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Dendritic Cell Subsets, Maturation and Function

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Abstract

Dendritic cells (DCs) are the most efficient and professional antigen-presenting cells of the immune system required for induction and dispersion of immune responses. DCs also have an important role in the induction and maintenance of tolerance. In response to infections, DCs drive the production of effector CD4⁺ T helper 1 (Th1) and CD8⁺ T cell-dominated immune responses. DCs can be designated to become tolerogenic and enhance regulatory T cells (Tregs) that regulate effector T cell responses, a process that is essential for the maintenance of immune homeostasis and control of autoimmune diseases and hypersensitivities. DCs can exist in three states: immature, semi-mature, and mature DCs. The difference between immature and mature DCs is distinctly based on variations occurring on a phenotypic level and functional level. Immature dendritic cells manifested characteristics of primitive cells, defined by expression of classical dendritic cell surface markers CD11c, CD11b and major histocompatibility complex class II (MHC-II). Phenotypic maturation is accomplished when DCs upregulate surface maturation markers such as CD80, CD83, and CD86.

Keywords: CD83, CD86, TLR, immunogenic, tolerogenic

1. Introduction

Dendritic cells (DCs) are rare, heterogeneous bone marrow (BM)-derived professional APCs that are disseminated ubiquitously in blood, lymphoid, and peripheral tissues, particularly at the gates of antigen entry. They originate from hematopoietic stem cells throughout specialized progenitor subsets and are essential in innate and adaptive immune capacity and in managing the balance between immunity and tolerance [1]. Under normal conditions, DCs are present throughout the body at low numbers representing $\approx 1\text{--}2\%$ of white blood cells [2].

In the steady state, DCs reside in immature or semi-mature states in the periphery where they regularly take up and process self-Ags and maintain self-tolerance [3]. Immuno-stimulatory DCs have undergone maturation after recognition of exogenous and endogenous danger signals by Toll-like receptors (TLRs). These signals include pathogen-associated molecular patterns in the form of microbial products, such as products of damaged or dying cells [4].

DCs are matured by CD40 ligation and by pro-inflammatory cytokines that can produce DC maturation *ex vivo*, detached of CD40 ligation. Maturation is correlated with up-regulation of cell surface MHC gene products, co-stimulatory molecules (CD40, CD80, and CD86 and CD83), and relevant chemokine receptors that improve the ability of DCs to migrate to secondary lymphoid tissue, where they present Ag to Ag-specific T cells and induce T-cell activation and generation. Consequently, activated T cells drive DCs toward terminal maturation [5].

DCs produce from Hematopoietic stem cells (HSCs) in the BM and are originated from both myeloid and lymphoid progenitors, as illustrated in **Figure 1**. Both subsets, conventional DC (cDC) and plasmacytoid DC subsets (pDC), are derived from a common CD34⁺ progenitor [6]. The hematopoietic growth factor fms-like tyrosine kinase 3 ligand (Flt3L) represents a fundamental function in steady-state DC expansion; this is evidenced by the preponderance of DC precursors being Flt3⁺ (CD135⁺) and culture with Flt3L appearing in cDC and pDC

