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Dendritic cell vaccine and its application in cancer therapy

Abstract

Dendritic cells (DCs) are the most potent antigens presenting cells in the immune system. They have a high capacity to trigger antigen-specific immune responses and promote both adaptive immunity and innate immunity. In the past decade, DC vaccine has been introduced as a new therapeutic strategy in cancer patients. DC-based immunotherapy is safe and can promote antitumor immune responses and prolonged survival of cancer patients. However, the current approaches of DC vaccination are far from optimal efficacy in advanced cancers. In this paper, we present recent findings about DC vaccine, its clinical application and efficacy in various cancers, as well as improved approaches in the preparation of DC vaccine.

Keywords: dendritic cells, function, *ex vivo* generation, vaccine, cancer treatment, efficacy

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Abbreviations: DC, dendritic cell; APC, antigen presenting cell; PRR, pathogen recognition receptor; TLR, toll like receptor; CLR, c-type lectin receptor; MHC, major histocompatibility complex; CDC, conventional DC; pDC, plasmacytoid DC; iDCs, inflammatory DC; ICAM-1, intracellular adhesion molecule-1; LFA-3, lymphocyte-function associated antigen-3; IL, interleukin; NK, natural Killer; NKT: Natural Killer T; PD-L: Programmed Death-Ligand; TRAIL: TNF-Related Apoptosis-induced ligand; TGF-β, transforming growth factor-β; IDO, indoleamine 2,3-dioxygenase; NO, nitric oxide; Treg, regulatory t cell; Breg, regulatory B cell; GM-CSF, granulocyte-macrophage colony stimulating factor; TSA, tumor specific antigen; TAA, tumor associated antigen; TSA, tumor specific antigen; Flt3, fms like tyrosine kinase 3; LPS, lipopolysaccharide; BCG, bacillus calmette-guerrin; IFN, interferon; TNF-α, tumor necrosis factor-α; USFDA, united states food and drug administration; CMV, cytomegalovirus; PAP, prostatic acid phosphatase; MART-1, melanoma antigen recognized by T Cell-1; NY-Eso-1, new york esophageal squamous cell carcinoma-1

Introduction

Cancer cells recruit several mechanisms to escape from immune systems.[1] Innovation of approaches to increase antitumor reactivity of effect or immune cells is essential for optimal antitumor immunity. DCs, as the most potent APCs, have a major application in cancer immunotherapy by presentation of tumor specific/associated antigens, activating antitumor lymphocytes, and augmenting innate immunity. More than two decades before, DCs were generated in the culture medium from bone precursor cells.[2] Afterwards, DC-based vaccines were studied in order to use as a therapeutic or prophylactic tool in malignant disorders. At present, DC vaccines are offered as a valuable instrument in cancer treatment. In this paper, we discuss anticancer DC vaccines, their application, safety, and clinical efficacy, as well as recent advances in DC vaccine preparation.

Immunophenotype and function of DCs

DCs are a heterogeneous population of cells with a widespread tissue distribution. They have a distinctive morphology with many veil-like projections and express PRRs, such as TLRs and CLRs, the endocytic receptor DEC-205, and FCγ receptors. DCs also express 10-100 fold higher levels of peptide-MHC complexes than other professional APCs, i.e. monocytes and B cells, on the cell surface. Indeed, DCs have a high ability in receptor-mediated endocytosis and macropinocytosis, antigen processing and presentation on the MHC class I and II molecules.[3,4] They promote induction of antigen-specific immune responses and also augment innate immunity. DCs are also important in induction of Immunological tolerance[5]

DC subsets

Myeloid DCs and plasmacytoid DCs: DCs can be categorized into two major subsets based on their origin: myeloid or conventional DCs (cDCs) and plasmacytoid DCs (pDCs). cDCs are derived from myeloid progenitor cells in the bone marrow and are characterized by expression of CD11c. cDCs can be subdivided into mono cyte-derived DCs, CD1a- interstitial DCs, and CD1a+ Langerhans cells. pDCs differentiate from lymphoid progenitor cells in the lymphoid tissues and characterized by expression of CD123 and production of a high levels of type I interferon. During inflammatory response, inflammatory DCs (iDCs) are originated from monocytes.[6]

