Progress in the development of cancer vaccines for lung cancer utilizing dendritic cells (Review)

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Abstract. Lung cancer is a major global health concern in terms of both incidence and mortality. Despite substantial advancements in targeted therapy and immune checkpoint inhibitor treatments, their overall effectiveness is limited. Dendritic cells (DCs) are crucial in innate and acquired immune responses due to their effective presentation of antigens. DC-based cancer vaccines have been identified as promising strategies for personalized cancer immunotherapy. The present review presents a thorough examination of the immunomodulation and associated mechanisms of DC vaccines in lung cancer, with a specific emphasis on the presentation of clinical trial data concerning the safety, feasibility and effectiveness of DC vaccines in the treatment of patients with lung cancer. The objective of this review is to highlight strategies and provide insights that may improve the development and clinical efficacy of DC vaccines for the treatment lung cancer.

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1. Introduction

According to the latest global cancer statistics, lung cancer has regained its position as the world's leading cancer in 2022. The 12.4% morbidity and 18.7% mortality rates place a considerable financial burden on public health systems around the world (1). Immunotherapy has made rapid advancements in the treatment of lung cancer, particularly with the development of immune checkpoint blockade (ICB) therapy, which has driven substantial advancements in the field, resulting in longer survival times and an improved quality of life for patients with lung cancer (2). Nevertheless, a small subset of patients shows an inadequate response to immunotherapy, with some patients experiencing severe immune-related adverse events that render it unfeasible to continue treatment (3). Therefore, the advancement of cancer immunotherapy by the development of personalized vaccines tailored to specific tumor antigens holds substantial clinical and scientific promise.

Vaccines were originally developed with the intention of preventing and treating infectious diseases, with the vaccinia vaccine being the first used to combat smallpox (4). However, vaccines have subsequently been developed for the management of various other illnesses, including cancer. Unlike traditional preventive vaccines that target pathogens before they cause disease, cancer vaccines function by activating the immune system by targeting tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), with the goal of destroying cancer cells and generating a lasting immune response (5). The efficacy of cancer vaccines relies primarily on their ability to activate antigen-specific $CD8^+$ T cells. Once activated, these T cells differentiate into effector or cytotoxic T lymphocytes (CTLs), which target and eliminate cancer cells displaying tumor antigens (6). The $CD8^+$ T cells induced by cancer vaccines exhibit a strong affinity for T-cell receptors (TCRs) and increased sensitivity to antigen stimulation, enabling the T cells to identify and bind to the immunogenic peptide-major histocompatibility complex class I (MHC I) complexes on cancer cells, facilitating their

effective eradication (7). Moreover, vaccines can be designed to promote the development and expansion of these memory $CD8^+$ T cells, ensuring their long-term functionality and effectiveness in guarding against tumor recurrence (8). Dendritic cell (DC) vaccines have shown significant effectiveness in clinical trials and are considered a leading approach for the treatment of early-stage cancer (9). The present review presents a thorough examination of the most recent advancements in research on lung cancer vaccines based on DCs, with a specific focus on the immunomodulatory and associated mechanisms of these vaccines in lung cancer. This review places particular emphasis on clinical trial data concerning the safety, feasibility and efficacy of DC vaccines in the treatment of patients with lung cancer, with the goal of providing insights that may improve the development and efficacy of DC vaccines for the treatment of this condition.

2. Biological features and subcategories of DCs

DCs are the most potent antigen-presenting cells (APCs) and play crucial roles in innate and acquired immune responses, such as the activation of antitumor T cells, the initiation of antigen-specific immune responses, and the regulation of immune tolerance and immunity (10). Additionally, DCs migrate to lymph nodes, where they interact with T and B cells. Therefore, DCs activate antigen-specific T cells through T cell TCR, DCs determines T cell expansion and differentiation through co-stimulatory signals and DCs maintains B cell memory through multiple antigen-antibody complexes and continuous stimulation (11). The essential function of DCs within the immune system has resulted in their frequent application in cancer vaccines and immunotherapies, with the goal of strengthening the inherent defense of the body against tumors and other illnesses.

