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REVIEW

BACTERIAL THERAPIES IN CANCER TREATMENT: ADVANCES, MECHANISMS, AND FUTURE PROSPECTS

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ABSTRACT

Cancer is one of the leading causes of death, and despite remarkable advances in treatment, chemotherapy remains the primary therapeutic approach. However, the emergence of drug resistance presents a major challenge, often limiting the efficacy of conventional treatments. As a result, developing novel therapeutic strategies has gained increasing importance in recent years. One such emerging approach is the use of bacteria in cancer therapy. Bacterial therapies offer unique mechanisms to target cancer cells and stimulate the immune response, providing a promising alternative to traditional treatments. This review aims to explore the potential of bacterial-based therapies in overcoming drug resistance and improving cancer treatment outcomes.

Keywords: Bacteria, cancer, immunostimulation, treatment

INTRODUCTION

Cancer is the second leading cause of death globally, after cardiovascular diseases (1). In 2020, an estimated 19.3 million cancer patients were newly diagnosed, and ten million deaths due to cancer occurred worldwide (2). The most frequent diagnoses included lung, prostate, colorectal, and breast cancers (3). Lung cancer, for instance, is the most prevalent form of cancer among men (1). These statistics underscore the urgent need to develop novel therapeutic approaches, and one such promising strategy is the use of bacterial therapies in cancer treatments (4). These strategies can be categorized into the following four sub-methods (5):

1. Bacterial vectors utilized for the targeted delivery of genetically engineered therapeutic agents.

2. Bacterial toxins for the inhibition of tumor growth.

3. Bacteria-mediated immunostimulation in cancer treatment.

4. Combination therapies integrating bacterial treatments with immunotherapy and chemotherapy.

Bacterial Vectors Utilized for the Targeted Delivery of Genetically Engineered Therapeutic Agents

Bacterial vectors have emerged as promising tools for the targeted delivery of genetically engineered therapeutic agents in cancer therapy. These vectors leverage the natural properties of bacteria to selectively home in on tumor sites, offering unique methods for localized treatment and minimizing damage to healthy tissues (6). A landmark study by Minton et al. (7) demonstrated that bacterial spores could inhibit cell growth, highlighting their potential in anticancer therapies. This early research laid the foundation for subsequent explorations into the use of bacterial vectors in cancer treatment.

Further advancements were made in a 1997 study by Pawelek et al. (8), in which the anticancer effects of a genetically modified *Salmonella* strain were observed. This study revealed that *Salmonella* could selectively colonize the tumor microenvironment (8). Once in the tumor, the bacteria activated the immune system and produced therapeutic genes and toxins that specifically targeted tumor cells, offering a novel approach to cancer treatment (8).

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Subsequent studies have demonstrated that bacteria selectively colonize tumor tissues, proliferate in hypoxic environments, and induce cancer cell destruction by producing enzymes and toxins (9). Genetic engineering techniques have enabled a more precise control of the bacteria's tumor-targeting abilities as well as the incorporation of novel functions to enhance their therapeutic potential (10).

Several different studies have been conducted in bacterial vector-based cancer immunotheraphy (Table 1).

Bacterial Toxins for the Inhibition of Tumor Growth

Bacterial toxins exhibit high cytotoxic effects and specific targeting capabilities, which make them promising agents in cancer treatment that selectively target specific surface receptors on cancer cells or exploit the characteristics of the tumor microenvironment (17). Treatment strategies employing these toxins include immunotoxins, targeted therapies, and gene therapy (18). Immunotoxins, which are generated through the conjugation of bacterial toxins with monoclonal antibodies, enable more precise targeting of cancer cells (19). In contrast, targeted therapies aim to modify tumor cells to enhance their binding to specific surface antigens, thereby reducing the likelihood of damaging normal cells (20). Additionally, incorporating bacterial toxin genes into gene therapy strategies facilitates the targeted production of toxins within tumor cells, a mechanism that can be categorized into three key subheadings (21).

