Chapter 1

Introductory Chapter: Dendritic Cells

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1. Introduction

Dendritic cells (DC) are critical antigen-presenting cells (APC) of the immune system due to their unmatched ability to sample antigens and initiate T cell responses [1]. In addition to the induction of primary immune responses, DC are also important cells for the maintenance of immunological tolerance. DC were discovered by Ralph Steinman and Zanvil Cohn in 1973 [2, 3]. However, the peak of publications focusing on DC as main sentinel cells of the immune system happened 20–30 years after their discovery. This chapter discusses major advances in our understanding of DC biology, subtypes, phenotypes, cell-cell interplay, and roles in several pathologic conditions such as infectious, autoimmune, and tumorous diseases (**Table 1**). These new discoveries in DC biology and contemporary approaches in directed and tightly controlled DC manipulations will help in the development of improved therapeutic and vaccination strategies to fight many diseases.

2. DC subtypes, phenotypes, and functions

A recent comprehensive review of published research on DC migration in health and disease also shows the phenotypic characteristics of DC in different tissues, namely, in skin, intestines, lungs, and CNS [4]. In contrast to other organs, where several DC subtypes exist simultaneously, in skin epidermis, for example, only one type of DC is present, CD207+ Langerhans cells. In contrast to that, several DC subsets were found in dermis, such as conventional (c) DC1 and cDC2, distinguished by the presence or absence of XC-chemokine receptor 1 (XCR1) expression, correspondingly. There is a third cDC subpopulation in skin dermis, so called double-negative cDC (lacking XCR1 and CD11b expression). These three dermal DC subtypes have different origin/cellular progenitors, and perform distinct functions during skin inflammation.

In contrast, intestinal cDC1 is characterized by CD103 expression. At the same time, intestinal cDC2 expresses CD11b in addition to CD103. Surprisingly, lamina propria CD103+cDC induce regulatory T cells, as for other organs it is a selective function of plasmacytoid (p) DC [4]. The authors admit the presence of yet uncharacterized DC phenotypes in human gut.

Lung-resident cDC and pDC subpopulations have been characterized previously in mice [5] and humans [6]; however, more recent findings show the existence of two cellular subpopulations within lung cDC. In addition to cDC, the presence of monocyte-derived (mo) DC, which can be discriminated in the lungs based on the expression of cell surface markers such as CD103 (Integrin aE), CD207 (langerin, a C-type lectin with mannose binding specificity), DNGR1 (C-Type Lectin Domain Containing 9A, CLEC9A, a receptor for necrotic cells required by DC to cross-prime CTLs against dead cell antigens), Signal regulatory protein α (SIRPa), MAR-1 (Fc epsilon receptor I alpha), and Ly6C (a mid-stage cell development differentiation antigen, GPI-anchored glycoprotein) [4]. Moreover, CD64 and MAR-1 are considered to be the most selective markers for the effective separation moDC from cDC. In addition to that, the GenChip technology application to DC research has recently demonstrated that DC subsets display different transcriptional factor's requirement in their development and function [7, 8]. Several transcription factors including PU.1 (E26 transformation-specific family transcription factor), Bcl11a (C2H2 type zinc-finger protein), Irf4 and Irf8 (Interferon Regulatory Factors 4 and 8, correspondingly), E2-2 (basic helix-loop-helix transcription factor E protein), Id2 (Inhibitor of DNA

Topic	References
DC development	[1, 7, 9–11, 13, 14]
Antigen processing and presentation	[1, 9, 13, 14, 16–19]
Phenotypes, cell surface markers	[4, 9–15]
Transcriptional control and classification	[1, 7, 8, 10]
Functional characterization	[8–10, 13–15]
DC cytokine profile	[14, 15]
Immune tolerance	[14, 30, 31, 35]
Tissue- and organ-resident DC	[5, 13, 19]
DC migration	[4]
Cell-cell interaction	[16–23]
DC and allergy	[5, 12, 14, 24]
DC and cancer	[14, 24, 32]
DC and autoimmunity	[4, 14, 15, 24, 35]
DC and infectious diseases	[15, 24–28]
DC in osteoimmunology	[33, 34]
Novel techniques in DC research	[11, 20, 21]

Table 1. Main topics of research and discussion covered by cited manuscripts.