DCs are part of the hematopoietic cell lineage, arising from hematopoietic stem cells (HSCs). The HSCs subsequently differentiate into common myeloid progenitor cells (CMPs), which further differentiate into DCs (12). In the presence of the Nur77 transcription factor, also known as nuclear receptor subfamily 4 group A member 1, CMPs can transform into common DC progenitor cells, which are precursors for both plasmacytoid DCs (pDCs) and conventional or classical DCs (cDCs) (13). DCs become activated upon the recognition of various exogenous danger signals, including components from foreign pathogens and altered cells such as tumor cells. Specifically, the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns occurs via receptors expressed by the membrane and cytoplasm of DCs (14). Activated DCs have unique properties that facilitate the effective capture and internalization of antigens, and their conversion into peptides. These peptides are presented following interaction with MHC I and MHC II molecules to form complexes that are recognized by the TCRs of both $CD8^+$ and $CD4^+$ T cells (15,16). The antigen-trapping DCs then migrate to lymphatic organs such as the spleen and lymph nodes, where they activate antigen-specific T cells by presenting the processed antigen to TCRs (17). DCs can also deliver costimulatory signals such as CD80/CD86 and programmed death-ligand 1 (PD-L1)/PD-L2 to T cells via B7 family proteins, leading to signal amplification and clonal selection (16). Additionally, DCs have the ability to influence the type and strength of T-cell responses via the secretion of cytokines that direct T-cell differentiation into various subsets, such as IL-12 p70 for the promotion of T helper (Th)1 responses, IL-4 for the production of Th2 cells, and IL-17 for the stimulation of Th17 responses (18).

DCs are a diverse population in the immune system and are commonly divided into cDCs, pDCs and monocyte-derived DCs (moDCs) on the basis of their ontogenetic and functional properties. cDCs include both cDC1 and cDC2 subsets, while pDCs and moDCs also play crucial roles within the DC family (19). The development of cDC1s is driven by the transcription factors basic leucine zipper ATF-like transcription factor 3 and interferon (IFN) regulatory factor 8, which regulate the expression of a variety of cell surface markers, such as X-C motif chemokine receptor 1, C-type lectin domain containing 9a, cell adhesion molecule 1, B and T lymphocyte associated, and CD26 (20). The cDC1 subset was first identified in the blood by the expression of CD141, a thrombomodulatory protein that facilitates the cross-presentation of antigens via MHC I to support essential immune responses (21). In addition to expressing various lectins, cDC1s contribute to the recognition of PAMPs through toll-like receptors (TLRs) 1-8 and the initiation and progression of immune responses against pathogens through the production of increased amounts of IL-12 p40 and IL-12 p70 (22). Thus, the cDC1 subset has distinct characteristics that allow these cells to fulfill critical functions in monitoring and responding to potential threats within the immune system. The cDC1 marker CD141 is not expressed by cDC2s, which facilitates the differentiation of cDC2s from cDC1s. Additionally, as CD301 and Fc e receptor 1A are highly expressed on cDC2s but not on cDC1s, they serve as valuable markers for the accurate identification of cDC2s (23). Myeloid cDC2s comprise an abundance of lectins (glycoproteins), TLRs, nucleotide-binding oligomerization domain-like receptors and retinoic acid-inducible gene-I-like receptors. In addition, cDC2s effectively present MHC II-associated antigens to $CD4^+$ T cells, thereby inducing the differentiation of Th1, Th2 and Th17 cell subsets (24). pDCs predominantly reside in lymphoid organs, where they are key generators of type I IFNs and play a critical role in antiviral and antitumor immune responses (25). While moDCs share characteristics and transcriptional properties with DCs, they have a number of phenotypic markers in common with monocyte-derived macrophages, such as CD1b, CD163, CD206 and CD209. Upon exposure to inflammation, moDCs differentiate and are recruited to sites of inflammation, including the tumor microenvironment (TME) (26).

3. Cancer vaccines based on DCs

Building on advancements in the understanding of DC biology, scientists have rigorously explored strategies for optimizing vaccine construction. The commonly used approaches for DC vaccine preparation involve the generation of antigen vector DCs *in vitro* and the direct delivery of antigens to DC receptors *in vivo* (27). The successful generation of mouse DCs from precursor cells in the bone marrow has facilitated the development of DC vaccines (28). At present, DCs can be acquired *in vitro* via four different techniques: Differentiation

of $CD14^+$ monocytes into DCs, differentiation of $CD34^+$ hematopoietic progenitor cells into DCs, expansion of circulating DCs, and the differentiation of dedifferentiated induced pluripotent stem cells into DCs (29-32). DCs can be loaded with TSAs *in vitro*, so that upon infusion into a patient, they trigger a targeted immune response against the tumor. The process of targeting antigens directly to DC receptors *in vivo* is known as receptor-mediated targeting. In addition, chimeric antigen-antibody complexes that target DC surface receptors are taken up into the endosomal compartments of DCs for MHC loading and the activation of T-cell responses (33). The complexity of this process is pivotal in the initiation of the immune system. This technology shows potential for increasing vaccine immunogenicity and improving vaccine efficacy. Compared with the generation or manipulation of DCs *ex vivo*, which is commonly performed but has notable drawbacks, including high costs, extensive personnel requirements, and challenges in standardization and scalability, the targeting of DCs *in vivo* allows for the production of vaccines on a larger scale. The targeting strategy of DCs *in vivo* is based on DC surface molecules and their receptor mechanisms, mainly including targeting Fc receptors, C-type lectin receptors and scavenger receptors (8).

