Reviews on the Role of Dendritic Cells in Induction and Regulation of Immunity

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Abstracts: Dendritic cells (DCs) are the most potent professional antigen presenting cells and they arise from both the myeloid and lymphoid lineages. The review is made to overview the role of dendritic cells in controlling immunity. Dendritic cells in the periphery capture and process antigens, express lymphocyte co-stimulatory molecules, migrate to lymphoid organs and secrete cytokines to initiate immune responses. They not only activate lymphocytes, they also tolerate T cells to antigens that are innate to the body (self-antigens), thereby minimizing autoimmune reactions. Tissue dendritic cells phenotypes that do have a function in primary defense will be activated to mature after encountering and ingesting of antigens. Up on activation they express major histocompatibility complex and co-stimulatory molecules, secrete different cytokines and migrate to the secondary lymphoid organ for initiation of adaptive immune response. The dendritic cells play a central role in control and regulation of immune response and immune tolerance. They have also been shown to be important target of designing of effective vaccines and provision of immunotherapy. Hence, continued research on the complexities of dendritic cells biology, as well as immunological functions should be encouraged.

Key words: Dendritic cells • Antigen presenting cells • Immunotherapy • Autoimmune

INTRODUCTION

The living animal body contains all the components necessary to sustain its life. As a result, animal tissues are extremely attractive to varies microorganisms. However, the tissues of living, healthy animals are resistant to microbial invasions due to the existence of difference mechanisms of immunity [1]. Pluripotent hemopoietic stem cell gives rise to the lymphoid progenitor and myeloid progenitor [2]. The immune response to the infection depends on the interaction innate and adaptive immune system [3].

The induction of adaptive immune response begins when a pathogen is ingested by antigen-presenting cells (APCs) particularly immature dendritic cells (iDCs). It is obvious that, none of the subset of immune system functions in isolate. Therefore APCs create a critical interaction between the innate and adaptive immune system. Dendritic cells (DCs) create this bridge by phagocytizing, processing and presenting the antigen (Ag) to recirculating naïve T cells in secondary lymphoid organs. Among the professional APC, DCs are the most potent APCs characterized by high ability to present antigen and play a critical role in triggering Ag specific T cell response. The activated T cells proliferate and differentiate into their effector T cells that are responsible for cell mediated immune response and regulatory activities [3].

Dendritic cells control the induction of T regulatory (T reg) cell and immune tolerance, acting as important adjuvant for effective vaccine development and also now a day, progress in manipulation of DCs revealed their importance in immunotherapy for the treatment of various diseases, such as cancer, autoimmune disease and treatment for organ transplantation. Once a neglected cell type, DCs can now be readily obtained in sufficient quantities to allow molecular and biological analysis. With knowledge comes the realization that these cells are a powerful tool for manipulating the immune system. Nevertheless sufficient document in exploitation of DCs function particularly in developing countries are still urgently required [4].

Therefore the Objectives of this Seminar Paper Are:

- To review the role of dendritic cells in controlling immunity.
- To give overview on consequence of immune tolerance and immunotherapy for monitoring immune disorder.

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Fig. 1: Dendritic cells arise from both the myeloid and lymphoid lineages.
Source: [1]

The Biology of Dendritic Cells

Dendritic cell Development: Dendritic cells (DCs) originally identified by Steinman and his colleagues [5] represent the pacemakers of the immune response. DC acquired its name because it is covered with long membrane extensions that resemble the dendrites of nerve cells. There are many types of DC, although most mature DCs have the same major function, the presentation of antigen to T\(_{\text{H}}\) cells. Four types of dendritic cells are known: Langerhans cells, interstitial dendritic cells, myeloid dendritic cells and lymphoid dendritic cells. Each arises from hematopoietic stem cells via different pathways and in different locations [6]. By contrast, follicular dendritic cells (FDC) are probably of mesenchymal rather than hematopoietic origin and do not express M\(_{\text{H}}\)C class II, but are so named because they are located in lymphoid follicles and have long dendritic processes [2].

