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Bacterial and viral vectors as vaccine delivery vehicles for breast cancer therapy

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ABSTRACT

Breast cancer is the frequently diagnosed cancer among women and it is the most lethal malignancy in women globally. With one million cases every year, breast cancer is the fast-growing cancer type that has a high prevalence rate in young women. The limitations and undesirable side effects of conventional therapies like chemotherapy and radiotherapy on malignant tumors necessitate the development of alternative therapeutic approaches. Gene therapy has emerged as a promising approach to cure a variety of malignant cancer types which involves the delivery of functional gene directly into the target tumor tissue. Efficient gene therapy approach relies on the effective delivery of therapeutic genes to the desired cell type. In this regard, biological and non-biological gene delivery vectors are used to protect the naked foreign DNA to mediate effective tissue entry of the desired gene of interest. In this review, the use of bacterial and viral vectors for breast cancer gene therapy was summarized.

1. Introduction

Cancer is defined as a group of diseases characterized by abnormal growth of cells that can invade other cells/tissues which may lead to mortality. Breast cancer is the fast-growing cancer type and most common non-cutaneous malignancy which accounts for18% of total female cancers having high prevalence rate in young women and occurs unfrequently in men (<1%) [1]. Almost 1.4 million breast cancer cases were reported worldwide [2]. In US, cancer accounts for the second most common cause of death (1 in every 4) next to heart disease. In 2015, more than 2, 00,000 new breast cancer cases were estimated in the US. In Mexico, breast cancer is the second leading cause of death in women over 20 years. In West Africa, breast cancer is the leading cause of death which accounts for >16,000 deaths in 2008; whereas in East Africa, the prevalence was significantly lower with 10,000 deaths in the same year [3,4]. In Europe, the incidence was much higher with >40,000 deaths in 2008. In contrary to other infectious diseases, cancer is prevalent mostly in developed countries like Europe and North America compared to the developing and underdeveloped countries in Eastern and Southern Africa.

Numerous risk factors are associated with the development of breast cancer including genetic, environmental, hormonal, and nutritional influences. The chance of occurrence of breast cancer increases with age, early menarche, late menopause, obesity in postmenopausal women and risk is even higher with a family history of the disease [5,6]. Age plays a crucial role in the incidence of breast cancer. The incidence of breast cancer is less common in younger women but the chances are higher with age till menopause (8%–9%), however after the menopause, the chance of incidence has been significantly reduced to 2–3% per year [7]. The incidence and presentation of the disease vary between European and African Women. The mean age of presentation is 48 years in Africa mainly in the premenopausal stage, whereas in Europe, postmenopausal women are reported to be more susceptible to the disease [8]. Genetic predisposition between European and African counterparts may also significantly attribute to the onset of disease.

At present, prevention of breast cancer largely encompasses

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reducing modifiable risks such as early detection through physical examination and mammograms, avoiding unnecessary post-menopausal hormone therapy, reducing alcohol consumption, loss of weight, increasing physical activity, and genetic testing for mutations of the type 1 and type 2 breast cancer susceptibility genes - BRCA1 and BRCA2, respectively [9,10]. In patients with advanced condition of cancer progression, where the patients are at high risk, the treatment strategies includes chemoprevention with raloxifene, tamoxifen, and aromatase inhibitors as well as prophylactic bilateral mastectomy and oophorectomy with adjuvant radiation or a combination of these [11,12]. With the technological advancements and due to the intense health risk of breast cancer and insufficiency of preventative efforts, recent research focus has been laid on immunotherapy and cancer vaccination. This has possibly been achieved by use of viral or bacterial vectors for the delivery of the target drug for breast cancer vaccination. These approaches include immunization with whole autologous or allogeneic tumors, as well as antigen-based strategies where immunization is achieved with overexpression of proteins or peptides in tumors and underexpressed in normal tissues [13,14]. Human epidermal growth factor receptor 2 (HER2) and mucin (MUC1) are the predominant antigens used in human breast cancer vaccine trials [15]. This review predominantly focuses on the use of bacterial and viral methods of vaccine delivery towards breast cancer therapy.

