

Review

Bacteria: Prospective Savior in Battle against Cancer

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Abstract. *Conventional anticancer therapies such as chemotherapy are losing their sheen in the battle against cancer. Therefore, strategies for treatment of cancer need to be constantly modified to fulfill the growing demands of alternative therapies. Several viral and non-viral vectors have been exploited for anticancer gene therapy. But over the years bacteria have been proven to be an important candidate for successful evasion of cancer. They serve as invaluable source of tumor-specific anticancer genes, toxins, polysaccharides for synthesis of nanodrugs and gene-delivery vectors. The current review assesses the role of important bacterial groups in different spheres of anti-cancer research.*

Bacteria have always attracted the attention of intense worldwide research. Their role in causing deadly infections in humans is well-acknowledged but it is duly accredited for its positive impact on human health also. Research has established a strong link between cancer and bacteria in both positive and negative ways. At one-point bacteria is the causal agent of cancer as evidenced by the example of gastric cancer caused by *Helicobacter pylori* (1). On the contrary, live bacteria or their products are also responsible for curing some of the deadliest forms of cancer, as explained by the anti-tumor effects of probiotic lactic acid bacteria (*Bifidobacterium*, *E. coli*, *Lactobacilli*) (2). Every year cancer is taking its global toll on humanity. Therefore, huge interest has been generated towards exploiting them for cancer therapy. This brief review article highlights the potential of using bacteria as promising anti-cancer agents.

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Historical Perspective of Bacterial Cancer Therapy

The link between bacteria and cancer was first observed few decades back by Busch and Fehleisen (3). They noticed tumor regression in cancer patients suffering from erysipelas infection caused by *Streptococcus bacteria*. The causal agent was identified as *Streptococcus pyogenes*. But it was not until the end of 19th century when William Coley, a bone sarcoma surgeon, intentionally used bacteria for cancer treatment. He made a mixture of heat-killed *Streptococcus* and *Serratia marcescens* to treat bone and soft tissue sarcoma patients. This combination was known as Coley's toxin (4). He hypothesized that a toxic material in the microbe elicited host immune response, which destroyed the tumor cells. He also reported positive results while treating patients suffering from various malignancies and carcinomas with this concoction. This observation was an important breakthrough in the history of bacterial cancer therapy. Lately the importance of bacillus Calmette- Guérin (BCG-attenuated strain of *Mycobacterium bovis*) was ascertained for treating bladder cancer (5). Thus, research and development in the use bacteria for cancer treatment has been accelerated with many important turning points.

Benefits of Utilizing Bacteria in Cancer Treatment

Chemotherapy is the forerunner of all therapeutic strategies employed for treating cancer. It has been accepted worldwide but is constantly drawing criticism due to its potential drawbacks. Most of the therapeutic drugs fail to completely penetrate the tumor environment, lack specificity and harm normal cells. Thus, they impart limited efficacy in treating cancer.

Bacteria offer multiple benefits over the conventional available drugs. Certain bacterial strains like *Clostridium* specifically proliferate well in tumor cells (6). These are highly active and motile in the anaerobic conditions prevalent in tumor cells. Certain auxotrophic strains are attracted to tumor cells for the metabolic nutrients available in the tumor environment. This allows infiltration of such

bacteria in the malignant cells, which are inaccessible or unresponsive to chemotherapeutic agents. Since they are metabolically very active in tumor cells, it is expected that they are excellent candidates for delivery of anticancer agents. This includes production of cytotoxins (bacterial toxins), enzymes that make prodrugs active and immunomodulating agents (cytokines, antigens). They can also deliver certain tumor anti-proliferating components and genes to the tumor tissue. Clinical trials have been carried-out for such bacterial products and have been found to be quite successful in tumor regression.

The preferential specificity and proliferation of certain bacteria in tumor tissues can be used in combination with chemotherapeutic drugs to enhance their efficacy. Nevertheless, antibiotics can be used to control bacteria when they are no longer required in the tumor. Thus, the use of bacteria can be clinically controlled.

