Review article

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CURRENT ACHIEVEMENTS OF DENDRITIC CELL-BASED IMMUNOTHERAPY

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Dendritic cells (DCs) are the key antigen-presenting cells and stimulators of the immune response. Numerous studies have proven DC-based tumor vaccines as the most effective form of tumor vaccines with good results in clinical trials. Due to the marked disproportion in the results of complete tumor curing in some patients using DC-based vaccines and modest results achieved in other patients, there is a need for improvement of preparation methods. This review summarizes the current protocols in creating DC-based tumor vaccines and future perspectives as well.

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Introduction

Dendritic cells (DCs) have been occupying the attention of immunologists all over the world for more than 40 years. During the last two decades, DCs have been shown as a useful tool in boosting the antitumor immune response (1-3).

In their resting state, DCs are considered to be immature but prepared to recognize and acquire antigens through numerous pattern-recognition receptors (PRRs). There are several groups of PRRs, including Toll-like receptors (TLRs), C-type lectins (CLRs), cytoplasmic retinoic acid–inducible gene-I-like receptors (RLRs) and nucleotide oligomerization domain-like receptors (NLRs) (4-6). Upon PRRs activation, DCs undergo phenotypic and functional maturational changes (7). They include the upregulation of chemokine receptors (CCR7), adhesion molecules (CD54), co-stimulatory molecules (CD80 and CD86), immunoproteosomes and major histocompatibility complex (MHC)-MHC class I and II molecules, all important for DCs migration to the lymphoid tissues and activation of the immune response (8). Co-stimulatory molecules and cytokines expressed by the DCs determine the immune response towards T helper 1 (Th1), Th2 or Th17 profile. Thanks to the production of different cytokines (IL-12, IL-15, type I IFNs), DCs also activate B cells (9), natural killer (NK) cells (10) and NKT cells (11).

Upon recognition, DCs take up antigens through pinocytosis, endocytosis, and receptor-mediated phagocytosis by Fc receptors, integrins, apoptotic cell receptors, CLRs and scavenger receptors (8). Antigens are further processed into peptides that are presented on MHC class I and II molecules via the endogenous pathway or exogenous pathway, respectively (12, 13). Endogenous pathway includes processing and presentation of intracellular antigens to $CD8^+$ T cells, whereas exogenous peptides are presented to $CD4^+$ T cells via exogenous pathway. In addition, DCs can process the exogenous antigens on MHC I molecules stimulating $CD8^+$ T cells via cross-presentation.

Following maturation, DCs migrate to the secondary lymph organs (lymph nodes, spleen, Peyer's patches) where they interact with T cells (14). T cells specifically recognize antigens expressed on MHC molecules through their T cell receptor (TCR). Duration and intensity of DC-T cell interaction seem o be of great importance in T cell activation. B cells are activated by DCs through their ability to stimulate T follicular helper cells and induction of B cell growth and antibody production. DCs process glycolipid antigens and present them on the CD1d molecule and activate NKT cells (11). Concluding, DCs are an important part in the orchestration of innate and adaptive arm of immune responses.

In humans, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) are considered as two main types of DCs in the blood (2). Both mDCs and pDCs express distinct TLRs and respond differently to pathogenic stimuli, suggesting their specific direction of the immune responses (15). The main role of mDCs

refers to immunity against fungi and bacteria (16) and detection and uptake of necrotic cells as well (17). pDcs produce high levels of type I IFNs in response to viral products, suggesting their important part in preventing viral infections (18). There are some studies indicating a synergistic act of mDcs and pDCs in antitumor response (19).

DC immunotherapy

In order to eliminate the malignant tumors by immune mechanisms, modern chemotherapeutic protocols are supplemented with immunotherapeutic procedures. Within active specific immunotherapy, the best clinical results are achieved using DC-based tumor vaccines (2, 8). DCs are key antigen-presenting cells and immune response stimulators. On the other hand, they are also important for immunological tolerance and maintaining the immune system nonreactive to its own antigens. One of the mechanisms by which the tumor evades the effector functions of the immune system is the stimulation of the tolerant properties of the DCs. Immature DCs are potentially tolerogenic and might even promote antigen-specific tolerance when used in DC vaccines (20). Therefore, the latest studies of tumor vaccine development are based on the preparation of mature DCs with immunogenic properties (21-23).

Methods of generating DCs

Current protocols for generating DCs include differentiation from monocyte precursors or $CD34^+$ hematopoietic precursors, *in vivo* expansion of circulating DCs and isolation and enrichment of circulating blood DC subsets (8).

Since the circulating number of human DCs is very low, most of the studies exploit *in vitro*-generated monocyte-derived DCs (MoDCs) obtained by cultivation of monocytes from peripheral blood mononuclear cells (PBMCs) (24, 25). Monocytes are induced to differentiate into immature MoDCs after 6 days in the presence of GM-CSF and IL-4, upon which the cells are stimulated to mature into the immunogenic MoDCs.