Maturation of Dendritic Cells: In most tissues, DCs are present in a so-called ‘immature’ state and are unable to stimulate T cells. Although these DCs lack the requisite accessory signals for T cell activation, such as CD40, CD80, CD86, they are extremely well equipped to capture antigen in peripheral sites [7]. Immature DCs (iDCs) have several features that allow them to capture Antigen. Firstly, they can take up particles and microbes by phagocytosis. Secondly, they can form large pinocytic vesicles in which extracellular fluid and solutes are sampled; a process called macropinocytosis. And thirdly, they express receptors that mediate endocytosis, including lectin receptors like the macrophage mannose receptor as well as FC receptors [8]. Once DCs have captured Ags, which also provide signal for maturation, it is clear that the maturation of DCs is crucial for the initiation of immunity. This process is characterized by reduced Ag-capture capacity and increased surface expression of M\(_{\text{H}}\)C and co-stimulatory molecules that interact with receptors on T cells to enhance adhesion and signaling (Co-stimulation); for example, B7-1/CD80, B7-2/CD86 and CD83 [9]. These co-stimulatory molecules bind the CD28 molecules on T lymphocytes. Expression of the co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) on the DCs are essential for the effective activation of T lymphocytes and for IL-2 production [10].

The Role of Dendritic Cells in Induction and Regulation of Immunity

Role of Dendritic Cell in Innate Immunity: Natural killer cells activation: Natural killer (NK) cells are lymphocytes of the innate immune system that potently contribute to infection eradication. NK cells exert their activity by producing high amount of IFN-\(\gamma\), that activates a strong inflammatory response and by having direct cytotoxic function. The functions of NK cells are regulated by a balance of activating and inhibiting signals. These signals are transmitted by inhibitory receptors, which bind M\(_{\text{H}}\)C class I molecules and activating receptors, which bind ligands on tumors and pathogen infected cells. Other than surface receptors, NK cell activated due to response to DCs derived cytokines, such as IL-2, IL-12, IL-18 and type 1 IFNs, they elicits IFN-\(\gamma\) production from NK cells [11, 12]. Role for DC in activation of NK cells has been described both in mouse and in man. The first place of
contact between NK cell and DC could be the site of infection where both resident and recruited DC would be able to activate NK cells [13]. Activated DC can migrate to the draining lymph nodes where they can probably stimulate resident and newly recruited NK cells. Indeed, in the T cell area of human lymph nodes, NK cells have been described to localize with DC. Moreover, it has been found that a subpopulation of NK cells enriched in lymph nodes is able to respond to DC derived stimuli such as IL-12, that elicits IFNγ production by NK cells and membrane bound IL-15, that induces NK cell proliferation [11].

Two pathways for DC-mediated NK cell activation have been described in mouse, one dependent on IL-4 and the other one dependent on microbial stimuli. DC differentiated in presence of IL-4 are strong producers of IL-12 following activation with inflammatory stimuli. This cytokine has been shown to be required to obtain optimal IFNγ production by NK cells. In the context of viral infections, another DC-derived cytokine able to promote efficient IFNγ production by NK cells is IL-18 [14].

In absence of DC exposure to IL-4 and in response to bacterial challenges or to bacterial cell products, DC-derived IL-2 plays a major role in eliciting IFNγ production by NK cells. The biological relevance of NK cell activation mediated by DC during bacterial infections resides mainly in the secretion of IFNγ, which activate macrophage for phagocytosis and lysis [12].

**Phagocytosis: Primary Defense:** Dendritic cells are involved in primary defense through their phagocytic activity to foreign antigens. This phagocytosis by DCs may be relegated to certain stage of their life history [1]. Tissue iDC phenotypes that are normally associated with low level of MHC proteins and lack co-stimulatory B7 molecules but they have ability to recognize and ingest pathogens through receptors that recognize features common to many microbial surfaces and are very active in taking up antigen by phagocytosis using receptors such as C-typelectin (Mannose receptor) and FC receptors [2].

