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Bacteria-based immunotherapy: A promising frontier in cancer treatment

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Abstract

Cancer remains a significant medical challenge, with uncontrollable cell growth leading to death. Bacteria-based cancer immunotherapy (BCiT) was first attempted in the 19th century and has shown promise in alternative treatments for cancer. Recent evidence suggests that BCiT can modulate immune responses via cellular and molecular pathways, with bacteria demonstrating an anticancer effect through toxins and cell membrane components. This study aims to investigate the progress of bacteria-based immunotherapy for cancer treatment, using data from previous studies. Bacterial-based immunotherapy harnesses immune cells to directly terminate tumor cells. through secondary analysis of previous research studies, comprehensive reviews of relevant literature were conducted. The PubMed, Science Direct and Frontiers databases were searched with the keywords “bacteria-based immunotherapy,” "bacteriotherapy,” and “cancer immunotherapy","bacteriotherapy,” and “cancer immunotherapy."

A literature review was conducted, focusing on articles published no later than 5 years old. The safety and efficacy of BCiT are achieved through synthetic biology tools for genetic engineering. Combining bacterial vaccines with conventional therapies could enhance therapeutic benefits against cancer. However, the clinical manifestation of bacterial-based immunotherapy is limited due to potential infection and biosafety-associated toxicity and uncertain behavior in vivo. This review demonstrates the role of bacteria in the tumor microenvironment and provides a summary of strategies for immunotherapy based on their potential for cancer management. We will also propose advancements towards facilitating clinical translation for bacteria-based immunotherapy

Keyword: Bacteria; Immunotherapy; Cancer; Tumor; Bacteria-based cancer treatment; Bacteriotherapy; Cancer immunotherapy

1. Introduction

In recent years of research, immunotherapy has become a progressive technique in cancer treatment through the harnessing of microorganisms to fight cancerous tumors. Bacterial-based immunotherapy is one of the promising frontiers in the development of powerful and focused cancer cures. Traditional remedies, which include chemotherapy and radiation, are most typically utilized in nowadays’s clinics. However, by focusing on the cancer cell and killing it effectively, they also kill the surrounding health cells as well. Bacteria-based immunotherapy pursuits operate via special mechanisms that simplest target the cancerous mobile, leaving the relaxation unharmed. Through attenuated traces and biochemically engineered pathogens of bacteria, this evaluation will display the underlying mechanisms through which microorganism-based immunotherapy is run to target and ruin cancer cells. By informing us of these mechanisms and their ability to spark off the immune system and target cancer cells efficaciously, we are able to, in addition, optimize the design and efficacy of bacteria-primarily based immunotherapy strategies for improvements in cancer remedies.

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2. Engineered Bacteria and Immune Activation for Cancer Treatment

The study of bacteria-based immunotherapy can be dated back to the 19th century with Dr. William Coley, the father of cancer immunotherapy [1] injecting live or heat-inactivated bacteria such as Streptococcus pyogenes and Serratia marcescens via tumor. Thus, the introduction of "Coley toxin" to the medical field. In following years, the advancements in bacteria-based immunotherapy for cancer patients has benefited from this, resulting in partial or full cancer regression. Several bacterial pathogens such as Salmonella, Clostridium, Escherichia Coli, Proteus, Listeria and Lactobacillus are studied as they have been known for their ability to specifically target and inhibit tumor growth. Other advancements include the Bacillus Calmette-Guerin (BCG), derived from Mycobacterium Bovis, originally developed as a vaccine for tuberculosis [2] Bacteria which are introduced into the body activate immune components including dendritic cells, macrophages, and T cells [3] .Stimulation release of interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), create an inflammatory environment for immune cell activation [4] In response, the activation of antigen specific T cell response attacks the cancer cell and kills the cancer cell through apoptosis induction. Immunomodulation of bacteria-based immunotherapy can alter the tumor microenvironment by regulating the expression of bacterial pathogens [5] However, different pathogens of bacteria colonise different specific tissues. Klebsiella pneumonia is a gram- negative, encapsulated pathogen that infects lung tissue. This means that specific bacteria can be used to target specific cancer sites. Klebsiella pneumonias outer membrane vesicle is incubated with doxorubicin, a chemotherapy drug, allowing for it to quickly reach the microenvironment of the lung tumor cell in mice. This resulted in induced tumor cell apoptosis [6] (Figure 1).