Immature DCs and Mature DCs: DCs are classified into "immature" and "mature" subsets based on their immunophenotype and function. Immature DCs have high capacity to capture antigens and are usually found in the peripheral non-lymphoid tissues. After antigen capture, they migrate into lymphoid tissues and become matured by up-regulation of expression of MHC molecules I and II, co-stimulatory molecules such as CD40, CD80, and CD86, and adherent molecules such as ICAM-1(CD54) and LFA-3(CD58) on the cell surface as well as secrete various soluble factors including various chemokines and cytokines such as IL-12. Consequently, mature DCs can present antigens in the lymphoid tissues and prime, activate, and expand effector immune cells.[7–9]

Immuno-stimulatory DCs and tolerogenic DCs: DCs have strong immune-stimulatory properties. They can activate CD4+ and CD8+ T cells, B cells, NK cells, NKT cells, γδ T cells, and other immune cells. But, DCs have also important roles in the induction of immunological tolerance through various mechanisms including expression of the immunosuppressive molecules such as PD-L1 and -L2, CD95 (Fas), TRAIL, and galectin-1, and secretion of immunosuppressive mediators such as IL-10, TGF-β, IDO, IL-27, arginase-1, heme oxigenase-1, and

NO. Both pDC and cDCs can be tolerogenic. These tolerogenic DCs suppress immune responses of different effector cells; for example, they induce T cell anergy or apoptosis and promote the development and expansion of Tregs and Bregs.[1,10]

Ex vivo generation of DCs

Differentiation of DCs from DC-precursor cells: DCs exist in a low frequency in the peripheral blood, at about 0.1% of white cells. Isolation of DCs from blood or other tissues is difficult due the low frequency of these cells. Currently, DCs are generated from precursor cells at large numbers *ex vivo*.[11–13] We and others generated DCs *ex vivo* with a high purity.[14] Various agents such as GM-CSF, Flt3 ligand, c-Kit, IL-3, and IL-4 have been used to differentiate and growth DCs ex vivo. Human DCs are usually generated *ex vivo* from peripheral blood CD14+ monocytes in the presence of GM-CSF or GM-CSF/IL-4. Also, CD34+ hematopoietic stem cells can be used for *ex vivo* generation of DCs. Mouse DCs are usually generated from bone marrow precursor cells.

Antigen loading of DCs: Antigen loading of DCs is an important process in *ex vivo* generation of DCs for clinical applications. TSAs/TAAs are suitable targets for loading on DCs. Synthetic peptides have been used for antigen loading of DCs.[15–17] However, synthetic peptides are only accessible for cancers with defined TSAs/TAAs. Tumor lysate is other approach for antigen loading of DCs. This approach has been used successfully in many studies.[18–21] Total antigen loading approaches have the potency to deliver self-antigens and immunosuppressive components, and ultimately reduce antitumor immune responses. Nevertheless, total tumor antigen vaccines contain all potential tumor specific antigens, both MHC class I- and MHC class II- restricted epitopes, therefore, these vaccines can produces multivalent CD4+ and CD8+ T cell responses. DCs pulsed with tumor lysate can expand autologous tumor reactive T cells, in vitro. Whole tumor lysate based vaccines also produced more clinical responses than highly specific vaccines. Recently, hypochlorous acid-oxidation has been presented as a new method for preparing tumor lysate and DCs pulsed with hypochlorous acid-oxidized tumor lysate were safe and elicited potent T cell responses against ovarian antigens.[22] DC loading of cancer stem cell lysate is appeared to be more effective than total tumor lysate.[23] DCs have also been successfully transfected with peptide- or total tumor-RNA/mRNA or DNA.[24–26] Tumor cells RNA- or mRNA-transfected DCs have induced CTLs and antitumor immunity.[24,27–29] In a recent study, total tumor mRNA-electroporated DCs were more potent than total tumor lysate-electroporated DCs in the induction of antitumor immune responses in vitro and in suppression of tumor growth in MC-38-carcinoembryonic antigen colon cancer-bearing mice.[30]

