Clinical Immunology 183 (2017) 181–190

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

# Hematologic neoplasms: Dendritic cells vaccines in motion

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ARTICLE INFO

*Article history:*
Received 27 February 2017
Received in revised form 28 July 2017
accepted with revision 29 August 2017
Available online xxxx

*Keywords:*
Dendritic cells
DC vaccine
Immunotherapy
Cancer vaccination
Hematological malignancies
Hematologic neoplasms

ABSTRACT

Dendritic cells (DCs) are bone-marrow-derived immune cells accounted for a key role in cancer vaccination as potent antigen-presenting cells within the immune system. Cancer microenvironment can modulate DCs maturation resulting in their accumulation into functional states associated with a reduced antitumor immune response. In this regard, a successful cancer vaccine needs to mount a potent antitumor immune response able to overcome the immunosuppressive tumor milieu. As a consequence, DCs-based approaches are a safe and promising strategy for improving the therapeutic efficacy in hematological malignancies, particularly in combinations with additional treatments. This review summarizes the most significant evidence about the immunotherapeutic strategies performed to target hematologic neoplasms including the tumoral associated antigens (TAA) pulsed on DCs, whole tumor cell vaccines or leukemia-derived DCs.



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*Abbreviations:* DCs, dendritic cells; TAA, tumor-associated antigens; APC, antigen presenting cells; mDCs, myeloid dendritic cells; pDCs, plasmacytoid dendritic cells; HLA, human leukocyte antigen; Ag Antigens, abs antibodies; PBMCs, peripheral blood mononuclear cells; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; Flt3, FMS-like tyrosine kinase-3; TNF, tumor necrosis factor; CD, cluster designation; CD40L, CD40 ligand; HLA, human leukocyte antigen; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; TLR, toll-like-receptor; IFN, interferon; IL-12p70, interleukin-12 p70; DCIR, DC immunoreceptor; DC-SIGN, DC-specific ICAM-grabbing non-integrin; Clec9A, C-type lectin domain family 9 member A; CML, chronic myeloid leukemia; LAA, leukemia-associated Ag; WT1, Wilms' tumors 1; CTLs, cytotoxic T lymphocytes; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor; KLH, keyhole limpet hemocyanin; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; mRNA, messenger RNA; CR, complete remission; hTERT, human telomerase reverse transcriptase; PRAME, preferentially expressed antigen in melanoma; PD1, programmed cell death protein 1; MM, multiple myeloma; Id, idiotype; M, protein myeloma protein; DC/MM cells, DCs fused with myeloma cells; MAGE3, melanoma-associated antigen 3; LEN, lenalidomide; CT7, cancer-testis antigen 7; BCL, B-cell lymphomas; FL, follicular Non-Hodgkin Lymphoma; poly-ICLC, poly-L-lysine and carboxymethylcellulose; SIIT, sequential intranodal immunotherapy; B-CLL, B-chronic lymphocytic leukemia; RHAMM, receptor for hyaluronic acid mediated motility; Apo-DC, apoptotic bodies of B-CLL cells; CTCL, cutaneous T-cell lymphomas; Tax-DC, tax peptide-pulsed DCs; ATL, adult T-cell leukemia/lymphoma; ALL, acute lymphoblastic leukemia; ELISPOT, enzyme-linked immunospot; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; CTLA4, cytotoxic T-lymphocyte antigen 4; PDL1, programmed death-ligand 1; ILTs, immunoglobulin-like transcripts; Tregs, regulatory T cells; MDSC, myeloid-derived suppressor cells; NK, natural killer cells; RT, radiotherapy; CT, chemotherapy.

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http://dx.doi.org/10.1016/j.clim.2017.08.016
1521-6616/

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## 1. Introduction

Vaccination is a new therapeutic approach for cancer [1,2] that aims at re-educating the immune system to identify and destroy malignant cells, concurrently inducing immunological memory to prevent cancer recurrence [1,2].

Cancer vaccines have shown minimal toxicity in clinical trials in comparison to other cytotoxic therapies. Positive results demonstrated slower tumor growth rate and improved overall survival while no substantial reductions in tumor burden or significant differences in time to progression [3].

DCs play a key role in the vaccination as potent antigen presenting cells (APC) [4–6]. In humans, two major blood circulating subsets, namely myeloid (mDCs) and plasmacytoid DCs (pDCs), have been described according to the origin, immunophenotype, and function. Both subsets express high levels of Human Leukocyte Antigen (HLA)-DR lacking the expression of lineage markers. mDCs are characterized by the expression of CD11c while pDCs are negative for CD11c and express high levels of CD123 [7,8].