Antitumor DC vaccines can be classified into two categories: DC gene vaccines and DC peptide vaccines. These vaccines are designed to increase antigen uptake, processing and presentation by DCs via the introduction of TSA-coding genes including tumor DNA or RNA, cytokines, costimulatory molecules and adhesion molecules. The import of these elements into DCs leads to the induction of specific CTLs which, when activated, secrete IFN-γ and granzyme B to eliminate tumor cells (33-37). This requires a tumor-specific platform for the stimulation of DCs, a vaccine to sensitize DCs to tumor cell lysis, a fusion vaccine for tumor cells and DCs, and a vaccine to load secreted body components into DCs (38-40). The primary approach involves the synthesis or screening of specific tumor antigen peptides, their binding to the surface of DCs, and the initiation of targeted immune responses against tumor antigens.

4. DC gene vaccine functions in regulating the immune response to lung cancer

Lymphotactin (Ltn) is a C-chemokine that specifically attracts T cells and natural killer (NK) cells and is produced by T and NK cells themselves (41). Modification of the Ltn gene in DCs can enhance their targeted chemotaxis towards T cells and NK cells, thus optimizing the microenvironment for antigen presentation and promoting the effective presentation of antigens to T cells by the DCs (42). Hence, a recombinant adenovirus vector containing the Ltn gene (rAd-Ltn) was fabricated, and DCs transfected with the rAd-Ltn were used to inoculate isogenic mice or treat tumor-bearing mice with preestablished spontaneous lung metastasis (43). The Ltn-modified DCs were shown to depend on $CD4^+$ and $CD8^+$ T cells during the induction and effector phases for the development of protective immunity. Furthermore, the activation of the CD28/cytotoxic T-lymphocyte associated protein 4 pathway by costimulated T cells and the presence of IFN-γ are essential for Ltn-DCs to initiate an effective antitumor immune response (44). A number of potential targets for the development of DC gene vaccines have been identified. These include cytokeratin 19 (CK19), which is classified as a type I CK and known for its upregulation in various types of human tumors, including lung cancer. It is an intermediate filament protein that is a component of the cytoskeleton (45). A DC vaccine was prepared by introducing CK19 into DCs via adenoviral transfection. When tested in an Lewis lung cancer (LLC) model, the CK19-transfected DCs induced the generation of potent CK19-specific CTLs with the ability to lyse LLC cells, and thereby effectively inhibited tumor growth (46). Ki-Ras mutations are frequently observed in lung cancer and have been shown to be associated with patient prognosis (47). On this basis, recombinant adenoviruses have been employed to create innovative tumor vaccines by the transfection of DCs with genes encoding the mutated Ki-Ras protein. These vaccines were shown to effectively promote the expansion of splenic lymphocytes and prompt specific CTL reactions against lung cancer cell lines harboring the corresponding gene mutations (48). In additional, livin is a member of the inhibitor of apoptosis protein family, which has been identified as playing a critical role in the development of drug resistance in lung cancer chemotherapy, with livin a exhibiting a particularly evident association with the progression of lung cancer (49). Therefore, scientists developed a recombinant adenoviral vector carrying the livin α gene (rAd-Livin α), and demonstrated that the introduction of rAd-Livin α into a DC vaccine effectively suppressed tumor growth in mice (50,51). Fibroblast-activating protein α (FAPα) is crucial in shaping the TME by influencing cancer-associated fibroblasts (CAFs). It achieves this through the modification of their cell surface proteases, which results in the suppression of antitumor immunity and the promotion of tumor growth and metastasis (52). Xie *et al* (53) utilized this method to develop a recombinant adenoviral vector containing FAPα and it was found that DC vaccines transduced by rAd-FAPα could effectively inhibit tumor growth and prolong overall survival time. However, in these two studies, the antitumor vaccine was not effective in completely eliminating the tumor in tumor-bearing mice.

Ye *et al* (54) investigated the impact of FAPα and livin α dual gene modification on the antitumor effect of DCs on LLC cells. The results indicated that the efficacy of the dual-gene-modified DC vaccine against LLC was greater than that of the respective single-gene-modified DC vaccines, potentially due to its enhanced ability to modulate the immune response of the TME by targeting CAFs. This approach inhibited tumor growth and extended the survival time of mice. In addition, DC vaccines transfected with ovalbumin via lentiviral vector have been shown to elicit potent T-cell-mediated immunity, with enhanced migration of the DCs to T-cell-rich compartments and increased activation of CTLs for the eradication of tumor cells (55).