2. Anti-tumor therapy for breast cancer

Although treatment and prognosis for breast cancer are available, it hugely depends on the diagnosis stage, biological characteristics of the tumor, age, and health of the patient. Anti-cancer therapy faces major hurdles since the treatment measures shouldn't affect the normal cells and organs, even if so, the side effects should bare minimum. Many cancer cases are diagnosed at the final metastases stage that generally leads to death. The limitations in conventional anticancer therapies like surgery, radiotherapy, or chemotherapy have their setbacks which include poor survival rates, lack of tissue specificity, inability to treat deep tumor tissue, development of drug/radio-resistance and adverse side effects prompted the need for alternative therapies [16]. The ultimate goal of cancer treatment is to target the tumor cells without destroying the healthy cells. The recent advancement in medical era showed gene-based vaccine therapy as a promising area for the cure for malignant diseases. Gene-based vaccine therapy is a boon for the cancer patients engaging the delivery of a functional gene to the target cells for the production of functional therapeutic proteins. The introduced gene may either directly kill the tumor cell or block the cell cycle and induce apoptosis. Instead, genes that inhibit metastatic cell progression or block new cell vessel formation could also be used [17]. However, targeting the functional gene on the site of the tumor safely and efficiently will make gene therapy as a successful treatment for cancer. Since the chances for cleaving the naked DNA/RNA by endonucleases or degradation by phagocytic cells are high, the DNA/RNA needs an effective delivery vehicle to protect and mediate effective delivery of gene of interest into the cell. The delivery vehicle used for the gene therapy can be either by using non-biological agents such as chemical and physical approaches of introducing plasmid DNA to mammalian cells or biological agents such as viruses and bacteria (Fig. 1).

3. Therapeutic approaches

The choice of a therapeutic approach as per the Clinical Practise Guidelines, is based on the existence of breast cancer molecular/immunohistochemical subtypes such as Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)/neu enriched, basal-like and triple-negative breast cancer (TNBC). Vaccine delivery for breast cancer is purely based on patient's immune system. This approach utilizes the high specificity of adaptive immune response and the immunological memory [18]. Variety of therapeutic approaches are available for inducing direct or indirect cell death in cancer cells. These includes cell-based vaccines (allogeneic, autologous, or dendritic cell-based), tumor-associated peptide or protein vaccines, heat shock proteins, DNA vaccines, and use of recombinant viral or bacterial vectors improving immunogenicity of vaccine preparations [19]. Fig. 2 illustrate different strategies using bacterial and viral vectors for the cancer therapy.

Use of competent bacteria or virus particles to infect, replicate in the tumor tissues enabling the destruction of cancer cells as a result of infection is the oncolytic approach. Bacterial vectors expressing cytotoxic proteins/immunogenic peptides has been used for killing the host cancer cells. *S. Typhimurium* with DNA sequence encoding the MHC class I-restricted peptide $p60_{217–225}$ could kill cancer cells through $CD8^+$ cell mediated antigen-specific tumor inhibition [20]. *Clostridium* species possess the natural oncolytic activity and are used as a vector for treating cancer in the clinical trial [21,22]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is one of the pro-apoptotic proteins inducing apoptotic cell death in the cancer cells. Systemic administration of attenuated *Salmonella typhimurium* engineered to express TRAIL under prokaryotic radiation-inducible RecA promoter reduced the tumor growth in xenograft model [23,24]. In other cases, bacterial genes expressing toxins (Diphtheria toxin or Pseudomonas exotoxin) or enzymes that convert the inactive pro-drugs to toxic substances are used to kill tumor cells. The spectrum of viral vectors are broad and the recent researches on oncolytic viruses have proved its potential in the cancer immune and gene therapy. The oncolytic viruses (OVs) such as the echovirus, adenovirus, and herpes simplex-1 virus have received the regulatory approval in Latvia, USA, China, and EU and many of the recombinant viruses are under clinical development [25].

The process of forming new blood vessels from existing microvessels is known as angiogenesis, which is a common phenomenon occurs during tumor progression. Strategies in targeting or preventing the angiogenesis process, thereby manipulating the formation of new blood vessels or inactivating pre-existing vessels can prevent tumor cell growth. Expression of endostatin or similar genes in *Bifidobacterium* as the delivery vehicle have been proven to prevent angiogenesis and controls cancer cell growth [26,27].

Immunotherapy by modulating cancer cell immune response in tumor microenvironment is another strategy in breast cancer therapy. Immunosuppressive cytokines secreted by the cancer cells weaken the production of cytotoxic lymphocytes, thereby creating an immune-suppressive microenvironment [28]. Expression of several immune molecules like CCL21, IL-18, Fas ligand and lymphotoxin by *S. typhimurium* significantly reduced the tumor size in murine xenograft model [29].