a. Direct Cytotoxicity

Certain bacterial toxins, such as diphtheria toxin and Pseudomonas exotoxin, can infiltrate cancer cells and disrupt essential cellular processes, particularly protein synthesis (22). This disruption ultimately leads to cell death. These toxins can be engineered to specifically target overexpressed receptors in cancer cells, thereby minimizing damage to healthy tissues.

b. Immune Modulation

Toxins such as superantigens are known for their ability to activate the immune system by triggering a significant release of cytokines (23). This cascade recruits immune cells, particularly T cells, to the tumor microenvironment, enhancing the immune-mediated destruction of tumor cells and inhibiting further tumor growth (24).

Table 1: Comparative objectives and outcomes of bacterial vector-based cancer immunotherapy studies.

Title	Objective	Results
Pleiotropic Immunomodulatory Functions of Radioactive Inactivated Bacterial Vectors for Enhanced Cancer Radio-immunotherapy	This study aimed to develop a safer IRT using inactivated bacterial vectors labeled with $^{125}I/^{131}I$, which were designed to retain radioactivity at tumor sites, target tumor cells and TAMs, and enhance the antitumor immune response (11).	*In vivo* studies showed that $^{125}I/^{131}I$-labeled bacterial vectors effectively targeted tumor cells and TAMs. They inhibited tumor growth and prolonged survival in a murine breast cancer model while enhancing TIL infiltration and anti-tumor immunity (11).
A Safe Bacterial Microsyringe for *in vivo* Antigen Delivery and Immunotherapy	This study aimed to engineer a novel antigen delivery system that utilizes the *Pseudomonas aeruginosa* T3SS as a microinjector, employing the "KBMA" strategy to enhance safety for potential human applications (12).	The study demonstrated the potential of an attenuated *P. aeruginosa* strain as a safe antigen delivery vehicle since it effectively targeted antigen-presenting cells and induced a strong anti-tumor immune response in a murine model (12).
Intracellular Bacterial Vectors That Induce CD8 (+) T Cells with Similar Cytolytic Abilities but Disparate Memory Phenotypes Provide Contrasting Tumor Protection	This study compared the efficacy of *Listeria monocytogenes* and *Salmonella typhimurium* in inducing functional CD8(+) T cell responses and tumor protection (13).	The study revealed that while both *L. monocytogenes* and *S. typhimurium* induced functional CD8 (+) T cells, only *Listeria* generated long-lasting memory T cells crucial for effective tumor protection (13).
Optimization of Antitumor Immunotherapy Mediated by Type III Secretion System-based Live Attenuated Bacterial Vectors	The primary objective of this study was to optimize the efficacy of live attenuated *P. aeruginosa* vectors, which utilize the type III secretion system for antigen delivery, inducing robust and durable anti-tumor immune responses (14).	This study demonstrated that optimized *P. aeruginosa* vectors can enhance CD8 (+) T cell responses and improve tumor rejection in murine models, highlighting their potential for clinical use in cancer immunotherapy (14).
Cancer Immunotherapy Using *L. monocytogenes* and Listerial Virulence Factors	This study explored the potential of *S. typhimurium* as a cancer immunotherapy agent by assessing its ability to selectively infect tumor cells and enhance immune responses (15).	The findings demonstrated that *S. typhimurium* efficiently targeted tumors, induced the release of tumor-associated antigens, activated CD8 (+) T cells, and promoted significant tumor regression, suggesting its potential for bacterial-mediated cancer immunotherapy (15).
Cancer immunotherapy using *L. monocytogenes* and listerial virulence factors	This study investigates the use of *Listeria monocytogenes* as a vector for cancer immunotherapy, focusing on its ability to deliver tumor-associated antigens directly into the cytoplasm of host cells to elicit robust CTL responses (16).	The study shows that *L. monocytogenes* targets tumor cells, promotes tumor antigen presentation via the MHC Class I pathway, and activates CTLs, leading to strong anti-tumor responses (16).