These findings indicate that DC-based gene vaccines can stimulate a targeted CTL immune response by modulating T cells, leading to the development of antitumor immunity against lung cancer. DC gene vaccines are anticipated to emerge as a significant modality for lung cancer immunotherapy.

A summary of the immunomodulatory effects of DC-based vaccines in lung cancer is presented in Table I.

Table I. Immunomodulatory effects of DC-based vaccines in lung cancer.

First author, year	Vaccine type	DC vaccine loading strategy	Vaccination program	Mechanism	Antitumor effect	(Refs.)
Zhang *et al*, 1999	DC gene	Transfection of Ltn recombinant adenovirus into DCs	-	Induced phase depended on $CD4^+$ T cells and $CD8^+$ T cells; stage effect depended on $CD8^+$ T cells	Significantly inhibited spontaneous lung metastasis of LLC in mice	(43)
Sun *et al*, 2015	DC gene	Transfection of CK19 recombinant adenovirus into DCs	Subcutaneous injection; $5x10^5$ cells administered 3 times, at 3-day intervals	Stimulated T-cell proliferation *in vitro*; induced cytolytic activity against tumor cells in splenic T cells	Average LLC tumor weight was 2.800 and 2.788 g, respectively, in mice immunized with empty vector-transfected and untransfected DCs, and 1.035 g in mice transfected with CK19 DCs ($P<0.01$)	(46)
Yu *et al*, 2004	DC gene	Transfection of Ki-Ras recombinant adenovirus into DCs	Intraperitoneal injection; $2x10^5$ cells administered twice, 1 week apart	Stimulated the proliferation of splenic lymphocytes and induced specific CTLs	Immunization of mice with the DC vaccine had a specific killing effect on LLC expressing the Ki-Ras gene	(48)
Chen *et al*, 2013	DC gene	Transfection of livin α recombinant adenovirus into DCs	-	Effectively induced human livin α-specific CTLs *in vitro*	Effectively sensitized homologous T lymphocytes and produced HLA-restricted anti-livin-related cytotoxic effects against lung cancer cells without autoimmune reactivity in normal lung cells	(50)
Xie *et al*, 2020	DC gene	Transfection of DCs with recombinant adenovirus encoding FAPα	Subcutaneous injection; $5x10^5$ cells administered 3 times, 5 days apart	Produced potent FAPα-specific CTLs to target and eliminate CAFs	In prophylaxis, vaccinated mice exhibited 100% survival; in therapy, the tumor volume of vaccinated mice was significantly reduced on days 13-23; 4/10 immunized mice survived to day 61, while the controls died naturally or were euthanized ($P<0.001$)	(53)
Ye *et al*, 2023	DC gene	Transfection of FAPα and livin-α into DCs via recombinant lentivirus	Subcutaneous injection; $5x10^5$ cells administered 3 times, 3 days apart	Promoted immune enhancement of the TME by killing CAFs	LLC tumor volume in mice immunized with the doubly gene-modified DC vaccine was decreased more than that in mice immunized with DCs modified with either single gene alone, and the survival rate was higher ($P<0.01$)	(54)
Jiang *et al*, 2017	DC gene	Transfection of OVA into DCs via lentivirus	Intratumoral and caudal vein injections; DC vaccine and T cells (DC: T, 1:10) were inoculated with $5x10^7$ cells/ml PBS	Stimulated strong T-cell-mediated immunity, enhanced homing to T-cell-rich compartments, and activated a greater number of CTLs	Mean tumor size of mice immunized with DC vaccine and T cells was significantly smaller than that of the controls, and overall survival was significantly extended ($P<0.01$).	(55)

Table I. Continued.