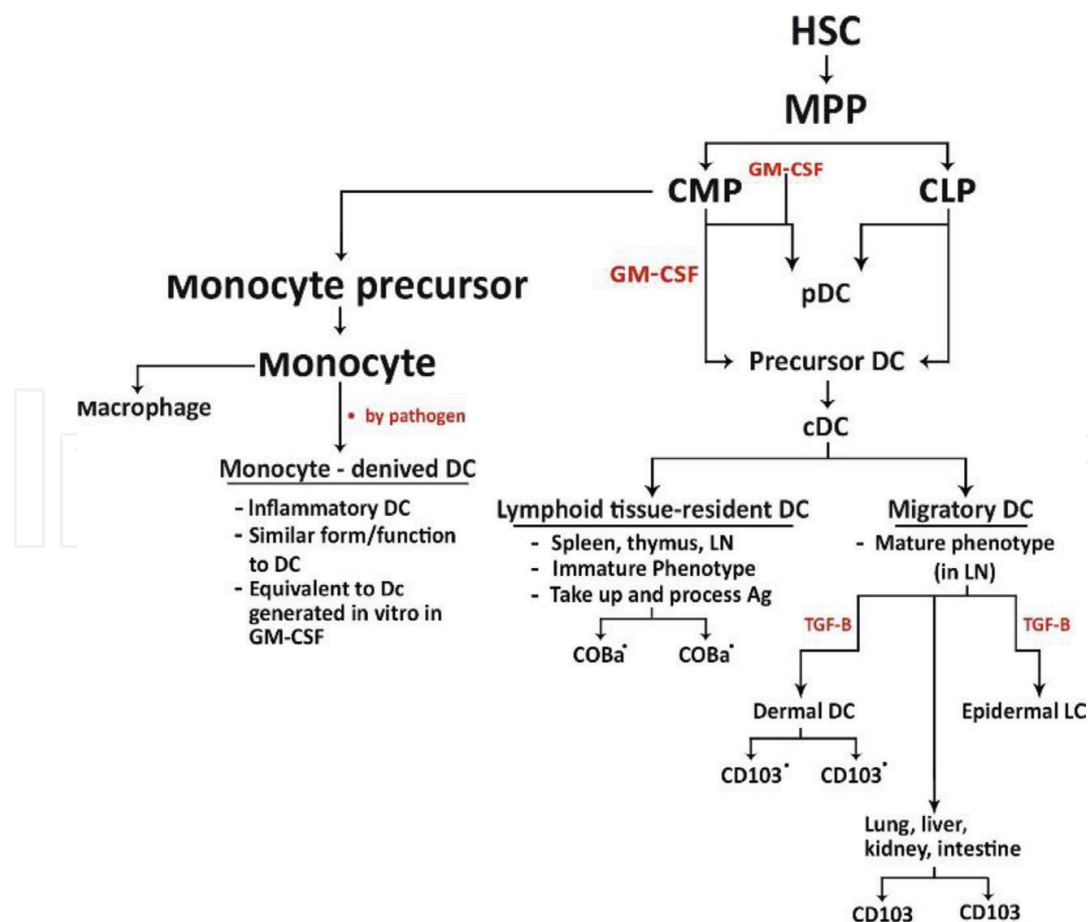


Figure 1. Dendritic cell hematopoiesis.

subsets. GM-CSF is also crucial in DC hematopoiesis, as it provides DCs from monocytes and immature progenitors in the deficiency of intact Flt3L signaling and provides DCs under inflammatory conditions [1].

DCs are divided into two principal cell populations, conventional DCs (cDCs) and plasmacytoid DCs (pDCs). In the steady state, cDCs present typical DC characteristics (e.g., cytoplasmic dendrites) and function (e.g., Ag uptake, processing, and exhibition). cDCs can be divided into migratory DCs, such as skin epidermal Langerhans cells (LCs), dermal DCs, which present Ag in lymph nodes following its uptake in peripheral tissue and resident DCs, which take up and process Ag within a lymphoid organ, such as splenic or thymic DCs [1]. Thymic DCs remove self-Ag-specific thymocytes and stimulate the expansion of immunoregulatory T cells (Treg). Thymic conventional DCs (cDC) readily received MHC class I and II from thymic epithelial cells (TEC), but plasmacytoid DCs (pDC) were less effective. Intercellular MHC shift was donor cell-specific; thymic DC readily gained MHC from TEC plus thymic or splenic DC, whereas thymic or splenic B cells were smaller donors [7].

Plasmacytoid DCs (pDCs) are a subset of precursor DCs which possess an immature phenotype in the steady-state and plasma cell morphology (e.g., lack dendrites). On activation, pDCs strictly match cDCs in form and function. Monocyte-derived DCs or inflammatory DCs are similar to cDCs in form and function and related to in vitro GM-CSF-generated DCs [3].

Under steady-state conditions, human pDCs display lower levels of MHC and costimulatory molecules compared with conventional myeloid DCs (mDCs). pDCs are less efficient in Ag processing and loading ability to excite T cells than mDCs. After their activation via TLR, pDCs produce high levels of type 1 interferon (IFN) and incite CD4⁺ and CD8⁺ T cells. This is in opposition to activated mDCs, which secrete IL-12 and enhance T-helper type-1 (Th1) cell differentiation and CD8⁺ cytotoxic T lymphocyte (CTL) responses [8]. Plasmacytoid DCs (pDCs) are a subset of precursor DCs which have an immature phenotype in the steady-state and plasma cell morphology (e.g., lack dendrites). On activation, pDCs closely resemble cDCs in form and function. Monocyte-derived DCs or inflammatory DCs are similar to cDCs in form and function and correlate with in vitro GM-CSF-generated DCs [3].

Under steady-state conditions, human pDCs display lower levels of MHC and costimulatory molecules compared with conventional myeloid DCs (mDCs). pDCs are less efficient in Ag processing and loading ability to stimulate T cells than mDCs. After their activation via TLR, pDCs secrete high levels of type 1 interferon (IFN) and stimulate CD4⁺ and CD8⁺ T cells. This is in contradiction to activated mDCs, which produce IL-12 and increase T-helper type-1 (Th1) cell differentiation and CD8⁺ cytotoxic T lymphocyte (CTL) responses [8].

pDCs have intrinsic tolerogenic features; in the steady position, human thymic pDCs provoke Treg, whereas liver and airway pDCs control oral and mucosal tolerance, respectively. pDCs have also been involved in the management of disease activity in experimental models of autoimmunity and revealed to exert disease-suppressing capacity [9].

