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A promising therapeutic approach of dendritic cell vaccines for ovarian cancer

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Abstract

Ovarian cancer (OC) remains one of the most lethal gynecological malignancies, primarily due to its often late-stage diagnosis and the development of resistance to conventional therapies. In recent years, significant advancements in immunotherapy have highlighted the potential of dendritic cell (DC) vaccines as a novel therapeutic approach. This review aims to thoroughly evaluate the current landscape and the future potential of DC vaccinations for OC therapy. Recent Studies have provided evidence that DC vaccines can generate specific T-cell responses, thereby enhancing the immunogenicity of ovarian tumors. Furthermore, combining DC vaccines with other therapeutic modalities, such as checkpoint inhibitors and chemotherapy, has shown considerable promise in overcoming the immune evasion mechanisms employed by tumors. However, several challenges remain, including optimizing antigen selection, improving DC maturation and migration, and countering tumor-induced immunosuppression. Continued research is essential for fully unlocking the potential of DC vaccines in improving outcomes for ovarian cancer patients.

Keywords: Ovarian Carcinoma, DC subsets, Immunotherapy, Dendritic Cell Vaccine, Hereditary Ovarian Cancer

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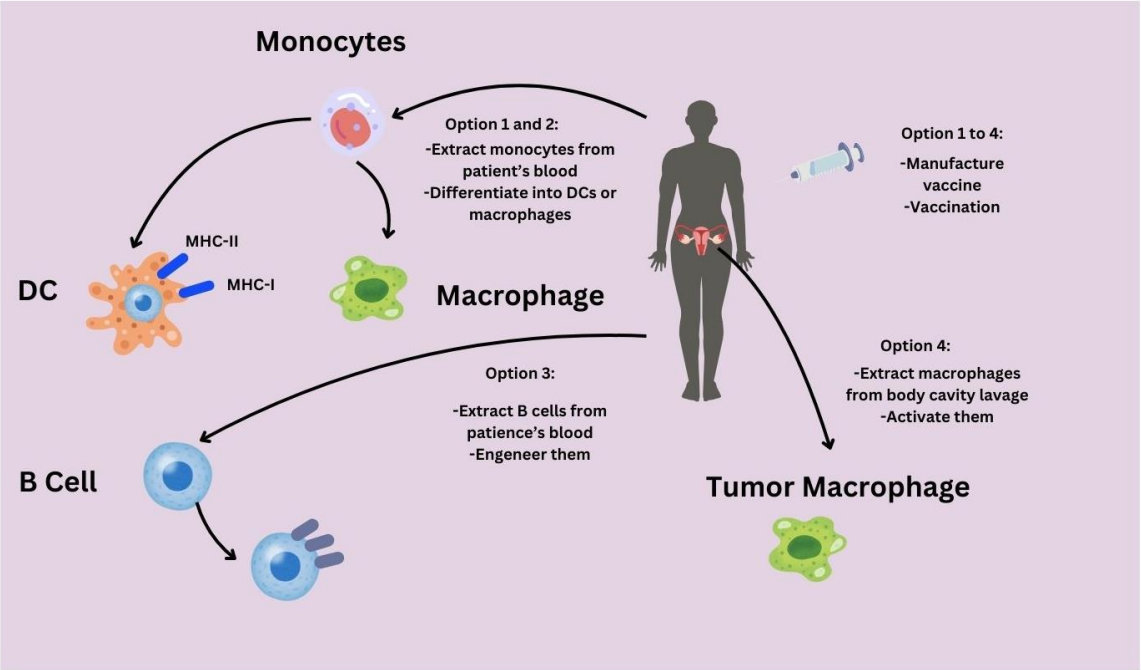
Graphical abstract



Introduction

Ovarian Cancer (OC), a malignant tumor that develops in the ovaries, is often referred to as the "silent killer" due to its subtle symptoms and late diagnosis. It ranks as the seventh leading cause of cancer-related deaths in women and is the deadliest among gynecologic cancers (1, 2). Among female patients, ovarian cancer makes up 4% of all malignancies and 25% of cancers affecting the female reproductive system. It leads to 5% of female deaths and more than 50% of deaths caused by cancer of the female genital tract. The main types of ovarian carcinomas are serous (40%), mucinous (10%), endometrioid carcinoma (20%), undifferentiated carcinoma (10%), and clear cell tumors (3).

Several elements contribute to the prognosis of a tumor, including tumor margin, vascular invasion, tumor grade and stage, expression of oncogenes, and the presence of estrogen and progesterone receptors (3, 4). Immune cells within the tumor, such as Dendritic Cell (DCs), may also serve as a prognostic factor. DCs are a rare immune cell population found in tumors and lymphoid organs, but they play a central role in initiating antigen-specific immunity and tolerance. Manipulating DCs has the potential to effectively induce anti-tumor immunity (5). DCs play a crucial role in the immune system by enhancing immunity or inducing tolerance. This is achieved through the presentation of antigens to T cells, and the delivery of immunomodulatory signals via direct cell-to-cell interactions and the secretion of cytokines (6).

The functions of DCs are influenced by their capacity to sense and respond to environmental stimuli, which are detected through various receptors located on the cell surface and within the cell for cytokines, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). Recent research underscores the unique functions of DC subsets in antitumor immune responses, offering important insights for therapy and making them a promising tool in vaccine development, especially for diseases like cancer, infectious diseases, and autoimmune disorders (7, 8). To initiate and maintain protective anti-tumor immunity, optimal DC function is necessary. However, aggressive cancers can effectively evade immune control by impairing normal DC functions (9). The understanding of DC subsets and their functions has predominantly been shaped by research in mice; however, there is an increasing interest in exploring the biology of human DCs (10,11). This article will delve into the primary functions of DCs in cancer immunology and examine the potential

therapeutic strategies involving the targeting of DCs in vaccines for patients with OC. Despite all these therapeutic advances, approximately 80–85% of the advanced-stage patients still relapse, indicating the urgent need for novel therapies against OC.