IRT: Internal radioisotope therapy, TAMs: Tumor-associated macrophages, TIL: Tumor-infiltrating lymphocyte, T3SS: Type III secretion system, KBMA: Killed but metabolically active, CTL: Cytotoxic T lymphocyte, MHC: Major histocompatibility complex, P. aeruginosa: *Pseudomonas aeruginosa*, L. monocytotogenes: *Listeria monocytogenes*, S. typhimurium: *Salmonella typhimurium*

c. Apoptosis Induction

Certain bacterial toxins can induce programmed cell death (apoptosis) in tumor cells (25). For instance, toxins produced by Clostridium perfringens can disrupt cellular membranes, promoting apoptosis, particularly in the hypoxic conditions often present in tumor cores (Table 2) (26).

Bacteria-Mediated Immunostimulation in Cancer Treatment

The entry of bacteria into the host initiates a rapid and robust immune system stimulation that leads to an immediate immune response critical for combating malignancies (Figure 1) (31). This response predominantly activates innate immune cells, such as macrophages, dendritic cells, and natural killer (NK) cells, which collectively enhance the body's defenses against cancer cells. Key molecular components found in bacterial cell walls, such as lipopolysaccharides (LPS) and peptidoglycans, function as pathogen-associated molecular patterns recognized by pattern recognition receptors on immune cells (32). This recognition triggers a cascade of signaling events that culminate in significant immune activation.

The immunostimulatory effects of bacteria are mediated through several mechanisms. First, bacteria can be directly introduced into the tumor microenvironment, where they induce local inflammation and attract immune effector cells to the tumor site (33). Second, certain bacteria can produce toxins capable of selectively inducing apoptosis in cancer cells, thereby reducing tumor burden and further stimulating the immune response (34). Third, bacteria can induce long-lasting immunological memory, enhancing the host's ability to mount a rapid response against recurrent tumors (35). Finally, innovative therapeutic strategies involving engineered bacteria exploit these mechanisms to enhance the efficacy of existing cancer treatments, including checkpoint inhibitors and other immunotherapeutic approaches (36).

In summary, bacteria-mediated strategies highlight the potential of leveraging microbial interactions to enhance immune function in cancer therapy. By targeting tumor cells directly and modulating the immune system, these approaches may establish a durable antitumor response, representing a promising avenue in the fight against cancer.

Combination Therapies Integrating Bacterial Treatments with Immunotherapy and Chemotherapy

Bacterial therapies are gaining attention in cancer treatment due to their ability to both directly target tumors and stimulate the immune system. These therapies, when combined with immunotherapy and chemotherapy, offer a synergistic approach, potentially enhancing therapeutic outcomes and addressing drug resistance (37).

Bacteria can activate the immune system through molecules like LPS and peptidoglycans that are present in their cell walls. These components are recognized by immune cells such as macrophages, dendritic cells, and NK cells, leading to a strong immune response (38). When used alongside checkpoint inhibitors, like Programmed cell death protein 1/Programmed death-ligand 1 (PD-1/PD-L1) blockers, bacterial therapies can further boost the immune system's ability to attack cancer cells, which helps to overcome immune evasion mechanisms (39).

Table 2: Several studies that have been conducted in the field of using bacterial toxins for inhibition of tumor growth.