It may be important after transplantation regarding donor engraftment (tolerance), which has clinical features that overlap with autoimmune disease. Epidermal LCs may be immunostimulatory or tolerogenic, depending on their state of maturity, inciting immunogen, and the cytokine environment [10].

DCs are characterized by high versatility, flexibility and multiple functional activities combined with their dual capacity to induce self-tolerance or trigger immune responses. The principal function of DCs is to scare the immune system toward heterogeneous and dangerous invasions and to defend self-tissues from destruction to keep self-tolerance [11]. The coordination of these supposedly multiple functions may open up new roads for stimulating or controlling immune responses and to promote defensive or therapeutic remedies for controlling inflammatory and autoimmune diseases or cancer, as well as designing unusual varieties of vaccines based on DCs biology [12].

A basic biological role of DCs relies on the constant sampling of their tissue environment, reacting to stress, risk signals and transducing the gathered molecular information to other cell classes of the immune system [13]. DCs are implemented with characteristics sets of pattern-recognition receptors, such as TLRs (Toll-like receptors), NLRs (NOD-like receptors), and RLRs (RIG-I-like receptors), which are specialized to recognize exogenous pathogen-associated molecular patterns (PAMPs) and endogenous danger signals, damage-associated molecular patterns (DAMPs) [14].

The response of DCs to MAMPs and DAMPs is achieved by the activation of pausing DCs by microbial components, noxious or toxic abuses. Activation of DCs sequences in the expression of costimulatory molecules, the generation of cytokines, chemokines and additional soluble mediators. Both are resting and stimulated DCs can switch their tissue position and transfer through peripheral and lymphoid tissues. Activation of DCs by MAMPs and DAMPs appears in the prompt, chemokine-mediated translocation of DCs to peripheral lymph nodes where they have the possibility to communicate naive T-lymphocytes to induct adaptive immune responses [15]. This process assures the transformation of molecular message obtained in the periphery toward other cell varieties of both innate and adaptive immunity such as neutrophils, granulocytes, NKs, killer T cells, T- and B-lymphocytes [16].

The response of DCs can be divided into the perception phase followed by phases of signal transduction pathways supported by adaptors and interfered by post-translational changes such as phosphorylation and ubiquitination reactions leading to the activation of transcription factors, and gene transcription followed by the secretions of soluble factors [17].

In this cascade, few receptor complexes ligated by their specific ligands allow substantial signal amplification. It has also been shown that the generation of fully active and stable DCs requires the parallel activation of multiple signaling pathways [18]. Signs through a particular receptor may produce partial stimulation only, which may be regressed by signals which promote the differentiation of regulative DCs. Signals produced by Toll-like receptors (TLRs), cytokines, chemokines, eicosanoids, free oxygen radicals, and several inflammatory mediators provide a signaling matrix and determine the phenotype and functional activities of DCs [19].

Five types of PRRs have been recognized: (i) transmembrane TLRs, which are combined to cell surface or endosomal membranes of different cell types, (ii) membrane C-type lectin receptors (CLRs) identified by the appearance of a carbohydrate-binding domain, (iii) three further classes of intracellular sensors, which are confined to the cytosol of multiple cell types and include NOD-like receptors (NLRs), RIG-like receptors (RLRs), and the latterly expressed AIM2-like receptors (ALRs), all with nucleotide recognition capacities [20].

Upon binding of their specific ligands, TLRs activate the NF- κ B/AP-1 and the interferon-regulatory factor 7/3 (IRF-7/3) pathways to coordinate innate and initiate adaptive immunity [21].

RLRs are crucial viral sensors in the cytoplasm and contain retinoic acid-inducible gene-I (RIG-I), melanoma differentiation-associated gene-5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), sequentially. RIG-I and MDA5 have been recognized as receptors toward double-stranded RNA [22].

Nucleotide-binding oligomerization domain (NOD)-like receptors mediate primarily antibacterial immunity through the activation of NF- κ B or inflammasomes, whereas RIG-I-like helicases have a fundamental role in the induction of antiviral immune responses [23] (**Figure 2**).

The collaboration of PRRs and the resulting secretion of type I interferons and inflammatory cytokines can be extremely potent toward pathogens. Following infections, innate defense mechanisms are stimulated immediately and support the expansion of adaptive immune responses. DCs perform a crucial role in the orchestration of humoral and cellular immunity and the initiation and sustaining of long-term immunological memory [24]. Interaction of microbes with the innate immune system involves the induction of multiple PRR pathways triggered simultaneously by various PAMPs of the whole pathogen [25].