Preclinical and clinical studies using DNA vaccines offered a promising outcome in treating cancer [30,31]. DNA vaccines activate the tumor immune response *via* activating the proliferation of cytotoxic lymphocytes and B cells thereby induces the expression of specific tumor antigen in the cancer cells and break the immune tolerance. Several bacterial species were reported to be effective in triggering the cancer immune response. Oral intake of *S. typhimurium* as the transgene carrier was phagocytosed by the monocyte. Release of the transgene containing plasmid during phagocytosis facilitates the expression of specific antigen and activates the immune system most particularly antigen-specific T cell activation and cytotoxic response. The approach has been used in many preclinical and clinical trials of cancer therapy [29,32,33].

4. Vaccine delivery methods

Non-viral vectors such as cationic lipids and polycationic polymers are used as DNA delivery agents in gene therapy [8,34]. These molecules form electrostatic interactions with DNA, thereby protects DNA from nucleases and cellular defense mechanism. In cationic lipids, the

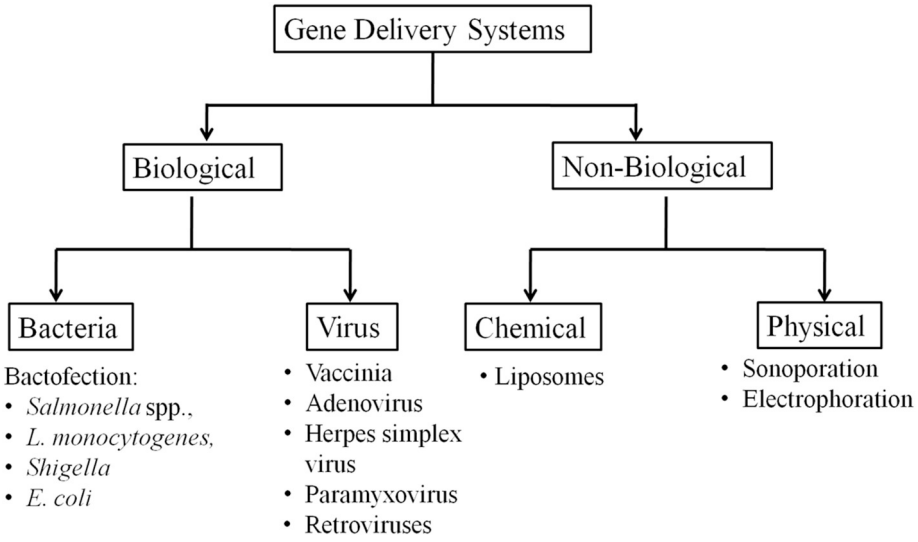

Fig. 1. Gene delivery systems used for anti-tumor treatment.

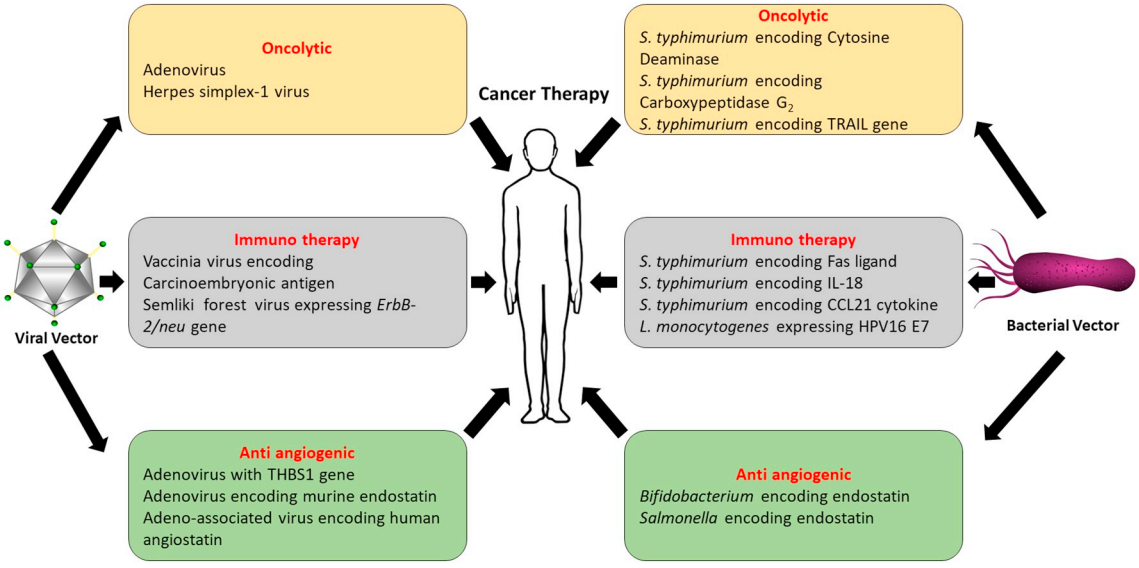

Fig. 2. Therapeutic strategies utilizing bacterial and viral vectors for cancer therapy.