1 .Ovarian Carcinoma

Among women, OC ranks seventh in terms of global cancer diagnosis, following breast, colorectal, lung, endometrial, thyroid, and non-Hodgkin's lymphoma (12). Approximately 239,000 new cases and 152,000 deaths are reported annually (13). Eastern and Central Europe record the highest rates, with 11.4 per 100,000 and 6.0 per 100,000, respectively (6, 13). As a worldwide concern, late diagnosis and the absence of an effective screening strategy contribute to the complexity of the issue. Moreover, newly diagnosed cancer is commonly managed through cytoreductive surgery and platinum-based chemotherapy (14).

Three main cell types - epithelial cells, stromal cells, and germ cells - are responsible for the formation of ovarian tumors, whether they are benign or malignant. In developed nations, more than 90% of malignant tumors are classified as sex cord-stromal tumors. While most epidemiologic research, including this review, emphasizes epithelial OC (15). For instance, granulosa ovarian tumors are derived from epithelial cells. Around 5% to 6% of tumors are cell tumors, like thecomas, whereas germ cell tumors, such as teratomas and dysgerminomas, make up approximately 2% to 3% (13, 16). OC is classified into five distinct histological subtypes, each with identifiable risk factors, cells of origin, molecular compositions, clinical features, and treatments. These subtypes include high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC; <5%) (15) (Figure 1) .

Among these subtypes, high-grade serous carcinoma is the most commonly diagnosed. In contrast, HGSC shares similarities with high-grade endometrioid carcinoma. Among the less frequent histologies, small-cell carcinoma is distinguished by its highly aggressive behavior, often seen in younger women who are diagnosed around the age of 25. The tissue origin of this type of cancer remains uncertain. Additionally, carcinosarcoma, another type of aggressive cancer, is also recognized in certain cases (14, 17). The exact cellular origin and pathogenesis of OC are still unclear. It is interesting to note that a significant proportion of tumors seem to arise from different gynecological tissues, primarily affecting the ovary. Studies on morphology and genetics have shown that the fallopian tube epithelium is the origin of both high- and low-grade serous neoplasms. Furthermore, endometriotic cysts are connected to CCOC and ENOC, while MOC is thought to come from transitional cell nests at the tubal-mesothelial junction. HGSOC and LGSOC are believed to stem from the tubal epithelium, albeit through separate pathways (18).

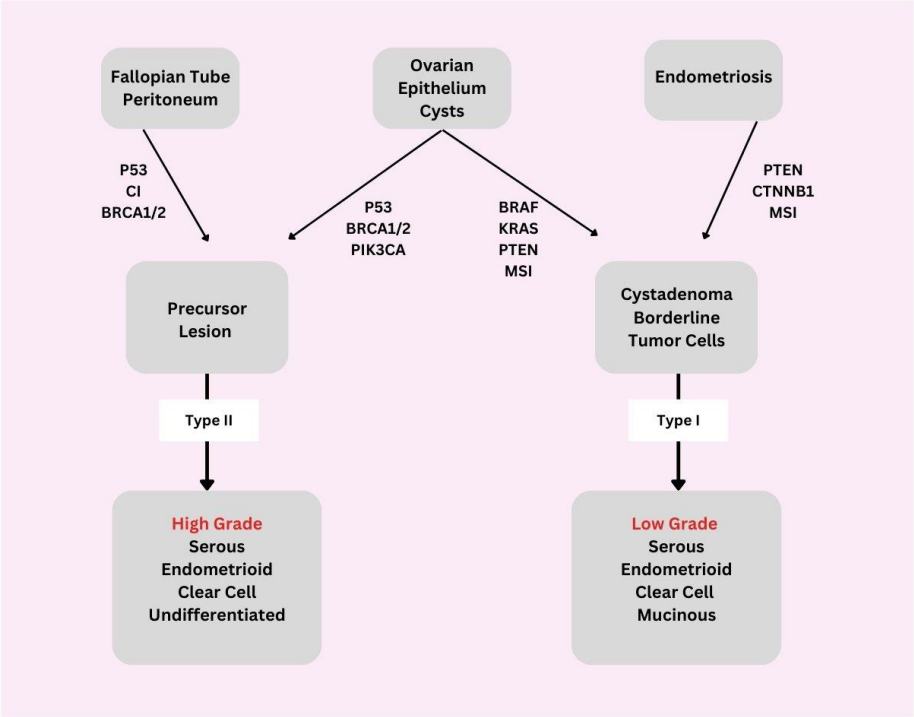


Figure 1. Two-pathway concept of ovarian cancer development (1).

The presence of serous tubal intraepithelial carcinomas, or tubal lesions in the fimbriated end of the fallopian tube, show similarities in morphology and TP53 signatures to tumors. This suggests that the progression of cancer may begin at these tube lesions and advance rapidly into the ovary (2-4,18). LGSOC tumors are identified across a range that signifies a clear progression from benign serous cystadenoma to borderline serous tumors and finally low-grade carcinoma. The glands of epithelial inclusion, believed to have derived from the cystadenoma, are situated in the ovary but display traits similar to those of the fallopian tube, indicating they may have developed from transplanted tubal epithelium (5,16,18). Current epidemiological studies on OC are delving deeper into the investigation of etiologic factors based on histopathologic and molecular subtypes, utilizing the approach of "molecular pathological epidemiology." The evidence from these studies shows that several risk factors have distinct correlations with the primary histotypes (7, 18).

2. Hereditary and Genetic of Ovarian Cancer

Hereditary OC syndromes appear to be genotypically and phenotypically heterogeneous diseases characterized by variable clinical courses (18,19,20). The role of genetic factors in the pathogenesis of OC is well documented. Hereditary OC accounts for at least 5–15% of ovarian carcinomas (18,19). OC risk is influenced by a range of distinct hereditary genetic anomalies (3,21); for example, mutations in the BRCA1 and BRCA2 genes, which are linked to breast cancer, contribute to approximately 90% of OC cases in individuals with a family history of hereditary breast-ovarian cancer. Individuals with BRCA1 mutations have a lifetime risk of OC of approximately 40–50%, while those with BRCA2 mutations have a risk of 20–30% (21). Furthermore, alterations in the BRCA genes elevate the susceptibility to various types of cancer, which include breast cancer, specifically BRCA1 and BRCA2 mutations; pancreatic cancer linked to BRCA2 mutations; prostate cancer associated with BRCA2 mutations; melanoma also connected to BRCA2 mutations; and potentially serous endometrial cancer related to BRCA1 mutations (7,21). Studies have shown that the presence of deleterious mutations in BRCA1/2 and other genes involved in repairing

double-strand DNA breaks is significantly correlated with an increased susceptibility to HGSOC, although these mutations can manifest in other subtypes of tumors as well (21, 22).