Maturation induction in DCs: Multiple components induce maturation of DCs. TLR ligands, including microbial components such as LPS, peptidoglycan, choleratoxin, filamentous hem agglutinin, inactivated BCG; and viral double stranded RNA, cytokines such as type I interferons, IFN-γ, TNF-α, IL-1β, TGF-β, and IL-10, PGE2, vitamin D3, FCγ receptors, necrotic cells, apoptotic bodies, heat shock proteins, urate crystals, T cells, NK cells, NKT cells, and γδT cells can stimulate/modulate maturation of DCs. However, IL-12 production by DCs, which have important roles in tumor immunity, is only induced by some factors. IFN-γ and IL-4 enhance IL-12 production while PGE2 and IL-10 have inhibitory effects. IL-1β, IL-6, TNF-α, and PGE2 have been used as a golden standard for maturation of DCs in cancer immunotherapy. But, these agents can reduce the production of IL-12 of DCs.[31,32] Furthermore, IL-10, vitamin D3, and the drugs dexamethasone and rapamycine induce immature DCs/tolerogenic DCs.

Route of DC vaccine administration, dose and repeats

The number of DCs, vaccination repeats, and the route of DC vaccination in patients influence the vaccine efficacy. In most studies, DCs have been injected intravenously, intraperitoneally, subcutaneously, or intradermal. Intratumor injection of DCs can also be used for the induction of antitumor immune responses. In a study by Schmidt et al.,[29] intratumoral injection of tumor RNA-pulsed DCs significantly produced more protective immunity as compared with subcutaneous or intravenous injections. In our study, intratumoral injection of un-mocked DCs into large established tumor led to enhanced tumor growth (our unpublished data), indicating that the tumor microenvironment has an enormous adverse effect on DCs. It should also be noticed that antigen-loaded DCs when injected to previously vaccinated hosts may be rapidly eliminated by antigen-specific CTLs.[33] Thus, increased numbers of DC vaccinations may not lead to enhanced T cell activation/expansion. On the other hand, once antigen-specific T cells in the periphery diminish to a level that they do not eliminate DCs; DCs can again re-stimulate T cell responses, emphasizing considering appropriate DC injection intervals. The frequency of DC vaccine injections should also be taken into account. Although repeated immunizations lead to increased frequencies of memory T cells, overstimulation can result in terminal differentiation and activation induced cell death (AICD) or exhaustion of T cells.[34]

Antitumor DC vaccines in animal models

In 1989, Shimizu et al.,[29] reported that vaccination with APCs pulsed with tumor antigens induces protective antigen-specific antitumor immunity in mice.[35] Since the mid-1990s, tumor antigen-pulsed DCs have been studied to treat tumors in mouse tumor models. In 1994, Flamand et al.,[36] observed that immunization with DCs pulsed with tumor antigen protected mice against subsequent tumor challenge in a B cell lymphoma model. Afterwards, induction of antitumor immunity was reported by vaccination with DCs pulsed with tumor peptide [15–17] and soluble protein[37] in different tumor models. DCs fused to tumor cells are able to stimulate naïve T cells and induction of protective immunity in vivo.[38] Tumor lysate, tumor cell RNA- or mRNA-transfected DCs have been capable to induce CTLs and antitumor immunity in several tumor models. In a myeloma mouse model, both idiotype protein- and tumor lysate-pulsed DC vaccines induced strong antitumor immune responses and protected mice against myeloma, but tumor lysate-pulsed DC (18-21) vaccine was more potent than idiotype-pulsed DC vaccine to promote antitumor immunity.[39] In a recent study, total tumor mRNA-electroporated DCs[24,27–29] were more potent than total tumor lysate-electroporated DCs in the induction of antitumor immune responses in vitro and suppression of tumor growth in MC-38-carcinoembryonic antigen colon cancer-bearing mice.[30]

