it an interesting candidate for therapeutic strategies, particularly in oncology. Its ability to replicate massively in tumor tissues, at a rate 1000 times higher than that observed in healthy tissues, as well as its ability to produce lipopolysaccharide (LPS), are among the factors that give it a unique therapeutic potential **(Figure 2)** [59].

S. Typhimurium is a motile, facultative intracellular bacterium capable of surviving and replicating within phagocytic cells. The LPS it produces plays an essential role in its virulence, allowing it to protect itself from its environment while stimulating an intense immune response. When invading the intestinal mucosa, this bacterium generates cellular lesions and triggers an inflammatory response marked by an influx of leukocytes, which can lead to symptoms such as diarrhea. These biological properties are exploited in the context of its therapeutic use, where phase I clinical trials have been conducted to evaluate its potential as an anti-tumor agent [60].

The ability of *S. Typhimurium* to survive in anaerobic conditions allows its intra-tumoral development, thus exploiting the hypoxic environments of tumors. However, this approach is associated with a risk of toxic shock due to the production of LPS. To overcome this problem, a modified strain of *S. Typhimurium*, called VPN20009, was developed. This strain is auxotrophic for purines, meaning that its metabolism is dependent on these molecules abundant in tumor environments due to cell lysis. In

addition, the VPN20009 strain is deleted from the msbB and purI genes, thus reducing virulence and the risk of toxic shock while retaining its ability to colonize tumors [61].

Clinical trials conducted in 1999 showed acceptable tolerance of the VPN20009 strain, but limited efficacy in terms of tumor regression. This low efficacy has been attributed to insufficient tumor colonization and rapid elimination of the bacteria by the body. In response to these limitations, new strains carrying tumor immunological targets, such as Tumors Associated Antigens (TAA), are being developed to improve the recognition and elimination of tumor cells by the immune system [62].

Another promising strain, named A1-R, was designed to be auxotrophic for leucine and arginine, limiting its proliferation to tumor tissues where these amino acids are abundantly available. This strain has shown notable efficacy in the colonization and destruction of lung tumors in mice, as well as anti-angiogenic activity, particularly beneficial in highly vascularized tumors [63].

The two strains described, VPN20009 and A1-R, are the most advanced in the development of *Salmonella Typhimurium*-based therapies. VPN20009 is currently the only strain to have reached the clinical phase, although obstacles remain. The results obtained so far suggest that S. Typhimurium could become a promising therapeutic agent or treatment vector in the fight against cancers. The future of this research focuses on improving tumor colonization, optimizing safety, and increasing the clinical efficacy of these modified strains [64].

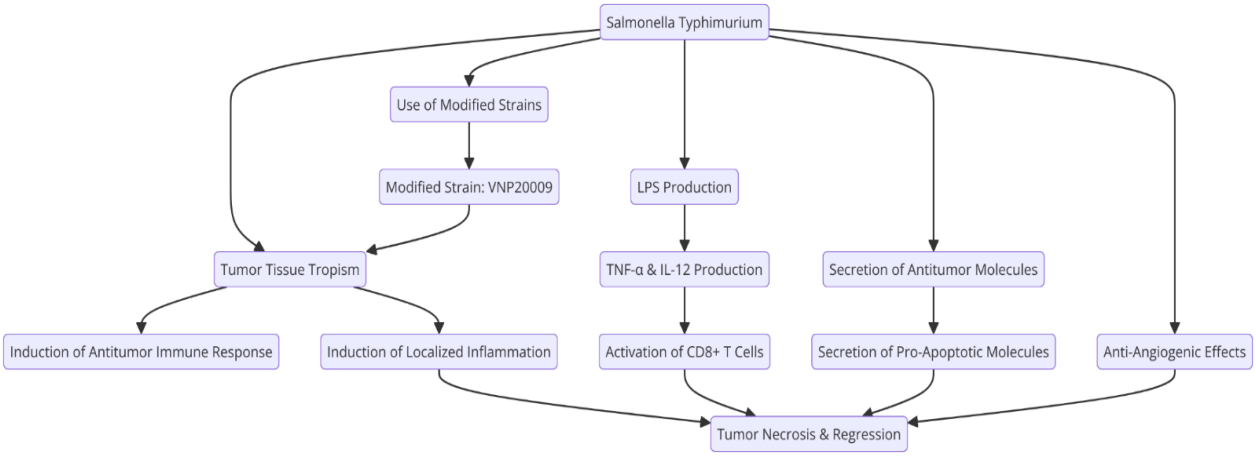

Figure 2. Therapeutic mechanisms of Salmonella Typhimurium.

Listeria monocytogenes

Listeria monocytogenes is a Gram-positive, non-spore-forming bacillus that is motile at 20°C, belonging to the Firmicutes group. Its facultative aero-anaerobic metabolism, combined with the presence of catalase and the production of β-hemolysis by listeriolysin O (LLO), allows this bacterium to survive in various environments, including at 4°C, which gives it a psychrophilic character. *Listeria* is widespread, found in soils, waters, and plants, and approximately 1 to 10% of the human population are thought to be healthy carriers at the intestinal level. Listeria monocytogenes is a pathogenic intracellular bacterium with a tropism for the central nervous system (CNS) and can cause serious infections, particularly in immunocompromised individuals, pregnant women, and newborns. Although listeriosis is relatively rare, with about 200 cases per year in France, it has a high mortality rate of 25 to 30%, even with effective antibiotic therapy. Human contamination occurs mainly through food, particularly via refrigerated products such as raw milk cheeses, cold meats, and seafood **(Figure 3)** [65].