Binding Protein 2), Batf3 (basic leucine zipper transcription factor ATF-like 3), IFN regulatory factors (IRFs), zbtb46 (zinc finger transcription factor 46), Notch RBP-J (the main transcriptional mediator of Notch signaling), Icaros (DNA-binding zinc finger protein), and others have been found to be differentially regulated in different DC subsets [7, 9, 10]. The comprehensive review by Murphy and associates [10] discusses DC origins, heterogeneity, functions, phenotypic and functional homology between mouse and human DC subsets, and the requirement of several transcription factors for DC subtypes' development. According to a contemporary view on DC presented in this chapter, DC are divided into two main subpopulations, namely, interferon regulatory factor of transcription 8 (Irf8+) cDC (CD8a+) and Irf4+ cDC (CD11b+). Moreover, two subpopulations can be clearly distinguished even within Irf4+ cDC based on their developmental dependency on either Notch-2 or Klf4. The authors discuss the functional differences between different DC subsets based on the *in vitro* studies and the *in vivo* specific gene-knockout mouse evaluation. They also discuss the DC origins and transcription factors necessary for DC subtype's development from a precursor cell. As an example, Nfil3 (nuclear factor, interleukin 3 regulated; another abbreviation for it is E4BP4) is required for CD8α+ DC development, whereas Id-2 is required for Irf8+ cDC. Furthermore, a recently published international comprehensive study has used a combination of single-cell messenger RNA sequencing (scmRNAseq) and cell cytometry by time-of-flight (CyTOF) contemporary technologies to study individual human DC subsets and their precursors among blood CD135+HLA-DR+ cells [11]. The authors created a panel of 38 labeled Abs based on DC-specific markers including CD2, CX3CR1, CD11c, and HLA-DR. This panel also included Abs to cDC-associated markers such as CD11c, CX3CR1, CD2, CD33, CD141, and reported the existence of individual DC lineage-committed subpopulations, intermediate DC clusters, previously unrecognized human pDC heterogeneity. It definitely brought new insights into DC therapeutic potential in many diseases. Lineage commitment is directly regulated by several hematopoietic cytokines, where Flt3L, M-CSF, GM-CSF, Lymphotoxin β and TGFβ1 play the major roles in the individual DC subset's development [9].

In conclusion, the previous simplistic division of mouse and human DC on cDC and pDC and definition of their function as: the inductors of CD4+ T cell immunity (CD11b+ cDC), efficient Ag cross-presenters to CD8+ T cells (CD8α+ cDC), and rapid producers of type I IFN to fight viral infections (pDC), has been upgraded significantly [4, 8, 9, 12–15]. Human pDC differs from cDC as they are $CD11c^{low}$ and the expression of other lineage-associated markers such as CD3, CD14, CD16, and CD19 is not detected on their surface; however, they express BDCA-2 (blood dendritic cell Ag–c-type lectin, CLEC4C (CD303)), CD4, CD68, CD123 (IL-3R), and immunoglobulin-like transcript 3 (ILT3), or ILT-7. Similarly to human pDC, mouse pDC are also $CD11c^{low}$, but they express Ly-6C (a GPI-anchored glycoprotein - lymphocyte Ag 6 complex) and Siglec-H (sialic acid-binding immunoglobulin-like lectin H), which is not found on mouse cDC. The pDC ability to induce tolerance through IDO production and Treg cell induction explains, in part, their protective role in allergic diseases and transplant rejection [15]. However, pDC play tissue-damaging type I IFN-associated pro-inflammatory functions in autoimmune diseases [15]. The latter chapter has divided human DC into four subpopulations such as CD141+ DC, CD1c+ DC, pDC, and moDC, correspondingly to the mouse subsets such as CD8/CD103+ DC, CD11b+ DC, pDC, and moDC. Human moDCs have been shown to serve as an effective inducer of Th1 responses, which partially overlaps with CD141+ DC and CD1c+ DC functions [15]. Functional specializations of different DC subsets as well as the

clinical syndromes associated with DC deficiency are being discussed in details in a review by Merad and colleagues published in 2013 [9], whereas a review by Mildner and Jung [13] focuses on functional similarities and differences of organ-specific DC.

