OPEN ACCESS

Ology Press

Mini Review

Vaccines and Immunology Open Access Journal

Dendritic cell-cancer vaccines – a promising antitumor strategy

Dr Tanja Dzopalic

Department of Immunology, Faculty of Medicine, University of Nis, Serbia

Correspondence: Dr Tanja Dzopalic, Department of Immunology, Faculty of Medicine, University of Nis, Serbia, Tel +381 642163 163, Email tanja.dzopalic@medfak.ni.ac.rs; tanjche80@gmail.com

Received: February 03, 2018 | **Published:** February 15, 2018

Introduction

Even since their discovery in 1973, dendritic cells (DCs) were the subject of intense research among immunologists. In the last 20 years, DCs emerged as a powerful tool for boosting antitumor immune response.[1-3]

DCs are the most potent antigen presenting cells conducting both, innate and acquired immune response.[4] Their unique function is manifested through uptake of exogenous antigens, their processing into peptides and sequential presentation to $CD4^+$T helper (Th) cells in MHC class II complexes. DCs also activate $CD8^+$ cytotoxic T lymphocytes (CTLs) by exogenous antigens during the process called cross-presentation.

In this way tumor antigens are presented to CTLs.

By virtue of different expression of pattern-recognition receptors (PRRs), DCs recognize numerous pathogen associated molecular patterns (PAMPs) on microorganisms.[5] The best described PRRs include Toll-like receptors (TLRs), C-type lectins (CLRs), cytoplasmic retinoic acid–inducible gene-I-like receptors (RLRs), nucleotide oligomerization domain-like receptors (NLRs).[6] Activation of PRRs leads to phenotypic and functional maturation of DCs upon which they migrate to lymphoid organs inducing optimal T-cell response (Th1, Th2, Th17).[1]

In humans, DCs comprise two functionally distinct subtypes, myeloid DCs (mDC) and plasmacytoid DCs (pDC). mDCs seems to be important for inducing immune response against fungi and bacteria[7] and also for detection and uptake of necrotic cells.[8] Thanks to IFN type I production, pDCs are mediating immune response against viral infections.[9] pDCs also exert tumoricidal activity.[10]

DC-cancer vaccines

Current protocols for treatment of malignant tumors comprise multilateral strategies. Achieving potent immune response is one of the most important approaches, where DC-based cancer vaccines play an unavoidable role. Namely, since the DCs are in the centrum of immune response initiation, DCs could be very effective in boosting antitumor immunity.[11] Most of the clinical studies exploit *in vivo* generated monocyte-derived DCs (moDCs) in their trials.[12] Such an approach includes cultivation of monocytes obtained from peripheral blood mononuclear cells (PBMCs) with GM-CSF and IL-4, which are able to differentiate them into immature moDCs after 5-6 days.[13] In order to boost effective immune response, DCs need to acquire mature state. Mature DCs exert up-regulated expression of costimulatory molecules (CD80 and CD86), MHC class II molecules, adhesion molecules (CD54), produce cytokines and chemokines necessary for migration to lymphoid tissues and activation of T cell responses.[14,15] Immature DCs are not able to induce immune response, therefore only mature DCs are included in clinical studies.[16]

Maturation of DCs can be achieved in various ways. Poly I:C (TLR3), LPS (TLR4) and loxoribine (TLR7) are well-known TLR agonists and activators of DCs.[17-19] MoDCs treated with such molecules exert mature phenotype and induce good Th1 and Th17 antitumor immune response. Cooperation between multiple TLRs, however, is necessary for more effective immunity. Therefore, numerous studies using simultaneous engagement of different TLRs were performed where much better results were achieved.[20,21] In addition, single TLR agonists could be delivered directly to DCs by new nanomaterial (nanotubes) inducing significant immunostimulatory effect. Functionalized multi-walled carbon nanotubes (MWCNTs) with low concentrations of TLR7 agonist potentiates strong Th1 and Th17 immune response, similarly as 10 times higher concentrations of soluble TLR7 agonist. These findings might have implications for potential use of MWCNTs functionalized with TLR7 agonist as a promising system for preparing more potent immunostimulatory DCs and improving the protocols for preparation of DC-based vaccines.[22] MoDCs matured in the presence of poly I:C, TNF-α, IL-1β, IFN-α and IFN-γ has been used in clinical trials. These cells named α-type-1 polarized DCs (αDC1) produce high amounts of IL-12p70, migrate in response to CCR7 ligand and induce CTL-mediated response against tumor-associated antigens (TAA).[23] Such αDC1 exerted good clinical outcome in patients with high-grade glioma for at least one year.[24] Co-ligation of TLRs with CLRs was also used as a maturation moDCs stimuli. Combination of TLR-3 and Dectin-1 agonists, poly I:C and curdlan, respectively,

up-regulated phenotypic maturation of moDCs with the capability to stimulate Th1 and Th17 immune response.[25]