But the absolute level of phagocytic activity of DCs is relatively lower than professional scavengers like macrophages. Typical immature DCs are the langerhans’ cell of the skin. These are actively phagocytic and contain large granules, known as birbeck granules, which is likely to be a type of phagosome. An infection triggers the maturation and migration of DCs to secondary lymphoid organs. Here they lose the ability to phagocytize antigen but they utilize phagocytosis, endocytosis and macropinocytosis primarly as a presentation mechanisms [15].

**Role of Dendritic Cell in Acquired Immunity**

**Role in Priming T Lymphocytes:** Mature circulating naïve T cells that have not yet encountered their specific antigens, require encountering specific antigens to participate in an adaptive immune response. This induction enables them to proliferate and differentiate in to cells that can contribute to the removal of antigen. Up on activation they act very rapidly on their target cells or their specific antigens and thus they are called effector T cells. Effector T cells detect peptide antigen derived from different type of pathogen [1]. Peptide from intracellular pathogen are carried to cell surface by MHC class I molecules and presented to CD8+ T cells that differentiate in to effector cytokotoxic T cells, while peptide antigen from pathogen multiplying in intracellular vesicle and those of ingested extracellular bacteria and toxin are carried to the cell surface by MHC class II molecules and presented to CD4+ T cells. These cells will differentiate in to two types of effectors CD4+ T cells namely T_{h1} and T_{h2} [2].

DCs play a central role in directing the differentiation of T cells in to T_{h1} and T_{h2}, during microbial infections. iDCs are able to recognize and ingest these pathogens and activated as a part of innate immune response. The ingested pathogens induce their migration to regional lymph node, where they synthesize new MHC molecules that present peptide at high levels and also express co-stimulatory molecules that stimulate naïve T cells [16].

Mature DCs instruct T cell to induce an efficient primary immune response and establish immunological memory. During this condition DCs and T cells interact through the formation of immunological synapse [13]. In this synapse, T cell receptors and co-stimulatory molecules congregate in a central area surrounded by a rising of adhesive molecule. Sustained signal via this synapse interaction is required for T cell to enter the first cell division cycle. Especially CD4+ T cells require more than 20 hours of continuous stimulation. Therefore stability and duration of synapse will determine the T cell function [17].

There are three types of activation signals. The first activation signal is signal for antigen specificity generated by the interaction between MHC-peptide-TCR, either within CD4+ T cell and MHC-II or with CD8+ T cell and MHC-I. The second signal, essential for activation is based on the interaction between CD80/86 on DCs and CD28 on T cells. Without the second signal, the T cell become inactivated and develops energy and tolerance to the respective antigen. Secretion or lack of secretion of factors by DCs, particularly IL-12, are instrumental in the final differentiation of T cells, in to T_{h1} and T_{h2}, respectively (Signal 3) [13].
Dendritic Cells Regulate B Cell: Dendritic cells, famous for their T-cell-stimulatory properties, are now known to have major effects on B-cell growth and immunoglobulin secretion. B cells and DCs are both APCs and both are essential for antibody responses but for entirely different reasons. DCs activate and expand T-helper cells, which in turn induce B-cell growth and antibody production. Naive B cells respond uniquely to the interstitial DC [18]. By secretion of soluble factors including IL-12, DCs stimulate the production of antibodies directly and the proliferation of B cells that have been stimulated by CD40L on activated T cells. DCs also orchestrate immunoglobulin class-switching of T-cell activated B cells: IL-10 and TGF-β can induce secretion of IgA. This cytokine especially TGF-β is primarily responsible for IgM to IgA class switch[19].