Application of DC vaccine in cancer patients and its efficacy

In the past decade, increased knowledge about DCs and the possibility of generation of large numbers of DCs ex vivo, led to use DC vaccines in cancer patients as a novel cancer therapy modality. Cancer immunotherapy with DCs represents greatest hope for patients with advanced cancers, which do not respond to the conventional cancer therapies. Vaccination with DCs pulsed with peptides or tumor lysates have induced therapeutic tumor-specific responses in some malignancies. DCs pulsed with tumor antigens have been well tolerated and autoimmunity has not been observed

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in vaccinated patients. In 1998, therapeutic responses were reported after vaccination with DCs pulsed with tumor lysate or a mixed of peptides in five of 16 patients with advanced melanoma; two patients with complete response and three patients with partial response.[40] Since 2000, clinical trials have been performed using DCs pulsed with tumor peptides or tumor lysate and DC-tumor cell hybrids in patients with melanoma, colorectal cancer, neuroblastoma, cutaneous T cells lymphoma, renal cell carcinoma, lung cancer, breast cancer, sarcoma, leukemia, pancreatic adenocarcinoma, collangiocellular carcinoma, hepatocelluar carcinoma, thyroid medullary carcinoma, non-Hodgkin's lymphoma, multiple myeloma, and prostate cancer. Immunological responses were induced in most vaccinated patients without obvious toxicity or autoimmunity. However, complete or partial clinical responses were rare.

Sipuleucel-T is a DC vaccine which has been approved by the USFDA in 2010 to treat patients with asymptomatic, or minimally symptomatic, metastatic hormone-refractory prostate cancer. This vaccine is the only DC vaccine that approved so far by U.S. FDA to treat cancer.[41] Sipuleucel-T helps to extend patient's lives by several months. This vaccine is composed from monocyte-derived autologous DCs that pulsed with the tumor antigen PAP.

In recent years, advancing the DC vaccine preparation protocols or combinational therapy has increased the efficacy of DC vaccines. PD-L-silenced and antigen mRNA-loaded DCs had improved immunogenic potency as they superiorly boosted *ex vivo* antigen-specific CD8+ T cell responses from transplanted cancer patients.[42] DCs pulsed with hypochlorous acid-oxidized tumor lysate were found to be safe and two of five vaccinated ovarian cancer patients experienced durable progression-free survival of 2years and more after DC vaccination.[22] Vaccination of 16 patients with head and neck squamous cell carcinoma with DCs loaded with the tumor peptide p53 was associated with two-year disease free survival of 88% of vaccinated patients.[43] Injection a tetanus/diphtheria toxoid in the vaccine site one day before vaccination with DCs pulsed with CMV phosphoprotein 65 RNA resulted in improved lymph node migration of DCs and prolonged survival of patients with glioblastoma. Preconditioning the vaccine site by this toxoid also enhanced DC vaccine efficacy in a mouse tumor model.[44] Administration of tumor lysate-pulsed DCs vaccine in combination with transfer of ex vivo-activated T cells after curative surgery led to prolonged recurrence-free survival and overall survival of patients with invasive hepatocellular carcinoma.[45] Vaccination with autologous MART-1-pulsed DCs together with adoptive transfer of TCR transgenic T cells resulted in tumor regression in nine of 13 patients with metastatic melanoma.[46] Patients with stage III/IV head and neck squamous cell carcinoma vaccinated intranodally with apoptotic tumor cell-loaded DCs survived disease-free for more than five years.[47]

Conclusion

DC vaccine is a promising approach in cancer therapy. However, vaccine-induced clinical responses were not satisfactory in patients with advanced cancers. Thus, more attempts are needed to improve the efficacy of DC vaccines in advanced cancers. DC generation protocol, route of antigen loading onto DCs, type and dose of tumor antigen(s), DC maturation status, DC migration potency, amount of cells administrated, number of injections, time of injections, and the route of vaccine administration can be optimized to improve clinical efficacy of DC vaccines as it is observed in more recent studies. Co-administration of agents that promote DCs survival and their immune stimulatory function may be beneficial. Furthermore, combinational therapy and modulation the immunosuppressive environment of the tumor, which suppresses antitumor activities of DCs, can increase DC vaccine efficacy.

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Conflicts of interest

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