cationic head group binds to DNA and the lipid tail forms DNA-lipid complex. Either naturally occurring proteins or synthetic molecules such as histones, protamines, polyhistidine or polylysine can be used as DNA condensing agents. Though non-viral vectors are safe for gene targeting, its low efficiency compared to viral vectors limits its application in cancer therapy [22]. Research advancements along years made use of bacterial and viral vectors or the combination of these with synthetic carriers to overcome the drawbacks associated with the use of non-viral vectors alone.

4.1. Viral vectors

Viruses are naturally immunogenic and their genetic materials can be engineered to carry any transgenes for their expression in the host cells. Several recombinant viruses are capable of infecting and expressing the transgene in immune cells like antigen-presenting cells (APCs), most specifically dendritic cells (DCs) [35]. Thereby, the greater presentation of tumor antigens to the immune system leads to an increased frequency and avidity of cytotoxic T-lymphocytes targeting tumor cells with the antigens expressed by the vaccine vector [36]. Based on the so far reports, it is apparent that recombinant viruses can be produced, administered and quality controlled more easily compared to other immunotherapy strategies. This was possibly achieved based on the understanding on the inherent characteristics of each virus with its own distinct merits and demerits, that determines its utility for a particular therapeutic strategy [37].

As viruses have the natural ability to infect human cells, it can be effectively used as vaccine delivery vehicles as it elicits host T cell responses and humoral responses [38–40]. Mainly, viruses can be used for direct killing of tumor cells by their oncolytic activity or used to trigger the tumor immune response by the expression of tumor-specific antigens.

Certain viruses have naturally oncolytic properties or can be engineered to target the tumor cells specifically. Oncolytic virotherapy (OVT) is the predominantly used strategy to treat cancer, as it has the potential to specifically lyse the tumor cells and elicit immune response against viral antigens as well as to tumor cell antigens which is long lasting in the form of memory T cells, and hence makes it as a promising candidate in cancer therapy [41]. Oncolytic viral administration triggers anti-viral and anti-tumor immunity. Anti-viral immune response can be innate and adaptive, which determine the efficiency of oncolytic viral therapy. Oncolytic virus infected cancer cell process and present

viral antigen to their surface, which are recognized by $CD4^+$ and $CD8^+$ T cells, resulted in T cell mediated cancer cell destruction. NK cells mediated cancer cell targeting also follows the same pattern in innate immunity [42]. Pathogen-associated molecular patterns (PAMPs) trigger a series of signaling events that stimulate the inflammasome and activate different transcription factors, resulted in release of many pro-inflammatory cytokines and Damage-associated molecular patterns (DAMPs). Inside the tumor microenvironment, released pro-inflammatory cytokines breaks the pro- and anti-inflammatory equilibrium, end up in tumor immuno suppression. Released pro-inflammatory cytokines attract other immune cells with additional effector function, increasing host antitumor immunity [43]. Apart from causing direct lysis to the cells, oncolytic viruses can also be genetically engineered with gene of interest and used as delivery vehicles for vaccine therapy. Upon infection and virus replication in the tumor cells, the gene of interest will be produced in larger amounts where it can exert its function. Due to its efficacy, many oncolytic viruses have been identified as potential therapeutic agents and moved towards clinical application in the recent decade. Strategical oncolytic virotherapy was reports in 1990s, in the xenograft models of human glioma where local administration of a thymidine kinase negative herpes simplex virus (HSV) showed promising results (Kokoris, Sabo, Adman, & Black, 1999).