In an innovative therapeutic strategy, *Listeria monocytogenes* has been exploited for its intracellular parasitism properties. The bacterium, thanks to its internalin surface protein, crosses the intestinal barrier and induces its phagocytosis by intestinal antigen-presenting cells (APCs). LLO, when paired with a phospholipase, permits a tiny percentage of bacteria to break free from the phagosome and proliferate in the cytoplasm. Because of its capacity to polymerize actin, Listeria can potentially spread to nearby cells, thus renewing the infectious cycle and effectively reaching tumor cells [66].

To minimize the risk of infection, an attenuated *Listeria* strain, deleted of the actA and plcB genes, was developed. These genes are respectively responsible for the intercellular mobility of the bacteria and the lysis of cell membranes. Although this strain is avirulent, it retains its ability to stimulate the immune system, making it a promising candidate for anti-tumor vaccination applications [67].

This approach has been successfully tested in mouse models, where *Listeria*-based vectors have been developed to carry specific tumor-associated antigens (TAAs) such as HPV16 (cervical cancer), Her2/neu (breast cancer), PSA (prostate cancer), and VEGFR-2 (tumor developmental antigen). Preclinical studies have shown that injection of these vectors can induce a strong immune response, sufficient to eradicate the corresponding tumors in many cases [68].

Clinical trials conducted by ADVAXIS on patients with metastatic carcinomas have also shown encouraging results, with tumor reduction observed in 30% of treated patients, although some side effects, such as hypotension and flu-like syndrome, were rapidly resolved by antibiotic and symptomatic treatment. In addition, *Listeria monocytogenes* has been explored as a vector for radiotherapy directed against breast cancers, offering a new

therapeutic perspective for the treatment of metastases. Listeria monocytogenes is therefore proving to be a very promising candidate for both therapeutic and prophylactic applications in oncology, thanks to its ability to target tumor cells and induce a robust immune response [69].

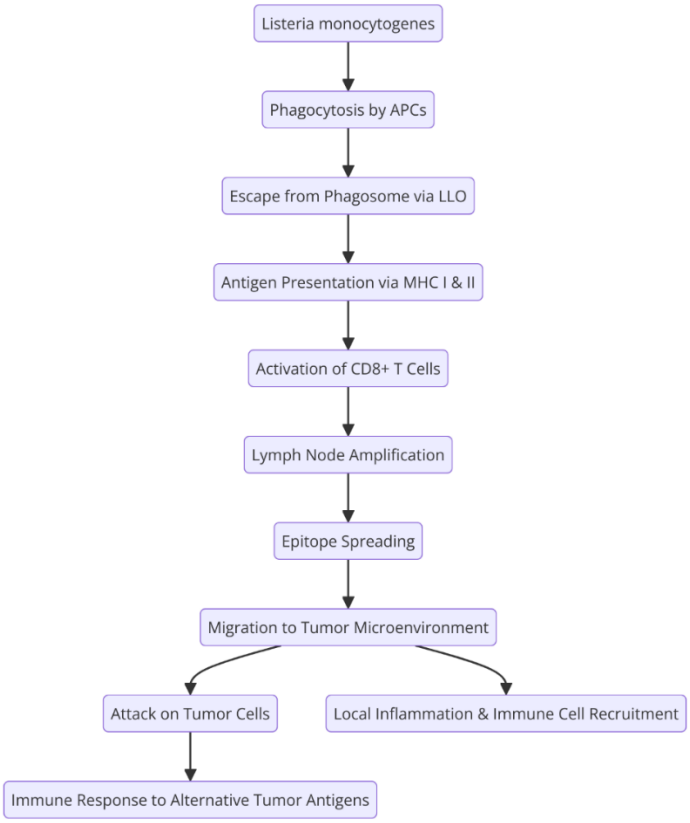

Figure 3. Schematic representation of the Listeria monocytogenes vaccination mode. (The bacteria are taken over by the APCs, which allow the expression of TAAs and stimulate an immune response directed against tumor cells.)

Mycobacterium bovis

Mycobacterium bovis is a strain related to Koch's bacillus (BK) and is used in the BCG (*Bacillus Calmette-Guérin*) vaccine. This slow-growing curved bacillus is characterized by its resistance to acids and alcohols, identifiable by the Ziehl-Nielsen stain, which classifies it among the Acid-Fast Bacilli (AFB). It has a membrane composed of mycophenolic acid, is non-sporulated, immobile, and strictly aerobic. These characteristics differentiate it from other bacteria studied for their anticancer therapeutic potential [70].

Due to its strict requirement for oxygen, *Mycobacterium bovis* cannot grow in the hypoxic environments typical of internal tumor tissues, unlike other bacteria. However, this strain is particularly effective in the treatment of external tumors, mainly at the bladder level. The therapeutic strategy consists of directly inoculating the bacteria into the bladder through a urethral catheter. This inoculation provokes an intense immune response, marked by the production of numerous cytokines (IL-2, IL-6, IL-8, IL-10, IL-12, TNF-α, INF-α, and γ) and by the activation of several types of immune cells, including CD4, CD8 and NK cells. This response leads to targeted apoptosis of cancer cells, mainly induced by TNF-α **(Figure 4)** [71].

Attempts to reproduce this immune reaction by direct administration of cytokines have been made, but the presence of the bacteria seems essential to obtain an optimal response. In addition, the administration of cytokines with BCG improves the therapeutic efficacy compared to inoculation alone, although this can sometimes cause irritation and allergic reactions [71].

BCG therapy, used since its introduction by Morales in 1976, is today the reference treatment for bladder tumors at high risk of recurrence and progression. In clinical practice, BCG therapy is often used as adjuvant treatment after transurethral resection or as an adjunct to conventional chemotherapy. This approach significantly reduces recurrences and improves 5-year survival of patients [72].