Another way of the DCs generation involves mobilization of $CD34^+$ precursors from the bone marrow upon which the cells are expanded *in vitro* in the presence of GM-CSF, Flt3L, TNF-α, TGF-β, and SCF. Such cells represent the mixture of MoDCs and myeloid cells at different stages of differentiation (26).

Maturation of DCs

Since immature DCs are not able to induce an mmune response, only mature DCs are included in clinical trials (23, 27). Maturation of DCs can be achieved in many different ways, but still, there is no consensus on adequate maturation stimuli. Gold standard for maturation of DCs used to include a well-known cocktail of proinflammatory cytokines TNF-α, IL-1β and IL-6 with PGE_2 (28). This way matured DCs highly express CD40, CD80, CD86, MHC class I and II, but fail to induce IL-12 production, important for the development of Th1 antitumor response. TLR agonists have also been used to mature DCs. Poly I:C (TLR3), LPS (TLR4), loxoribine and resiquimod (TLR7) are well-known TLR agonists and activators of DCs (29-31). Simultaneous engagement of different TLRs potentiates more effective antitumor immune response through the maturation of DCs (32, 33). Additionally, single endosomal TLR agonists could be effectively delivered to DCs by nanomaterials (carbon nanotubes) inducing very potent immunostimulatory effect (34). Co-activation of TLRs and CLRs by TLR3 and Dectin-1 agonists can also be used as a good maturation DC stimulus. Such treated DCs express mature phenotype and polarize immune response in Th1 and Th17 direction (35).

Tumor Antigens and Loading of DCs

In order to exert good immune response, MHC molecules of DCs should be loaded with adequate tumor antigens. For the induction of a strong and sustained antitumor T-cell response, it would be of great interest to activate both, $CD4^+$ and $CD8^+$ T cells (36, 37). Several methods of loading of DCs with tumor epitopes have been described.

DCs are usually loaded through incubation with peptides, proteins, RNA or autologous/ allogeneic tumor cells before maturation process (8, 38). Peptides loading do not require antigen processing, therefore they can be directly placed on the MHC molecules on the surface of the DCs. However, such an approach is HLA-type dependent and antigen identification is required for these specific haplotypes. Clinical trials using peptides as a loader, exerted satisfactory results in patients with cervical (39, 40), ovarian (41) and colorectal cancer (42) where $CD4^+$ and $CD8^+$ T cell responses were induced.

DCs loading with proteins and tumor cell lysates does not need antigen identification, thus multiple epitopes can be presented on MHC molecules of different haplotypes (43). The best results were achieved in multiple myeloma and ovarian cancer patients where DCs were fused with tumor lysates and both $CD4^+$ and $CD8^+$ T cell responses occurred (44, 45). A study in the mouse model of high-grade glioma exerted an increased survival accompanied by the immunostimulatory switch from regulatory T cells to Th1 and Th17 (46).

Currently, RNA transfection of DCs is a very useful method in achieving potent antitumor immunity by encoding specific antigens and maturation factors (47, 48). Clinical benefit among patients with metastatic clear cell renal cell carcinoma and non-small cell lung cancer was achieved by RNA transfected DCs (47, 49). Recent investigations using neoantigen-loaded DCs showed promising results by the promotion of neoantigen-specific T-cell response (50).

Administration and migration of DCs

The biological potential of the DCs to stimulate the antitumor immune response also depends on their migration to the lymph nodes (2). Therefore, the optimal route of administration of DCs needs to be established. Current immunization strategies include subcutaneous, intradermal, intranodal, intrave-

nous and intratumoral administration (8). So far, the best systemic response was achieved via a combination of the intradermal and intravenous application of DC vaccines in the treatment of patients with melanoma (51, 52).

In Vivo Targeting of DCs

In vivo DC targeting represents a novel approach that involves targeting specific receptors, such as Fc receptors, CD40, and CLRs (3). CLRs are the most attractive targets since DCs express a variety of CLRs (Clec9a, DEC205, Langerin) involved in recognition of glycosylated antigens (53). Targeting of Clec9a in animal models induced good antitumor response through cellular and humoral immunity (54, 55). Clinical trials of DEC205 targeting are currently ongoing in ovarian cancer, acute myeloid leukemia, and melanoma (8).

Delivery of tumor antigens via RNA lipoplexes is the newest approach for *in vivo* DC targeting (8). Such combination protects RNA from degradation, while the RNA itself activates pDCs and induces the release of IFN type I. There is an ongoing clinical trial with melanoma patients where high amounts of IFNα production and antigen- specific T cell response were observed (56).

DC-derived exosomes

Another new approach in cancer immunotherapy involving DCs refers to DC-derived exosomes (DC-Exo). It has been shown that DC-Exo turns cancer cells into more immunogenic targets, which can contribute to the effectiveness of DC vaccines (3, 57).