Viral strains including Vaccinia, Adenovirus, Herpes simplex virus, Paramyxovirus, and Rhabdoviruses are evaluated as potential delivery vehicles (Table. 1) [44]. Adenovirus is the most studied oncolytic viral platform in the recent breast cancer research and therapeutic approach against breast cancer treatment. The therapeutic value of traditional replication-defective adenovirus is limited as it is not specific to target tumor cells. The specificity can be increased by placing the gene responsible for viral growth/replication under tumor- or tissue-specific promoters. Briefly, the gene responsible for adenovirus replication is placed downstream to the E2F-1 promoter, as E2F-1 expression is higher in breast cancer tissues than the normal ones [45,46]. Yan et al. [47] has reported replication selective virotherapy by developing a novel recombinant adenovirus vector with E2F-1 promoter and an immune regulatory factor Interleukin-15 (IL-15). Zhu et al. [48] has constructed recombinant type five adenovirus with human telomerase reverse transcriptase (hTERT) promoter to regulate the adenoviral *E1A* gene and hypoxia response element (HRE) promoter containing IL-24 gene to control the adenoviral *E1B gene*. IL-24 inhibits growth of tumor cells and induces tumor-specific apoptosis.

Adeno-associated viruses (AAV) infect a diverse variety of human and non-human cells and have shown a great promise as a potential platform for vaccine delivery for many infectious diseases including HIV [49–51]. Oral vaccination by AAV expressing truncated neu oncogene in a neu-positive murine TUBO breast cancer model induced both humoral and cellular immune responses and significantly improved the mice survival [49].

Retroviruses are RNA viruses, which can be used as DNA delivery vectors for cancer therapy after removing the viral proteins gag, pol and env. Wei et al. [52] was the first to report the possibility of using retroviruses as vectors for delivering DNA transgenes. Although retroviral vectors possesses its attention for safety concerns like oncogene activation in normal cells and insertional mutagenesis, they are advantageous with a tendency to occupy higher molecular weight transgenes and long-lasting transgene expression in the host cell. Tumor cell-specific transgene expression of recombinant retroviral vectors were reported by McCrudden and McCarthy [53]. Recombinant retroviruses are used for gene-directed enzyme prodrug therapy (GDEPT), in which an enzyme metabolizes the inactive drug to active toxic metabolite in the cancer cells [54]. MetXia-P450 is a recombinant retroviral vector for human cytochrome P450 type 2B6 gene, which potentiates the cyclophosphamide metabolism to produce active phosphoramide mustard and acrolein. MetXia-P450 retroviral vector have been reported to sensitize T47D breast cancer cells to cyclophosphamide and reduced the tumor size of tumor tissue in MDA-MB-231 breast tumor xenograft model [55,56]. Rexin-G is another recombinant replication-incompetent retroviral vector-based vaccine regimen used against many solid tumors including breast cancer [2]. Rexin-G codes for the expression of engineered human cyclin G1 transgene which induces apoptosis and prevents angiogenesis [2,57].

Parvovirus-H1 (H1PV) are non-pathogenic to humans, but immunogenic and tends to multiply in transformed cells and destroy it [3,58]. Parvovirus-H1 can stimulate the human immune system through Toll-like receptors (TLRs) 3 and 9, which leads to the activation of NF-κB-dependent adaptive immune response [59,60]. H1PV shows a higher affinity towards primary breast tumor cells established from the tumors of breast cancer patients rather than the normal cells. Primary cultures from high-grade tumors were reported to exhibit significant sensitivity to H1PV [61]. Recombinant HIPV has also been used for cancer immunotherapy. Genetically engineered HIPV with transgenes for inflammatory cytokines (TNFα and IFN-γ), synergistically improved the therapeutic effect [62].

Herpes simplex virus (HSV), a dsDNA virus belongs to the family Herpesviridae, is one of the well-studied oncolytic virus that are relatively safe and proved to be a valuable tool in oncolytic therapeutics. The U.S. Food and Drug Administration (FDA) approved Talimogene

Table 1
Oncolytic viruses used for vaccine delivery.