Generally, tumor environment escapes the effects of host immune system due to its lower immunogenicity leading to their acceptance as self-antigens by the body. Bacteria can act as potent immune-stimulating agents in such conditions. The bacterial cell wall components or conserved sequences like pathogen-associated molecular patterns (PAMP) initiate innate as well as adaptive immune responses. PAMPs activate toll-like receptors (TLRs), interleukin (IL)-12, interferon (IFN)- γ and tumor necrosis factor (TNF) (7). These attract dendritic cells to the tumor site that results in the presentation of tumor antigens to T-cells leading to inflammatory reaction in tumor cells (8). Thus, bacteria are very effective in exposing the tumor to immune reactions resulting in its destruction. Figure 1 illustrates various components of bacteria, which can be utilized in developing therapeutic strategies for treatment of cancer.

Overall, bacteria truly present a very promising future in cancer treatment. The following cases shed light on the various approaches of utilizing bacteria in cancer therapy.

Attenuated Bacteria as Anticancer Agents

The majority of cancer treatments using chemotherapeutic agents today are facing efficacy problems. This is primarily due to the fact that a tumor consists of large poorly-vascularized regions, which prevents the intrusion of common drugs. It has been investigated that anaerobic bacteria can be exploited to proliferate in these hypoxic regions of the tumor and facilitate its destruction. Intense research focused upon the role of *Clostridia* spp. proved its potential of penetrating and colonizing tumor (9). The clostridial spores had the tendency to germinate and multiply in necrotic areas of solid tumor. One of the earliest finding was the potential of *C. butyricum* M55, a non-pathogenic soil isolate, to colonize mice bearing ascites tumor and cause oncolysis (10).

For a long time *Clostridium* spp. were considered to be ideal candidates but the idea was abandoned because of their toxicity to normal cells. To mitigate this problem, Dang *et al.* designed an attenuated strain of *C. novyi* by deleting a lethal toxin gene by inactivating the phage carrying the gene in the spores of *C. novyi* wild strain. The spores of this attenuated strain proliferated well in necrotic areas of the tumor and initiated inflammatory reactions leading to tumor destruction (6). Further, the administration of a combination of *C. novyi*-NT spores with one or more chemotherapeutic agents, such as mitomycin-C or docetaxel, was found to be more anti-tumorigenic. This mode of anti-neoplastic effect was named combination bacteriolytic therapy or COBALT (6).

Realizing the inability of obligate anaerobes like *Clostridium* to completely regress large tumors in the absence of anoxic conditions the role of facultative anaerobes like *Salmonella* spp. has been investigated. Disruption of *msbB*, *purI*, *Xylose (xylI)* and antibiotic resistance genes has generated an attenuated strain of *Salmonella typhimurium* (VNP20009) (11). This strain retains its tumor inhibiting potential and has undergone Phase I clinical trials for treatment of patients with metastatic cancer by intravenous administration (NCT00004988). Similarly, a Leu/Arg auxotrophic green fluorescent protein (GFP) expressing *S. typhimurium* A1 has been tested with prostrate PC3 cancer cells (12), lung fibrosarcoma (13) and MDA-MB-435 breast cancer (14). In these its role in tumor regression and inhibition was successfully ascertained. To ensure the complete prevention of damage to normal tissues by the bacteria, a novel biosynthetic approach has been devised. In this a *Salmonella typhimurium* SL7207 strain has been engineered to survive only in anaerobic condition by placing an essential gene, *asd*, under the control of hypoxia conditioned promoter (YB1 strain). It had the ability to infiltrate the MDA-MB-231 breast cancer cells and induce apoptosis (15).

Traditionally, lactic acid bacteria are well-known for their anticancer properties. Studies upon the effects of probiotic bacteria like *Bifidobacterium longum* have established their strong antitumor activity. This lactic culture is capable of inhibiting colon cancer by modulating the factors associated with colon carcinogenesis (16). Aso *et al.* have ascertained that the oral administration of *Lactobacillus casei* (biolactis powder) prevented the recurrence of superficial bladder cancer (17). Similarly, probiotic *Bacillus polyfermenticus* inhibits the growth of colon cancer cells such as HT29 by suppressing the expression of ErbB2 and ErbB3 receptors (18). Chiu *et al.* described that soluble factors (Lcr5) secreted by *Lactobacillus casei rhamnosus* induced apoptosis in a human monocytic leukemia cell line (19). The complete eradication of cancer using live or attenuated bacteria has still not been successfully achieved, but alternative ways of utilizing it have been devised.