In order to induce an optimal immune response in cancer patients, MHC molecules of a mature DCs should be loaded with adequate tumor antigens. To date, several methods of DCs' antigen loading have been performed. They include incubation of DCs with peptides lysates of autologous or allogeneic whole tumors or tumor cell lines.[26-28] Such an approach stimulated CTL and Th1 immune response in ovarian cancer patients.[29] RNA transfection of DCs is another way in achieving potent immunity by encoding specific antigens and maturation factors. Combination of amplified RNA and synthetic CD40L RNA with *Sunitinib* exerted clinical benefit among 62% of treated patients with metastatic clear cell renal cell carcinoma.[30] Recent investigations using neoantigen-loaded DCs showed promising results by promotion of neoantigen-specific T-cell response.[31]

DCs need to migrate to lymph nodes in order to activate T cells. Therefore, optimal route of administration of DC vaccines need to be established. So far, the best systemic response was achieved by common intradermal and intravenous administration or by direct intranodall application.[32]

Novel approaches in cancer immunotherapy include CTLA-4 and PD-1 blocking antibodies as immune checkpoint inhibitors.[33,34] Their combination with DCs could direct T-cell response in a specific manner. Namely, DC vaccination should enhance tumor-specific immune response while check point inhibitors increase the number of circulating T cells. Clinical benefit in 38% of melanoma patients was observed.[35,36]

Development of new technologies contributes to differentiation of new DCs from human pluripotent stem cells upon the addition of growth factors, BMP-4, VEGF, GM-CSF, SCF, Flt3L and IL-4 at key intervals of differentiation.[37] Another genetic engineering technology involving Cas9 endonuclease can manipulate DCs to prevent expression of inhibitory molecules (PD-L1) and cytokines (IL-10) thus improving their effectiveness *in vivo*.[38]

Taken together, DC-based cancer vaccines represent a powerful tool in immunotherapy. So far, only specific types of tumors have been studied, mainly due to the lack of appropriate tumor antigens or the absence of sufficient tumor material.[2] Additional investigations need to be performed in order to achieve fully effective results.

Aknowledgement

The author thank to the support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (project number 175102).

References

1. Sabado RL, Bhardwaj N. Directing dendritic cell immunotherapy towards successful cancer treatment. *Immunotherapy.* 2010;2(1):37–56.
2. Bol KF, Schreibelt G, Gerritsen WR, et al. Dendritic cell-based immunotherapy: State of the Art and Beyond. *Clin Cancer Res.* 2016;22(8):1897–1906.
3. Constantino J, Gomes C, Falcao A, et al. Dendritic cell-based immunotherapy: a basic review and recent advances. *Immunol Res.* 2017;65(4):798–810.
4. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature.* 1998;392(6673):245–252.
5. Medzhitov R, Janeway CA Jr. Decoding the patterns of self and nonself by the innate immune system. *Science.* 2002;296(5566):298–300.
6. Underhill DM. Collaboration between the innate immune receptors dectin–1, TLRs, and Nods. *Immunol Rev.* 2007;219:75–87.
7. Liu YJ. Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. *Cell.* 2001;106(3):259–262.
8. Sancho D, Joffre OP, Keller AM, et al. Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. *Nature.* 2009;458(7240):899–903.
9. Cella M, Jarrossay D, Facchetti F, et al. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat Med.* 1999;5(8):919–923.
10. Tel J, Smits EL, Anguille S, et al. Human plasmacytoid dendritic cells are equipped with antigen-presenting and tumoricidal capacities. *Blood.* 2012;120(19):3936–3944.
11. Sabado RL, Balan S, Bhardwaj N. Dendritic cell-based immunotherapy. *Cell Res.* 2017;27(1):74–95.
12. Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. *J Exp Med.* 1994;179(4):1109–1118.
13. Colic M, Stojic-Vukanic Z, Pavlovic B, et al. Mycophenolatemofetil inhibits differentiation, maturation and allostimulatory function of human monocyte-derived dendritic cells. *Clin Exp Immunol.* 2003;134(1):63–69.
14. Banchereau J, Briere F, Caux C, et al. Immunobiology of dendritic cells. *Annu Rev Immunol.* 2000;18:767–811.
15. Schnare M, Barton GM, Holt AC, et al. Toll-like receptors control activation of adaptive immune responses. *Nat Immunol.* 2001;2(10):947–950.
16. Constantino J, Gomes C, Falcao A, et al. Antitumor dendritic cell-based vaccines: lessons from 20 years of clinical trials and future perspectives. *Transl Res.* 2016;168:74–95.
17. Rouas R, Lewalle P, El Ouriaghli F, et al. Poly(I:C) used for human dendritic cell maturation preserves their ability to secondarily secrete bioactive IL-12. *Int Immunol.* 2004;16(5):767–773.
18. Colic M, Mojsilovic S, Pavlovic B, et al. Comparison of two different protocols for the induction of maturation of human dendritic cells in vitro. *Vojnosanit Pregl.* 2004;61(5):471–478.
19. Dzopalic T, Dragicevic A, Vasilijic S, et al. Loxoribine, a selective Toll-like receptor 7 agonist, induces maturation of human monocyte-derived dendritic cells and stimulates their Th-1- and Th-17-polarizing capability. *Int Immunopharmacol.* 2010;10(11):1428–1433.
20. Napolitani G, Rinaldi A, Bertoni F, et al. Selected Toll-like receptor agonist combinations synergistically trigger a T helper type 1-polarizing program in dendritic cells. *Nat Immunol.* 2005;6(8):769–776.
21. Dzopalic T, Rajkovic I, Dragicevic A, et al. The response of human dendritic cells to co-ligation of pattern-recognition receptors. *Immunol Res.* 2012;52(1-2):20–33.
22. Čolić M, Džopalić T, Tomić S, et al. Immunomodulatory effects of carbon nanotubes functionalized with a Toll-like receptor 7 agonist on human dendritic cells. *Carbon.* 2014;67:273–287.
23. Lee JJ, Foon KA, Mailliard RB, et al. Type 1-polarized dendritic cells loaded with autologous tumor are a potent immunogen against chronic lymphocytic leukemia. *J Leukoc Biol.* 2008;84(1):319–325.
24. Okada H, Kalinski P, Ueda R, et al. Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by