Follicular dendritic cells (FDCs) directly sustain the viability, growth and differentiation of activated B cells. They also organize the primary B-cell follicles. FDCs differ from ordinary DCs: they are not bone-marrow-derived, they lack the leukocyte marker CD45 and they display a unique set of molecules at their surface, including all known complement receptors. With their receptors for complement and FC, FDCs capture antibody–antigen complexes and display whole complexes, rather than processed antigens, at their surface for long periods [20]. FDCs are abundantly present within antigen-stimulated B-cell areas. There, proliferating B cells undergo somatic mutation, after which they stop dividing and wait to be triggered by an immune complex on FDCs. B cells that recognize an immune complex with high affinity process the antigen and present it as peptide–MHC complexes to antigen specific T cells. The T–B-cell interactions ensure the survival of these high-affinity B cells, while the non-stimulated low-affinity B cells apoptosis and phagocytosed by macrophages [21].

Antigen Processing and Presentation: The foreign antigens that trigger an immune response are of two distinct types. The first type of foreign material is made within the infected target cells of the body and appears as pathogen induced new proteins called endogenous antigens. These antigens have been shown to bind to MHC class I molecule and presented to cytotoxic T cells [1]. The second foreign antigens are either invading organisms like bacteria or those materials found free in the circulation for a time. These foreign materials are called exogenous antigens. These antigens are known to be processed by specialized professional antigen-processing cells, such as Macrophage, DCs or B cells [13].

The type of APCs employed probably depends on the nature of the antigens, the route by which the antigens enter the body and presence of previous exposure. DCs are unique among all APCs in adult immune system in many critical ways. They express high levels of both class II MHC molecules and members of the co-stimulatory B7 family. For this reason, they are more potent antigen-presenting cells than macrophages and B cells, both of which need to be activated before they can function as antigen-presenting cells. Unlike macrophage or B cells, DCs primary function appears to be antigen presentation [22].

Antigen processing by macrophage is inefficient, since much of the endocytized antigen is destroyed by lysosomal proteases. However DCs play a central role in efficient presentation of antigens to T lymphocytes and controlling Th1 versus Th2 differentiation during microbial infection [23]. DCs also do have unique distribution with in lymphoid organs, accumulating in regions where macrophage and B cells are generally excluded. DCs are restricted to the area where naïve T cells reside [24].
Immature Dcs are specialized in antigen capture, then process antigens via different pathways such as: Macropinocytosis where fluid from extracellular milieu is taken up into pinocytic vesicles and antigen is concentrated by expelling excess water. Endocytosis via lectin receptors, FCR and complement receptors (CR3) can mediate efficient internalization of immune complexes of bacteria. Phagocytosis of apoptotic and necrotic cell fragment, TLRs in pathogen recognition including LPS, lipothaicoic acid and lipoprotein [25].

After antigen uptake, DCs rapidly migrate to the secondary lymphoid organs. During this migration, they undergo a maturation process which is characterized by down regulation of the capacity to capture antigen (phagocytosis and endocytosis) and up regulation of antigen processing and presentation, expression of co-stimulatory molecules and DCs morphology [22].

In addition to the above distinct antigen handing and homing properties, DCs exhibit a variety of other features that greatly enhance their capacity as APCs. Among these are exceptionally high levels of MHC-II and co-stimulatory molecules, certainly as compared to macrophage in most tissues. DCs also express CD86 fivefold higher density than B cells. In addition, the extensive fold and dendritic extension, characteristic of DCs enables them to form close contact with multiple T cells simultaneously [26].

Induction of immune tolerance and t regulatory cells: Tolerance is the inability of the immune system to respond to specific antigens. The induction of T reg cells and tolerance is essential for maintenance of immune homeostasis and for the prevention of autoimmune disease. To induce tolerance, the immune system uses several mechanisms, including the deletion of auto reactive T cells, the induction of energy and active suppression of auto immune response [27].

Immune tolerance has two mechanisms (Central and peripheral tolerance) that control and maintain by DCs. Central tolerance occurs in the thymus for T cells and the bone marrow for B cells. The primary mechanism for central tolerance in T cells is the induction of T cell apoptosis. DCs are found in abundance in the thymus, where newly produced T cells are educated to become functional CD4+T cells and CD8+T cells and undergo selection to eliminate immunity against self cells. Low affinity reactive T cells are positively selected and allowed to survive and reach the periphery. T cells that respond to DCs carrying self-peptides are destroyed in the thymus by negative selection. This process involves T cells which recognize MHC/peptides with high avidity [27].