Bacterial Vectors Associated with Cancer Treatment

The advantage of using bacteria in tumor biology has been exemplified in the previously discussed investigations. The toxicity of bacteria at the required dosage level is the major roadblock for their use as anticancer agents. Therefore, the focus has been shifted towards the genetic modification of bacteria to express genes of therapeutic interest. They can serve as vehicles to carry anticancer agents like proteins, peptides and enzymes.

The investigators exploit the basic underlying property of utilizing those bacteria, which selectively proliferate in tumors. *B. adolescentis* has been used as a vector to transport endostatin, a potent anti-angiogenic agent to hypoxic regions of a tumor (20). Similarly, bacterial ghosts can be utilized to deliver the requisite drugs to a specific site. Bacterial ghosts are non-denatured envelope-derived from gram-negative bacteria, which retain the original morphological and structural features of a normal bacterium (21). One such example is the site-specific delivery of doxorubicin (DOX) to human colorectal adenocarcinoma cells (Caco-2) using bacterial ghosts derived from *Mannheimia hemolytica*. These DOX-ghost cells exhibited strong anti-proliferative activity against Caco-2 cells. Furthermore, bacteria can be equipped with genes expressing therapeutic molecules like cytokines, apoptosis inducing factors, short hairpin RNAs (shRNA), which are able to silence the genes of interest associated with cancer. An attenuated *Salmonella enterica serovar typhimurium* carrying a plasmid encoding small interfering RNA targeting the STAT3 transcription factor, essential for tumor survival, has been designed. This combination significantly decreased tumor growth and extended the life of mice bearing prostate tumor (22). Another example is the use of *S. typhimurium* expressing the CCL21 chemokine that induces an inflammatory response within tumors in immunocompetent mice challenged with multidrug resistant CT-26 colon, D2F2 breast and B16 melanoma cancer cells (23).

Certain bacterial redox proteins have the potential to induce apoptosis and inhibition of cell cycle in mammalian cells. Azurin is one such protein involved in electron transfer during de-nitrification by *Pseudomonas aeruginosa* (24). It has been observed that it could inhibit melanoma and breast cancer tumor growth by increasing the intracellular levels of p53 and Bax inducing apoptosis. Therefore, Zhang *et al.* has used *E. coli* Nissle 1917 to deliver azurin to B16 mouse melanoma and 4T1 breast tumor, which resulted in suppression of tumor growth and inhibition of pulmonary metastasis (25).

The recent trend of utilizing a theranostic approach (a combination of diagnostics and therapy) for tumor evasion has come up with a new technology of developing Bacteriobots (Bacteria-based microrobots) (26). These can be loaded with peptides, antibodies and nucleic acids having

anti-tumor effects. The prototype of a bacteriorobot involves a combination of polystyrene bead and flagellated bacteria. A bacteriorobot composed of *S. typhimurium* attached to a microstructure containing drugs has been synthesized. The bacteria enable the microstructure to move towards the tumor. This combination of robotics and biotechnology presents a new phase of anticancer therapy.

The inability of bacteria to completely regress tumor proliferation is the major limitation encountered in cancer research. This has been overcome by genetically modifying the bacteria to express heterologous enzymes, which can convert non-toxic prodrugs into potent anti cancer agents. Several studies are being carried out in this direction. A clostridial strain, *C. sporogenes* is known for its high tumor colonizing efficiency. This strain has been transformed with the *E. coli* cytosine deaminase (CD) gene. The systemic injection of this bacterial spores resulted in the expression of the cytosine deaminase enzyme in the tumor, which converted the non-toxic prodrug 5-fluorocytosine (5-FC) to anticancer 5-fluorouracil (5-FU) drug (27). A new approach known as tumor amplified protein expression therapy (TAPET) utilizes the *S. typhimurium*VNP2009 strain carrying the *E. coli* (codCD) directed against tumors. This enhances the therapeutic efficiency of *S. typhimurium*VNP2009 (28). The same strain has been exploited to express the herpes simplex virus (HSV)-thymidine kinase (*hsv-tk*) gene in melanoma tumors that converts the prodrug ganciclovir enhancing, thus, its antitumor activity (29). Sometimes bacterial genes can be made to express in mammalian cells to produce enzymes that can convert non-toxic prodrugs to active anticancer agents. This gene can be transfected using retrovirus, naked DNA, liposomes, *etc.* This approach of gene-directed enzyme pro-drug therapy (GDEPT) has been utilized to express the bacterial enzyme carboxypeptidase (CPG2), which enhances the sensitivity of tumors to prodrugs, like CMDA (4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-L-glutamic acid) (30).