First author, year	Vaccine type	DC vaccine loading strategy	Vaccination program	Mechanism	Antitumor effect	(Refs.)
			into the tumor on days 12 and 16, and into the tail vein on day 20 after tumor cell inoculation		Median survival time after tumor inoculation was 67 days vs. 44 and 37 days in empty vector and untransfected DC groups ($P<0.05$ and $P<0.001$, respectively)	
Pan *et al*, 2022	Tumor-specific epitope stimulated DC	MUC1-Vax containing PD-L1 generated by a peptide assembly method was loaded onto DCs	Foot pad injection; $2x10^6$ cells administered twice, 7 days apart	Induction of the activation and cytokine secretion of spleen T lymphocytes results in enhanced and prolonged resistance to PD-L1 antibody, and the activation of Th cells and MUC1- and PD-L1-specific CTLs	Survival rate of immunized mice was significantly improved and the survival time was prolonged; tumor size of mice in the DC vaccine group was significantly smaller than that in the control group at the same time point, and one tumor was completely eliminated	(61)
Teramoto *et al*, 2013	Tumor-specific epitope stimulated DC	Loading of DCs with MHC I and pan-MHC II peptides	Subcutaneous injection; $1x10^6$ cells administered 4 times, 3 days apart	Increased the number of IFN-γ producing $CD4^+$ T cells in the spleen and decreased the number of Tregs	Immunization significantly reduced the tumor load of mice and significantly increased IFN-γ in tumor tissue	(62)
Shinagawa *et al*, 2008	Tumor-specific epitope stimulated DC	Pulsing of immature DCs with gp96	Subcutaneous injection; $5x10^5$ cells pulsed with 3 μg/ml gp96 administered 4 times,	Tumor cells are killed by the immune response of $CD8^+$ CTLs and NK cells	Tumor size of mice immunized with gp96 pulsed DC vaccine derived from LLC-OVA was significantly smaller than that of the control group ($P<0.05$)	(63)
Wculek *et al*, 2019	Tumor cell lysate sensitized DC	Loading of cDC1 vaccine tumor cell lysate	Intravenous and intradermal injection; $2\text{-}10x10^5$ cDC1 cells	Number of PD-1^+ $CD8^+$ and $CD4^+$ T cells in tumor draining lymph nodes was increased, and the pool of anticancer T cells was expanded	Mice vaccinated with the cDC1 vaccine showed a significant reduction in tumor growth and improved survival compared with control mice	(66)

CAF, cancer-associated fibroblasts cDC1, classical DC 1; CK19, cytokeratin 19; CTL, cytotoxic T lymphocyte; DC, dendritic cell; FAPα, fibroblast-activating protein α; HLA, human leukocyte antigen; IFN, interferon; LLC, Lewis lung cancer; Ltn, lymphotactin; MHC, major histocompatibility complex; MUC1, mucin 1; NK, natural killer; OVA, ovalbumin; PD-L1, programmed death-ligand 1; Th, T helper; TME, tumor microenvironment; Treg, regulatory T cell.

5. Role of DC polypeptide vaccines in modulating lung cancer immunity

As potent APCs, DCs are capable of carrying a diverse range of tumor antigens, including TSAs, TAAs and whole tumor cell antigens for delivery (56). Mucin 1 (MUC1) is a heavily glycosylated transmembrane protein with considerable potential as a TAA that is upregulated in various types of tumors, including lung, pancreatic and breast cancers (57,58). PD-L1 is a transmembrane protein that is highly expressed in diverse tumor types. PD-L1-specific T cells have been shown to be capable of augmenting the immune response of T cells, either directly or indirectly, by inducing the release of cytokines or TAAs from tumor cells during their destruction, thereby intensifying the immune response (59). A novel peptide assembly method (60) was used by Pan *et al* (61) to generate a specific MUC1-Vax tumor vaccine containing PD-L1, which was loaded onto DCs to produce a DC vaccine. This innovative DC vaccine exhibited the ability to stimulate the activation of T lymphocytes in the spleen and the secretion of cytokines. In addition, vaccinated mice exhibited the elevated and long-lasting production of anti-PD-L1 antibodies, as well as the activation of Th cells and MUC1- and PD-L1-specific CTLs. Teramoto *et al* (62) administered a DC vaccine containing TAA-derived MHC I and pan-MHC II peptides to mice bearing LLC tumors. This led to a significant increase in the population of IFN-γ-producing $CD4^+$ T cells in the spleen, along with a reduction in regulatory T cell (Treg) levels, which effectively inhibited tumor growth. Tumor-derived gp96 has been indicated to lead to the elimination of tumor cells in mouse models. Specifically, in a murine LLC model, Shinagawa *et al* (63) demonstrated that a vaccine comprising immature bone marrow-derived DCs pulsed with tumor-derived gp96 elicited the eradication of tumor cells through an immune response mediated by CD8 CTLs and NK cells. Cytidine phospho-guanosine oligonucleotides (CpG-ODNs) exhibit strong immunostimulatory properties (64). A highly effective *in vivo* antitumor immune response was obtained when a DC tumor vaccine, created by the fusion of CpG-ODN stimulated mature DCs with tumor cells, was used to immunize LLC-bearing mice. The researchers suggested that this was accomplished primarily through the promotion of DC maturation (65). An enhanced understanding of the role played by the DC subpopulation is crucial for advancing the development of next-generation DC vaccines. Wculek *et al* (66) primed the primary cDC1s isolated from the spleens of mice with tumor cell lysates that had been induced to undergo immunogenic cell death through ultraviolet irradiation. The utilization of the TCL-loaded cDC1s in murine cancer models was observed to augment the population of PD-1^+ $CD8^+$ and $CD4^+$ T cells in the tumor-draining lymph nodes, thereby expanding the reservoir of anticancer T cells. In addition, they exerted a synergistic antitumor effect when combined with anti-PD-1 blockade.

