

# Dendritic cell therapy: a proactive approach against cancer immunotherapy

## Abstract

Cancer is one of the biggest challenges of modern medicine. Though there are different therapies in general like chemotherapy, radiation and surgery. Further, cancer is highly heterogeneous. Two persons, who suffer from the same type of cancer, can show totally different variations and ways of progress. That makes it hard to treat the cancer and just for that reason oncology is one field where personalized medicine is advancing extremely fast. The more that treatments can be tailored to the single patient, the higher are the chances of treating that patient's cancer effectively. Personalization creating a special tailored therapy for everybody wasn't possible before. The goal is to allow patients a pain free time at least for a while, to improve the quality of life and to dam up the growth of the tumor. To reach that goal, now researchers concentrate on the power of the human immune system and its improvement to treat cancers with immunotherapy. Dendritic cells (DCs) play a central role in the initiation and regulation of innate and adaptive immune responses and have increasingly been applied as vaccines for cancer patients. *In vitro* generation of dendritic cells from monocytes and antigen loading into immature dendritic cells to proper maturation, with the aim of imprinting different DC functions that are essential for their subsequent induction of a T cell-mediated immune response against tumor.

**Keywords:** dendritic cell, immunotherapy, MHC, lymph nodes, antigen uptake, cross presentation, mucosa, chemical barriers

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**Abbreviations:** DC, dendritic cell; MHC, major histocompatibility complex; TCR, t cell receptor; LNs, lymph nodes; CTLA-4, cytotoxic t lymphocyte antigen; IFN, interferon; IL, interleukin; DC-SIGN, dendritic cell-specific intracellular adhesion molecule 3 grabbing non-integrin; PGE2, prostaglandins; GM-CSF, granulate macrophage colony stimulating factor

## Introduction

The primary body defense mechanism is the immune system. Innate or natural immunity is the first line of defense and a type of general protection, including physical barriers of the body (e.g. skin, mucosa), chemical barriers (e.g. secretions and enzymes), and other soluble factors (e.g. cytokines, chemokine and the complement system). It also includes innate leukocytes such as natural killer (NK) cells, mast cells, and phagocytic cells (e.g. monocytes, dendritic cells (DCs), macrophages and neutrophils).<sup>1</sup> Among the phagocytes, DCs have powerful key functions in the immune system. Among the innate leukocytes, T Lymphocytes mediate cellular immunity and B lymphocyte mediate humoral immunity. T lymphocytes need presentation of antigen in a processed form to activate their killing. Presentation of antigen is carried out by Antigen presenting cells. Among the various antigens presenting cell dendritic cells are most potent and were first recognized for their unique dendritic morphology in 1973 by Steinman and Cohn. In 2011 Steinman got the Nobel Prize for this discovery. Dendritic cells assume great importance as they are adapted to process antigen material and present it on the cell surface for recognition by other cells of the immune system.<sup>2</sup> The processes of the dendritic cells embrace other cells of the immune system and with their constant movement deliver antigens and other signals that

are key to initiate immune responses. This review focuses on the cancer immunotherapy by the use of dendritic cells to generate T-cell mediated active anti-tumor immune responses.

## Dendritic cell vaccine

Vaccines act through dendritic cells (DCs) that induce, regulate and maintain T-cell immunity. Therefore, understanding the DC system is essential for the design of novel cancer vaccines with improved clinical efficacy.<sup>3</sup> *Ex vivo*-generated DCs have been used as therapeutic vaccines in patients with metastatic cancer for over a decade.<sup>4</sup> Importantly, a number of studies have shown that DCs can expand in patients T cells specific for non-mutated self-proteins that are over-expressed in cancer.<sup>5</sup> The DCs vaccine is prepared by either using bone marrow cells (CD34+) or peripheral blood monocytes (CD14+), cells are separated by density gradient centrifugation using Ficoll Hypaque or by magnetic beads. Cells are incubated with GM-CSF and IL-4 cytokine, after several days cells differentiated into immature dendritic cells, immature dendritic cells in the presence of maturation stimuli like Poly I: C, KLH, CD40L, FLT3 TNF- $\alpha$ , they uptake the antigen and become mature.<sup>6-10</sup> The surface marker characterizations very important to sort the cells, before administration of mature DCs to the patient vaccine should go under functional assessment like extracellular and intracellular CD marker (CD83, 80, 86, CCR7) expression for DC migration and activation of naive T cells with a strict quality control process to identify any endotoxin and mycoplasma contamination.<sup>11</sup> This, together with key progresses in tumor immunology and unraveling molecular pathways regulating T-cell immunity (for example, CTLA-4 and PD1, will allow us to refine and improve the immunogenicity and clinical efficacy of DC vaccination.<sup>12,13</sup>