Apart from BRCA1 and BRCA2, there are other genetic mutations in genes involved in DNA repair that can raise the chances of developing OC, including genes within the Fanconi anemia-BRCA pathway like RAD51C, RAD51D, BRIP1, BARD1, and PALB2 (22,23). The presence of inherited mutations in other genes involved in DNA repair, namely CHEK2, MRE11A, RAD50, ATM, and TP53, may also contribute to an increased likelihood of OC development (7, 22, 23).

Other inherited disorders, such as Lynch syndrome, are also responsible for an additional 10–15% of hereditary ovarian carcinomas (18,20). The syndrome is characterized by the inheritance of a germline mutation predominantly caused by mutations in four mismatch repair genes (MLH1, MSH2, MSH6, and PMS2), representing 65–85% of cases (23,24). Studies have provided evidence that individuals with Lynch syndrome are more likely to develop endometrioid and clear-cell carcinomas in comparison to the expected occurrence in cases of sporadic OC (7, 25). Despite the involvement of both the BRCA and DNA mismatch repair pathways in DNA repair, the specific reasons behind the occurrence of cancers in particular organs associated with these inherited mutated genes remain understudied (26).

3. Dendritic cells Subsets and Functions in OC

The prognosis of OC is dependent on a variety of factors, including tumor margin, vascular invasion, tumor grade and stage, oncogene expression, and estrogen and progesterone receptor status (9,26). Additionally, the presence of immune cells within the tumor, such as DCs, can serve as an additional prognostic factor (10,27). Considered the most effective antigen-presenting cells, DCs serve as a bridge between the immune system of the host and tumor cells, reflecting their intricate interaction (11,12,27), and despite their limited presence in the body, these cells play a crucial role in triggering antigen-specific immunity and tolerance, making them the predominant cell type (8).

DCs are developed from CD34+ hematopoietic stem cells situated in the bone marrow. Following this, they undergo differentiation into diverse subtypes in the peripheral blood and nonlymphoid organs and tissues, ultimately reaching maturation in the lymphoid organs (13-15). Immature dendritic cells show lower levels of toll-like receptors (TLRs), major histocompatibility complex (MHC) molecules, costimulatory molecules, and adhesion molecules. Consequently, these cells are found in peripheral tissues and have restricted antigen-presenting functions (7, 9, 21).

TLRs are recognized as the key receptors involved in the detection of PAMPs and DAMPs (15,28). Through the activation of DCs, PAMPs stimulate the innate immune response, which serves as a crucial defense against infectious diseases. In the context of tumors, DCs are activated in response to DAMPs released by tumor cells via TLR signaling (12,16,26). Immature DCs respond to chemokine ligands CCL19 and CCL21 by migrating towards the lymph nodes. The maturation of these DCs involves the up-regulation of chemokine receptors CCR7 and CCR8, which enhance their migration (17). While situated in the lymph nodes, they undergo a progressive change into a mature state, marked by an elevated expression of MHC I molecules, MHC II molecules, costimulatory molecules, and adhesion molecules (17,18,28). There are three main subsets into which DCs can be divided: conventional or classical DCs (cDCs, also called myeloid DCs), monocyte-derived DCs (moDCs), and plasmacytoid DCs (pDCs) (8,12,14). cDCs can be further classified as cDC1, cDC2, and migratory DCs (migDCs) (12,13,29) (Figure 2).

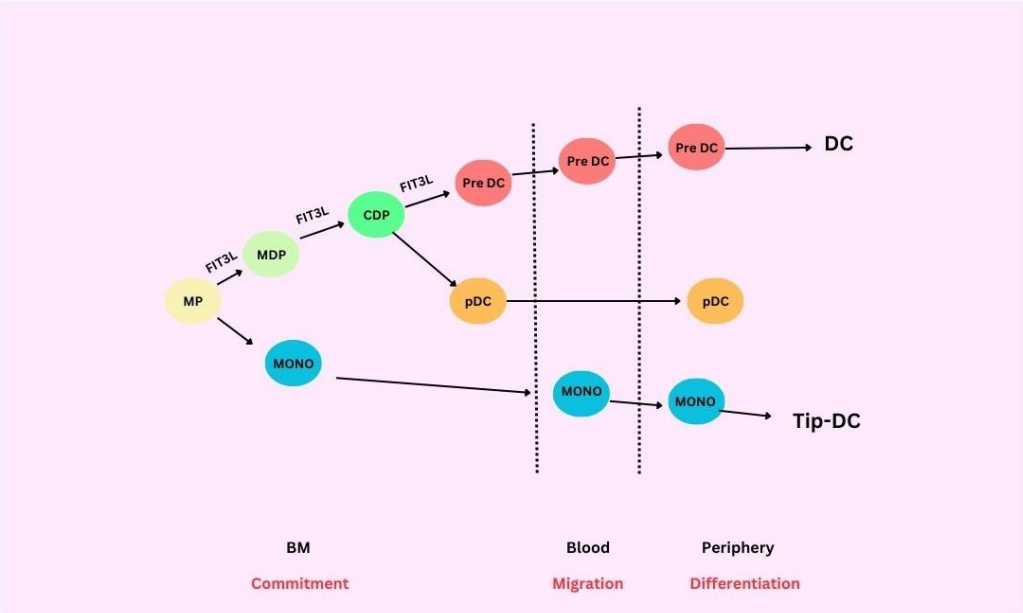


Figure 2. Dendritic cell and monocyte origin and development (29).

3.1 cDC1

cDC1 serves as the primary DC subtype responsible for regulating cancer immunotherapy responses by activating CD8+ T cells via the antigen cross-presentation mechanism (9, 13). They are of utmost importance in facilitating the early activation of CD4+ T cells against tumor-derived antigens via MHC-II, and their role in delivering CD4+ T cell assistance to CD8+ T cells cannot be underestimated (18.29). However, the absence of CDC1s during viral infections disrupts the proper differentiation of memory CD8+ T cells, resulting in unfavorable outcomes (12, 19). cDC1s are also potent in their production of interleukin-12 (IL-12) and have the capability to induce NK and CD8+ T-cell cytotoxicity as well as the generation of interferon-gamma (IFNγ) (19). IFNγ contributes to a positive feedback loop that increases cDC1-mediated IL-12 production, ultimately bolstering antigen cross-presentation (20).