In terms of protocols, induction treatment consists of weekly instillation for 6 weeks, followed by maintenance treatment. However, the protocols for this maintenance treatment are not standardized, and the dosage must sometimes be reduced to improve tolerance. The French Society of Urology recommends a complete assessment before installation, including a complete biological assessment [73].

Although BCG therapy is widely used with success, some aspects, such as the harmonization of protocols, could still be improved to optimize the tolerance and efficacy of the treatment. Nevertheless, *Bacillus Calmette-Guérin* remains a concrete example of the daily use of a bacterium to effectively treat bladder cancer, which is the sixth most common cancer in France [74].

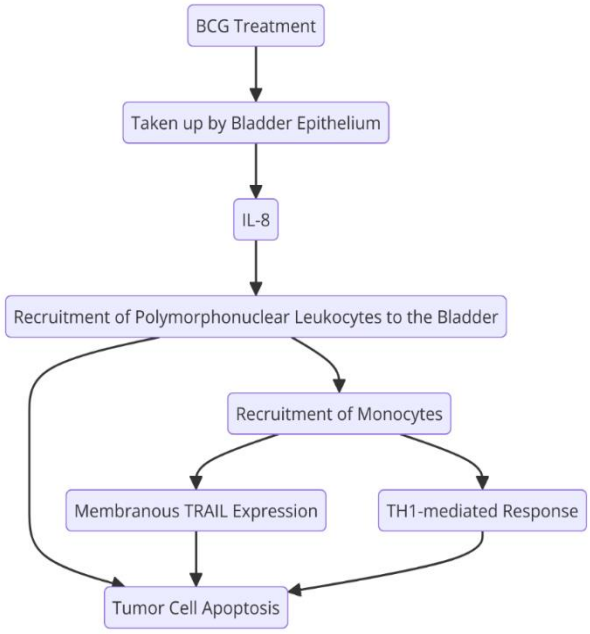

Figure 4. Schematic representation of the mode of action of BCG therapy.

Bifidobacterium spp.

Bifidobacterium is a genus belonging to the class Actinobacteria, characterized by Gram-positive, strictly anaerobic, non-sporulating, and nonmotile bacilli. These fermentative bacteria are mainly found in the mammalian colon and constitute an essential part of the human intestinal microbiota. Bifidobacterium is non-pathogenic and often used for its probiotic properties. Its fermentation produces lactic acid, lowering the pH and inhibiting the growth of other microorganisms. This ability is exploited in food preservation, particularly in fermented dairy products, although its main role remains oriented toward marketing applications. The therapeutic strategy using Bifidobacterium relies on its anaerobic character to target tumor tissues, particularly in hypoxic environments. Unlike other bacteria studied for their anticancer potential, Bifidobacterium is avirulent, meaning that it does not trigger inflammation or significant immune response, thus limiting its direct efficacy for tumor reduction. However, this feature makes it a potential vector for in situ drug or therapeutic agent delivery **(Figure 5)** [75].

An innovative application of this strategy is to use Bifidobacterium strains carrying a plasmid encoding Cytosine Deaminase (CD), a bacterial enzyme capable of converting the prodrug 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU), a potent anticancer agent. 5-FU, by inhibiting the metabolism of pyrimidine bases such as uracil, blocks the synthesis of nucleic acids, thus preventing tumor cell proliferation. By using Bifidobacterium to perform this conversion specifically at the tumor tissue level, this approach could significantly reduce the side effects associated with systemic 5-FU administration, while increasing the selectivity of treatment [76].

Preclinical studies in animal models, including tumor-bearing mice and rats, as well as toxicity tests in monkeys and guinea pigs, have not revealed any signs of significant toxicity or adverse reactions, suggesting that Bifidobacterium is a safe vector for this type of therapy. One of the major challenges remains industrial development, due to the large molecular size of this vector, which limits the delivery options, although oral administration is being considered [77].

Studies have shown that strains of *Bifidobacterium breve*, administered orally to mice, can migrate to tumors, where they multiply specifically without inducing toxicity or translocation of other bacterial populations. This targeted colonization of tumors seems promising, suggesting that Bifidobacterium could play a key role in the development of new therapeutic strategies against cancer [78, 79].

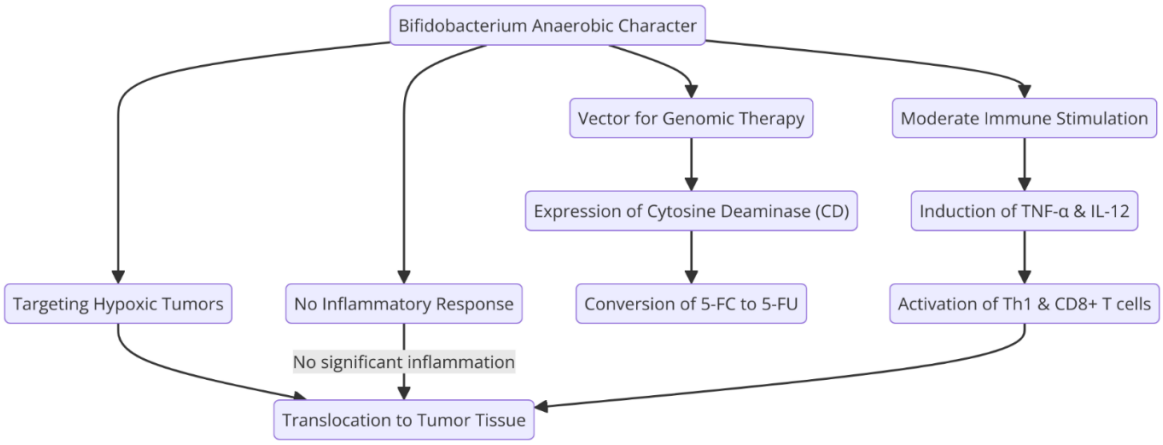

Figure 5. Therapeutic mechanism of Bifidobacterium.

