Minireview: Optimization of Human Dendritic Cells for Antitumor Vaccination

Abstract

Dendritic cells are professional antigen presenting cells and provide a link between innate and adaptive immunity. Encounter with the antigen in the periphery primes dendritic cells to migrate to the lymph nodes, where they present antigens to naive B and T-cells for the induction of suitable immune response. Owing to their capacity to induce T-cell mediated cytotoxic responses in antigen-specific manner, dendritic cells have long been envisioned as suitable candidates for cancer immunotherapy.

Ex vivo generated, antigen-loaded DCs present a powerful cell-based immunization technique for the induction of specific antitumor immunity, and various DC-based vaccines are now in the clinical phase trials. In this mini review, we describe the existing methods to generate and activate clinical grade DCs for cancer immunotherapy.

Keywords: Immunotherapy; Dendritic cells; Vaccination; Cytokines; GM-CSF; Tumor

Mini Review

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Abbreviations: DCs: Dendritic Cells; APC: Antigen Presenting Cells; IL-12: Interleukin-12; SCF: Stem Cell Factor

Introduction

The immune system is essential protective machinery and is crucial for the survival of an organism. The cells of both innate and adaptive immune responses function in a concerted manner to endow the protection against both extrinsic and intrinsic pathogenic factors. Dendritic cells (DCs) are the professional antigen presenting cells (APC) of the immune system and provide a link between innate and adaptive immunity [1]. DCs are sparsely distributed in the periphery in their immature phenotype, which is highly specialized for antigen capture and processing. Pathogenic encounter activates immature DCs into mature APCs which migrate to lymph nodes to present antigens to naive B and T-cells for the induction of suitable immune response [2].

For the generation of a successful T-cell mediated immune response, the interaction between mature DCs and naive T-cells requires three signals:

a. Immunogenic peptide display in context of MHC molecules

b. Engagement of costimulatory molecules expressed on the surface of DC and T cell

c. Production of interleukin-12 (IL-12) for a polarized T cell response [2].

DCs have long been envisioned as suitable candidates for immunotherapy against various cancers and viral infections, owing to their property of efficient antigen capture, processing and its display in context of MHC molecules to stimulate both $CD4^+$ helper and $CD8^+$ cytotoxic T cell response to generate a long lasting immune response [3].

In addition to sense the presence of exogenous antigens, immune system is also able to recognize the tumor-associated antigens and eliminate the neoplastic cells-a process called immunosurveillance [4]. Tumor cells proliferate in an immunosuppressive microenvironment, which renders their efficient clearance by the immune system inefficient [5]. DCs, owing to their excellent capacity for antigen-presentation and T-cell stimulation, have been considered as potential candidates for immunotherapy. *Ex vivo* generated, antigen-loaded DCs present a powerful cell-based immunization technique for the induction of specific antitumor and antiviral immunity, and various DC-based vaccines are now in the clinical phase trials [6,7]. In a clinical setting, DCs intended for cancer vaccines can be generated from hematopoietic precursors or blood monocytes upon *in vitro* culture with cytokine combinations over a period of 2 to 7 days [8]. The crucial requirement for *ex vivo* generated DC lies in the optimum maturation protocols and antigen stimulation of DCs in order to stimulate potent $CD4^+$ and $CD8^+$ immune responses against tumor antigens [9].

Dendritic cell subtypes

DCs are highly polymorphic cells found both in circulation and periphery, where they constantly survey the tissues in the search of pathogens. Various subtypes of DCs have been described in both human and mice and are distributed in different anatomical locations to perform specialized functions, and influence both humoral and cell-based adaptive immune responses [10]. Two primary DC subtypes can be found in human blood: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). Further classification of circulating DC subsets is based on the expression of three surface markers: BDCA1 (CD1c), BDCA2 (CD303) and BDCA3 (CD141) [11]. $CD303^+$ pDCs are potent mediators of the antiviral responses due to their capacity to secrete enhanced levels of type-I interferons in response to virus infection [12]. $CD303^+$

pDCs contain intracellular stores of pre-synthesized MHC class-I molecules in the early endosomal compartments for peptide loading and immediate presentation to $CD8^+$ T cells to generate cytotoxic immune response [13]; and MHC class-II molecules in the late endosomal compartments to present the processed peptides to $CD4^+$ helper T cells [7]. In addition, virus-stimulated $CD303^+$ pDCs also activate plasma cells to secrete antibodies, by producing high levels of type-I interferons and IL-6 [12]. Thus, $CD303^+$ pDCs can control both cellular and humoral immune responses against viral pathogens.