The possible interaction of two or more signaling pathways in biochemical systems can either be potentiating or hampering. For example, in moDCs and monocyte-derived Langerhans cells (moLCs), co-ligation of TLR3/TLR7 and TLR3/Dectin-1 lead to increased Th1/Th17 responses, in contrast to TLR3 and Langerin ligation, which had an opposite effect [26].

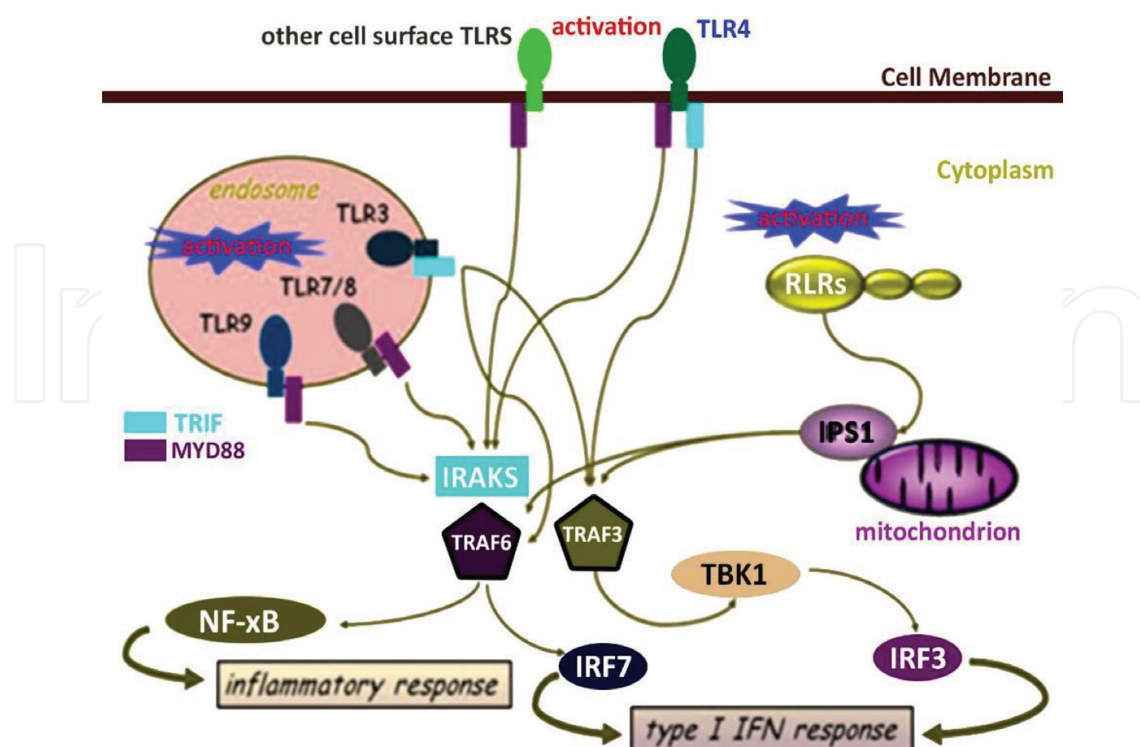


Figure 2. TLR and RLR signaling.

Similarly, another group found that RLR/TLR co-activation caused decreased Th1/Th17 responses upon bacterial infection. This cross-interference of RLR and TLR signaling might have significant implications in the design of future vaccination strategies, and the possible spectrum may be expanded to other non-immune cell types as well [27].

In vaccine construction, a primary purpose is to produce efficient, specific T-cell responses. This is accomplished by targeting antigen to cell surface molecules on DCs that efficiently direct the antigen into endocytic chambers for packing onto MHC molecules and stimulation of T-cell responses. Toll-like receptors (TLRs) expressed on DCs employed as intentions for antigen presentation for cancer and different disorders [28].

Depending on phenotypic and functional requirements, DCs may develop immunogenic or tolerogenic responses. Although several Toll-like receptors, such as TLR3, TLR4, TLR5, TLR7, and TLR8, provoke immune activation, others can quiet immune responses by tolerance initiation in DCs. Under certain conditions, TLR2 activation can lead to IL-10 production or Treg cell activation via repression of TLR7/TLR9 signaling and prevention of IFN- α and - β secretion from pDCs [29].