Probiotics

The gut microbiota represents a complex ecosystem, hosting a large bacterial population that actively interacts with its environment, including the immune system (IS). It has been shown that maintaining a balanced microbiota, through a diverse and healthy diet, combined with the avoidance of toxic substances, can potentially support and enhance IS stimulation, thus playing an important role in preserving the cellular integrity of the body. Consequently, prophylactic interventions are possible [80, 81].

Research has revealed that the targeted introduction of certain microbiota bacteria, absent in individuals with specific pathologies, could offer notable clinical benefits. Fecal microbiota transplantation has shown promising results in the management of chronic inflammatory bowel diseases (IBD). Regarding oncology, various avenues have been explored to adjust or improve the microbiota's anti-tumor stimulation [82, 83].

The mode of action of probiotics in cancer therapy is based on several key mechanisms. Probiotics, which are beneficial bacteria naturally present in the gut, can modulate the gut microbiota and interact with the immune system (IS) to promote anti-tumor immune responses. They can stimulate the production of pro-inflammatory cytokines, enhance the activation of T cells and NK cells, and promote the differentiation of Th1 lymphocytes, which are essential for an effective immune response against tumor cells. In addition, some probiotic strains can inhibit tumor growth by regulating the tumor microenvironment, reducing chronic inflammation and thus limiting the proliferation of cancer cells. These bacteria can also serve as vectors to deliver therapeutic agents directly into tumor tissues, increasing the specificity and reducing the side effects of conventional treatments. Studies on cancer have revealed the translocation of intestinal bacteria, including Enterococcus hirae, Lactobacillus johnsonii, and Lactobacillus murinus, to secondary lymphoid organs in mice harboring colonic tumors. This phenomenon is attributed to the inflammation triggered by the alkylating agent cyclophosphamide (CTX). This translocation initiated an anti-tumor immune response sufficient to eradicate tumors in mice. The presence of these bacteria was found to be essential for therapeutic efficacy, with a reduction in efficacy observed in mice with disrupted microbiota [84, 85].

Enterococcus hirae, a Gram-positive cocci, was studied to better understand its properties related to anti-tumor action. Phenotypic analyses showed few significant differences in terms of virulence, antibiotic resistance, and response to environmental stresses between different E. hirae strains. However, comparative genomic analysis identified strain-specific genes capable of translocation, absent in other strains. These results suggest new potential applications, highlighting the importance of E. hirae and Barnesiella intestinihominis in improving the efficacy of CTX anti-tumor treatment. E. hirae demonstrated the ability to restore CTX efficacy after oral administration, while B. intestinihominis promoted a protective Th1-type immune differentiation, similar to a vaccine effect, in the presence of CTX [86, 87].

Optimization of bacterial therapies by genetic engineering

Genetic engineering and biochemical synthesis are key tools to optimize bacterial therapies, reducing their toxicity while increasing their antitumor efficacy. For this, *Salmonella typhimurium* was modified to express cytosine deaminase, an enzyme that converts cytosine to uracil, facilitating the destruction of tumor cells [88, 89].

In addition, *Clostridium novyi-NT* spores were genetically modified to eliminate toxic genes while retaining their ability to proliferate in hypoxic environments and induce tumor necrosis. This approach improves the safety of therapies while maintaining their efficacy [90, 91].

Advances in synthetic biology also enable the creation of customizable multifunctional therapeutic platforms. These platforms can be designed to meet the specific therapeutic needs of each patient, for example by combining the expression of pro-inflammatory cytokines, cytotoxic molecules, and immunostimulatory factors in a single bacterial strain.

Clostridium novyi-NT and *Salmonella Typhimurium* are recognized for their ability to infiltrate hypoxic tumor regions; Clostridium generates enzymes that enzymatically degrade tumor tissues, while Salmonella is genetically engineered to express tumor-

associated antigens or cytotoxic enzymes. *Listeria monocytogenes* is notable for its capacity to induce a potent immune response via T-cell activation, especially when leveraged as a vector for tumor-specific antigens, though it may elicit flu-like symptoms and hypotension, both of which are manageable with antibiotic therapy. *Mycobacterium bovis* (BCG), extensively utilized in bladder cancer therapy, triggers a robust localized immune response, leading to cytokine production, yet it may also incite localized inflammatory reactions. *Bifidobacterium spp.*, despite being avirulent, functions as a vector for delivering therapeutic agents, such as converting prodrugs into active anti-cancer compounds directly at the tumor site, with minimal immune stimulation and negligible toxicity. Lastly, *Enterococcus hirae* and *Barnesiella intestinihominis* enhance chemotherapy efficacy by potentiating specific immune responses, with no significant toxicity observed. This synthesis highlights the diverse mechanisms by which these bacterial strains are harnessed for their therapeutic potential in oncology, alongside their safety profiles [92-94].