Virus	Characteristics	Replication	Examples of virus strain and targeted malignancy	References
Adenoviruses Ad5	It has double-stranded DNA (dsDNA) genome with the medium transgene insertion capacity of about 7.5 kb. Biologically safe.	Nucleus	LOAd703 (Pancreatic), CG0070 (Bladder), DNX-2401 (Brain), VCN-01 (Solid tumors), ONCOS-102 (melanoma).	[52,99,101]
Poxviruses Vaccinia virus	It is large enveloped virus with a dsDNA genome of about 190 kb that has the capacity to pack large foreign inserts and also having broad host range.	Cytoplasm	Pexastimogene Devacirepvec (Pexa-Vec) (Hepatocellular, Colorectal, Solid tumor, breast cancer)	[4]
Herpesviruses HSV1, HSV	It has linear double stranded DNA (dsDNA) that has the capacity to pack large quantities of DNA even up to 30 kb.	Nucleus	Talimogene Laherparepvec (T-Vec) (Melanoma, Breast cancer)	[102]
Paramyxoviruses Newcastle disease virus, Measles virus	It has negative-sense ssRNA with a medium packaging capacity of about 6 kb	Nucleus	MV-NIS (multiple myeloma, Ovarian and CNS cancer)	[103]
Rhabdoviruses Rabies, Vesicular stomatitis virus	It has small ssRNA genome with a medium packaging capacity of about 6 kb	Nucleus	VSV-IFNb-NIS (Solid tumor, Endometrial cancer)	[104]
Reovirus	It has double-stranded RNA genome that selectively targets and replicate in transformed cells with an activated Ras signaling pathway.	Cytoplasm	Reolysin (Colorectal, Bladder, Pancreatic, Multiple Myeloma, Plasma cell myeloma)	[105]
Picornaviruses Coxsackievirus	It has small ssRNA genome that can pack small foreign inserts	Cytoplasm	PVSRIPO (CNS cancer, Melanoma)	[106]

laherparepvec or T-VEC by the trade name Imlygic™, the first oncolytic Herpes Simplex Virus in 2015 [63].

Another important strategy in virus mediated vaccine delivery is the viral vector-DC vaccine, virus vector-Car T. Targeting transgene expression to dendritic cells (DCs) has become a promising approach for guiding the immune system towards immunity or tolerance. This can be achieved on a transcriptional level by using DC-specific promoters or by retargeting the tropism of the virus vectors [64]. The main merit of using viral vectors for genetically modifying DCs is the associated stimulation of DC maturation [65]. Recombinant adenoviral vectors were the most common used vector for transduction of tumor antigens into DCs because of their high efficacy in inducing both humoral and cell-mediated immune responses [66]. Transduction of Human DCs with recombinant adenovirus vectors for up-regulated CD83 and down-regulated CD14, characterizing the mature phenotype of DCs, and also down-regulated IL-10 production of the cells [65]. A report by Chen et al. [67] evidenced that *ex vivo* transduction of DCs with an Ad5 expressing ErbB-2/neu gene offered genetic immunization by induction of protective and therapeutic immunity against a ErbB-2/neu over-expressing breast tumor cell line. In addition, co-transducing DCs with Ad5 expressing IL-12 further enhanced the protection.

Adoptive transfer of chimeric antigen receptor (CAR)-modified T cells with the synergistic effect of the oncolytic viruses for directing/targeting solid tumors gained much importance in the recent research towards cancer therapy [68]. In addition to the potential effect of CAR-modified T cells which were reported to benefit patients of hematological malignancies with significant results, synergism with viral vectors improved the effector functions of tumor-specific T cells with the optional utility to deliver gene-based vaccines/therapeutic transgenes selectively to the tumor microenvironment of solid tumors [69]. A recent report by Bajgain et al. [70] showed CAR T cells directed against mucin1 (MUC1), when co-expressed for an inverted cytokine receptor linking the IL4 receptor exodomain with the IL7 receptor endodomain (4/7ICR) in order to transform the suppressive IL4 signal enhanced the anti-tumor effects of CAR T cells at the tumor site of breast cancer model *in vivo*.

4.2. Bacterial vectors

The link between cancer and bacteria have been reported first by Busch and Fehleisen [71] where, reduced tumor growth was observed with erysipelas infection by *Streptococcus pyogenes* in a cancer patient. Then, William Coley in the 19th century used an attenuated mixture of *Streptococcus* and *Serratia marcescens* for treating bone and soft tissue sarcomas. This mixture was known as Coley's toxin [72]. This lead to the focus on discovering and using bacterial strains or its products in treating a variety of cancers [73]. Infection of poorly antigenic tumors with certain facultative or obligate anaerobic bacteria preferentially facilitates its accumulation and proliferation in tumors, initiates anti-tumor immune responses and promote tumor killing effects. This happens by changing the function of different cellular components of the immune system, such as CD4+ and CD8+ T cells, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and their activation. Also, it has been reported that several conserved bacterial ligands acts as agonists for innate immune system receptors, example, toll-like receptors (TLR), and when binding, initiates an intracellular signaling cascade thereby, leading to the production of proinflammatory cytokines. Additionally, some bacterial components, like exotoxins, have been reported to initiate anti-tumor activities by their direct action on tumor cells rather than their indirect effect.