3.2 .cDC2

Classically, cDC2 releases IL-10, IL-12, IL-23, and TNF-b to promote the development of CD4+ helper T cells (9, 13), particularly T helper type 2 (Th2) (18,28) and T helper 17 (Th17) cells (20, 21). These cells are distinct from cDC1s and are unable to functionally fill in for cDC1 deficiencies (12). Studies have indicated that cDC2s can increase the activation of existing CD8+ T cells during anti-CD40 therapy (22). The understanding of cDC2 functions is obstructed by three fundamental hindrances. First, the absence of a definitive marker specific to cDC2 poses a challenge in elucidating the contribution of cDC2s to tissue immune responses in vivo through conditional depletion models. Second, a resemblance can be seen in the present cDC2 markers and phenotypic characteristics with alternative myeloid compartments such as moDCs and macrophages, which poses challenges in isolating the specific contribution of cDC2s in functional inferences compared to other myeloid cells (23,30). Third, the cDC2 compartment is known for its heterogeneity, housing diverse sub-populations. This suggests that each subset within this compartment may possess unique functionalities (10, 24, 25). Various immune contexts have led to the identification and categorization of cDC2 sub-populations, with some overlap in their characteristics. To gain a better understanding, further investigation is necessary. This is especially important for DC vaccines, as targeting the most potent cDC2 subpopulation could potentially improve patient outcomes compared to targeting the entire cDC2 compartment, which may contain some anti-inflammatory sub-populations (23, 29, 30).

3.3. migDC

Migratory DCs, also known as migDCs, DC3, mregDC, or LAMP3+ DCs, are a unique type of fully developed cells that can be found in both cDC1s and cDC2s when they detect or absorb antigens (25, 26). MigDCs are dendritic cells found in non-lymphoid tissues that travel to the tdLN through the lymphatic system instead of the bloodstream. In inflammation, migDCs loaded with antigen move to T-cell regions in LNs to activate CD4+ and CD8+ T cells. They upregulate MHC-II and costimulatory molecules and secrete inflammatory cytokines to enhance T-cell responses (27, 28).

4. Dendritic Cell Dysfunction in The Tumor Microenvironment

Within OC lesions, there is a notable presence of DC infiltration; nevertheless, the infiltrated DCs exhibit a decreased efficacy in antigen presentation owing to DC tolerance. This tolerance is distinguished by the reduced expression of costimulatory molecules on the DC cell surface, leading to a compromised antigen-presenting capability. DCs can assist tumor cells under specific conditions (27, 30). In the absence of tumors, hematopoietic precursors differentiate into progenitors that further specialize into immature DCs. Immature DCs mature and specialize in antigen presentation after meeting an antigen or "danger signal." Nonetheless, differentiation of DCs is commonly disrupted in the tumor microenvironment, resulting in a buildup of defective and immature DCs. In mouse melanoma, tumor-infiltrating DCs contained both myeloid and plasmacytoid DC populations (31). Most of these DCs appeared immature, but about a third expressed a mature phenotype (32).

DC dysfunction can be impacted by immune checkpoint signaling. When PD-1 on T cells interacts with PD-L1 on tumor cells, it can lead to the death of T cells. PD-1 inhibitors could enhance the antitumor effect of DCs in OC (33). Through the release of TGF-b and PGE2 into the microenvironment, OC cells can stimulate the upregulation of PD-L1 in DCs, which strengthens their ability to suppress the immune response of T cells (33,34). Immunosuppressive cells and specific DCs have a direct interaction that affects the body's ability to combat tumors. In ovarian carcinoma, the interaction between pDCs and regulatory T cells (Treg cells) is facilitated by the expression of the ICOS ligand, leading to tumor progression (34). Additionally, insulin-like growth factor (IGF) influences dendritic cells (DCs) in ovarian cancer, impacting cell proliferation, protein synthesis, and growth through the activation of the RAS-ERK and PI3K-AKT pathways. In the presence of IGF, DCs fail to mature and secrete higher levels of IL-10 and TNF-a, considered immunosuppressive factors in the OC microenvironment (35, 36). The insulin-like growth factor type I receptor (IGF1R) is prominent in OC. This receptor has a negative correlation with the differentiation of DCs into cDCs. By utilizing IGF1R inhibitors, the DC-mediated antitumor effect can be rebuilt. This suggests that the IGF axis may be responsible for inducing dysfunction in DCs (36,37). To conclude, immunosuppressive signals contribute to DC dysfunction in OC. By infusing functional DCs into the body, they can engage with T cells in lymph nodes rather than the tumor microenvironment, potentially restoring their ability to present tumor antigens and induce antitumor effects (38, 39).

5. DCs Vaccine in OC

Cancer vaccines are divided into various groups based on how they deliver the chosen TAAs. These groups include cell-based vaccines, peptide/protein vaccines, and genetic vaccines (Table 1) (31, 35).

5.1 cell-based vaccines

Cell-based vaccines can use DCs to help connect innate and adaptive immunity (40). The goal is to trigger cytotoxic T lymphocytes to target and destroy cancer cells using tumor antigens (41,42). DCs are essential for immunosurveillance, which underscores the immune system's vital role in recognizing and removing pathogens and cancer cells. However, the slow progression of malignancy during its initial phases can result in occasional failures of immunosurveillance (39). In the early stages, tumors can occasionally inhibit an immune response or fail to produce the essential signals for immune system activation. Cell-based vaccination aims to fix this problem by reversing the immune system's lack of knowledge about cancer cells (43).