Title	Bacterial toxin	Objective	Result
CRM197 (NT diphtheria toxin): Effects on Advanced Cancer Patients	NT diphtheria toxin	The primary objective of this study was to investigate the therapeutic potential of CRM197, a non-toxic mutant of diphtheria toxin, as a novel immunotherapeutic agent for various advanced cancers (27).	This clinical trial showed that subcutaneous CRM197 administration induced a strong immune response, was well-tolerated, and demonstrated promising anti-tumor activity in patients with advanced cancers, suggesting its potential as a novel immunotherapy (27).
Safety, Tolerability, and Tumor Response of IL4-*Pseudomonas Exotoxin* (NBI-3001) in Patients with Recurrent Malignant Glioma	P. exotoxin	The primary objective of this open-label, dose-escalation study was to evaluate the safety and efficacy of intratumorally administered IL-4 *P. exotoxin* (NBI-3001) in patients with recurrent malignant glioma (28).	Intratumoral administration of NBI-3001 was well-tolerated in patients with recurrent malignant glioma and showed promising anti-tumor activity, indicated by an increased tumor necrosis on MRI (28).
Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Treatment-refractory Advanced Solid Tumors	*C. novyi*-NT	The primary goal of this clinical trial was to evaluate the safety and efficacy of intratumoral injection of *C. novyi*-NT, an attenuated bacterial strain, in patients with advanced solid tumors (29).	Intratumoral injection of *C. novyi*-NT showed promising anti-tumor activity with tumor regression and systemic immune response, but it caused significant toxicities, including sepsis and gas gangrene at higher doses (29).
Major Cancer Regressions in Mesothelioma After Treatment with an Anti-mesothelin Immunotoxin and Immune Suppression	*P. exotoxin* A (with anti-mesothelin)	The study aimed to assess the efficacy of an anti-mesothelin immunotoxin combined with immune suppression for treating mesothelioma (30).	In preclinical models, the combination treatment resulted in major tumor regressions. Clinical trial results indicated that the anti-mesothelin immunotoxin was well-tolerated and showed significant therapeutic potential, with some patients experiencing tumor shrinkage. Immune suppression was found to enhance the response by mitigating immune-mediated resistance (30).

MRI: Magnetic resonance imaging, NT: Non-toxic, IL: Interleukin

Additionally, bacterial therapies complement chemotherapy by localizing within the tumor microenvironment, allowing for more targeted drug delivery. This improves drug efficacy while minimizing side effects on healthy tissue. Bacteria also help disrupt the tumor's physical barriers, enhancing drug penetration and overall treatment effectiveness (40).

Genetically engineered bacteria add further precision to this approach. Modified bacteria can deliver chemotherapeutic agents directly to tumors, ensuring higher concentrations at the target site while reducing systemic toxicity (41). This targeted delivery is particularly beneficial for combating resistant tumors and improving the safety profile of chemotherapy (42). A comprehensive treatment strategy is achieved by combining bacterial therapies with immunotherapy and chemotherapy (Figure 2). While immunotherapy amplifies the immune response against cancer, chemotherapy directly attacks proliferating tumor cells, and bacteria enhance these effects by improving immune activation and drug targeting. This multi-pronged approach can reduce the likelihood of resistance, a major challenge in cancer treatment.