Conclusion

The conflicting involvement of the gut microbiota in the development of cancer has exposed a complicated duality in which certain bacteria have been shown to have pro-carcinogenic properties while others have been shown to have anti-carcinogenic properties. On the one hand, bacterial strains such as Fusobacterium nucleatum, Bacteroides fragilis, and Escherichia coli have been strongly associated with the development of various types of cancers, including colorectal cancer. These bacteria have contributed to carcinogenesis through several mechanisms. They induced chronic inflammation, produced DNA-damaging toxins, modulated gene expression epigenetically, and disrupted host immune responses. These actions created a favorable environment for tumor cell proliferation and cancer progression. On the other hand, some bacteria, such as Bifidobacterium infantis, Listeria monocytogenes, and Salmonella typhimurium, have demonstrated significant anticancer properties. These bacteria were able to stimulate innate and adaptive immune responses, modulate the tumor environment to promote cancer cell destruction and improve the efficacy of anticancer therapies. They colonized hypoxic tumor microenvironments, induced tumor necrosis, and, in some cases, prolonged patient survival. The anticancer properties of these bacteria have been exploited in several clinical and preclinical studies, where they have shown promising potential to treat different types of tumors. Genetic engineering of bacteria has enhanced their anticancer effects while reducing their toxicity, opening the way to innovative therapeutic strategies. These advances have shown that bacterial therapies, in combination with immunotherapies, could offer targeted therapeutic options, capable of directly attacking tumors while exploiting the patient's natural immune responses. The gut microbiota has therefore been recognized as exerting both pro-oncogenic and anti-cancer influences, highlighting the importance of balanced management of gut health in the fight against cancer. A better understanding of these opposing mechanisms could lead to significant advances in cancer prevention and treatment, using the microbiota as both a therapeutic target and a treatment tool.

Acknowledgments: We express our deep gratitude to the Institut Supérieur des Sciences de la Santé (ISSS), Djibouti City P.O. Box 2530, Djibouti, and the Medicinal Research Institute, Center for Research and Study of Djibouti, for their invaluable support and essential contribution to the completion of this research. Their expertise and assistance were crucial to the success of this study.

Conflict of interest: None

Financial support: This project benefited from financial support from ICGEB within the framework of the CRP/DJI22-01 project.

Ethics statement: None

References

1. Ahmed U, Khan F. Understanding the gut microbiome: implications for human health. Res Med Sci Rev. 2023;1(01):47-56.
2. Lin D, Medeiros DM. The microbiome is a major function of the gastrointestinal tract and its implication in micronutrient metabolism and chronic diseases. Nutr Res. 2023;112:30-45.
3. Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. Nat Rev Clin Oncol. 2023;20(7):429-52.
4. Zhao LY, Mei JX, Yu G, Lei L, Zhang WH, Liu K, et al. Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications. Signal Transduct Target Ther. 2023;8(1):201.
5. Pandey M, Bhattacharyya J. Gut microbiota and epigenetics in colorectal cancer: implications for carcinogenesis and therapeutic intervention. Epigenomics. 2024;16(6):403-18.
6. Mignini I, Ainora ME, Di Francesco S, Galasso L, Gasbarrini A, Zocco MA. Tumorigenesis in inflammatory bowel disease: microbiota-environment interconnections. Cancers. 2023;15(12):3200.
7. Mendes I, Vale N. How can the microbiome induce carcinogenesis and modulate drug resistance in cancer therapy? Int J Mol Sci. 2023;24(14):11855.
8. Reyes ME, Pulgar V, Vivallo C, Ili CG, Mora-Lagos B, Brebi P. Epigenetic modulation of cytokine expression in gastric cancer: influence on angiogenesis, metastasis and chemoresistance. Front Immunol. 2024;15:1347530.
9. Yang J, Cao F, Shen J, Zeng Y, Bai Y, Zhou C, et al. Bile acids modified by the intestinal microbiota promote