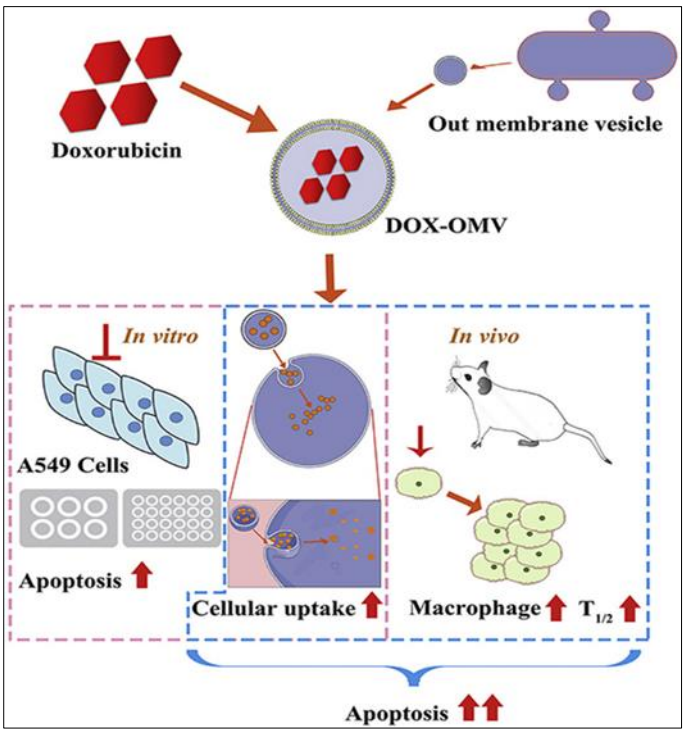

Figure 1 Klebsiella pneumonia outer membrane vesicle acts as a biological drug delivery carrier for transporting the chemotherapy drug, doxorubicin into the non-small cell lung cancer cells (NSCLS). Collected from: Recent Advances in Bacteria-Based Cancer Treatment

3. Mechanism of Targeting used by Bacteria

Through new advancements, the preclinical trials included animal models of cancer, such as mice with syngeneic tumours. Mouse models are used to ensure proper reliability before administering to humans. Through data already collected by previous review, the most used modes of colonisation of bacterial vaccines in preclinical research are oral, subcutaneous, intraperitoneal, intravenous, intratumor and intradermal [7] (Figure 2). In oral bacterial vaccines, breast cancer mice were orally given the salmonella typhi vaccine strain, CVD915, to assess its functionality against tumours [8]. Thus, since the positive preclinical outcome the creation of VXM01 became the first oral cancer vaccine for prostate cancer patients. Intravenous bacterial vaccines have been deemed the most used for cancer treatment due to their minimal toxicity and side effects [7] With intravenously bacterial vaccines, they can be genetically modifying pathogens

of Salmonella Typhimurium which can be intravenously colonised in both mice and humans with breast cancer [8]. Intratumoral injection can directly inject the bacterial therapeutic agents into the tumor site. Intratumoral injections of bacterial vaccines have shown significant tumor effects in preclinical studies, for example, engineered pathogen *E. Coli SYNB1891* colonised into four diverse types of tumors. This resulted in the activation of innate immune stimulating pathways [10]. Intraperitoneal injection of bacterial vaccine delivery method involves the administering of the injection directly in the peritoneal cavity. Due to the large surface are of the peritoneum, the intraperitoneal injection is absorbed quickly and is of ease to use. The attenuated bacterium into the peritoneum allows for the stimulation of immune response to target tumor cells. Through subcutaneous bacterial vaccine, the therapeutic effect can be prolonged due to their absorption nature. The intradermal injection of bacterial vaccine has been commonly used in the administration of the antitumor vaccine BCG to treat non-invasive bladder cancer [11].