Bacterial Toxins

Paul Ehrlich first introduced the concept of exploiting bacterial toxins in early 1900s. He established that the antibodies coupled with toxins could serve as 'magic bullets' for destroying cancer cells. The toxins used in this strategy are either chemically conjugated or genetically fused with tumor cell-binding ligands such as antibodies or growth factor. These are widely known as immunotoxins. Commonly used bacterial toxins are *Pseudomonas* exotoxin A, *Diphtheria* toxin. These inhibit protein synthesis by ADP ribosylation of elongation factor 2 (EF-2), which is post-translationally modified to a diphthamide residue leading to cell death (31).

Human IL-2 coupled with truncated diphtheria toxin with deletions in the binding region is useful in treating hematological malignancies. One such example is a fusion

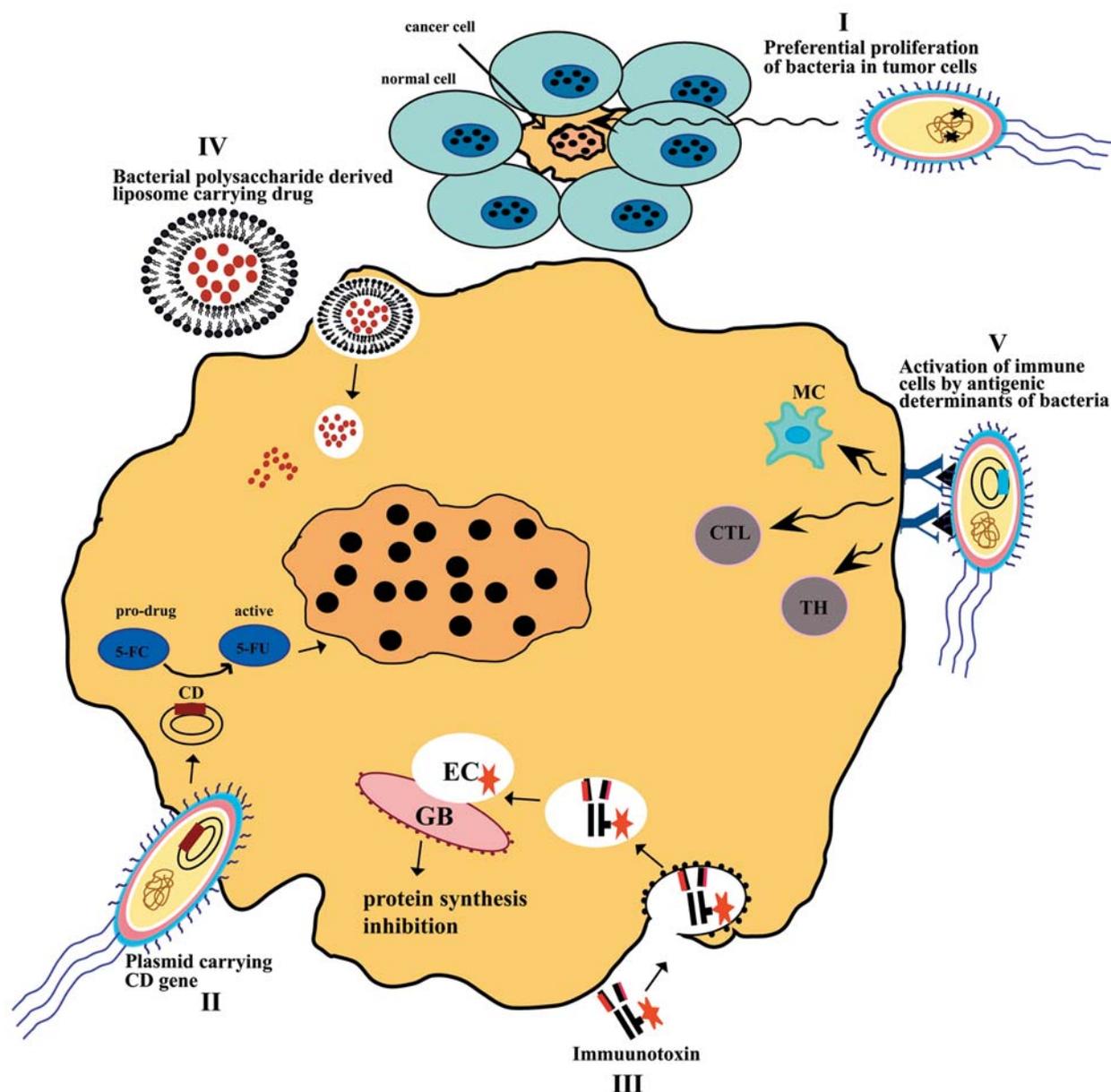


Figure 1. Schematic summary of the various components of bacteria utilized in anti-cancer therapy. I. Attenuated anaerobic (*Clostridium*) and facultative anaerobic (*Salmonella*) bacteria specifically target the anaerobic regions of tumor and proliferate initiating inflammatory reactions causing tumor destruction. II. Bacteria (*C. sporogenes*) expressing the cytosine deaminase enzyme that converts the non-toxic prodrug 5-fluorocytosine to active anticancer drug 5-fluorouracil. III. Bacterial toxins coupled with antibody to generate immunotoxin that binds to antigen on the surface of cancer cell. It enters the cell through coated pits and is cleaved into two fragments, which travel to the cytoplasm and block protein synthesis. EC, endoplasmic compartment; GB, Golgi body. IV. Polysaccharide derived from bacteria is used to synthesize liposomes and nanoparticles for the delivery of cancer cell specific drugs. V. Bacteria attracted towards the malignant cells are genetically engineered to express cytokines and tumor-associated antigens to enhance the immune response against the tumor.

toxin DAB389IL-2 known as Denileukin diftitox created by deleting amino acids from the binding region approved for the treatment of cutaneous T-cell lymphoma. Another instance is the use DAB389EGF specific for the epidermal growth factor receptor (EGFR) antigen on tumor cells used

in the treatment of lung cancer (32, 33). It has also been observed that ‘receptorless’, Diphtheria toxin lacking carboxy terminal receptor binding domain (R), are essential for toxin internalization; the DT385 toxin was still toxic to a variety of cancer cell lines (34).