colorectal cancer growth by suppressing CD8 T cell effector functions. Immunity. 2024;57:1-14.
10. Wang J, Zhu N, Su X, Gao Y, Yang R. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. Cells. 2023;12(5):793.
11. Gomes S, Rodrigues AC, Pazienza V, Preto A. Modulation of the tumor microenvironment by microbiota-derived short-chain fatty acids: impact in colorectal cancer therapy. Int J Mol Sci. 2023;24(6):5069.
12. Yang Q, Wang B, Zheng Q, Li H, Meng X, Zhou F, et al. A review of gut microbiota-derived metabolites in tumor progression and cancer therapy. Adv Sci. 2023;10(15):2207366.
13. Wu H, Forslund S, Wang Z, Zhao G. Human gut microbiome researches over the last decade: current challenges and future directions. Phenomics. 2023:1-7.
14. Arbabi F, Shapoury R, Haghi F, Zeighami H, Pirzeh R. Investigating the bacterial profiles of lactobacillus, bifidobacterium, actinobacteria, fusobacterium, firmicutes, and bacteroides in stool samples from patients with severe depression and healthy individuals. Psychoneuroendocrinology. 2024;107090.
15. Bensch HM, Tolf C, Waldenström J, Lundin D, Zöttl M. Bacteroidetes to firmicutes: captivity changes the gut microbiota composition and diversity in a social subterranean rodent. Anim Microbiome. 2023;5(1):9.
16. Guo XJ, Dai SX, Lou JD, Ma XX, Hu XJ, Tu LP, et al. Distribution characteristics of oral microbiota and its relationship with intestinal microbiota in patients with type 2 diabetes mellitus. Front Endocrinol. 2023;14:1119201.
17. Suárez-Martínez C, Santaella-Pascual M, Yagüe-Guirao G, Martínez-Graciá C. Infant gut microbiota colonization: influence of prenatal and postnatal factors, focusing on diet. Front Microbiol. 2023;14:1236254.
18. Zapała B, Pustelnik J, Dudek A, Milewicz T. Differences in the composition of akkermansia species and families of christensenellaceae and ruminococcaceae bacteria in the gut microbiota of healthy polish women following a typical western diet. Diversity. 2023;15(10):1103.
19. Liu Z, Good BH. Dynamics of bacterial recombination in the human gut microbiome. PLoS Biol. 2024;22(2).
20. Yin Z, Liang J, Zhang M, Chen B, Yu Z, Tian X, et al. Pan-genome insights into adaptive evolution of bacterial symbionts in mixed host-microbe symbioses represented by human gut microbiota bacteroides cellulosilyticus. Sci Total Environ. 2024;927:172251.
21. Shanahan F, Ghosh TS, O'Toole PW. Human microbiome variance is underestimated. Curr Opin Microbiol. 2023;73:102288.
22. Oluwaloni FO, Yakubu OF, Adebayo AH, Koyejo OD, Lawal AK. Review of the gut microbiota dynamics in type-2 diabetes mellitus (T2DM): a focus on human-based studies. Trop J Nat Prod Res. 2023;7(6):3059-79.
23. Rong X, Shen C, Shu Q. Interplay between traditional Chinese medicine polysaccharides and gut microbiota: the elusive "polysaccharides-bond-bacteria-enzyme" equation. Phytother Res. 2024;38(9):4695-715.
24. Fusco W, Lorenzo MB, Cintoni M, Porcari S, Rinninella E, Kaitsas F, et al. Short-chain fatty-acid-producing bacteria: key components of the human gut microbiota. Nutrients. 2023;15(9):2211.
25. Dicks LM. Our mental health is determined by an intrinsic interplay between the central nervous system, enteric nerves, and gut microbiota. Int J Mol Sci. 2023;25(1):38.
26. Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. Intern Emerg Med. 2024;19(2):275-93.
27. Wiredu Ocansey DK, Hang S, Yuan X, Qian H, Zhou M, Valerie Olovo C, et al. The diagnostic and prognostic potential of gut bacteria in inflammatory bowel disease. Gut Microbes. 2023;15(1):2176118.
28. Pessôa R, Clissa PB, Sanabani SS. The interaction between the host genome, epigenome, and the gut–skin axis microbiome in atopic dermatitis. Int J Mol Sci. 2023;24(18):14322.
29. Marques TM, Ganda-Mall JP, Forsgård R, Wall R, Brummer RJ, De Vos WM. Correlating the gut microbiome to health and disease. In: The Gut-Brain Axis. Academic Press; 2024. p. 1-36.
30. Chu J, Feng S, Guo C, Xue B, He K, Li L. Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: a review. Biomed Pharmacother. 2023;164:114985.
31. El Tekle G, Garrett WS. Bacteria in cancer initiation, promotion, and progression. Nat Rev Cancer. 2023;23(9):600-18.
32. Singh S, Sharma P, Sarma DK, Kumawat M, Tiwari R, Verma V, et al. Implication of obesity and gut microbiome dysbiosis in the etiology of colorectal cancer. Cancers. 2023;15(6):1913.
33. Qu R, Zhang Y, Ma Y, Zhou X, Sun L, Jiang C, et al. Role of the gut microbiota and its metabolites in tumorigenesis or development of colorectal cancer. Adv Sci. 2023;10(23):2205563.
34. Dougherty MW, Jobin C. Intestinal bacteria and colorectal cancer: etiology and treatment. Gut Microbes. 2023;15(1):2185028.
35. Nawab S, Bao Q, Ji LH, Luo Q, Fu X, Fan S, et al. The pathogenicity of fusobacterium nucleatum modulated by dietary fibers—a possible missing link between the dietary composition and the risk of colorectal cancer. Microorganisms. 2023;11(8):2004.
36. Lichtenstern CR, Lamichhane-Khadka R. A tale of two bacteria—bacteroides fragilis, escherichia coli, and colorectal cancer. Front Bacteriol. 2023;2:1229077.
37. Sadeghi M, Mestivier D, Sobhani I. Contribution of pks+ Escherichia coli (E. coli) to colon carcinogenesis. Microorganisms. 2024;12(6):1111.
38. Anderson SM, Sears CL. The role of the gut microbiome in cancer: a review, with special focus on colorectal

