

# Dendritic cell-cancer vaccines – a promising antitumor strategy

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## 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.<sup>1-3</sup>

DCs are the most potent antigen presenting cells conducting both, innate and acquired immune response.<sup>4</sup> Their unique function is manifested through uptake of exogenous antigens, their processing into peptides and sequential presentation to CD4<sup>+</sup>T helper (Th) cells in MHC class II complexes. DCs also activate CD8<sup>+</sup> 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.<sup>5</sup> 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).<sup>6</sup> 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).<sup>1</sup>

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<sup>7</sup> and also for detection and uptake of necrotic cells.<sup>8</sup> Thanks to IFN type I production, pDCs are mediating immune response against viral infections.<sup>9</sup> pDCs also exert tumoricidal activity.<sup>10</sup>

## 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.<sup>11</sup>

Most of the clinical studies exploit *in vivo* generated monocyte-derived DCs (moDCs) in their trials.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14,15</sup> Immature DCs are not able to induce immune response, therefore only mature DCs are included in clinical studies.<sup>16</sup>

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.<sup>17-19</sup> 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.<sup>20,21</sup> 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.<sup>22</sup> MoDCs matured in the presence of poly I:C, TNF- $\alpha$ , IL-1 $\beta$ , IFN- $\alpha$  and IFN- $\gamma$  has been used in clinical trials. These cells named  $\alpha$ -type-1 polarized DCs ( $\alpha$ DC1) produce high amounts of IL-12p70, migrate in response to CCR7 ligand and induce CTL-mediated response against tumor-associated antigens (TAA).<sup>23</sup> Such  $\alpha$ DC1 exerted good clinical outcome in patients with high-grade glioma for at least one year.<sup>24</sup> 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.<sup>25</sup>

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.<sup>26-28</sup> Such an approach stimulated CTL and Th1 immune response in ovarian cancer patients.<sup>29</sup> 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.<sup>30</sup> Recent investigations using neoantigen-loaded DCs showed promising results by promotion of neoantigen-specific T-cell response.<sup>31</sup>

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 intranodal application.<sup>32</sup>

Novel approaches in cancer immunotherapy include CTLA-4 and PD-1 blocking antibodies as immune checkpoint inhibitors.<sup>33,34</sup> 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.<sup>35,36</sup>

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.<sup>37</sup> 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*.<sup>38</sup>

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.<sup>2</sup> Additional investigations need to be performed in order to achieve fully effective results.

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