It is generally observed that the CD25 out-numbers CD122 and CD132 in most malignant cell types. An anti-CD25 monoclonal antibody called anti-Tac with Pseudomonas exotoxin A (PE) has been exploited for the treatment of adult T-cell leukemia (ATL) and hairy cell leukemia (HCL). In this a recombinant single chain Fv was constructed wherein a variable heavy domain is fused with a light domain *via* a peptide linker and this is fused to truncated PE and anti-Tac (35). Similarly, the causative agent of gastroenteritis, *Clostridium perfringens* produces enterotoxin. This enterotoxin known as CPE (*C. perfringens*) shows high specificity towards a tight junction (TJ) receptor, claudin-4 (CLDN4). This receptor is overexpressed in ovarian (36) and pancreatic cancer cells (37). Therefore, the CPE toxin's cytotoxic effect of the N-terminal domain and CLDN-4 specificity of the C-terminal domain have been exploited for enhancing the sensitivity of prostate and ovarian cancer cells to taxol and carboplatin (38).

Apart from these, combination therapy involving both diphtheria toxin (DT) conjugates and cytotoxic drugs results in greater efficacy in the treatment of cancer. This has been proved by use of DT toxin fused with human granulocyte-macrophage colony-stimulating factor (GM-CSF) along with arabinose C (Ara-C) exerting synergistic toxicity against human acute myeloid leukemia (AML) HL-60 cells (39, 40).

Bacterial Polysaccharides

An effective means of delivering drugs to a target site remains a challenging mission. In this respect, polysaccharides derived from bacteria are playing a promising role. Mauran, a sulfated polysaccharide extracted from halophilic bacteria; *Halomonas maura* has been utilized for the synthesis of nanoparticles along with chitosan (41). The group has confirmed the effectiveness of mauran-chitosan combination for sustained and prolonged release of 5-fluorouracil (5-FU). The mauran-chitosan-enclosed 5-FU was observed to be non-toxic to normal cells and effective in killing breast adenocarcinoma cells. Chen *et al.* have identified that the exopolysaccharide extracted from an endophyte, *Bacillus* spp. (MD-b1) had anti-tumor activity against certain gastric carcinoma cell lines. They observed potential cell damage and morphological abnormalities being induced by the exopolysaccharide in tumor cells (42).