$CD1C^+$ and $CD141^+$ DCs belong to myeloid lineage and participate in mediating antiviral immune responses by cross-presentation of viral antigens to $CD8^+$ T cells [14]. Human $CD141^+$ DCs have high capacity to capture and process exogenous antigen and presentation in context of MHC -class I to the naive $CD8^+$ Tc cells. $CD141^+$ DCs express XCR1 chemokine receptors in response to XCL1 chemokine secreted by NK cells and activated $CD8^+$ T cells, which guide their migration to the lymph nodes for the antigen presentation to naive T-cells [14]. Taking the specialized immunostimulatory function into account, $CD141^+$ DCs are good candidates for antitumor vaccines to induce robust antitumor cell-mediated immunity.

Human skin contains two subtypes of mDCs: epidermal Langerhans cells and dermal interstitial cells. Dermal DCs can be further subdivided into $CD1a^+$ and $CD14^+$ dermal DCs based on the expression of respective surface markers [15]. $CD14^+$ dermal DCs in humans participate in the control of humoral immunity by activating B cells, and may induce the differentiation of $CD4^+$ T_H cells into follicular T_H cells (T_{FH} cells) [16]. Langerhans cells are efficient in the capture of exogenous antigen in the skin and its cross presentation on MHC I to $CD8^+$ T cells, leading to their activation and differentiation into the effector cytotoxic T-lymphocytes (CTLs) against target cells, including tumor cell lines.

Over the last decade, several methods for *ex vivo* DC generation have been described to produce suitable DC subsets to engender effective tumor antigen-specific cytotoxic responses.

Sources of human DCs for vaccination studies

DCs comprise only a small fraction of total cellular population in the blood (0.1-1%) and are sparsely distributed in the circulation. Thus, obtaining DCs in numbers sufficient to be used for immunotherapy creates a challenge. *Ex vivo* generation and expansion from precursors is the most common method for obtaining DCs for vaccination. DC precursors can be isolated from various sources, including bone-marrow, cord blood and peripheral-blood mononuclear cells (PBMCs). In the mouse model, Inaba et al. [17] pioneered the method of *ex vivo* generation of DCs from bone-marrow precursors in response to GM-CSF [17]. DCs generated in this way displayed functional and phenotypic properties typical to their naturally occurring counterparts, including high expression of MHC class I and II molecules. The findings were extended to humans, as shown by Reid et al. [18], where *in vitro* cultures of $CD34^+$ human bone-marrow cells differentiated into mature DCs in the presence of GM-CSF and TNFα Reid et al. [18]. These results from studies using cytokine-directed bone-marrow cell differentiation confirmed that the $CD34^+$ compartment of the bone-marrow is an excellent source for the *ex vivo* generation of DCs intended for immunotherapy.

In addition to bone-marrow, $CD34^+$ stem cells are also present in human neonatal cord blood, and provide another potential source for obtaining hematopoietic precursors to develop DC for immunotherapy. *In vitro* cultures of enriched fractions of $CD34^+$ cells isolated from neonatal cord blood were able to differentiate into mature DCs in response to GM-CSF and TNFα [19,20]. A common $CD34^+$ progenitor might be responsible for the development of different DC subsets. For example, Caux et al. [21] showed that $CD34^+$ progenitors from human cord blood were able to generate DCs with both Langerhans cells (LCs) and dermal DC phenotypes, in response to different exposure times to GM-CSF and TNFα [21]. Furthermore, $CD34^+$ cord blood progenitors may retain the pleuripotency over cryopreservation, as reviving a culture with a cytokine mixture of GM-CSF, stem cell factor (SCF) and TNFα, was shown to induce the differentiation of mature DCs from the thawed pools of $CD34^+$ cord blood cells [22]. Recently, some studies have also explored the potential of pluripotent cells for their differentiation into DC populations upon culture in a cytokine milieu containing GM-CSF and IL-4. In this regard, both mouse embryonic cells [23] and human fibroblasts-derived induced pluripotent cells [24] have been used to produce DCs capable of antigen processing and stimulating T-cell responses.