Using bacteria as a vector for delivering therapeutically important transgenes offers many advantages. Certain Bacterial strains example, Clostridium are highly active and motile in the prevalent anaerobic/hypoxic conditions of the tumor cells [74]. Some auxotrophic strains example, Salmonella are attracted and infiltrated in high amounts due to the increased availability of metabolic nutrients in the tumor microenvironment [75]. Because of these merits and due to their high metabolically active state in tumor cells, they are considered as potential candidates for delivery of anticancer agents/gene-based vaccines for treating tumors as they can access the tumors at remote areas and that are insensitive to chemotherapeutic agents [76]. They have been proved as an excellent candidates for production/delivery of cytotoxins or bacterial toxins, prodrugs converting enzymes, immune-modulating agents (examples, cytokines, antigens), to deliver certain tumor anti-proliferating components, small interfering RNAs (siRNAs) and genes to the tumor tissue [16,77]. Bacterial mediated delivery of foreign DNA into mammalian cells employing bacterial vector is termed as bactofection based gene therapy [78].

Most common species of bacteria used for breast cancer vaccination are *Salmonella typhimurium* [79], *Listeria monocytogenes* [80], *Clostridium novyi* [81], *Clostridium acetobutylicum*, *Bifidobacterium longum*, *Bifidobacterium adolescentis*, and *Escherichia coli*.

Cancer therapeutic approach using bacteria can also be categorized into two kinds; (1) either by introducing the cytotoxic/desired gene into the cancer cell or (2) through oncolysis. Oncolytic strategies rely on using the natural oncolytic property of the replication-competent bacteria to achieve therapeutic responses. *Clostridium* and *Salmonella* are reported to be used as oncolytic vectors [57,82]. Expression of the cytotoxic genes (Suicide genes) in the host cell were reported with administration of attenuated *S. typhimurium* and *Bifidobacterium longum* with vectors for expressing molecules like tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) which reduced the tumor progression significantly [23,83].

Redox proteins produced by certain bacterial strains were reported to kill the cancer cells by inducing apoptosis and cell cycle arrest. Azurin protein produced by *Pseudomonas aeruginosa* kills the cancer cells by inhibiting cell cycle and initiating apoptosis [84] by expression of p53 and Bax, thereby prevents the progression of breast cancer and melanomas. Genetically engineered *E. coli* Nissle 1917 with recombinant transgene for azurin targeted and restrained B16 mouse melanoma and 4 T1 breast tumor cells and inhibits metastasis [85]. Genetically modified obligate anaerobic *Salmonella typhimurium* YB1 strain to survive in hypoxic condition using hypoxia conditioned promoter effectively infected MDA-MB-231 breast cancer cells and induced apoptosis [86].

Loeffler et al. [87] constructed a recombinant *S. typhimurium* VNP20009 strain for immunotherapy with transgene for a cytokine called LIGHT (also known as TNFSF14 or HVEM-L) to study its efficacy in D2F2 breast carcinoma model in Balb/c mice. Endoglin (CD105), is a co-receptor in the TGF-beta receptor complex. When attenuated *Salmonella typhimurium* VNP20009 strain carrying endoglin was orally administered, it effectively inhibited the angiogenesis in D2F2 breast carcinoma xenograft by breaking the peripheral T cell tolerance [88]. *S. typhimurium* RE88 with DNA vaccine encoding Fra-1 and IL-18 activated immune cells (T cells, NK cells, and DCs), inhibited angiogenesis and resulted in the prevention of breast cancer growth and metastasis [89]. Oral administration of engineered *S. typhimurium* SL3261 with human granulocyte/macrophage colony-stimulating factor (hGM-CSF) prevents the growth of 4 T1 breast cancer *in vivo* [90].