Despite the immunogenic capability of DCs in mounting immune responses, which has been assigned to the only target in the immune system, they have also been ascribed several roles in tolerance installation and silencing of immune responses. DCs express a fundamental role in the induction of several subsets of T cells, such as Th1, Th2, Th17 and regulatory T cells (Tregs). In the steady state, DCs play a critical role in the induction of tolerance against self-antigens. Complete ablation of DCs breaks self-tolerance of CD4⁺ T cells and results in fatal autoimmunity [30] (Figure 3).

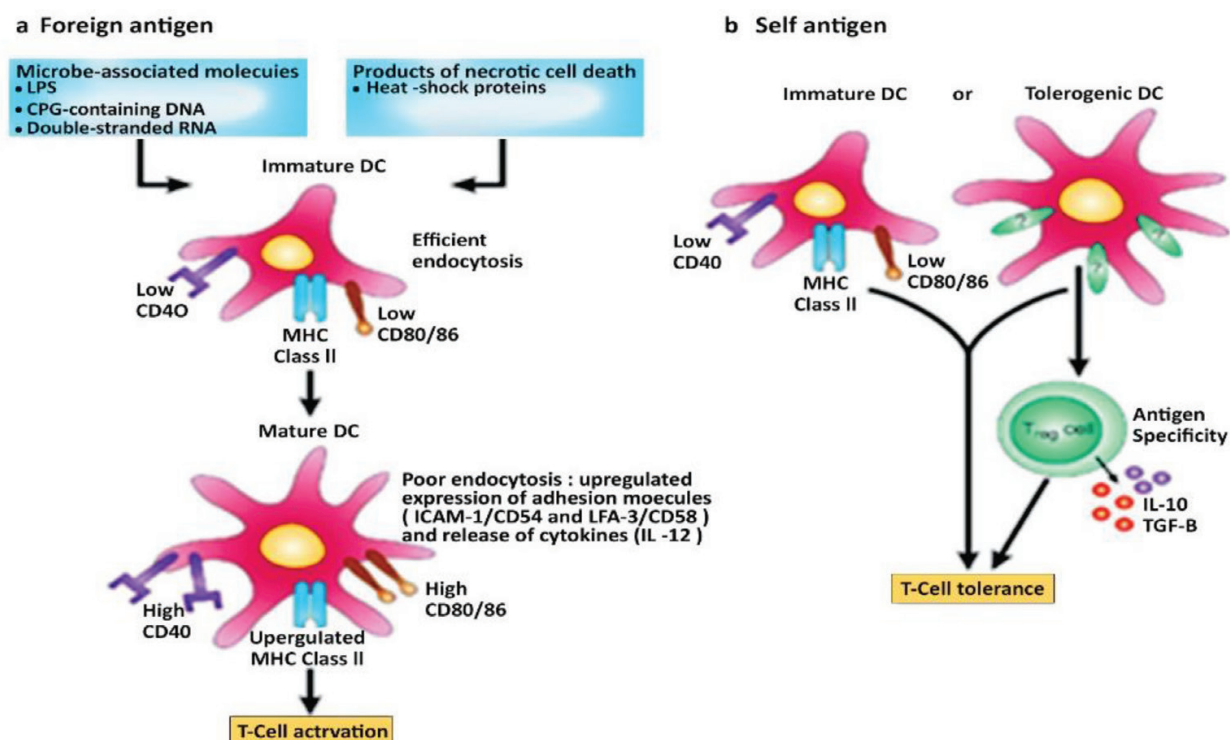


Figure 3. Dendritic cells in the choice between immunity and tolerance.

Although the general state of knowledge considers cDCs as inducers of immunity, while pDCs serve as the inducer of tolerance [31], their functions in the immune response to a diverse range of antigens are more complex.

pDCs are believed to be the critical effector cells in the early antiviral innate immune response by providing large quantities of type I interferons upon viral infection. pDCs increase immune responses by cross-talking with cDCs by the secretion of IFN- α , through performing a crucial role in active stimulation of adaptive immunity as well. In the interest to IFN- α secretion, it has been described that pDCs also express CD40L, which stimulates cDCs to secrete IL-12 [32] (**Figure 4**).

An association between the appearance and deficiency of multiple surface markers has been employed to identify DC subsets. These include the presence of significant expression of class II MHC antigens and the insufficiency of several progenitors' markers such as CD3 (T cell marker), CD14 (monocyte marker), CD19 (B cell marker), CD56 (natural killer cell marker) and CD66b (granulocyte marker). DCs further express a modification of adhesion molecules including CD11a (LFA-1), CD11c, CD50 (ICAM-2), CD54 (ICAM-1), CD58 (LFA-3), and CD102 (ICAM-3). DCs also represent costimulatory molecules including CD80 (B7.1), and CD86 (B7.2), which are upregulated through DC activation. CD86 designates to be a marker of primary DC maturation, while CD80 only increases in mature DC. Two additional markers of mature DC in humans are CD83 and CMRF-44. CD83 also is exposed by stimulated B cells, and CMRF-44 will also be exposed by macrophages and monocytes [33].

