CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Dendritic cell-based therapeutic cancer vaccines: past, present and future

Clin Exp Vaccine Res 2014;3:113-116
http://dx.doi.org/10.7774/cevr.2014.3.2.113
pISSN 2287-3651 • eISSN 2287-366X

Md. Selim Ahmed, Yong-Soo Bae
Department of Biological Science, Sungkyunkwan University, Suwon, Korea

Received: February 28, 2014
Revised: March 10, 2014
Accepted: March 10, 2014

Corresponding author: Yong-Soo Bae, PhD
Department of Biological Science, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon 446-740, Korea
Tel: +82-31-290-5911, Fax: +82-31-290-7087
E-mail: ysbae04@skku.edu

No potential conflict of interest relevant to this article was reported.

Dendritic cells (DCs) are professional antigen presenting cells, which play a pivotal role in antigen-specific (Ag-specific) T cell immunity. Malignancies have the capacity to inactivate DCs and effector T cells or to evade circulating antitumor immunity by expressing immune inhibitory molecules and/or secreting immunosuppressive cytokines. For this reason, *ex-vivo*-generated DCs [1] or *in-vivo*-DC-targeting [2] has been studied intensively over the past decade or development as a potential therapeutic cancer vaccine. Understanding how DCs induce, regulate, and maintain T cell immunity is essential for the design of novel cancer vaccines with improved clinical efficacy. Once activated, antigen-pulsed DCs are geared toward the launching of Ag-specific immunity, leading to T cell proliferation and differentiation into effector T cells. DCs are also important in triggering humoral immunity partly due to their capacity to directly interact with B cells and to present unprocessed antigens. There are examples of DC-based tumor vaccines being used successfully in clinical practice. Sipuleucel-T, the first Food and Drug Administration (FDA)-approved DC vaccine (Dendreon Corp.) has been found to be somewhat effective in the treatment of human prostate cancer [3]. As of 2014, 289 clinical studies of DC-based cancer vaccines are registered and under investigation (2014, http://www.clinicaltrials.gov). Among the 289 cases, 2 are in phase IV, 6 in phase III, 3 in phase II & III, 74 in phase II, 76 in phase I & II, 109 in phase I, and 3 in phase 0, underscoring the potential clinical significance of this therapy. In this editorial, we will discuss the evolution of DC-based cancer vaccine strategy, and future implications, with an emphasis on the efficacy and limitations of DC-based vaccine. Better understanding of DC biology and manipulation of activated DCs will allow DC scientists to produce the next generation of highly efficient cancer vaccines for cancer patients.

First Generation DC Vaccines

For the first generation of DC vaccines, patient-isolated or *ex-vivo*-generated monocyte-derived DCs (MoDCs) were used without additional modifications. Those primary DC vaccines were loaded with tumor lysates, recombinant tumor antigens or synthetic peptides. The early clinical trials of DC vaccines established the safety and feasibility of DC-based cancer vaccines, with relatively lower toxicity when compared with chemotherapy or radiation therapy. However, these unmodified MoDC vaccines only led to a tumor regression rate of 3.3% in patients with cancer. Because of this, peptide-loaded DCs were utilized, and demonstrated an improved tumor regression rate

of 7.1% [4]. Though not firmly established, the first generation DC vaccines were also some what effective in the induction of antitumor immunity, leading to tumor prevention in a mouse challenge model and to inhibition of tumor recurrence or metastasis after surgery in tumor-bearing mice [5]. Some clinical trials of early DC vaccines demonstrated significant tumor responses in patients with renal cell carcinoma, non-Hodgkin's lymphoma or melanoma [4,6]. DCs derived from $CD34^+$ hematopoietic progenitor cells showed better clinical outcome than those by MoDCs. Despite these successes, a number of obstacles still hindered the effectiveness of the first generation DC vaccines. In general, immunological therapy has not manifested linear dose-response effects like conventional chemotherapy. Instead, DC vaccine therapy depends on the complex interaction of a large number of variable factors, some of which are difficult to test, including the route of vaccine administration (intravenous, subcutaneous, intradermal, intra-tumoral, etc.), dose effects, vaccination schedule (weekly, monthly, multiple times in a week or month), adjuvant type, state of immunological competence, etc. [7]. Most of the earlier DC vaccine studies were performed in late-stage metastatic patients who had progressed despite standard chemotherapy. Immune target complexities also hampered the DC vaccination strategy. Most of the cancer tissues in later stages are heterogeneous in their expression of tumor antigens, rendering single epitope-targeting vaccines less effective. Because of this, the assessment of tumor antigens and their associated immune responses in patients should be investigated prior to vaccination. It has been reported that Treg cells from the tumor microenvironment are one of the main hurdles in cancer immunotherapy. Among the immunosuppressive cytokines in the tumor microenvironment, transforming growth factor-β was found to be a key factor in the inhibition of immune-mediated antitumor activity against renal cell carcinoma in DC-based immunotherapy [5]. Despite a few encouraging early reports, the first generation of DC vaccines fell short of expectations in the demonstration of dramatic tumor response for many of the aforementioned reasons. Nonetheless, the silver lining was that the first generation of DC vaccines did prove to have minimal toxicity.