6. Clinical utilization of DC vaccines in the treatment of lung cancer

Following the application of DC-based cancer vaccines in individuals diagnosed with lymphoma and melanoma (67), autologous DCs have since been utilized in immunotherapy for a range of malignancies, including prostate cancer (68), renal cell carcinoma and malignant glioma (69). Sipuleucel-T, also known by the trade name Provenge, was demonstrated to be effective as an autologous DC-based vaccine in a phase III study, and was the first therapeutic cancer vaccine to obtain approval by the US Food and Drug Administration for the treatment of metastatic castration-resistant prostate cancer (68). Although the potential of DC vaccines to induce an immune response in lung cancer has been confirmed by preclinical trials, further comprehensive evaluations are necessary to investigate their safety and efficacy for clinical application. In one such trial. in which the tolerance and immune response to DC vaccines of patients with non-small cell lung cancer (NSCLC) was evaluated, researchers administered a mature autologous DC vaccine derived from DC/T-cell-derived maturation factor, to 16 individuals diagnosed with stage IA-IIIB NSCLC after undergoing radical treatment (70). During the study, no unexpected or serious adverse events were reported, and an antigen-specific response was detected in 6 patients. In a follow-up study, the team administered the immature autologous DC vaccine to 14 subjects with NSCLC. Once again, no serious adverse events occurred and 9 subjects exhibited an enhanced response to T-cell IFN-γ (71). Thus, in patients with NSCLC, DC vaccines have demonstrated favorable tolerability and marked biological efficacy. Notably, Chang *et al* (72) pulsed DCs with autologous tumor cells isolated from the pleural effusion of patients diagnosed with advanced lung cancer and administered the DCs directly into the inguinal lymph nodes under ultrasound guidance. An increase in the T-cell IFN-γ response was observed in 3 of the 8 patients treated in the study, and the T-cell response was found to be more pronounced in the patients with the longest disease control times (72). In a separate study of 5 patients with NSCLC who received autologous DC vaccines, 3 of the patients experienced prolonged survival. Notably, 2 patients exhibited a survival time nearly twice that of the anticipated average, and these patients were the only individuals whose tumors concurrently expressed HER2 and CEA (73).

Building on the relevance of CEA in tumor response, a separate study stimulated DCs with pulses of CEA652, a human leukocyte antigen (HLA)-A24-restricted 9-mer peptide derived from CEA. These DCs were subsequently administered to 18 patients diagnosed with metastatic gastrointestinal cancer or lung adenocarcinoma expressing both CEA and HLA-A24 (74). Throughout the trial, the vaccine exhibited good tolerability. No instances of toxicity associated with the treatment were observed, and although there was no clear tumor shrinkage, some patients experienced either long-term disease stabilization or a significant reduction in serum CEA levels. Since then, researchers have used the tumor antigens MUC1 (75,76), Wilms tumor protein 1 antigen peptide (77), recombinant melanoma antigen gene-3 plus recombinant survivin peptide (78), and a recombinant adenoviral vector expressing the chemokine (C-C motif) ligand 21 gene (79) to generate DC vaccines. When administered to patients with lung cancer, certain individuals have experienced beneficial effects, such as stimulation of the T-cell IFN-γ response, a reduction in Tregs, or enhancement of tumor T-cell infiltration without experiencing any significant adverse events.

Table II. Clinical application of DC-based vaccines in lung cancer.