The identification of DCs by surface phenotyping may be accomplished by merely demonstrating a high level of MHC class II or a costimulatory molecule such as CD80 and the absence of lineage markers [34].

The conventional or myeloid DCs (cDCs) are characterized by a high exhibit of the phenotype LIN-CD11c and low HLA-DR + CD123, while plasmacytoid DCs (pDCs), derived from a lymphoid precursor, manifest low expression of the phenotype LIN-CD11c and high HLA-DR + CD123 [35]. The maturation state of DCs can categorize DCs. Immature DCs are located mainly in peripheral tissues, where they capture antigens, initiate their maturation and migrate to lymphoid organs, where they become mature to present antigen and stimulate naive T lymphocytes [36].

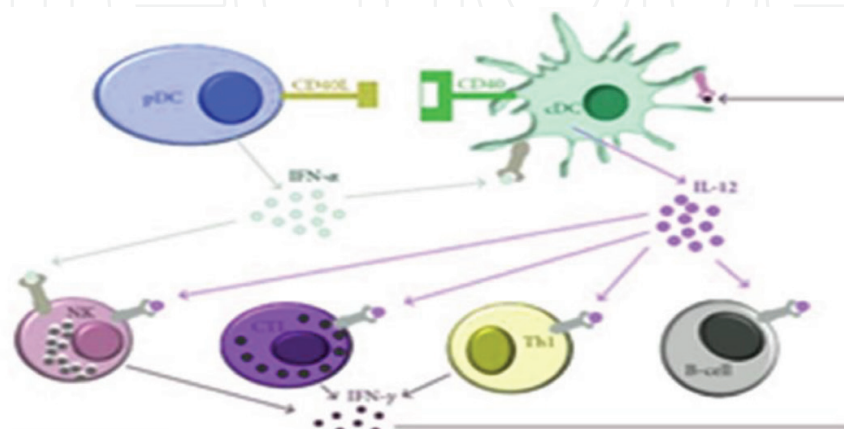


Figure 4. Cooperative action of different DC subsets to tackle both innate and adaptive immunity.

Buckley et al. [37] revealed that macrophages and DCs are positioned in the same splenic anatomical sections and yield monocyte-macrophage markers, proposing that both cell classes are relevant and probably originated from a familiar precursor. Vandenabeele et al. [38] illustrated in human thymus main classes of DCs, showing the low of the phenotype CD11b-CD11 + CD45RO, great CD83, CD86, HLA-DR and fewer DCs with high CD11b + CD11c, CD45RO population. They also recorded the appearance of pDCs with great CD123 in the thymic cortex. The role of DCs is tightly correlated to their anatomical location. In secondary lymphoid tissues, mature DCs present antigens, caught in the periphery, to naive T cells and produce immunity, while in the thymus DCs present self-antigens, produce negative determination of autoreactive T cells and improve the positive selection of regulatory T cells [39].

DCs can be generated via culturing CD34+ cells in the presence of several cytokines. One procedure which has been developed includes depleting the CD34+ cells of differentiated ancestors and next culture the cells in the presence of GM-CSF and IL-4 ± TNF- α . CD34+ cells can be collected from bone marrow or cord blood. Further procedure is to generate DC-like cells by culturing CD14+ monocyte-enriched peripheral blood mononuclear cells [40]. In the presence of GM-CSF and IL-4, these cultures lead to large numbers of DC like cells. These monocyte-derived DCs require additional conditioning *in vitro* with either TNF- α or lipopolysaccharides added to culture media to enable adequately function as a DC accomplished of preparing antigen-specific T cell responses [41].

Because of the established role of DCs in maintaining the balance between immunity and tolerance, tolerogenic (tol)DCs might be novel therapeutic targets to prevent undesirable (auto-) immune responses. The idea behind tolDC therapy is that it is a highly targeted, antigen-specific treatment that only affects the auto-reactive inflammatory response [42]. A tolerogenic state in DCs can be induced using several pharmacological agents, such as cyclosporine A, rapamycin, dexamethasone, vitamin A, vitamin D or other cytokines and growth factors [43].

Isolation and culture of leukocytes (buffy coats) obtained from heparinized human peripheral blood provide a valuable model for studies on DCs biology and may help uncover new means to manipulate DCs differentiation and function in therapeutic settings [44]. The buffy coat layer from human peripheral blood was cultured in the presence of GM-CSF and IL-4 to generate dendritic cell populations which were allowed to differentiate into mature DCs by TNF- α within 9 days [45] (**Figure 5**).