neoplasia and clostridioides difficile. Clin Infect Dis. 2023;77(Suppl_6).
39. Wang Q, Liu Y, Chen W, Chen S, Su M, Zheng Y, et al. Uterine commensal Peptostreptococcus species contribute to IDO1 induction in endometrial cancer via indoleacrylic acid. Biomedicines. 2024;12(3):573.
40. Huang Z, Wang C, Huang Q, Yan Z, Yin Z. Hungatella hathewayi impairs the sensitivity of colorectal cancer cells to 5-FU through decreasing CDX2 expression. Hum Cell. 2023;36(6):2055-65.
41. Zhang W, Xu X, Cai L, Cai X. Dysbiosis of the gut microbiome in elderly patients with hepatocellular carcinoma. Sci Rep. 2023;13(1):7797.
42. Taylor JC, Kumar R, Xu J, Xu Y. A pathogenicity locus of Streptococcus gallolyticus subspecies gallolyticus. Sci Rep. 2023;13(1):6291.
43. Kato I, Minkevitch J, Sun J. Oncogenic potential of Campylobacter infection in the gastrointestinal tract: narrative review. Scand J Gastroenterol. 2023;58(12):1453-65.
44. Fusco W, Bricca L, Kaitsas F, Tartaglia MF, Venturini I, Rugge M, et al. Gut microbiota in colorectal cancer: from pathogenesis to clinic. Best Pract Res Clin Gastroenterol. 2024;72:101941.
45. Hurst R, Brewer DS, Gihawi A, Wain J, Cooper CS. Cancer invasion and anaerobic bacteria: new insights into mechanisms. J Med Microbiol. 2024;73(3):001817.
46. Mi Z, Yao Q, Qi Y, Zheng J, Liu J, Liu Z, et al. Salmonella-mediated blood-brain barrier penetration, tumor homing and tumor microenvironment regulation for enhanced chemo/bacterial glioma therapy. Acta Pharm Sin B. 2023;13(2):819-33.
47. Song L, Xiong D, Wen Y, Tan R, Kang X, Jiao X, et al. Transcriptome sequencing reveals salmonella flagellin activation of interferon-β-related immune responses in macrophages. Curr Issues Mol Biol. 2023;45(4):2798-816.
48. Morrow ZT, Sauer JD. Type I interferon signaling on antigen-presenting cells blunts cell-mediated immunity toward listeria monocytogenes. Infect Immun. 2023;91(7):e0054022.
49. Pei B, Peng S, Huang C, Zhou F. Bifidobacterium modulation of tumor immunotherapy and its mechanism. Cancer Immunol Immunother. 2024;73(5):94.
50. Guo L, Ding J, Zhou W. Harnessing bacteria for tumor therapy: current advances and challenges. Chin Chem Lett. 2024;35(2):108557.
51. Gong T, Wu J. Synthetic engineered bacteria for cancer therapy. Expert Opin Drug Deliv. 2023;20(7):993-1013.
52. Kim JS, Park JE, Choi SH, Kang SW, Lee JH, Lee JS, et al. ECM-targeting bacteria enhance chemotherapeutic drug efficacy by lowering IFP in tumor mouse models. J Control Release. 2023;355:199-210.
53. Sharafabad BE, Abdoli A, Abdolmohammadi Khiav L, Meskini M, Jamur P, Dilmaghani A. Therapeutic potential of clostridium novyi-NT in cancer: current knowledge and future perspectives. Curr Cancer Drug Targets. 2023;23(9):682-96.
54. Din SRU, Saeed S, Khan SU, Arbi FM, Xuefang G, Zhong M. Bacteria-driven cancer therapy: exploring advancements and challenges. Crit Rev Oncol Hematol. 2023;104141.
55. Theys J, Patterson AV, Mowday AM. Clostridium bacteria: harnessing tumor necrosis for targeted gene delivery. Mol Diagn Ther. 2024;28(2):141-51.
56. Profir M, Roşu OA, Creţoiu SM, Gaspar BS. Friend or foe: exploring the relationship between the gut microbiota and the pathogenesis and treatment of digestive cancers. Microorganisms. 2024;12(5):955.
57. Staedtke V, Sun N, Bai R. Hypoxia-targeting bacteria in cancer therapy. In: Semin Cancer Biol. Academic Press; 2024.
58. Dailey KM, Small JM, Pullan JE, Winfree S, Vance KE, Orr M, et al. An intravenous pancreatic cancer therapeutic: characterization of CRISPR/Cas9n-modified clostridium novyi-non toxic. PLoS ONE. 2023;18(11).
59. Mettlach JA. Regulatory mechanisms of Salmonella enterica lipopolysaccharide biosynthesis. PhD Thesis, The University of Oklahoma Health Sciences Center; 2023.
60. Pérez Jorge G, Gontijo MTP, Brocchi M. Salmonella enterica and outer membrane vesicles are current and future options for cancer treatment. Front Cell Infect Microbiol. 2023;13:1293351.
61. Chen J, Qiao Y, Chen G, Chang C, Dong H, Tang B, et al. Salmonella flagella confer anti-tumor immunological effect via activating flagellin/TLR5 signaling within the tumor microenvironment. Acta Pharm Sin B. 2021;11(10):3165-77.
62. Al-Saafeen BH, Fernandez-Cabezudo MJ, Al-Ramadi BK. Integration of Salmonella into combination cancer therapy. Cancers. 2021;13(13):3228.
63. Yang Z, Zou L, Yue B, Hu M. Salmonella typhimurium may support cancer treatment: a review. Acta Biochim Biophys Sin. 2023;55(3):331.
64. Lu Y, Mei N, Ying Y, Wang D, Li X, Zhao Y, et al. Bacteria-based nanoprobes for cancer therapy. Int J Nanomed. 2024:759-85.
65. Ding YD, Shu LZ, He RS, Chen KY, Deng YJ, Zhou ZB, et al. Listeria monocytogenes: a promising vector for tumor immunotherapy. Front Immunol. 2023;14:1278011.
66. Nguyen HM, Oladejo M, Paulishak W, Wood LM. A listeria-based vaccine targeting ISG15 exerts anti-tumor efficacy in renal cell carcinoma. Cancer Immunol Immunother. 2023;72(9):2889-903.
67. Wiktorczyk-Kapischke N, Skowron K, Wałecka-Zacharska E. Genomic and pathogenicity islands of listeria monocytogenes—overview of selected aspects. Front Mol Biosci. 2023;10:1161486.