Adjuvant DC vaccines have proven to be effective in the long run for people with melanoma, glioblastoma, prostate cancer, and renal cell carcinoma. However, it

is important to note that these improvements have only been demonstrated in a small number of patients (44, 45). DC vaccination is considered safe and typically causes fewer side effects than chemotherapy and ICBs (39). Choosing the appropriate DC subtypes is a key factor in successful vaccination. The chosen subtypes of autologous DC used in vaccine production display different levels of antigen-presenting potential, potentially influencing the effectiveness of DC vaccines. In the study of DC vaccines for tumors, scientists select particular DC subtypes from peripheral blood cells using apheresis. These subtypes, such as MoDCs, cDCs, and Langerhans cell-type DCs, are assessed in preclinical and clinical studies (36, 45). Various DC subtypes are being targeted to improve immune responses against tumors in vaccines that target DC within and outside the body, and these may vary depending on the cancer types (46,47). To manufacture vaccines that target DCs in the body, there is no need for apheresis to gather autologous DCs. Instead, specific antigens that target receptors on DCs are injected directly into the body. For example, the vaccine CDX-1401 is formulated to target DEC205+ cDC1s in multiple tumors, such as OC. This vaccine includes the DEC205 antibody fused with NY-ESO-1 and a TLR agonist (48, 49). The development of vaccines that target DCs externally involves the use of peripheral blood cells obtained through apheresis (50).

MoDCs are the preferred subtype for this purpose due to the limited number of DCs in peripheral blood cells for vaccine production. On the other hand, a larger number of DCs can be generated from monocytes when cultured in vitro compared to other sources (45). When it comes to vaccinations, cDCs are more potent than MoDCs in inducing long-lasting and broad immune responses. Furthermore, cDCs can enhance the efficacy of immune checkpoint inhibitors (51). The presence of cDC1, cDC2, and pDC in OC has been previously noted. The ratio of cDC and pDC varies in peripheral blood, ascites, and tumor sites. Among DC subsets, pDC is most frequently found in ascites (40) and tumor sites (10), while cDC is more abundant than pDC in the peripheral blood (35). This indicates that peripheral blood could be a valuable resource for the production of DCs (52). Due to the limited number of cDCs available for vaccine manufacturing, MoDCs are commonly used in clinical studies on DC vaccines (27). After isolation from peripheral blood using apheresis, mononuclear cells are cultured in vitro with GM-CSF and IL-4 for a specific duration. The evaluation of markers on DCs, including CD11c+, HLA-DR+, HLA-ABC+, CD40+, CD80+, CD83+, CD86+, and CCR7+, is performed to monitor the cellular composition of the DC vaccine (53). However, these markers are not effective in distinguishing MoDCs from other DC subtypes, resulting in the DC vaccine being a combination of DCs and a small proportion of other peripheral blood cells (11, 27) (Figure 3).

5.2 Peptide/Protein-Based Vaccines

Autologous cancer vaccines, such as DCs or whole tumor cells, are limited by the need for patient samples and the complex process of making personalized vaccines. Recombinant vaccines have an advantage in this respect. Peptide- or protein-based vaccines typically utilize specific TAAs and are given with an adjuvant or immune modulator to enhance uptake by DCs (3,53). Many different peptides have been experimented within OC to find out if they can target HER-2/neu. HER-2/neu is a member of the HER/EGFR/ERBB family, and if it's amplified in breast cancer, it makes the cancer more aggressive. That's why it's an important target for around 20%–30% of patients (54). The presence of HER-2/neu overexpression or amplification has been detected in OC cases (19), suggesting it as a potential target for cancer vaccination. Nevertheless, studies using HER-2/neu peptides have not shown any immune response (14, 36), and there is no clinical data available (31). The most efficient outcomes in OC treatment through peptide-based vaccines have been achieved by employing a personalized peptide vaccine (PPV). This method consists of mixing four peptides (selected from a set of 31) that have been tested for immune response in every patient and then injecting them subcutaneously in Montanide ISA51VG (19, 31, 35). The study revealed that platinum-sensitive patients had a median survival time of 39.2 months, while platinum-resistant patients had 16.2 months. Standard of care patients had 18–30 months (platinum-sensitive) and 8–12 months (platinum-resistant). Notably, PPV not only enhanced immune responses to specific peptides but also extended to other peptides, resulting in longer survival (50). The findings indicated that selecting and administering vaccine antigens based on the patient's

pre-existing immunity before vaccination could extend overall survival in advanced OC patients (55).

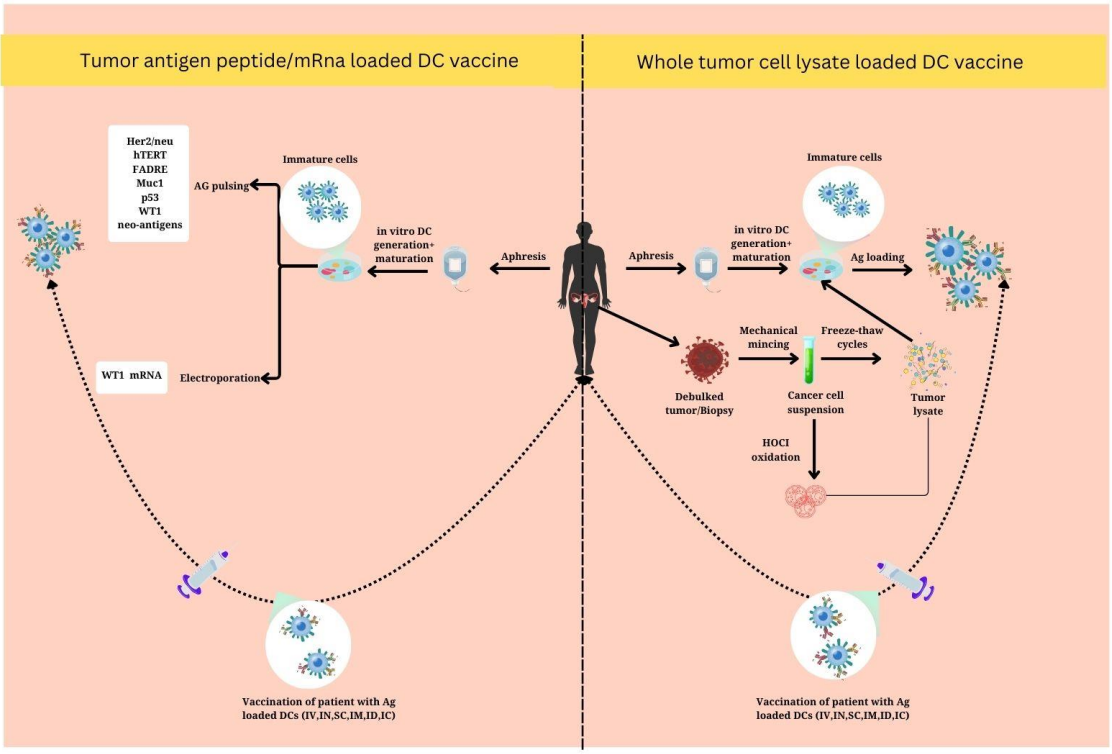


Figure 3. An overview of dendritic cell vaccination strategies used in ovarian carcinoma. Ag, antigen; HOCl, hypochlorous acid; IV, intravenous; IN, intranodal; SC, subcutaneous; ID, intradermal; IC, intracutaneous.