The anti-tumor effects of cell-bound exopolysaccharide (cb-EPS) from *Lactobacillus acidophilus* 606 on colon cancer cells have been investigated using HT-29 colon cancer cells. This cell-bound exopolysaccharide isolated from the bacteria could inhibit the proliferation of colon cancer cells by activating autophagic cell death-inducing factors like Beclin-1 and GRP78 (43).

Polysaccharide-anchored liposomes have been found to be stable and site-specific targets for the delivery of

chemotherapeutic drugs. Polysaccharide-anchored liposomes carrying adriamycin directed by a monoclonal antibody fragment (anti-sialosyl lewis, IgMs) has been analyzed for their tumor cell binding ability against the human lung cancer cell line (PC-9). Shinkai *et al.* constructed magnetoliposomes in which liposomes carrying drugs were anchored with hydrazide pullulan. This pullulan provides an anchor for immobilization of specific monoclonal antibodies onto magnetoliposomes. The cancer cells readily took up this construct (44). Therefore, bacterial exopolysaccharides are excellent candidates for drug delivery.

Bacteria as Immune Modulating Agents

Today, cancer is the focus of intense research because it has been the major cause of maximum number of death worldwide. The tendency of the tumor to evade host immune response is the main concern among researchers. This is attributed to the low antigenicity and high tumorigenicity of the tumor cells making them aggressive. The idea of using bacteria to make tumors vulnerable to immune response is an interesting field. Attenuated *S. typhimurium* that retain their invasiveness have been shown to infect malignant cells and make them express antigenic determinants of bacterial origin. This triggers immune responses leading to the release of anti-Salmonella specific T-cells that destroy the malignant cells infiltrated with *Salmonella* (45). Genetically-engineered *S. typhimurium* expressing cytokines like IL-2 (46) and IL-18 (47) have been observed to be more potent elicitors of an immune response against tumor cells.

Similarly, *Listeria monocytogenes* has been exploited to deliver tumor-associated antigens (TAA) eliciting immune responses leading to destruction of cancer cells. *L. monocytogenes*, due to its intracellular localization, delivers antigens to antigen presenting cells (APC) resulting in processing and presentation of antigen to immune system (48). A replication deficient strain of *L. monocytogenes* expressing CD24 has been designed, which enhanced the levels of IFN- γ secreting CD8⁺ T-cells and IL-4, IL-10 secreting Th 2 cells. This reduced the tumor size in mice inoculated with Hepa-1-6-CD24 indicating its plausible role in treating hepatic cancer (49). Again, the genes which are dominantly expressed by the tumor have been targeted as in the case of an attenuated *Salmonella typhimurium* strain carrying the DNA vaccine-encoding human tumor endothelial marker 8 (TEM8). This xenogenic DNA vaccine could generate TEM8-specific CD8⁺ cytotoxic T-cell response in tumor cells overexpressing the TEM8 marker leading to inhibition of tumor angiogenesis and reduction of tumor growth (50). Similarly, Jasosz *et al.* have described the use of an oral DNA vaccine against endoglin, a crucial tumor angiogenesis factor (51). Lately, bacillus Calmette- Guérin (BCG-attenuated strain of *Mycobacterium bovis*) has been the most successful bacterial agent for the

Table I. Important therapeutic approaches utilizing bacteria.