Future approaches

Combination of DCs with immune checkpoint inhibitors (CTLA-4 and PD-1 blocking antibodies), should direct T-cell response in a specific manner. This novel approach is still under investigations, where the increase in the number of circulating T cells is expected (58, 59).

There are ongoing studies using new technologies in the differentiation of DCs from human pluripotent stem cells and embryonic stem cells with the addition of growth factors, BMP-4, VEGF, GM-CSF, SCF, Flt3L and IL-4 at key intervals of differentiation (60).

Additionally, new genetic engineering technologies using Cas9 endonuclease, can modulate DCs and delete expression of inhibitory molecules (PD-L1) and cytokines (IL-10). Such modulated DCs express improved efficiency *in vivo* and drive $CD8^+$ T cell differentiation (8).

A recent study by Woo et al. has demonstrated that activation of the STING (Stimulator of Interferon Genes) pathway in tumor-resident host DCs is required for induction of a spontaneous $CD8^+$ T cell response against tumor-derived antigens *in vivo* (61). Activation of this pathway and the subsequent production of IFNβ lead to potent and systemic tumor regression and immunity, which can be potentiated with co-administration of a natural STING agonist (62).

Schematic presentation of current and future approaches in DC-based immunotherapy is pictured in Figure 1.

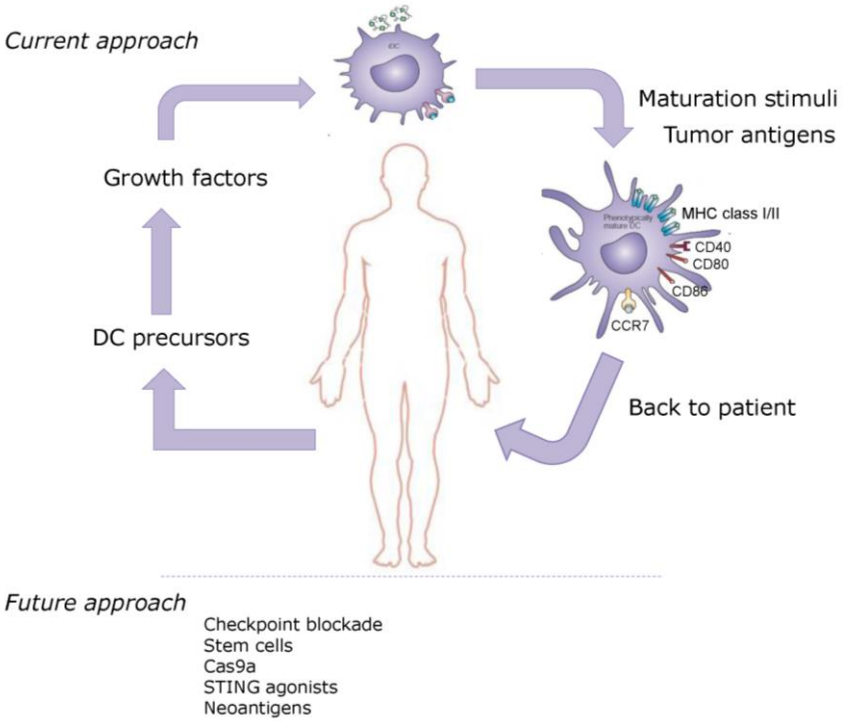

Figure 1. Current and future approaches in dendritic cell-based immunotherapy

Conclusion

Recent studies have shown the treatment of malignant tumors by tumor vaccines as an acceptable and harmless way of immunotherapy along with surgical treatment, radiotherapy, and chemotherapy. DC-based tumor vaccines, as the most potent tumor-specific immune response stimulants, are the most effective form of tumor vaccines. There are great expectations of numerous ongoing clinical studies involving DCs as cancer vaccines, as Karolina Palucka and Jacques Banchereau stated: *Just as immunotherapy is moving to the forefront of cancer therapy, DC-based therapy is moving to the forefront of cancer immunotherapy.*

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SAVREMENA DOSTIGNUĆA U IMUNOTERAPIJI TUMORA ZASNOVANOJ NA DENDRITSKIM ĆELIJAMA

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Dendritske ćelije (DĆ) glavni su antigen prezentujuće ćelije i pokretači imunskog odgovora. Brojne studije i klinička ispitivanja pokazali su da vakcine zasnovane na DĆ predstavljaju najefikasniji vid imunoterapije tumora. Zbog izrazite disproporcije u odličnim rezultatima potpunog izlečenja tumora kod nekih bolesnika primenom DĆ vakcina i skromnih rezultata koji se postižu kod drugih bolesnika, nameće se potreba da se priprema DĆ vakcina unapredi. U ovom preglednom članku navedeni su savremeni protokoli generisanja DĆ i kreiranja vakcina, kao i buduća razmišljanja.

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Ključne reči: *dendritske ćelije, imunoterapija, tumorske vakcine*