One crucial factor is the ease of availability of the precursor cells, targeted for the *ex vivo* generation of DCs. While hematopoietic cells derived from bone-marrow, neonatal cord blood, or stem cells provide a choice for the undifferentiated cells that can be cultured to produce DCs, their availability is relatively limited. Blood monocytes are readily available in higher number than hematopoietic precursors obtained from other methods, and therefore, provide the most common method to produce DCs for cancer immunotherapy. Romani et al. [20] demonstrated that adult blood-derived monocytes cultured in the presence of GM-CSF and IL-4, successfully differentiate into immature DCs over a period of 5-7 days [20]. The combination of GM-CSF and IL-4 was further confirmed as an essential cytokine combination for directing the cultured monocytes for their differentiation into immature DC capable of antigen capture and presentation [25-27]. The final DC population generated from the myeloid precursors is dictated by the cytokine milieu in which they mature. Various studies have explained the potential of human blood monocytes for their differentiation into mature DCs subtypes based on the cytokines used for the final maturation [28-31]. A recent study described the cytotoxic role of human monocyte-derived DC subset capable of killing tumor cells and stimulating effective CTL responses following LPS activation [32].

Different sources have been described for the isolation of DC precursors; however, for the clinical purposes, a rapid and cost-effective isolation would be a preferred choice to obtain DC precursors. In this context, leukapheresis is the current method of choice to recover monocytes as DC precursors for generation of antitumor vaccines in preclinical studies as described in several reports [33-40].

Cytokine cocktails for DC activation

Research over the last decade indicates that *ex vivo* generated DCs are efficient stimulators of T-cell mediated response against tumor antigens. The potential of APC-based cancer

immunotherapy is evident from the recent successful phase III clinical trials against metastatic prostate cancer, which resulted in overall extended median survival [41].

The combination of both cytokines and TLR agonists is essential for the overall maturation of *ex vivo* generated DCs to stimulate a robust T cell mediated anticancer response [9]. An ideal DC vaccine- must encompass the complete spectrum of DC responses including:

a. Efficient antigen presentation and expression of co-stimulatory molecules for T-cell stimulation

b. Lymph node migratory ability based on responsiveness to chemokines

c. Production of IL-12 for the induction of T_H-1 polarized immune response for the expansion of $CD4^+$ T helper cells and $CD8^+$ cytotoxic T cells against tumor antigens [6].

Various cytokine-based maturation protocols have been developed to activate *ex vivo* generated DCs from different sources. The so called classic cytokine cocktail consists of TNF-α, IL-1β, IL-6 and prostaglandin E2 (PGE-2), was first proposed by Jonuleit and coworkers [42], and has been used by several groups as a 'gold standard' to generate DCs intended for clinical use (sDC). However, a phase III clinical using monocyte derived sDC matured in the cytokine cocktail (TNF-α/IL-1β/IL-6/PGE2) has failed to show significant efficacy when compared to dacarbazine chemotherapy [43]. The limitation of sDC vaccination to generate suitable anticancer immunity underlies the importance of the constituents of the maturation cytokine cocktail involved. PGE2 is a powerful immuno-modulator and has been shown to enhance migratory potential in mature DCs and their responsiveness to chemokines secreted by lymph nodes [44]. However, evidence also supports an immunosuppressive role of PGE2 in context of tumor environment, where PGE2 might promote the down-regulation of IL-12p70 shifting the immune response to TH-2 type, and differentiation of DCs to secrete the immunosuppressive cytokine IL-10 [45]. In this context, it has been shown that sDC vaccination was capable of increasing regulatory T cell levels in cancer patients [46].

To overcome the limitation of sDC and to instruct the development of IL-12 producing *ex vivo* generated DCs; a new maturation protocol including IFN-γ was suggested to promote DC differentiation into stable, type 1 polarized effector population [47]. Furthermore, Mailliard et al [48]. developed a serum free DC maturation cocktail containing TNFα/IL-1β/IFN-γ/IFN-α and a TLR-3 ligand polyinosinic: polycytidylic acid (Poly I: C), to generate α-type1polarized DCs (α-1DCs) capable of producing IL-12p70 and expanding CTLs against tumor antigens [48]. The α-1DC cytokine protocol was able to successfully promote IL-12p70 secreting DCs in high numbers with optimum migratory potential, and potent stimulation of anticancer CTL responses *in vitro* [49]. Recently, phase I/II clinical trials using α-1DC-based vaccination against malignant glioma has shown favorable results [33,50], but further testing is required to establish α-1DCs for the candidate vaccines for other malignancies.