5.3 Genetic Vaccine

The use of genetic vaccines, whether they are DNA, RNA, or virus-based, can activate the expression of chosen TAAs within somatic cells like keratinocytes, myocytes, or DCs that infiltrate muscle or skin at the vaccination site. This can result in either cross-priming or direct antigen presentation to infiltrating T-cells. Genetic vaccines make it easy to deliver multiple antigens in one immunization, activate different branches of immunity, and have a more cost-effective and standardized manufacturing process (30). Two viral vaccines have been tested for OC: One team is concentrating on the "cancer-testis" antigen NY-ESO-1, which has been integrated into vaccinia (rV) as the initial vaccine and fowlpox (rF) as the follow-up vaccine. The second genetic vaccine tested for ovarian cancer, PANVAC-C + PANVAC-V, is a Poxviral vaccine. It involves engineering CEA-MUC1-TRICOM (B7.1, ICAM-1, LFA-3) into vaccinia (PANVAC-V) as the prime and fowlpox (PANVAC-C) as the booster vaccination (37, 38). A Phase I clinical trial with 25 patients with CEA- or MUC1-expressing metastatic cancers, including three with OC, showed limited clinical activity. Ongoing studies are investigating different genetic vaccines for treatment (56,57,58).

Table 1. Published results from therapeutic vaccines tested in ovarian cancer from 2000 to 2024.

Class	Name	Description	Clinical Development Phase	No. of Pts (OvCa Pts)	Clinical Result	Ref
DCs	APCEDEN	DCs loaded with whole-tumor lysate	Phase II	38 pts (9 OvCa pts)	No CR observed; ORR was 28.9% (11/38) and irRC was 42.1%	**(35)**
	DCVax-L	DCs loaded with autologous oxidized tumor lysate, combined with bevacizumab and metronomic Cy	Pilot	6 OvCa pts	4/6 pts (66%) achieved clinical benefit (including 2 PR and 2 SD)	**(37)**
	OCDC	DCs loaded with autologous oxidized tumor lysate	Pilot	5 OvCa pts	2/5 pts (40%) demonstrated PFS2 > PFS1	**(30)**
	DC-MFP	DCs loaded with mannan-MUC1 fusion protein (MFP)	Phase I	9 pts (2 OvCa pts)	2/9 pts (22%) in progression at entry were stable after therapy, for at least 3 years	**(33)**
	DC-wtl	DCs loaded with crude whole tumor lysate	Phase I	8 pts (6 OvCa pts)	Data suggested a positive correlation with disease stabilization	**(33)**
	Lapuleucel-T, Neuvenge, APC 8024	DCs loaded with BA7072, a fusion protein HER-2/neu linked to GM-CSF	Phase I; HER-2+ tumors	18 pts (4 OvCa pts)	2/18 pts (11%) had SD lasting > 48 weeks	**(24)**
	HER-2/neu; MUC1 peptides	DCs loaded with synthetic peptides derived from HER-2/neu or MUC1 peptides	Phase I; HER-2+ or MUC1+ tumors	10 pts (3 OvCa pts), HLA-A*02+	No data	**(24)**
	hTERT; HER-2/neu; PADRE peptides	DCs loaded with synthetic peptides derived from hTERT; HER-2/neu; PADRE	Phase I/II	14 OvCa pts, HLA-A*02+	3 years-OS was 90%; 3 years-PFS was 80% (with Cy)	**(24)**
	WT-1; MUC1; CA125	DCs loaded with syntheticpeptides derived from WT-1; MUC1; CA125	Phase II	56 OvCa pts	DCR and ORR were 29% and 3.6%, respectively	**(35)**
Peptides/ proteins	Mixture of peptides (comparison)	Predesigned peptides vs. PPV (personalized peptide vaccine); admixed with Montanide ISA-51	Pilot	14 pts (5 OvCa pts), HLA-A*02+ or HLA-A*24+	No clinical response with predesigned; 3/5 cervical cancer pts (60%) showed objective	**(41)**

				tumor regression	
Mixture of different peptides	OvCa-associated peptides plus a helper peptide from tetanus toxoid protein, admixed with Montanide ISA-51 and GM-CSF	Phase I	9 OvCa pts, HLA-A*01+, -A*02+ or A*03+	One participant remained disease-free at 19 months after active treatment	**(41)**
Mixture OvCa-associated peptides	OvCa-associated peptides admixed with Montanide ISA-51 and GM-CSF	Pilot	15 pts (8 OvCa pts); HLA-A*02+	With median follow-up of 492 days, 4 OvCa pts had relapsed and 3 died (expected relapse rate 18–22 mo in 75% of pts)	**(42)**
HER-2/neu	Epitope p369–377, admixed with GM-CSF	Phase I; HER-2/neu++ Tu	6 pts (2 OvCa pts), HLA-A*02+	No data	**(42)**
HER-2/neu-ICD	ICD protein, aas 676–1255, His-tagged	Phase I; HER-2/neu++ Tu	29 pts (1 OvCa pt)	No data	**(45)**
NY-ESO-1	Epitope p157–170, admixed with Montanide ISA-51	Phase I	18 OvCa pts, HLA-DPB1 *0401+ or *0402+	Median PFS of 19.0 mo (vs. 16–18 weeks in pts receiving 2nd line chemo)	**(46)**
NY-ESO-1 OLP	NY-ESO-1 overlapping long peptides, +/´ Montanide and Poly-ICLC	Phase I	28 OvCa pts (HLA indep)	Pts NY-ESO-1+ receiving OLP + Montanide + Poly-ICLC showed delayed time to recurrence	**(57)**
NY-ESO-1 protein	NY-ESO-1 protein + Montanide + CM-CSF +/´ decitabine	Phase I	12 OvCa pts	5/10 (50%) pts had SD (median duration 6.3 mo), and 1/10 (10%)had PR (duration 5.8 mo)	**(57)**
P53	Wt p53: 264–272 peptide admixed with GM-CSF and Montanide ISA-51, either SC (Arm A) or loaded into DCs (Arm B)	Phase II; p53++ Tu;	21 OvCa pts, HLA-A*02:01+	No significant difference between arms in median OS (40.8 mo vs. 29.6 mo, p = 0.26), nor in PFS (4.2 mo vs. 8.7 mo, p = 0.94)	**(68)**
P53-SLP	Ten synthetic peptides 25–30 aa long overlapping peptides (aas 70–248 in	Phase II	18 OvCa pts	2/18 (11%) of pts with SD, not clearly	**(35)**