Current DC-Based Cancer Vaccine Studies

Presently, the major focus of the DC vaccine approach is the enforcement of DC immunogenicity by modification of MoDCs to induce strong cytotoxic T lymphocyte (CTL) after vaccination [8]. In order to enforce the immunogenicity of DCs, they are matured and activated in the presence of specially designed cytokine cocktails and pathogen-derived agonists. Single or combined immunostimulating Toll-like receptor (TLR) ligands are used for generating DC vaccines. Poly I:C, imiquimod and/or CpG oligodeoxynucleotides are used as synthetic ligands for TLR3, TLR7, and TLR9, respectively, to confer DC maturation and interleukin 12 (IL-12) production efficiently. Together with TLR ligand agonists, prostaglandin E2 has been used to improve DC migration to regional lymph node. The use of Rv0577—a TLR2 agonist—is controversial as TLR2 ligation promotes the induction of Tregs rather than Th1 or Th17 cells. Combined TLR stimulation with Pam3Cys and Poly I:C enhances Flt3L-DC activation for tumor therapy. Maturation cocktail containing OK432 has a synergistic effect when combined with interferon-γ and promotes the antitumor immunogenicity of DC vaccines. Targeting the MHC and co-stimulatory molecules using ligand agonists enhances the DC potentiality to induce CTL. Combined DC vaccine and 4-1BB (CD137) agonistic antibody demonstrated superior therapeutic potential in metastatic colon cancer. DC vaccination with recombinant adenovirus enhanced the efficacy of DC vaccines. The combination of oncolytic adenovirus coexpressing IL-12 and granulocyte-macrophage colony-stimulating factor with DC vaccines provides synergistic antitumor immunity [4]. Indoleamine-pyrrole-2,3-dioxygenase inhibitor (1-MT) was effective in inducing tumor cell-fused DC vaccine potency. Cyclophosphamide and Cox2 inhibitors spotentiated DC vaccine efficacy. Tumor antigen-loaded DC vaccine in combination with IL-15 and p38 mitogen-activated protein kinase inhibitor confers strong CTL activation. Targeting DC surface lectins DCIR, DC-SIGN, dectin 1, CLEC9A and langerin promotes humoral and cellular immune responses including both $CD4^+$ and $CD8^+$ T cells. DEC-205 targeting is an attractive and effective method to deliver antigen to circulating DCs *in vivo* in anticancer vaccine strategies. Targeting Clec9A molecules on circulating DCs with Clec9A antibody provides a promising DC-based immunotherapy. Cancer-testes antigen NY-ESO-1-fused antibody targeting to mannose receptor or DEC-205 on circulating DCs elicits both $CD8^+$ and $CD4^+$ T cell responses. Adjuvant use of DC vaccine therapy is more effective than as the first-line treatment for primary solid tumors. As shown in animal experiments [5], DC immunotherapy has a strong potential for the inhibition of tumor metastasis or recurrence following surgery. DC vaccination combined with radiotherapy induces potent local and

 http://dx.doi.org/10.7774/cevr.2014.3.2.113

systemic antitumor immune responses in tumor bearing mice. Gemcitabine chemotherapy following DC vaccination enhanced the survival rate of patients with pancreatic cancer. Gene modification in DCs affects the DC immunogenicity against tumor. Cytokine inducible SH-2 containing protein as found to play a critical role in DC-mediated CTL activation as a positive regulator [9], while early growth response gene 2 (Egr2) acts as a negative regulator in DC mediated immunogenicity [10]. Egr2-silencing enhanced DC vaccine efficacy in the inhibition of tumor growth, suggesting that Egr2 could be an attractive molecular target for the development of more effective DC vaccine.