Indeed, several groups have described the combination of cytokine cocktails with TLR agonists as a suitable maturation protocol to achieve mature DC population capable of producing IL-12p70 to activate a T_H-1 polarized immune response. More frequently used molecules include TLR-3 ligand Poly I:C [49,51,52], TLR-4 ligand lipopolysaccharide (LPS) [53,54] and/or monophosphoryl lipid A (MPL-A) [55,56]. Recently, a MPL-A/IFN-γ based α type-1 DC-maturation cocktail has been proposed to produce activated DCs producing higher levels of IL-12p70 but with lower migratory capacity than sDC [55]. Furthermore, MPL-A/ IFN-γ maturation protocol also resulted in the induction of superior $CD8^+$ CTL-mediated anticancer responses compared to sDC [56]. More recently, a comparative study assessed various existing cytokine protocols including sDC (TNF-α/IL-1β/IL-6/PGE2), α-1DC (TNFα/IL-1β/IFN-γ/IFN-α), MPL-A/IFN-γ α-1DC and a combination of MPL-A/IFN-γ and PGE2, for the potential to generate clinical-grade DCs for immunotherapy [57]. In this study it was concluded that α-1DC and MPL-A/IFN-γ matured α-1DC remained the suitable options of choice for immunotherapy, since the mixture of MPL-A/IFN-γ and PGE2 caused elevated expression of inhibitory molecules compared with sDCs [57].

Three days vs. 7 days DC differentiation protocols

Standard protocols for the the generation of *ex vivo* immature DC require 6-7 days of culture in the presence of GM-CSF and IL-4 [20-25,49-56], followed by maturation with a pro-inflammatory cytokine cocktails for further 1-2 days. The rationale for the longer protocols was to generate immature DCs in higher number with full potential for T cell-stimulation, while retaining the capability to capture antigen, high expression of MHC class-I and II, and co-stimulatory molecules. However, rapid methods to generate clinical grade immature DCs over shorter incubation times have been proposed. For example, Dauer et al. [58] introduced a method to generate mature DCs over a period of 48 h.

To accomplish this, human monocytes are grown in the presence of GM-CSF and IL-4 for 24 h follwed by maturation in a cytokine cocktail (TNF-α/IL-1β/IL-6/PGE2) for another 24h [58]. The so called 'fast-DCs' obtained by this protocol were functionally similar to that generated by the standard 7-day protocols, expressed mature DC surface markers CD83, CD86 and CD80, were able to interact with CCR7 agonists. These DCs produced IL-12p70 when stimulated with CD40L in the presence of IFN-γ, and where capable of stimulating T_H-1 polarized immune response [58,59]. The clinical efficacy of the rapid DC-maturation protocols to induce tumor antigen-specific $CD8^+$ cytotoxic response was found to be favorable [54], suggesting the potential of fast DCs as an alternative to the conventional methods. Furthermore, a clinical trial targeting HER-2/neu-overexpressing breast carcinoma by DCs matured in the presence of GM-CSF, IFN-γ and LPS for about 2 days, caused tumor regression through the induction of HER-2/neu specific $CD4^+$ and $CD8^+$ T cell responses. Although, monocyte derived fast-DCs may appear to be a superior method of choice due to their complete T-cell immuno-stimulatory potential, more vaccination studies are required to address to the possible limitations involved.

Conclusion

DCs are excellent candidates for cellular vaccines against cancer due to their capacity to activate antigen-specific T cells. Due to their scarcity in circulation, methods are needed to differentiate and activate DCs *ex vivo*. Most comminly, DCs are differentiated from blood monocytes and loaded with tumor antigen before re-

introduction to the patient. Although, a one-week differentiation process in the presence of cytokines has been the standard procedure, recently shorter differentiation times are proposed. In addition, over the years different methods of activating DCs *in vitro* have been proposed. Latest studies show the reliance of toll-like receptor ligation plus interferon treatments in order to achieve cells that have high presentation capacity *in vivo*.

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