The *in vitro* effect of dexamethasone (DEX) on generation and differentiation of DCs through microscopic and phenotypic analysis was studied. The addition of DEX to the culture on day 0 prevented the differentiation of DCs to be tolerogenic. On the other hand, addition of DEX to the culture on day 7 or 8, either preceded or followed by addition of TNF- α , resulted in significant increase of CD83 expressing DCs; the greatest percent of tolerogenic DCs was obtained in the culture media to which DEX (1 μ M) was added on day 8 and TNF- α (10 ng mL⁻¹) was added on day 7. Although the addition of TNF- α to the culture 1 day prior to addition of DEX enhanced the differentiation of DCs (high percent of CD83 expressing DCs), TNF- α did not affect the morphological changes of DCs which became mature even in the absence of TNF- α . Opposite studies were reported that TNF- α is a maturation factor essential for the appearance of the morphological characteristics of DCs [46].

CD83 is an important marker for activated/mature DCs. It was recorded that both stimulated DCs and B cells secrete soluble form of CD83 and so low concentration of soluble CD83 are present in normal human sera [47]. The CD83 seems to possess regulatory roles for immune response. The soluble form of CD83 can repress immune responses, while being strongly up-regulated during DCs maturation and activation [48].

Fujimoto and Tedder (2006) revealed that CD83 has immunosuppressive roles such as the inhibition of surface molecules, such as MHC-II, reducing the dendritic cell-mediated T cell stimulation. The allogeneic stimulatory capacity of the DCs and immunosuppressant mechanisms of CD83 were illustrated significantly inhibiting anti-donor antibody responses [49]. The study of Ge et al. [50] reported that CD83 is capable of down-modulating expression of various DC [50]. The elevated CD83 expression suggests the possibility of DEX-generated cells to initiate a Th2-biased response where CD83 is able to inhibit DCs mediated T cells stimulation [51]. Furthermore, dexamethasone treated DCs possessed the capacity to convert CD4⁺ T cells into IL-10-secreting Treg potentially suppressing the proliferation of responder T cells [52].

The CD83 is a surface marker that distinguishes immature and mature human dendritic cell populations. The CD83 is type 1 glycoprotein belonging to the immunoglobulin superfamily