Future of DC-Based Cancer Vaccine

The next generation of DC-based therapeutic cancer vaccines should be prepared on the basis of DC subsets that are well suited to promote $CD8^+$ T cell responses. $CD141^+$ DCs targeting antigen delivery would allow the expansion of highly potent CTLs. On the other hand $CD1c^+$ targeting antigen delivery in tissues would allow the generation of $CD103^+CD8^+$ memory T cells. $CD4^+$ T cells regulate the $CD8^+$ T cell immunity in both priming and effector stages. Therefore, the knowledge of DC subsets could be helpful to design new vaccines directing the differentiation of antigen-specific $CD4^+$T cells towards a desired functionality. DC-mediated CTL activation will face some obstacles, including intrinsic negative regulators (CD28-CTLA4, PD1-PDL1, and ILTs), extrinsic regulators like Treg cells or myeloid derived suppressor cells, and tumor antigen alteration. To overcome these obstacles, some approaches have already been reported, such as the use of an antagonist to CTLA4 or PD-1. Antibody engineering could be another approach to create polyvalent vaccines targeting specific DC subsets to elicit strong anticancer immune responses. DC transcriptome analysis would provide another breakthrough for DC-based immune therapy. A list of candidate genes involved in type-1 cytokines may provide informative and predictive biomarkers of immune and/or clinical response. This approach may also identify patient-to-patient variation of immunologic significance [4]. Another innovative use for tumor vaccination has been suggested recently, focusing on the prevention of cancer development in high risk groups without current disease. The DC-based preventative vaccine, DC-Ad-GMCAIX, significantly delayed tumor development and reduced tumor growth of renal cancer in vaccinated mice [11]. Muc-1 peptide-pulsed DC vaccine showed preventative properties against advanced colonic adenoma. These data support the potential use of DC vaccines in tumor prevention.

Conclusion

DC-based cancer therapeutic vaccines have been studied for over a decade. However, the only DC vaccine that has been approved by the US FDA is the Dendreon's Provenge against prostate cancer in 2010. Research for this promising therapy has developed several novel methods to improve the efficacy of DC vaccine against cancer. From its inception, DC vaccine was expected to become one of the most promising approaches against cancer. However, it will take time to overcome the discovered limitations for general and effective cancer vaccination. Currently most of the DC-based vaccines are being developed in the context of adjuvant setting to create a synergistic effect with established cancer treatments. Several improved DC vaccines are currently in clinical trials, some of which will likely be approved by the FDA. We also hope that DC vaccines will be developed as a preventative vaccine against cancer.

ORCID

Md. Selim Ahmed *http://orcid.org/0000-0002-9601-8031*
Yong-Soo Bae *http://orcid.org/0000-0002-2233-9449*

References

1. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer 2012;12:265-77.
2. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu Rev Immunol 2012;30:1-22.
3. Wesley JD, Whitmore J, Trager J, Sheikh N. An overview of sipuleucel-T: autologous cellular immunotherapy for prostate cancer. Hum Vaccin Immunother 2012;8:520-7.
4. Butterfield LH. Dendritic cells in cancer immunotherapy clinical trials: are we making progress? Front Immunol 2013;4:454.
5. Lim DS, Kim JH, Lee DS, Yoon CH, Bae YS. DC immunotherapy is highly effective for the inhibition of tumor metastasis or recurrence, although it is not efficient for the eradication of established solid tumors. Cancer Immunol Immunother 2007;56:1817-29.
6. Kim JH, Lee Y, Bae YS, et al. Phase I/II study of immunotherapy using autologous tumor lysate-pulsed dendritic

cells in patients with metastatic renal cell carcinoma. Clin Immunol 2007;125:257-67.
7. Figdor CG, de Vries IJ, Lesterhuis WJ, Melief CJ. Dendritic cell immunotherapy: mapping the way. Nat Med 2004;10:475-80.
8. Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. Immunity 2013;39:38-48.
9. Miah MA, Yoon CH, Kim J, Jang J, Seong YR, Bae YS. CISH is induced during DC development and regulates DC-mediated CTL activation. Eur J Immunol 2012;42:58-68.
10. Miah MA, Byeon SE, Ahmed MS, Yoon CH, Ha SJ, Bae YS. Egr2 induced during DC development acts as an intrinsic negative regulator of DC immunogenicity. Eur J Immunol 2013;43:2484-96.
11. Birkhauser FD, Koya RC, Neufeld C, et al. Dendritic cell-based immunotherapy in prevention and treatment of renal cell carcinoma: efficacy, safety, and activity of Ad-GM.CAIX in immunocompetent mouse models. J Immunother 2013;36:102-11.

 http://dx.doi.org/10.7774/cevr.2014.3.2.113