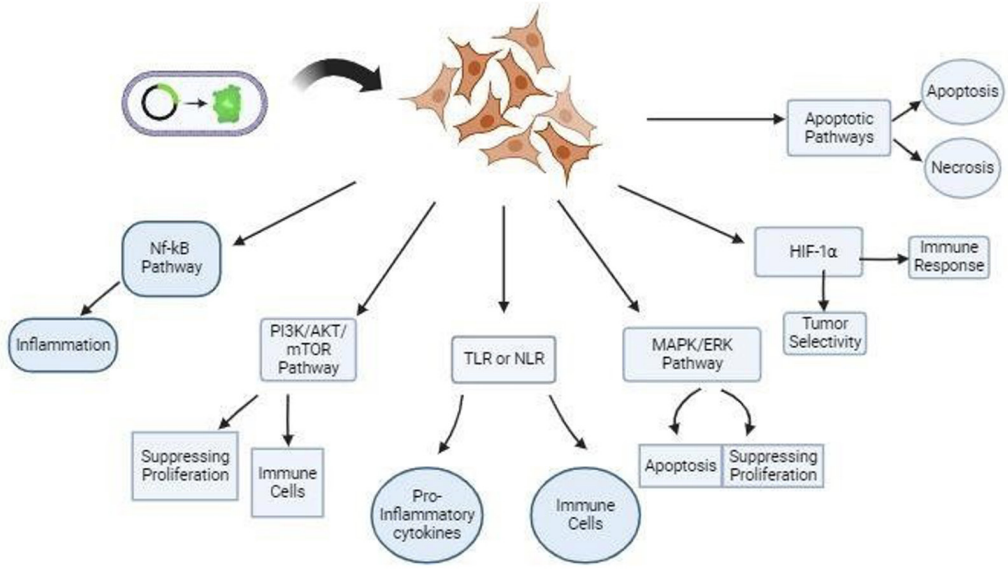

Figure 1: Mechanisms of host signaling pathway modulation by bacterial vectors in cancer therapy.
Nf-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells, Pl3k: Phosphoinositide 3-kinase, Akt: Protein kinase B, Mtor: Mammalian target of rapamycin, TLR: Toll-like receptor, NLR: Nod-like receptor, MAPK: Mitogen-activated protein kinase, ERK: Extracellular signal-regulated kinase, HIF-1a: Hypoxia-inducible factor 1-alpha

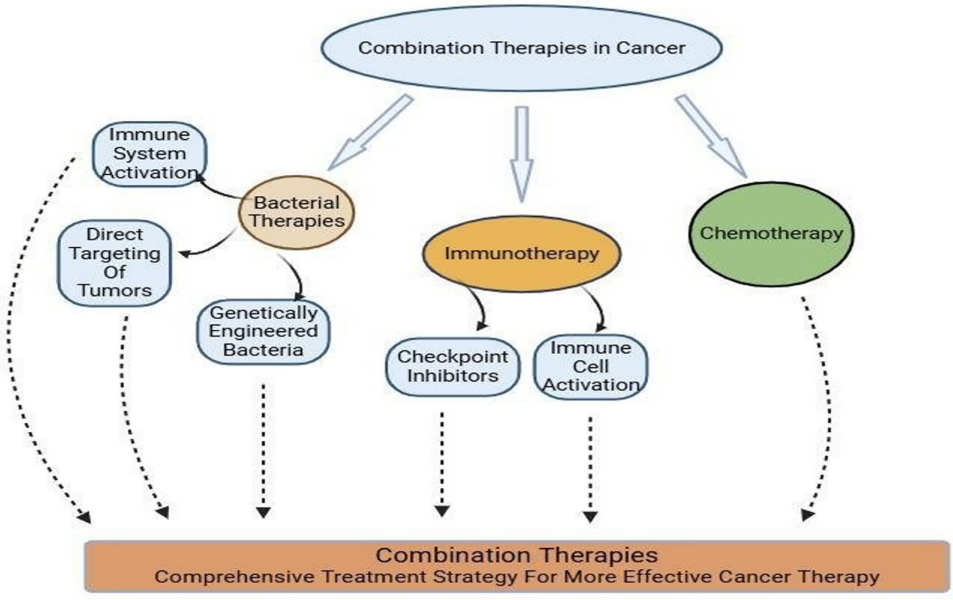

Figure 2: Combination therapies in cancer: integration of bacterial therapies, immunotherapy, and chemotherapy.

CONCLUSION

Bacterial treatment methods are emerging as promising alternatives in cancer therapy. Through various strategies such as tumor targeting, immunotherapy, gene therapy, and oncolytic bacteria, bacterial vectors can be effective in eliminating cancer cells. In particular, bacterial treatment methods offer significant advantages alongside traditional therapies by enhancing the immune system, modulating the tumor microenvironment, and providing targeted therapeutic approaches.

However, several challenges and limitations exist in the clinical applications of bacterial treatment methods. Issues such as the control of bacterial infections, minimizing side effects during treatment, and determining appropriate dosages should be the focal points of research. Furthermore, it is essential to integrate bacterial treatment methods with immunotherapies to enhance their effectiveness.

Future research should focus more on both preclinical and clinical studies to improve the efficacy and safety of bacterial treatment methods and deepen the knowledge in this field. In conclusion, bacterial treatment strategies open a new horizon in cancer therapy and play a significant role in the fight against cancer through a multidisciplinary approach.

Ethics

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Informed Consent: *N/A.*

Footnotes

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