Serial no.	Bacteria	Species	Component	Approach	Reference
I	Clostridium		Attenuated bacteria	Preferential proliferation in hypoxic region of tumor leading to tumor regression	9
		<i>Butyricum</i> M55	Attenuated bacteria	Colonize mice Ehrlich ascites	10
		<i>Novyi</i>	Attenuated bacteria	Preferential proliferation and degradation of necrotic regions	6
		<i>Acetobutylicum</i>	Vector	Expression of TNF α toxic to tumor cells	53
		<i>Perfringens</i>	Purified enterotoxins	Cytotoxic effect against pancreatic cancer cells	36
		<i>Sporogenes</i> <i>Beijerinicki</i>	Vector	Expression of cytosine deaminase (CD) gene in tumor Expression of <i>E. coli</i> nitroreductase (ntr) gene sensitizing tumor cells to prodrug CB-1954 leading to cell death	27 59
II	Mycobacterium	<i>Bovis</i>	Attenuated strain	Cell wall skeleton induces IFN- γ secretion in the treatment of bladder cancer	52
III	Pseudomonas	Not specified	Exotoxin A	Truncated exotoxin fused with antibody toxic for treating hairy cell leukemia	35
IV	Lactobacillus	<i>Acidophilus</i>	cb-EPS	Activation of autophagic cell death inhibiting tumor growth	43
		<i>Casei</i>	Probiotic	Prevent recurrence of superficial bladder cancer	17
V	Salmonella	<i>Typhimurium</i>	Vector	Expression of HSV thymidine kinase (hsv-tk) gene enhancing the antitumor activity of the prodrug ganciclovir	29
		<i>Typhimurium</i> VNP2009	Attenuated strain	Toxic with antitumor effect undergoing phase I clinical trials	11
		<i>Typhimurium</i>	Vector	Chemokine CCL21 expression inhibiting tumour growth	23
		<i>Typhimurium</i>	Carrier	Microbots carrying anti-tumor compounds	26
		<i>Typhimurium</i>	Vector	<i>Trail</i> gene expression causing apoptosis of cancer cells in murine breast cancer model	54
		<i>Choleraesuis</i>	Vector	Tumor specific expression of thrombospondin-1 (thbs1) gene delaying tumor growth	58
VI	Bifidobacterium	<i>Longum</i>	Attenuated strain carrying DNA vaccine	TEM-8 inhibit tumor angiogenesis and growth	50
		<i>Adolescentis</i>	Probiotic	Inhibition of colon cancer	16
			Vector	Endostatin expression having anti-angiogenic properties in tumor	20
VII	Listeria	<i>Monocytogenes</i>	Vector	Delivery of tumor associated antigens to kill cancer cells	48

treatment of bladder cancer. BCG-cell wall skeleton induces IFN- γ secretion and stimulates skin Langerhans cells to convert into dendritic cells. Thus, it acts as a potent adjuvant for immunotherapy (5). This BCG-cell wall skeleton has been reported to be a promising strategy for enhancing the effects of radiation therapy in colon cancer cells by inducing autophagic cell death (52).

An upcoming approach is exploiting the properties of tumor necrosis factor (TNF) to induce apoptosis of growing tumor cells. A recombinant *Clostridium acetobutylicum* strain has been designed, which carries TNF- α cDNA under the control of the radio-inducible Rec-A promoter. This was found to be toxic for tumor cells (53). But due to a certain level of toxicity of TNF- α to normal tissue, Ganai *et al.* have utilized the TNF-related apoptosis-inducing ligand (TRAIL) (54). It selectively induces apoptosis in cancer cells rather than in normal cells. The system consists of the *Trail* gene coupled to radio-inducible promoter sequence for RecA in *S. typhimurium* vector, which could suppress tumor growth in syngeneic murine breast cancer model.

Therefore, the aforementioned facts clearly indicate the huge potential of utilizing bacteria in immunotherapy in combination with other conventional methods for combating cancer.

Conclusion and Future Prospects

Researchers worldwide have accepted the indispensable role of bacteria as anticancer agents. Table I further exemplifies this fact. It is also proved by the recent surge in the number of research articles published on bacterial cancer therapy. Many successful clinical trials have also been undertaken. Mixed bacterial vaccines containing heat-inactivated *S. pyogenes* and *S. marcesans* popularly known as Coley's toxins is undergoing clinical trials in cancer patients expressing NY-ESO-1 (55). The incidence of deaths due to cancer is increasing worldwide so is a need to generate effective means to control this menace. Different combinations of drug systems are required to treat certain emerging incurable malignancies. The inherent properties of bacteria can be

modified and exploited for this purpose. But still more extensive research is essential to bring bacteria in the forefront. Therefore, bacteria are truly going to add a new aspect of treating cancer in the coming years.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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