Mature DCs are crucial arbiters of the host immune response against tumors regulating the effector cells of innate immunity [9–11]. Also, DCs orchestrate adaptive immune responses by the cross-presentation of TAA to T lymphocytes [4,12,13]. Cancer microenvironment can modulate DCs maturation and activity, leading to their accumulation into functional states associated with a reduced antitumor immune response. In this regard, a successful cancer vaccine requires an effective TAA cross-presentation within costimulatory molecules to overcome the immunosuppressive tumor milieu [14,15]. In particular, vaccination exploits the DCs ability to infiltrate tumor lesions and eradicate malignant cells by the activation of T lymphocytes and NK cells [16,17].

In the last decade, DCs have become a promising tool for cancer immunotherapy, including hematological malignancies, which has favored the development of greatly improved clinical protocols [18].

Hereunder, we will discuss the different DC-based strategies used in pre-clinical and clinical studies for enhanced immunization against hematological neoplasms.

## 2. Current strategies of DC immunotherapy in cancer

Many avenues of DC-based vaccinations against cancer are currently being performed, notably 1) vaccines composed of ex-vivo-generated DCs loaded with distinct types of antigens 2) *in vivo* vaccines consisting of chimeric proteins composed by an antigen (Ag) coupled with antibodies (Abs) specific to DC receptors [15].

### 2.1. Ex vivo DC strategies

The ex-vivo approach was developed to bypass possible impediments in therapeutic efficacy due to the dysfunction of endogenous DCs present in cancer patients [19].

Ex-vivo DCs are mainly obtained from peripheral blood mononuclear cells (PBMCs) in the presence of granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-4, IL-13 [20] or FMS-like tyrosine kinase-3 (Flt3)-ligand cytokine [21]. This production process is complicated and full of technical and logistic difficulties. The qualities of such produced DC vaccines are highly variable due to unpredictable and uncontrollable patient-to-patient variation. Alternatively, $CD34^+$ derived DCs represent a novel alternative cell source which has the potential for large scale production. A strategy standardizable and patient blood cell-independent can expand DCs in culture from $CD34^+$ progenitor cells by using GM-CSF, IL-4, tumor necrosis factor (TNF), Flt3-ligand, and CD40 ligand (CD40L) [22]. In this regard, new protocols can generate $CD34^+$ derived DCs possessing a superior capacity to stimulate tumor-reactive T cells and NK cells [23]. Also, cultures of B cells, in the presence of CD40L, result in a dramatic expansion of cells capable of Ag presentation with the required costimulatory molecules [24]. Subsequently, ex-vivo generated DCs can be loaded with TAAs, activated and then injected back into the patients [21]. A successfully isolation and expansion of mature DCs permits investigators to introduce distinct experimental Ags into these cells, possibly inducing an effective immune response to a malignancy. Several studies have evaluated peptide-based vaccines [25,26] often with an immune adjuvant [26], DNA or RNA coding for a specific Ag [27,28], viral/fungal vectors expressing tumor Ags [29,30] or tumor apoptotic bodies [31,32]. However, the reduced immunogenicity of the selected Ags, the HLA restriction in peptide-based approaches, and the downregulation of specific TAAs represented a significant issue of these strategies that could favor tumor evasion of the immune response [33]. These limitations enforced the development of other methods for priming DCs, particularly the whole intact tumor cells [34], leukemia-derived DCs [35], cell lysates [36], whole cell DNA or RNA [37]. In this regard, whole tumor cell approaches were polyvalent sources of TAAs able to elicit a broader immune response [38,39]. The rationale behind this vaccination strategy is to overcome the obstacle of Ag choice by containing a wide selection of TAAs, including neoantigens peculiar to a given patient's disease [38–40]. The neoantigens are peptides derived from somatic mutations that are not present in non-malignant cells. The development of RNA sequencing technologies has led to identifying a complete range of mutation-derived antigens from the primary tumor and metastases allowing to tailor therapeutic vaccines that stimulate an expansion of high-affinity $CD8^+$ T lymphocytes specific for the patient's neoplasm [40–42].

In this regard, early clinical trials reported that DCs-based vaccines should present a “mature” state to stimulate better an Ag-specific immune response upon T-cell encounter [43]. Thus, to enforce the immunogenicity, a new generation of clinical trials have used cytokines cocktails to activate DCs. Currently, maturation cocktails can comprise specific pathogen-derived molecules, Toll-like-receptor (TLR) ligands and other “type 1” polarizing agents including interferons (IFNs) [44]. As a consequence, mature DCs acquire an activated phenotype, respond to the homing signals from lymph nodes, secrete moderate amounts of IL-12p70, and induce the Ag-specific effector T cells [44–46]. The new DCs-based vaccines demonstrated objective clinical response rates with a range between 7.7% and 12.7%, and overall clinical benefit rate of 30–54% [47,48].

### 2.2. In vivo DC strategies

A remarkable alternative approach was to deliver an Ag to DCs directly *in vivo* by chimeric proteins constituted of a specific Ab for a DC