However, many self antigens may not get access to the thymus since they need for peripheral tolerance, which occur in the lymphoid organs. The mechanisms of peripheral tolerance include T cell death, anergy (Unresponsiveness) and active suppression by T reg cells. DCs could contribute by inducing apoptosis in T cells and by producing IL-10 and TNF-β; a cytokine that stimulates T cells and induces T reg cells [17].
Dendritic Cells Serve as Important for Effective Vaccine Development: Due to the ability of DCs to regulate immune responses, much effort has been put in the generation of DC-based therapies for the treatment of various diseases, such as cancer and autoimmune disease, as well as treatment for organ transplantation. Numerous studies in mice showed that DCs loaded with tumor antigens are able to induce protective antitumor response and produce significant therapeutic immunity to tumors [29].

Furthermore, exploitation of the potential adjuvant ability of in vitro antigen loaded DCs will be a powerful and efficient approach for promotion of anti-tumor immunity and this property of DCs can also be used in microbial vaccines as whole [30]. Several requirements can be defined for the generation of suitable DCs for vaccination such as: Expanding DC number, Concurrent activation and matured of expanded DCs that can express the desired co-stimulatory receptors and produce the appropriate cytokines and chemokines in order to effectively activate the T-cell response, Prophylactic use of DCs and Reinforcing Dcs antigen delivery and presentation. Each of these requirements, needed for successful DC vaccines [31].

In spite of the above facts, when tested, DCs can be superior and safe than other vaccination strategies. The most popular way to generate DC vaccine is to culture blood monocyte with GM-CSF and IL-4, which yield a uniform population of iDCs, followed by IFN-γ, then; specific Ag exposure also resulted in a high IL-12 production upon interaction with T cell. Maturing Dcs with TNF-α and cytokines, such as IL-1 and IL-6, leads to efficient upregulation of co-stimulatory molecules, which are indicative of a mature DC [30].

For immunotherapy applications, DCs would ideally traffic directly to a lymph node to interact with T-cells upon transfer into the patient. Use of the same maturation agents leads to efficient upregulation of the chemokine receptors, CCR7 and CCR4; two ligands for CCR7, namely CCL19 and CCL21, are known to be expressed throughout the lymphatic system [32]. Furthermore, CCR7 and CCR4 are known to also be expressed on naive T cells, further supporting the co-localization of mature DCs and naive T cells to allow for their interaction. Additionally, CCR7 signaling is known to support DC survival, dendrite process formation and antigen uptake, leading to more efficient T cell responses [33].

To apply DCs for immunotherapy of malignancies by introduce tumor antigen ex-vivo into DCs derived from peripheral blood or bone marrow, so that the engineered DCs were inoculated into the patient as a vaccine to present the tumor antigens to host T cell. IL-12 which strongly promotes the differentiation of T\(_{1}\) cells, enhances IFN-γ and granzyme production, prolongs T-cell survival and enhances immune recognition of tumor antigen-expressing cells [28]. T\(_{1}\) cells involved in antitumor responses by secretion of IFN-γ. IFN-γ used to control the growth or eliminate the tumors, notably the recruitment and activation of cells of the innate immune system and enhancing the production of anti-tumor chemokines [32].

Control of viral infection in vivo requires a rapid and efficient cytotoxic T lymphocyte response. In preliminary investigation on therapeutic DC based vaccine, 18 chronically HIV-1 infected and untreated individuals showing stable viral loads at least for 6 months were immunized with autologous monocyte derived DC loaded with autologous aldrithiol-2-inactivated HIV-1. Plasma viral load levels where decreased by 80% over the first 112 day following immunization [32].