		wt-p53) admixed in Montanide ISA-51		(HLA indep)	attributable to vaccination	
	Flt3-L	Truncated glycoprotein Flt3-L (Fms-like tyr kinase-3-ligand, which increases DCs and monocytes), either i.p. or s.c.	Pilot	15 pts (9 OvCa pts)	No objective responses were observed	**(35)**
	PPV	Personalized peptide vaccine: mixture of 4 peptides (from a panel of 31) previously tested for immunity in each pt, admixed in Montanide ISA51VG	Phase II	42 OvCa pts (HLA-dep)	Median survival time (MST) was 39.2 mo in platinum-sensitive pts, vs. 16.2 mo in platinum-resistant	**(58)**
Whole tumor cells	Fang vaccine, Vigil™ Ovarian, Gemogenovatucel-T	Autologous tumor cells eletroporated with FANG vector, a plasmid encoding GM-CSF and a bi-shRNA targeting furin convertase, thereby downregulating TGF-b1 and b2	Phase I	27 pts (5 OvCa pts)	23/26 pts (88%) showed SD at month 2 or later	**(32)**
Genetic vaccines	PANVAC-C + PANVAC-V	Poxviral vaccine: CEA-MUC1-TRICOM (B7.1, ICAM-1, LFA-3) engineered into vaccinia (PANVAC-V) as prime and fowlpox (PANVAC-C) as booster vaccination	Pilot; CEA+ or MUC1+ Tu	25 pts (3 OvCa pts)	1 OvCa pt (1/25: 4%) had durable (18 mo) clinical response	**(39)**
	rV-NY-ESO-1 + rF-NY-ESO-1	NY-ESO-1 engineered into vaccinia (rV) as prime and fowlpox (rF) as booster vaccination	Phase I; NY-ESO-1+ Tu	36 pts (1 OvCa pt)	7/9 pts with stage II/IV MEL survived 17–63+ mo	**(39)**

Abbreviations: aas, aminoacids; CR, complete response; DCR, disease control rate (SD + PR + CR); irRC, immune-related response criteria; mo, months; MST, median survival time; ORR, objective response rate (PR + CR); OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; Pt(s), patient(s); SD, stable disease; TTP, time to progression.

6. DCs in the cancer therapy

DCs have the potential to influence the efficacy of cancer therapies currently employed in clinical practice. This review delves into the impact that DCs can have on the response to such treatments (7).

6.1 Chemotherapy and DCs

Traditionally, chemotherapeutic treatments such asbortezomib, doxorubicin, epirubicin, idarubicin, and Mitoxantrone and oxaliplatin have long been thought to provide anti-cancer benefits by either directly killing cancer cells or causing a permanent cessation of the cell cycle, and these responses depend on DCs (16,59). It was believed that chemotherapy could target rapidly dividing cells, including immune cells, and cause immunosuppression. Many chemotherapy drugs used in clinics are not immunogenic or have immunosuppressive side effects. They can directly inhibit or kill effector cells or indirectly cause energy or immune paralysis. As a result, the immune system's role in anticancer therapy has been largely ignored (18). It is now commonly believed that certain chemotherapy drugs and anticancer medications can trigger the body's immune system to fight tumors (19, 60).

One way they do this is by making tumor cells more visible to the immune system, which leads to an immune response against the tumor. This has been shown in experiments with mice that have a healthy immune system. Additionally, immunogenic cell death (ICD) may be induced by specific physical methods like UV-C irradiation, hypericin-based photodynamic therapy, and high hydrostatic pressure, while certain oncolytic viruses possess the intrinsic capacity to initiate ICD. These were among the chemotherapeutic drugs used in clinical practice: anthracyclines (doxorubicin, epirubicin, and idarubicin), mitoxantrone, oxaliplatin, CTX, and bleomycin (BLM) (29, 60). The efficacy of these stimulants in triggering an immune response against tumors relies on the development of adaptive stress reactions that facilitate the synchronized release of endogenous danger signals from apoptotic cells. These signaling molecules, referred to as DAMPs, interact with various receptors found on dendritic cells to activate the adaptive branch of the immune system (61). Multiple DAMPs have been identified as characteristic elements of ICD, specifically the initial presentation of the endoplasmic reticulum (ER) chaperone calreticulin (CRT) and heat-shock proteins (HSPs) HSP70 and HSP90; the spontaneous release of molecules like high mobility group box 1 (HMGB1); and the excretion of adenosine triphosphate (ATP) (10, 31, 62). In addition, some chemotherapy drugs can induce tumor cells to produce type I interferons (IFNs). Although type I IFNs are not DAMPs specifically, they have strong immune-boosting effects and are crucial for chemotherapy-induced cell death to be recognized as immunogenic. To conclude, the activation of the immune system is supported by DAMPs, as demonstrated in many in vitro tumor cell line models and in vivo mouse immunization experiments. Recent reports also suggest that monitoring DAMPs in cancer patients may have prognostic or predictive value (30, 32).