## Antigen uptake, migration and cross presentation

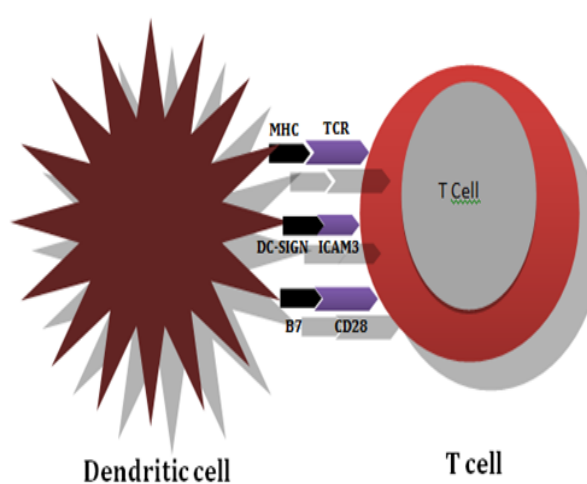
DCs capture the antigens processed them in peripheral tissues and migrate to secondary lymphoid organs, where they may provide cells of the adaptive, also called specific immunity, such as T and B lymphocytes with pathogen-related information from the affected tissue and thereby activate suitable antigen specific immune responses.<sup>14</sup> Dendritic cells are professional antigen-presenting cells (APC) capable of activating T cell responses against tumour antigens. These antigens are subsequently processed into small peptides as the DCs mature and moves towards the draining secondary lymphoid organs to antigen presentation.<sup>15</sup>

Normally, this is achieved by presenting a class of protein such as MHC class I which stimulates CD8<sup>+</sup> cytotoxic T cells and the antigen or protein is taken up by phagocytosis or receptor mediated endocytosis into the cytosol of the T-cell.<sup>16,17</sup> The antigens are further degraded in the cytosol via proteasome and enter the endoplasmic reticulum where peptides bind to newly synthesized MHC class I molecules for presentation on the cell surface. In case of MHC class II presentation, CD4<sup>+</sup> T helper cells are stimulated, and antigen is taken up by phagocytosis or receptor-mediated endocytosis to endosomes

where some proteolysis occurs. The peptides enter a vesicle containing MHC class II where they bind and are transported to the cell surface.<sup>18</sup>

Immature DCs expressing modest amounts of MHC and co-stimulatory molecules efficiently capture antigens through pinocytosis of receptor mediated endocytosis. DCs developmentally regulate the expression of chemokine receptors (CCR7) to facilitate their migration from the peripheral issue to regional LNs. High densities of CCR7, receptor for CCL19 and CCL21 are expressed on mature DCs but not immature DCs, whereas CCL3, a ligand for CCR1 and CCR5, is active on immature DCs but not mature DCs.<sup>19–21</sup> Expression of CCR7 is not sufficient for DC migration, some factors present at inflammatory sites, such as PGE2 and HMGB1 protein, have been shown to induce migration of mature DCs. PGE2 increases CCR7 sensitivity to CCL19/CCL21 signaling.<sup>22</sup>

Antigen presentation is crucial for the initiation and maintenance of T-cell-mediated immune responses. Dendritic cells cross presents the antigen that activates both CD4<sup>+</sup> and CD8<sup>+</sup> T cells.<sup>23</sup> The antigenic protein expressed by dendritic cells includes costimulatory molecules such as CD80 and CD86 that bind CD28 on T cells, MHC class I and class II binds to the TCR receptor, whereas CD40 and DC-SIGN (CD209) bind with the CD40L/CD154 and ICAM3 on T cells respectively (Figure 1).



**Figure 1** Antigen presentation and T cell activation. On encountering a dendritic cell presenting a tumor derived antigen epitope through MHC to TCR, DC-SIGN to ICAM3 and B7 co-stimulatory molecules (CD80, CD86) to CD28 receptor.

## T cell activation and immune response

This process is critical for interaction between DCs and T cells in the T cell area, which initiates adaptive immunity. Naïve T cells first enter in the lymph nodes by their migratory property and they made contact with antigen bearing dendritic cells. There are three distinct phase for T cell activation in LNs. The phase I period around 8h, in this phase T cell starts expressing activation marker such as CD44 and CD69. The duration of phase II is 8–20h, in this phase T cells form a contact with antigen bearing dendritic cells and overexpression of CD25 marker, IL-2 receptor and they start secretion of IFN- $\gamma$  and IL-2 cytokines.<sup>24–26</sup> In the phase III, T cells start their migration from LNs to blood circulation and start their proliferation. After activation, they start to differentiate into different types of T cells.<sup>27</sup> Cytokines released from the DCs or surrounding cells that initiate separate but complementary signaling cascade that enhances the induction and amplification of the antigen specific T cells. CD4 T cells can

subdivided into Th1, Th2, Th17 and Treg subsets on the basis their pattern of cytokine production. Protective Th1 related cytokines (IL-2, IFN- $\gamma$ ) are involved in cellular immune responses.<sup>28</sup> Whereas, Th2 related cytokines (IL-4 and IL-10) are associated with the humoral immunity and anti-inflammatory properties. Th17 cytokine (IL-17) is identified as a cell that recruited neutrophils and macrophage to participate and amplify the inflammatory reaction.<sup>29,30</sup>

## Conclusion

Many studies have been carried out on the function of DC in different arms of the immune response. It is widely accepted that DCs are the most educated and potent professional antigen presenting cells for priming naïve T cells and activate antigen-specific T cell response. The amount of antigen and its proper loading is the main concern for effective dendritic cell immunotherapy to get the proper immune response from the T cells. The receptor mediated endocytosis by targeting different endocytic receptor is a good approach to

internalization of the antigen. The nano-delivery of antigen will be a promising and proactive approach to increase the efficacy of dendritic cell vaccine for cancer immunotherapy.

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## Conflict of interest

The author declares no conflict of interest.

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