First author/s, year	Vaccine specification	Clinical study design	Vaccination program	Immune surveillance	(Refs.)
Hirshowitz *et al*, 2004	Mature autologous DC vaccine derived from DC/T-cell maturation factor	Patients with stage IA to IIIB NSCLC after radical treatment	Intradermal injections were administered twice to the thigh, with an average dose of $8.2x10^7$ for the first injection and $7.9x10^7$ for the second injection, with an interval of 1 month.	Increased IFN-γ production by T-cells in response to tumor lysate observed in 6/16 (37.5%) patients	(70)
Hirshowitz *et al*, 2007	Mature autologous DC vaccine derived from DC/T-cell maturation factor	Patients with stage IA-IIIB NSCLC after radical treatment	Intradermal injections were administered twice to the thigh, with an average dose of $8.2x10^7$ for the first injection and $7.9x10^7$ for the second injection, with an interval of 1 month.	Increased IFN-γ production by T-cells in response to tumor lysate observed in 9/14 (64.3%) patients	(71)
Chang *et al*, 2005	Immature DCs pulsed with autologous tumor cell lysate from pleural effusion	Phase I study of advanced refractory NSCLC	Ultrasound-guided injections to the inguinal lymph nodes; 4 doses at 1-week intervals followed by 2 doses at 2-week intervals	Mild-to-moderate increase in the T-cell response to tumor antigens was observed in 6/8 (75%) patients	(72)
Perroud *et al*, 2011	Mature antigen-pulsed autologous DCs	Patients with inoperable stage III or IV NSCLC and the HLA-A2 phenotype	Subcutaneous and intravenous injections; 2 doses with a 15-day interval, each comprising $5x10^7$ cells by subcutaneous injection and $5x10^7$ cells by intravenous injection	Anticipated survival duration surpassed by 3/5 patients, 2 of whom had a ~2-fold increase in survival duration compare with the anticipated average and were the only patients with both HER2 and CEA expression	(73)
Ueda *et al*, 2004	DCs pulsed with CEA derived HLA-A24 restriction 9-mer peptide	Patients with metastatic CEA- and HLA-A24-positive gastrointestinal cancer or lung adenocarcinoma	Administration to the inguinal region; 9 doses administered 2 weeks apart, each with $0.5\text{-}5x10^7$ cells	Positive response to DTH skin test in 5/11 (45.5%) patients; CEA-specific CTL responses observed in 6/11 (54.5%) patients	(74)
Teramoto *et al*, 2017	MUC1-pulsed DC vaccine	Patients with refractory NSCLC	Subcutaneous injection in the axilla or supraclavicular fossa; $1x10^7$ cells per dose at 2-week intervals, 1-42 doses	MUC1-specific cytotoxic immune responses were observed in 7/7 patients (100%)	(75)
Kontani *et al*, 2003	MUC1-pulsed DC vaccine	Patients with advanced or metastatic breast or lung cancer	Subcutaneous or pleural cavity injections were administered 3-12 times, 2 weeks apart, and each vaccine contained $4\text{-}10x10^6$ cells	Marked clinical effects observed in 7/9 (77.8%) patients, such as reduced tumor size or tumor marker levels, or disappearance of malignant pleural effusion	(76)
Takahashi *et al*, 2013	WT1 peptide-pulsed DC vaccine	Previously treated patients with inoperable or postoperative recurrence of NSCLC	Intradermal vaccination near the axillary and/or inguinal lymph nodes; $1x10^7$ cells per dose at 2-week intervals; median of 10 vaccinations (range, 4-31)	Clinical response based on RECIST observed in 31/62 (50.0%) patients: Complete response, n=1 (1.6%); partial response, n=4 (6.5%); stable disease, n=26 (41.9%)	(77)

Table II. Continued.

First author/s, year	Vaccine specification	Clinical study design	Vaccination program	Immune surveillance	(Refs.)
Li and He, 2018	DC vaccine pulsed with rMAGE-3 and rSurvivin peptide	Patients with stage I-IIIB NSCLC	Intradermal injection into the thigh; 2 doses administered with a 1-month interval, at doses of $9.1x10^7$ and $8.2x10^7$, respectively	In 11/16 (68.8%) patients with stable disease, peripheral T-cell production of IFN-γ increased	(78)
Lee *et al*, 2017	CCL21 gene-modified DC vaccine	Patients with stage IIIB/IV NSCLC	CT or bronchoscope-guided intratumoral injections; 2 vaccinations with a 1-week interval, and a maximum dose of $3x10^7$ cells per vaccination	T-cell IFN-γ response to TAA increased in 6/16 (37.5%) patients; tumor T-cell infiltration induced in 7/13 (53.8%) patients	(79)
Ge *et al*, 2017	DC vaccine pulsed with survivin and MUC1, silenced with SOCS1 and immunostimulated with flagellin	Stage I-IIIA resected NSCLC	Intravenous injection; administered 3 times at 1-week intervals, $1x10^6$ cells injected per dose	Number of Tregs decreased significantly in 2/15 (13.3%) patients, and TNF-α and IL-6 increased	(80)
Takahashi *et al*, 2016	Peptide-pulsed DC vaccine	Patients with advanced NSCLC	Intradermal vaccinations near the axillary and/or inguinal lymph nodes; median of 7 (range, 5-34) vaccinations at 2-week intervals, each comprising $1x10^7$ cells	Patients with lung adenocarcinoma had prolonged survival times and higher rates of erythema response	(82)

CCL21, chemokine (C-C motif) ligand 21; CT, computed tomography; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DTH, delayed-type hypersensitivity; HLA, human leukocyte antigen; IFN, interferon; MUC1, mucin 1; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors; rMAGE3, recombinant melanoma antigen gene-3; SOCS1, suppressor of cytokine signaling 1; TAA, tumor associated antigen; Treg, regulatory T cell; WT1, Wilms tumor protein 1.