6.2 Radiation therapy and DCs

Highly proliferating cells are the preferred targets of radiation treatment. While this therapy's primary function is to directly kill cancer cells, this explanation falls short of explaining the therapy's overall effect on tumor growth. Radiation therapy's anti-tumor efficacy also involves local bystander effects, such as the release of DAMPs and cytotoxic mediators, the alteration of the immunological TME, and the in situ generation of reactive oxygen species (63, 64). Additionally, radiation therapy can generate distant effects, referred to as out-of-field or abscopal effects, that are correlated with the promotion of systemic immune responses against cancer, facilitated by the induction of immunogenic cell death and the activation of CD8+ T cells by cDC1 Following radiation therapy, cancer cells release cytosolic DNA that acts as a DAMP, signaling through cGAS-STING to stimulate type I interferon production by DCs, thus aiding in antitumor immunity (55). However, high radiation doses prompt the expression of DNase TREX1, which breaks down cytosolic DNA, limiting interferon production and the immunostimulatory impact on cDC1s (54).

6.3 Small-molecule inhibitors and DCs

Small-molecule inhibitors have been developed to target important oncogenic signaling pathways such as STAT3 and mitogen-activated protein β-catenin signaling (26). These pathways are associated with decreased cDC1 tumor infiltration and a lack of response to immune checkpoint blockade therapy. Nevertheless, the transfer of preactivated in vitro-generated cDC1-like cells with poly(I:C)5 was effective in reversing this non-responsiveness (8). Moreover, the combination of vaccination with naturally existing cDC1s loaded with immunogenic cell death-derived whole tumor antigen and anti-PD1 treatment reveals a synergistic outcome. The synergy between TLR-induced activation of DCs and ICB can be heightened by FLT3L-induced expansion of DC populations. Recent discoveries suggest that cDC1 is vital for cross-priming, as evidenced by WDFY4-deficient mice being incapable of rejecting immunogenic tumors due to a defect in a vesicular transport pathway necessary for cross-presentation (18, 32). Enhancing the function of DCs may result in improved and expanded responsiveness to ICB regimens. Both cGAS and STING are crucial for intrinsic antitumor immunity and effective responses to anti-PDL1, with DCs playing a key role in mediating these responses. (33). The activation of type I interferons to stimulate cDC1s can potentially improve the response to anti-PDL1 treatment, indicating a potential requirement for the activation of tumor DCs to support effector T cell activity triggered by ICB.

Enhancing the production of chemokines like CXCL9 and CXCL10 by DCs, possibly through epigenetic modifications, may also enhance the efficacy of ICB therapy (32, 34).

7. Safety of Dendritic Cell Vaccines

The safety of DC vaccines has generated significant interest due to their potential to modify immune cell, cytokine, and chemokine levels in the body. Thankfully, most OC patients involved in clinical studies have responded well to DC vaccines. Most reported side effects are grade 1 or 2 and include common symptoms like local skin reactions, fatigue, pain, flu-like symptoms, muscle aches, fever, nausea, and vomiting (32). Numerous studies have reported serious toxicity associated with DC vaccines, especially when used in combination with other treatments. During the phase II trial of a p53 peptide cancer vaccine and DC vaccine, every one of the 21 patients encountered a localized skin response. Among the participants who were administered a combination DC vaccine containing p53 peptide, a minimum of 3 patients documented lymphopenia and fatigue (32). Additional toxicities related to the grade III/IV vaccine consist of increased ALT and AST levels, fever, hypocalcemia, memory impairment, and rigors (53). It is important to highlight that notable toxicity was connected to the IL-2 treatment in the subgroup examination of this research. This was noted during a phase I clinical trial of the DC vaccine for the maintenance therapy of ovarian carcinoma (39, 40). Additionally, two patients suffered from hypertension. More evidence is necessary to determine if these toxicities are related to DC vaccines in OC patients undergoing chemotherapy. To conclude, DC vaccines are usually well tolerated, but combining them with chemotherapy or immunotherapy should be done carefully (Table 2) (23, 65,66).

Table 2. Issues and challenges in cancer vaccine development (35).

Issues	Challenges
Personalised vaccination (e.g., patient tumour/ immune cells)	A. Development of a robust and standardisable vaccination platform technology Poor/undetectable immune response B. Generation of a strong immune response against tumour antigens without inducing unwanted auto-immune reactions
Immune tolerance and tumour escape	A. Counteract mechanisms of immune evasion by cancer B. Absence of efficacy biomarkers C. Establishment of immune surrogates of anti-tumour efficacy
Immunotherapy as single agent	A. Development of rational combination therapies B. Efficacy driven by tumour shrinkage endpoint C. Design clinical trials that incorporate new concepts of immune-related response criteria
Self-limited immunity	A. Maintenance of anti-tumor immune response over time

8. Future of the DC Vaccines

DC vaccines have exhibited promise in the realm of immunotherapy for ovarian carcinoma. However, there exists untapped potential that necessitates exploration through the use of new technologies, cohort studies, and biomarkers. Tumor immunosuppressive signals have been found to impair dendritic cells, leading to compromised immunological function and metabolism, thereby resulting in issues related to antigen presentation and tumor growth (40). The rise in popularity of personalized DC vaccines can be attributed to their effectiveness in activating T cell responses that target tumor antigens specific to individual patients, facilitated by next-generation sequencing and bioinformatics analysis. Nonetheless, challenges such as complex preparation techniques, limited tumor samples, and difficulties in selecting tumor antigens need to be addressed. While clinical experiments have validated the safety of DC vaccines,

their efficacy varies depending on the manufacturing technique and study strategy. The identification of an ideal biomarker is essential in this context (41).

Conclusion

Advances in cancer immunotherapy, notably for ovarian carcinoma, have demonstrated their significance in the battle against cancer. Cykine therapy, peptide vaccines, monoclonal antibodies, dendritic cell-based vaccines, adoptive T cell transfer, immune checkpoint inhibitors, and various nanoparticles are all being studied for ovarian cancer treatment. Combining these tactics with individual therapy can help boost the immunological response. However, there is still potential to enhance treatment options, such as by studying tumor biology, immune-suppressive networks, and immunomodulatory techniques. Polymeric and lipid-based nanoparticles are being created to deliver antigens, immune stimulants, and immunoadjuvants in a sustained-release manner. More research is needed to create accurate biomarkers and successful treatment combinations.

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