vaccinations with {alpha}-type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. *J Clin Oncol.* 2011;29(3):330–336.

25. Dragicevic A, Dzopalic T, Vasilijic S, et al. Signaling through Toll-like receptor 3 and Dectin-1 potentiates the capability of human monocyte-derived dendritic cells to promote T-helper 1 and T-helper 17 immune responses. *Cytotherapy.* 2012;14(5):598–607.
26. Barrou B, Benoit G, Ouldkaci M, et al. Vaccination of prostatectomized prostate cancer patients in biochemical relapse, with autologous dendritic cells pulsed with recombinant human PSA. *Cancer Immunol Immunother.* 2004;53(5):453–460.
27. Salcedo M, Bercovici N, Taylor R, et al. Vaccination of melanoma patients using dendritic cells loaded with an allogeneic tumor cell lysate. *Cancer Immunol Immunother.* 2006;55(7):819–829.
28. Mahdian R, Kokhaei P, Najar HM, et al. Dendritic cells, pulsed with lysate of allogeneic tumor cells, are capable of stimulating MHC-restricted antigen-specific antitumor T cells. *Med Oncol.* 2006;23(2):273–282.
29. Chiang CL, Kandalaft LE, Tanyi J, et al. A dendritic cell vaccine pulsed with autologous hypochlorous acid-oxidized ovarian cancer lysate primes effective broad antitumor immunity: from bench to bedside. *Clin Cancer Res.* 2013;19(17):4801–4815.
30. Amin A, Dudek AZ, Logan TF, et al. Survival with AGS-003, an autologous dendritic cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): Phase 2 study results. *J Immunother Cancer.* 2015;3:14.
31. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science.* 2015;348(6236):803–808.
32. Lesterhuis WJ, de Vries IJ, Schreibelt G, et al. Route of administration modulates the induction of dendritic cell vaccine-induced antigen-specific T cells in advanced melanoma patients. *Clin Cancer Res.* 2011;17(17):5725–5735.
33. Zarour HM. Reversing T-cell dysfunction and exhaustion in cancer. *Clin Cancer Res.* 2016;22(8):1856–1864.
34. Sanchez-Paulete AR, Cueto FJ, Martinez-Lopez M, et al. Cancer immunotherapy with immunomodulatory anti-CD137 and anti-PD-1 monoclonal antibodies requires BATF3-dependent dendritic cells. *Cancer Discov.* 2016;6(1):71–79.
35. Ribas A, Comin-Anduix B, Chmielowski B, et al. Dendritic cell vaccination combined with CTLA4 blockade in patients with metastatic melanoma. *Clin Cancer Res.* 2009;15(19):6267–6276.
36. Wilgenhof S, Corthals J, Heirman C, et al. Phase II study of autologous monocyte-derived mRNA electroporated dendritic cells (TriMixDC-MEL) plus ipilimumab in patients with pretreated advanced melanoma. *J Clin Oncol.* 2016;34(12):1330–1338.
37. Li Y, Liu M, Yang ST. Dendritic cells derived from pluripotent stem cells: Potential of large scale production. *World J Stem Cells.* 2014;6(1):1–10.
38. White MK, Khalili K. CRISPR/Cas9 and cancer targets: future possibilities and present challenges. *Oncotarget.* 2016;7(11):12305–12317.