Table III. Application of personalized neoantigen DC vaccines in lung cancer.

NCT number	Phase	Participants, n	Source of DCs
NCT04078269	I	6	Monocytes
NCT02956551	I	20	-
NCT03871205	I	30	-
NCT03208930	I/II	20	Peripheral blood

DC, dendritic cell; NCT, National Clinical Trial.

To improve the efficacy of DC vaccines and address challenges in antigen presentation, Ge *et al* (80) developed a novel antigen peptide. The DC vaccine was generated using pulses of survivin and MUC1, regulated by suppressor of cytokine signaling 1, and immunologically stimulated with flagellin. This modified DC vaccine led to a significant reduction in the number of $CD3^+CD4^+CD25^+FOXP3^+$ Tregs and an increase in TNF-α and IL-6 in 2 of the 15 patients tested. Long-term follow-up revealed that the vaccine effectively prevented lung cancer recurrence. TNF-α is involved in numerous physiological and pathological processes, primarily by binding to TNF receptors. This triggers the activation of a cascade of signaling events, which can lead to apoptosis (81).

Notably, a multicenter study (82) demonstrated that patients with lung adenocarcinoma who received a DC vaccine exhibited longer survival times and a higher rate of erythema response when compared with patients with other subtypes of NSCLC who also received the same vaccine, indicating the potential enhanced susceptibility of lung adenocarcinoma to DC vaccines.

These clinical studies suggest that DC vaccines exhibit favorable tolerability and biological activity in the treatment of lung cancer, as well as significant antitumor effects. Thus, they represent a promising therapeutic approach for lung cancer.

A summary of the clinical application of DC-based vaccines in lung cancer is presented in Table II.

7. Prospects of personalized neoantigen DC vaccines for lung cancer treatment

Tumors of the same type can vary considerably, and personalized neoantigens, which are specific to each tumor, are present only in proliferating tumor cells and not in normal tissues. Therefore, treatment using personalized neoantigens is a suitable approach to ensure a tailored immune response for each individual cancer (83). The use of fast and efficient high-throughput or next-generation sequencing, or whole-exome sequencing, can be used to compare the DNA sequences of tumor tissue and normal tissue in order to identify personalized neoantigens (84,85). The development of personalized neoantigen-pulsed DC vaccines is a promising strategy that may enhance the efficacy and safety of DC vaccines.

In 2020, Ding *et al* (86) recruited 12 patients with advanced lung cancer and isolated and identified 12-30 peptide-based personalized neoantigens from the tumor tissue in each case. At the same time, peripheral blood mononuclear cells were collected from each patient and induced to differentiate into DCs. The DCs were then pulsed with the corresponding selected neoantigen peptides to form a personalized vaccine for each patient. The disease control rate observed was 75%, with a median progression-free survival time of 5.5 months and median overall survival time of 7.9 months. This trial was the first to test the use of personalized neoantigen DC vaccines in patients with lung cancer, and provides evidence that this novel approach has potential as a treatment for this disease. Several clinical trials of personalized neoantigen DC vaccines in patients with lung cancer are currently ongoing (Table III). Although these trials are only at phase I, they involve innovative treatments and hold promise for the advancement of lung cancer treatment.

8. Conclusions and prospects

As pivotal APCs, DCs play a vital role in the immunotherapy of lung cancer. Preclinical and clinical studies have demonstrated that DC-based cancer vaccines targeting lung cancer exhibit low toxicity and are capable of eliciting the desired immune response; thus, these vaccines have clear clinical promise. The current investigations of DC vaccines in lung cancer are predominantly phase I clinical trials, owing to a multitude of factors. First, the process for the preparation of DC vaccines is intricate, and numerous factors impact the presentation of DC antigens, including the quantity of pulsed DC peptides and their maturation state. Second, the availability of autologous tumor cells is limited, and the identification of TSAs is challenging. Third, the effectiveness of DC vaccines may also be impacted by the diverse approaches to administration; currently, there is no universally established treatment method. Finally, there is a scarcity of reliable biomarkers for evaluating the efficacy of DC vaccines and evaluating the prognosis of patients treated with them. The future challenge lies in the development of personalized DC vaccines tailored to individual patients. Furthermore, the currently used combined treatments for lung cancer have exhibited marked improvements in therapeutic effectiveness (87). In the future, the combination of DC vaccines with other therapeutic approaches, such as medications, ICB therapies and ACTs should be considered to enhance the immune response, improve the elimination of tumors, and increase the overall quality of life of individuals with cancer.

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Availability of data and materials

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Authors' contributions

HH and WC contributed to the concept and design. HH, WC, CS and JX participated in the drafting and revision of the

manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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