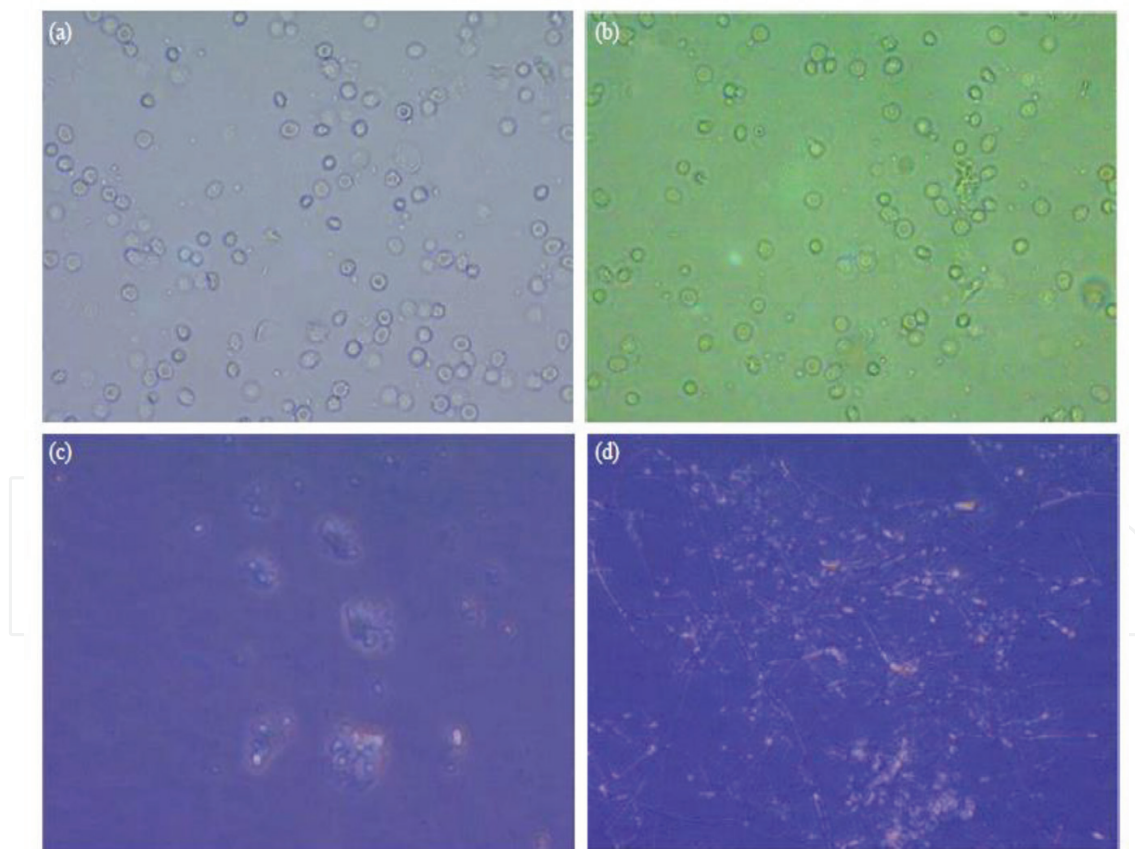


Figure 5. Morphological changes during generation and differentiation of DCs (40 \times), (a) adherent monocytes on day 0, (b) transforming monocytes on day 3, (c) generated DCs on day 7 and (d) mature DCs on day 9. The culture of buffy coat layer from human peripheral blood leads to generation of dendritic cell populations that in response to granulocyte-macrophage colony-stimulating factor (GM-CSF) plus interleukin-4 (IL-4) in 7 days and differentiate into mature DCs in response to maturation stimulus tumor necrosis factor- α (TNF- α). Morphological changes were examined under inverted microscope Carl Zeiss® using ZEN 2012® software, Germany.

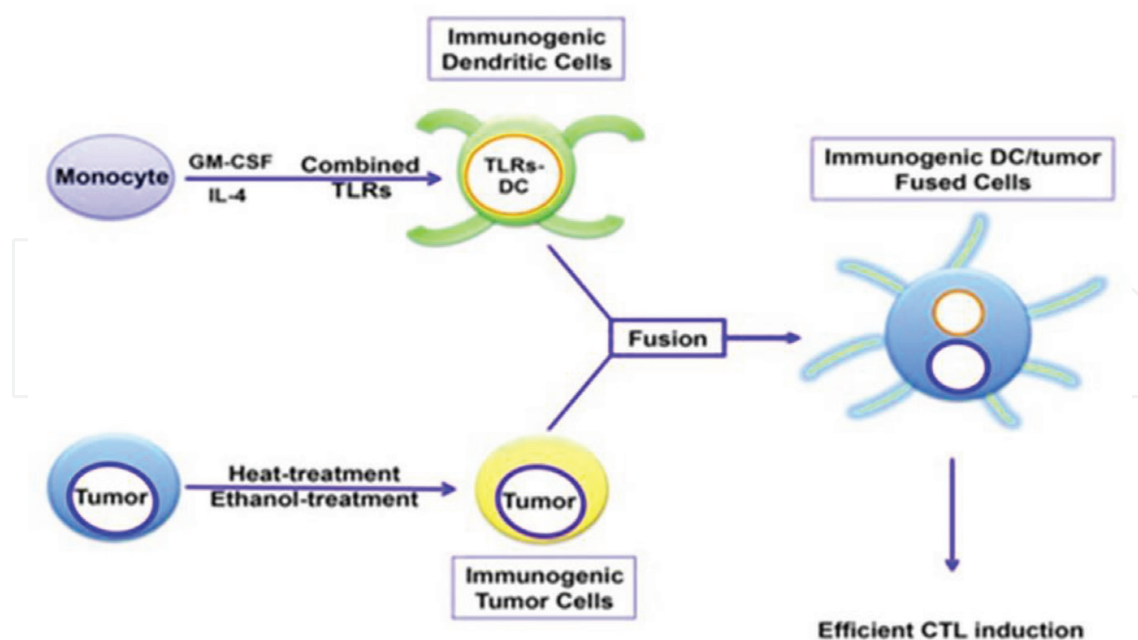


Figure 6. Generation of immunogenic cancer cells fused to activated dendritic cells.

and has been known to be one of the best markers. There is an outstanding deal of attention in how DCs might be developed as a manner of immunotherapy. DCs are being examined as adjuvants for vaccines or as a principal therapy to aggravate immunity against cancer. That DCs may show valuable in cancer has been most often studied in animal models. DCs burdened with tumor lysates, tumor antigen-derived peptides, MHC class I modified peptides, or whole protein have all been shown to yield anti-cancer immune responses and actions, including in some cases the ability to begin broad relapse of existing tumor [53] (**Figure 6**).

In conclusion, there is a pronounced hope to study these strategies and use tumor-antigen bearing DCs as a vaccine in humans. Human clinical investigations are continuing in numerous institutions to use DCs to initiate immunity to antigens against breast cancer, lung cancer, melanoma, prostate and renal cell cancers [54]. The study of immune-mediated mechanisms could be of value in avoiding and managing main immune disorders [45].

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