68. Zhang Y, Liu S, Chen M, Ou Q, Tian S, Tang J, et al. Preimmunization with Listeria-vectored cervical cancer vaccine candidate strains can establish specific T-cell immune memory and prevent tumorigenesis. BMC Cancer. 2024;24(1):288.
69. Jangra N, Kawatra A, Dhankhar R, Gulati P. Bacteria and bacteria-based products in cancer therapy: current status and future advances. In: Role of Microbes in Sustainable Development: Human Health and Diseases. Singapore: Springer; 2023. p. 441-70.
70. Arsuffi S, Cambianica A, Di Filippo E, Ripamonti D, Tebaldi A, Arosio MEG, et al. Vascular graft infections caused by mycobacterium bovis BCG after BCG immunotherapy for non-muscle-invasive bladder cancer: case report and review of the literature. J Clin Tuberc Other Mycobact Dis. 2023;31:100360.
71. Ji N, Long M, Garcia-Vilanova A, Ault R, Moliva JI, Yusoof KA, et al. Selective delipidation of Mycobacterium bovis BCG retains antitumor efficacy against non-muscle invasive bladder cancer. Cancer Immunol Immunother. 2023;72(1):125-36.
72. Gupta S, Yadav S, Kumar P. Efficacy of bacillus calmette-guérin in cancer prevention and its putative mechanisms. J Cancer Prev. 2024;29(1):6.
73. Haselager D, Dorigo-Zetsma W, Schröder M, Heidt J. An 80-year-old man with respiratory insufficiency after intravesical Mycobacterium bovis BCG immunotherapy. Chest. 2023;164(2).
74. Gellings P, Galeas-Pena M, Morici LA. Mycobacterium bovis bacille calmette–guerin-derived extracellular vesicles as an alternative to live BCG immunotherapy. Clin Exp Med. 2023;23(2):519-27.
75. Sharma D, Gajjar D, Seshadri S. Understanding the role of gut microfloral Bifidobacterium in cancer and its potential therapeutic applications. Microbiome Res Rep. 2024;3(1):3.
76. Vosough P, Vafadar A, Naderi S, Alashti SK, Karimi S, Irajie C, et al. Escherichia coli cytosine deaminase: structural and biotechnological aspects. Biotechnol Appl Biochem. 2024;71(1):5-16.
77. Taniguchi SI. In situ delivery and production system (iDPS) of anti-cancer molecules with gene-engineered bifidobacterium. J Pers Med. 2021;11(6):566.
78. Malik M, Hussain A, Hashmi A, Khan W. Protocol for randomized, two arm parallel, clinical trial for effectiveness of THR products in LMIC. Arch Pharm Pract. 2023;14(4):1-5.
79. Dicks LM, Vermeulen W. Do bacteria provide an alternative to cancer treatment and what role does lactic acid bacteria play? Microorganisms. 2022;10(9):1733.
80. Ha S, Zhang X, Yu J. Probiotics intervention in colorectal cancer: from traditional approaches to novel strategies. Chin Med J. 2024;137(01):8-20.
81. Vornic I, Pop O, Pascalau A, Andreescu G, Beiusan C, Manole F, et al. Assessing the role of Bcl-2 and p53 in apoptotic mechanisms in spontaneous abortions. Pharmacophore. 2024;15(2):1-6.
82. Wu R, Xiong R, Li Y, Chen J, Yan R. Gut microbiome, metabolome, host immunity associated with inflammatory bowel disease and intervention of fecal microbiota transplantation. J Autoimmun. 2023;141:103062.
83. Xia B, Liu X, Li Z, Ren J, Liu X. The effects of microbiota-targeted approaches in inflammatory bowel disease: probiotics, probiotic foods, and prebiotics. Curr Opin Food Sci. 2023;49:100956.
84. Rousseaux A, Brosseau C, Bodinier M. Immunomodulation of B lymphocytes by prebiotics, probiotics and synbiotics: application in pathologies. Nutrients. 2023;15(2):269.
85. Hima N, Benarous D, Louail B, Hamadi W. The effect of social media on purchasing behaviour through E-marketing: empirical study for algerian university students. J Organ Behav Res. 2024;9(2):73-86.
86. Yang Q, He Y, Tian L, Zhang Z, Qiu L, Tao X, et al. Anti-tumor effect of infant-derived Enterococcus via the inhibition of proliferation and inflammation as well as the promotion of apoptosis. Food Funct. 2023;14(4):2223-38.
87. Khazri A, Mendili M, Aouadhi C, Khadhri A. Promising aromatic and therapeutic plants from tunisia: phytochemical analysis, antioxidant, and antibacterial properties. J Biochem Technol. 2024;15(3):25-31.
88. Bhardwaj S, Bhatia S. Microbes used as anticancer agents and their potential application in biomedicine. In: Recent Advances and Future Perspectives of Microbial Metabolites. Academic Press; 2023. p. 173-215.
89. Grin NA, Platova EG, Dukaev MV, Magomedovic AM, Gairbekov MK, Sulimanova KI, et al. Assessment of effectiveness of teeth fillings modified with silver nanoparticles at low resistance of hard tissues. Ann Dent Spec. 2024;12(3):53-8.
90. Rodrigues R. Using spore-forming bacteria to treat cancer: recent advancements in clostridial-based therapies. Sci Rev Biol. 2023;2(2):30-9.
91. Lin L, Dai H, Jomeen J, Puts M, Tian L. Nonpharmacological interventions in the treatment of cancer-related fatigue. Clin Cancer Investig J. 2024;13(1):34-9.
92. Pyla M, Kankipati S, Sumithra B, Mishra PK, Mishra B, Mandal SK, et al. Bacterial proteins and peptides as potential anticancer agents: a novel search for protein-based therapeutics. Curr Med Chem. 2024.
93. Dias FCR, de Torres SM, de Figueiredo Pereira M, Morais DB, da Silva WE, de Silva Junior VA. Bioconjugate based on cisplatin and bacterial exopolysaccharide with reduced side effects: a novel proposal for cancer treatment. J Trace Elem Med Biol. 2024;83:127374.
94. Yarahmadi A, Zare M, Aghayari M, Afkhami H, Jafari GA. Therapeutic bacteria and viruses to combat cancer: double-edged sword in cancer therapy: new insights for future. Cell Commun Signal. 2024;22(1):239.