Despite these, the tumor-associated antigens [91] and the epitope markers [92] present exclusively on the breast cancer cells have also been reported to be an excellent vaccine candidate for cancer treatment which can elicit an immune response against tumor cells. Mammaglobin-A (MAM-A) protein is a key vaccine target, which is over-expressed in 80% of the breast cancer cells [93,94]. In the Phase-I trial, the Mam-A DNA vaccination to breast cancer patients with stage IV metastasis elicited strong CD4 cellular effector immune responses offering a promising strategy towards the breast cancer vaccine development [94]. Human epidermal growth factor receptor 2 (HER2) is associated with an aggressive form of variety of epithelial cell cancers. The monoclonal antibody trastuzumab specific to HER2 binds directly

Table 2
Bacterial systems used for vaccine delivery.

Bacteria	Antigens/target	Animal model	Examples of Bacterial/plasmid Strain and Targeted malignancy	References
S. typhimurium	Vascular endothelial growth factor receptor-2, transcription factor Fos-related antigen-1, and the anti-apoptosis proteins survivin and legumain,	Mouse	pcDNA3.1-Flk-1 (melanoma, colon, and lung), pUb-Fra-1 pIL-18 and (breast carcinomas)	[89,107]
S. typhimurium	TRAIL	Mouse	VNP pRA-TR and VNP pRA-ZsG (Breast)	[83]
S. typhimurium	IL-8	Mouse	pGEN206-IL-18 (Breast and Colon)	[109]
S. typhimurium	L-Asparaginase	Mouse	pASN (SKS1002/pASN) (Breast, colon and pancreas)	[110]
S. typhimurium	RGD peptide	Mouse	$pOmpA^{RGD}$ (Melanoma and breast)	[79]
B. longum	Cytosine deaminase	Rat	pAV001-HU-eCD-M96 (Breast)	[111]
L. monocytogenes	Fusion of fetal liver kinase-1 and listeriolysin-O	Mouse	*Lm*-LLO-Flk-1 (Breast)	[112]
L. monocytogenes	Truncated listeriolysin O (LLO)	Mouse	LM-LLO-Mage-$b_{311–660}$ (Breast)	[80]

to its extracellular domain and inhibits the function of HER2. However passive immunotherapy provides treatment to 30% of patients with breast cancer. While on the other hand, active immunotherapy with E75 peptide from the HER2 is effective in treatment from 75% to 80% of women with breast cancer [95].

Attenuated *Salmonella* strains have wide application in human and veterinary medicine as live vectors. Attenuated species of *Salmonella* used for vaccine delivery (*S. typhimurium* and *S. typhi*) are proved to elicit a good immune response in humans [96]. *Listeria monocytogenes*, a gram-positive bacterium is capable of escaping from the phagosome to the cell cytosol by the action of the pore-forming hemolysin, listeriolysin O and phospholipases enabling more efficient gene transfer and makes it as a versatile vector for vaccine delivery. Unlike L. *monocytogenes*, both *Salmonella* and *E.coli* spp. are trapped in the cell phagosome post-invasion. Several reports showed the effectiveness of L. *monocytogenes* as delivery vehicles for cancer treatment [97]. Reports showed by Wood et al. [98] used *Listeria*-based vaccines (Lm-LLO-CD105A, and Lm-LLO-CD105B) against CD105, to treat breast cancer in a mouse model. The vaccines stimulated a robust anti-angiogenesis effect and an antitumor immune response that inhibited primary and metastatic tumors. Certain examples of using bacteria for delivery of vaccine candidates were described in Table 2.

5. Conclusion

Different strategies, new compounds, and physical or biological vectors (bacteria and viruses) are proposed continuously for gene delivery, as there is no one-size-fits-all solution. The development of efficient non-toxic gene delivery vehicles and strategies that can carry and deliver foreign DNA to specific cell types is the ultimate goal in gene therapy. Using recombinant bacteria and virus have shown to be promising and currently being broadly investigated. In viral vectors, vaccines carrying tumor-specific antigens are the extensively studied strategy, which activate host tumor immune response through T-cell-specific immune responses. Cancer therapy by oncolytic viruses kills the cancer cell directly along with the stimulating immune response by releasing tumor-specific antigens and inflammation. Oncolytic therapy combined with other therapies like radiation therapy [99], immunotherapy [4], chemotherapy [100] and thermal radiofrequency [5] has been proven to possess synergistic effect to combat cancer. Genetic modification in the bacterial and viral vectors allows their improvements in efficacy of cancer therapy. Improving the efficiency and clinical safety of recombinant bacterial and viral vectors could help in accepting these vaccines for therapeutic use. Producing a suitable vaccine delivery vehicle is a challenge which needs to be overcome for the gene therapy to be accepted and get regulatory approval for treating breast cancers.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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