Fig. 4: Dendritic cells serve as vaccine development.
Source: [28]
Prolonged suppression viral load of more than 90% was seen in 8 individuals for the last 1 year. The suppression of viral load was positively correlated with HIV-1 specific IL-2 or IFN-γ expressing CD4+ T cells and with HIV-1 gag specific perforin expressing CD8+ effector cells, suggesting that a robust virus-specific CD4+ T,1 response is required for inducing and maintaining virus specific CD8+ effector to contain HIV-1 in vivo. The results suggest that inactivated whole virus pulsed DC vaccines could be a promising strategy for treating people with chronic HIV-1 infection [23].

Organ transplantation is the main alternative to the loss of vital organ function from various diseases. However, to avoid graft rejection, transplant patients are treated with immunosuppressive drugs that have adverse side effects. A new emerging approach to reduce the administration of immunosuppressive drugs is to co-treat patients with cell therapy using regulatory cells. Tolerogenic DC (TolDC) therapy appears to be a promising strategy for the treatment of autoimmune diseases and transplantation [34].

Several protocols have been described for the generation of human TolDC. In these studies, TolDC have been derived from monocytes using the cytokines GM-CSF and IL-4. However, as described for tolerogenic bone marrow-derived DC in animal models, different drugs or cytokines could be added to GM-CSF/IL-4 culture to manipulate human DC in vitro, to obtain TolDC with specific features [35]. TolDC can be generated with vitamin D3 (VitD3). VitD3-treated DC has the properties of tolerogenic DC or generation of VitD3-TolDC together with dexamethasone (Dex) in order to increase their tolerogenic potential; the cells are maturation resistant, produce IL-10 and induce low proliferation T cells [36].

In order to favor their migration to the draining lymph nodes and their antigen presentation to T cells, VitD3-DC or Dex/VitD3-DC can be matured in vitro with LPS. Such cells are described as alternatively activated DC and induce memory T cell hypo-responsiveness and naïve T cell proliferation associated with low IFN-γ and high IL-10 production [34]. Another protocol to generate TolDC with IL-10 consists of culturing monocytes with IL-10 (in addition to GM-CSF and IL-4) from the initiation of culture. In this case, TolDC express CD83, CD80 and CD86, similar to activated/mature cells. Furthermore, this TolDC secrete high levels of IL-10 and induce hypo-responsiveness in T cell [35].

A key characteristic of DC generated with IL-10 is their ability to induce the differentiation of regulatory T cells. Unfortunately, another property of IL-10 producing DC is a decreased trafficking of these cells to the lymph nodes. The chemokine CCR7 participates in the migration of DC to the lymph nodes and generating mouse DC with IL-10 down-regulates their expression of CCR7 and impairs there in vivo homing to lymph nodes. In a model of mouse cardiac all transplantation, showed that injection of DC co-expressing IL-10 and CCR7 induced a significant prolongation of graft survival [18].

CONCLUSION AND RECOMMENDATIONS

The tissues of healthy animals resist many microbial invasions through a vast array of defense mechanisms. In spite of numerous invaders, the body cannot rely on single mechanism of defense. Clearly, the defense of the body from a complex system of overlapping and interlinking mechanisms that together becomes able to destroy or control almost all invaders. Due to their key position in connection innate and adaptive immune response, DCs represent a logical target for such interventions. Recent intensive researches on DCs biology imparted significant understanding of DCs function and their major role in maintaining homeostasis through the induction of protective immune response against pathogens and tumors, regulation adaptive immune response and in maintenance of peripheral tolerance. This rapidly expanding knowledge of the function of DCs, suggests new possibilities for the development of effective vaccines and therapeutic strategies. However, it is still unclear how different DCs populations with distinct lineage are generated in vivo and in vitro, how they migrate and accumulate under steady state of conditions.

Therefore, based on the above facts the following recommendations are forwarded:

- Continued research on the complexities of DCs biology, as well as immunological functions should be encouraged.
- Manipulation of immune response through exploitation of DCs function has to be evaluated and used as immunotherapy of infectious diseases and immune related disorders.
- Availability of sophisticated technologies is necessary.

REFERENCES