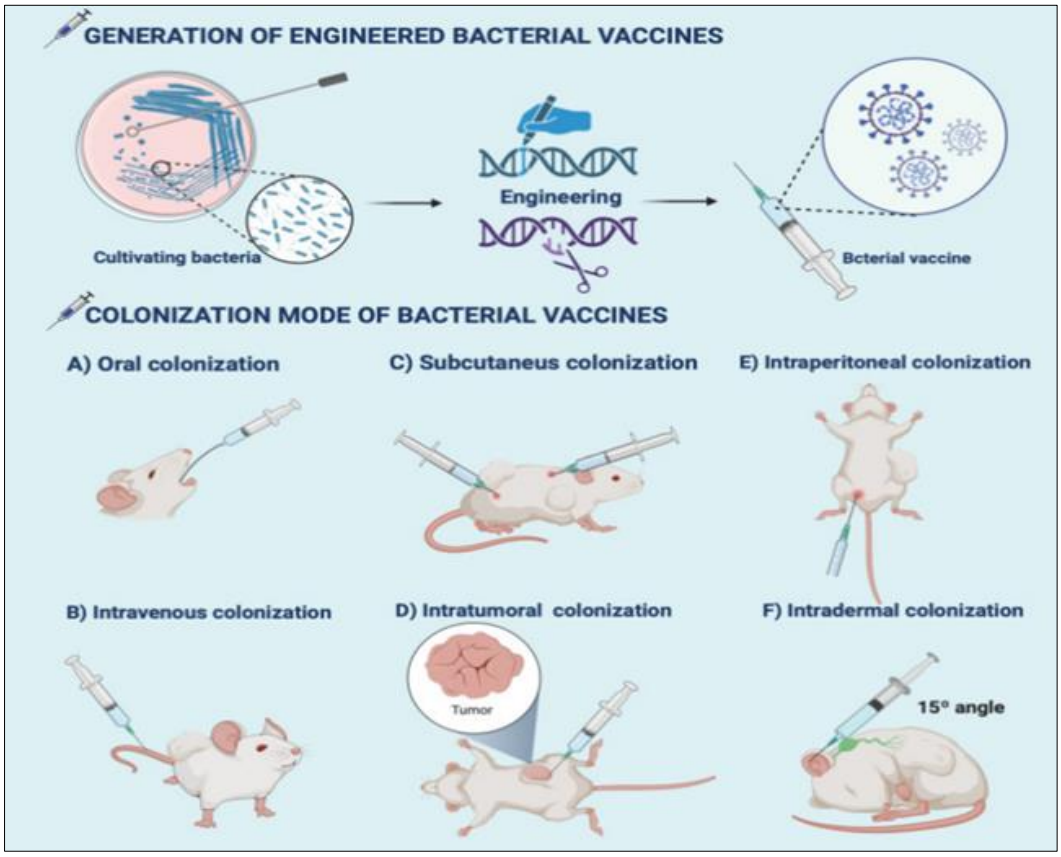

Figure 2 The different types of mechanisms of bacterial vaccines. These bioengineered techniques facilitate bacterial vaccines. Most commonly used modes include (A) oral, (B) intravenous, (C) intratumor, (D) subcutaneous, (E) intraperitoneal and (F) intradermal injections. Collect from: *Recent Advances in Bacteria-Based Cancer Treatment*

Colonisation of the tumors through various methods by bacteria allows for the improvement of rates of response. While there are many preclinical trials still ongoing both at a late stage and early, there have been significant improvement in successfully merging tumor targeting bacterial with cancer immunotherapy. Various methods used are indicated in Table 1.

Table 1 Examples of ongoing and late-stage preclinical trials of bacteria-based immunotherapy. Figure of data collected from [12]

Bacterial species	Clinical trial Identifier	Treatment	Cancer type	Phase	Number of enrolled patients	Treatment outcome/s
Clostridium novyi-	NCT03435952	Clostridium novyi-NT (IT) combination with Pembrolizumab (IV)	Solid tumors	I	16 [A]	Objective response rate =25% (n=PR,n=1CR = (Nelson et al. 2023)

NT						
Salmonella enterica	NCT03750071	VXM01 (oral) combination with Avelumab (IV)	Glioblastoma	I/II	28 [A]	Objective response rate for non-resectable tumors (n = 25) = 12% (n = 3 PR) (Wick et al. 2022)
	NCT04589234	Salmonella typhimurium expressing IL-2 (oral)	Pancreatic	II	60 [E]	N = 1 patient with CR for pulmonary metastases & PR for primary cancer (Saltzman 2021)
	NCT03762291	TXSVN vaccine (oral) against TAA Survivin	Multiple myeloma	I	1 [A]	N/A
E. coli Nissle 1917	NCT04167137	E. coli producing CDA (IT) monotherapy or combination with Atezolizumab (IV)	Solid tumors	I	32 [A]	SD observed in four patients (Luke et al. 2023)
	NCT03847519	ADXS-503 (IV) combination with Pembrolizumab (IV)	NSCLC	I/II	17 [A]	Objective response rate = 12% (n=2 PR), n = 6 patients with SD (Gerstner et al., 2022))
Listeria monocytogenes	NCT03006302	CRS-207 (IV) combination with Pembrolizumab (IV)	Pancreatic	II	40 [A]	N/A
	NCT05014776	CRS-207 (IV) combination with Pembrolizumab (IV) & Ipilimumab (IV)	Pancreatic	II	20 [E]	N/A

IV: intravenous; IT: intratumoural; CDA: synthetic cyclic diadenyl monophosphate, a STING agonist; E: estimate; A: actual; PR: partial response; CR: complete response; SD: stable disease; N/A: not available

Through bioengineering methods, like genetic engineering, it enables the development of bacterial vaccines. With prior literature reviews, research papers and data sources on bacteria-based immunotherapy. As a result of gathering information on this topic, secondary research has been carried out in order to understand the mechanisms by which cancer is treated via bacteria based immunotherapy. I particularly picked studies with pre-existing data, participant characteristics, outcomes and safety profiles. Mostly concentrating on recent publications as they are more up-to-date meaning that they can be used for further validation and knowledge enhancement concerning the topic under investigation. Selected graphs and figures express my findings in detail.[7]

4. Opportunities, Limitations, and Perspectives of Bacterial Therapy

From these studies, the positive results of bacteria-centered cancer treatment can be interpreted to provide insight into its hopes and possible mechanisms. The findings and information presented in this paper illustrate how bacteria are related to the demand for bacteria vaccines. Advancements made thereafter have helped clarify these mechanisms, which could help future researchers improve their strategies and outcomes when treating patients's tumors. Nonetheless, it should be noted that the study is limited by various types of cancer, variations in the protocols of treatment, and clinical translation hurdles [13] To develop this, future investigations may concentrate on genetically modifying bacteria for better tumor targeting [5] This avenue of improvement will streamline the bacterial targeting mechanism to amplify specificity and efficiency for targeting tumor sites. The bacteria are engineered to express surface ligands that bind these receptors of the tumors, thereby improving their ability to selectively accumulate in the tumor microenvironment. With further research and inventions, bacteria-based immunotherapy may become a breakthrough and a new dawn in cancer therapy. [15_18]

5. Conclusion

Finally, a hopeful novel strategy for cancer therapy could be bacteriocentric immunotherapy, which exploits the host microbe to immunologically involve the native immune system to cure cancer. Studies in this area of research have illuminated an extraordinary process of engagement between microbes to provoke immunogenic responses that translate to tumor regression and, hopefully, longer survival times for cancer patients. They identified these harmful bacteria as Salmonella and Bacillus Calmette-Guerin (BCG), and they can have cancer partially or wholly resolved due to the infections. Moreover, the bacteria-based immunotherapy also induced changes in immune cell activation and tumor microenvironment during invasion, which contributed to the reduction of tumor burden. Animal models of preclinical studies as well as syngeneic tumors in mice have been highly developed for the efficacy and safety of anti-cancer bacterial vaccinations. Animal models are used as a fundamental tool for predicting the fidelity and translational power of results from experimental systems for human patients. Although these and other challenges, such as off-target effects, safety concerns, and translation to clinical practice, need to be overcome, current research is aimed at addressing these challenges to develop more effective and targeted therapies in the future. At the same time, many exciting clinical developments are ongoing with the use of engineered live bacteria therapeutics that may advance the therapeutic armamentarium. Thus, in the future, robust preclinical validation and well-planned clinical trials will be needed to fully demonstrate the power of bacteria-based immunotherapy and to provide insights into how they could transform cancer care. Only with further innovation and an unyielding spirit will we continue to turn the tide on cancer through bacteria-based immunotherapies, thereby animating the horizons of cancer treatment. Through further exploration and development, bacteria-based immunotherapy could revolutionize the field of cancer therapy, providing fresh possibilities to tackle this intricate ailment and enhance the overall state of health amongst patients. In this review, we provide an in-depth overview of the different types of colonization of bacterial strains reported in preclinical research to date for use as vaccines to treat cancer. It collates and summarizes the results of previous studies about the effectiveness, safety, and feasibility of different delivery methods (orally, subcutaneously, intravenously, and/or intratumorally, intraperitoneal, and intradermally)

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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