3. The role of cell-cell interplay in DC activation and function

DC uptake Ag, process it, and present it to T cells as Ag-derived peptide in the context of specific MHCI or MHCII molecules [1]. DC are subdivided on immature, Ag-sampling, and mature, Ag-presenting, cells. After Ag uptake, DC undergo maturation and migrate to the T cell areas of lymph nodes. In the lymph nodes, DC present Ag to T cells, which effective stimulation depends on two critical signals, MHC-TCR and costimulation. Several recent studies consider the necessity of a third, so called "polarization" signal, for an optimal T cell activation [16–18]. Such signal can be provided by certain cytokines [17, 18] or semaphorins [16]. A recent review by Federika Benvenuti [19] focuses on the structural and functional composition and significance of DC-T cell cross-talk, on the formation of an immunological synapse between these two immune cells and a synapse composition. The interesting current technical developments aimed to analyze DC-T cell interaction and resulting corresponding cell activation include two-photon intravital imaging technique [20] and Labelling Immune Partnerships by SorTagging Intercellular Contacts (LIPSTIC) [21]. Both techniques can be used to study cell activation *in vitro* and *in vivo* and beneficiary complement each other. Activation of T cells can be additionally analyzed by the use of dynamic *in situ* cytometry, Ca+ influx analysis, and/or transcription factor translocation [20].

Direct cell-cell contact between DC and other immune cells can significantly modulate DC themselves and the resulting DC-induced immune response to Ag. DC-macrophage interaction and its role in the immune response activation have been described for CD169+ (siloadhesin, Siglec-1) macrophages and BATF3-dependent CD8α+ DC [21]. Specific viral Ag targeting to CD169+ macrophages led to Ag transfer to cross-presenting CD8α+ DC and subsequent T cell activation. A review by Walzer and colleagues [22] discusses the activation of NK cells by DC after a direct cell-cell contact, DC maturation induced by such interaction, immature DC lysis by activated NK cells, and other effects of such interaction, which have all important consequences for antimicrobial response. A direct interaction of DC with neutrophils, critical cellular fighters of bacterial infection and regulators of immune response on the infection site, has been reported previously as the interaction between Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Nonintegrin (DC-SIGN or CD209) with Mac-1 or CEACAM1 on neutrophils [23]. These cell-cell interaction pathways play important connecting roles between innate and adaptive immunity. The communication of different DC subsets between themselves and the resulting changes/modifications in the immune response has never been addressed although such cellular cross-talk might significantly influence the outcome of immune response.

4. DC and infections

The main role of DC in infection is to induce an immune response leading to microbe elimination. DC are equipped with numerous Ag uptake receptors such as DEC-205, mannose

receptor CD206, CD209 (DC-SIGN), CD207 (langerin), CLEC4A (DCIR), which bind a whole array of microbes (reviewed in [24]). Following Ag uptake, CD8α+ DC cross-present Ag on MHCI to stimulate CD8+ T cells to kill infected cells. In addition to that, a protective Th1 response is generated over effective Ag presentation to CD4+ T cells. However, numerous microbial agents are capable of blocking DC maturation. Those include *Herpes simplex* virus, vaccinia virus, varicella zoster, CMV, measles, *Salmonella typhi*, *Plasmodia*, *Coxiella burnettii*, and others. Some microbial agents, such as *Yersinia pestis* or *Salmonella typhi*, can selectively destroy DC by injecting toxins into cells thus avoiding recognition by a host immune system. *Mycobacterium tuberculosis* blocks the expression of CCR7 on DC thus interfering with DC migration step. *Aspergilus fumigatus*, malaria and hepatitis C viruses modify DC function in such way that DC induce a Th2 type of immune response instead of a protective Th1 response. Furthermore, several microbes can multiply/replicate within DC cytoplasm, which leads to infection spreading. Those DC-disseminating microbes include, but not limited to, HIV-1, LCMV, *Toxoplasma gongii*, *Bacillus anthracis*, CMV, and Ebola virus. The *in vitro* pathogen invading study has been done in human myeloid DC cultures. As the numbers of pDC are significantly lowered in the blood of people with HIV, HTLV-1 and RSV infections, it is highly likely that these microbes can evade pDC as well. pDC produce a large amount of type I IFNs in response to either viral (HIV) [25] or nonviral (*Aspergillus fumigatus*) [26] pathogens. Besides pathogens, however, the healthy microbiota representatives, such as *Lactococcus lactis* [27] and *Bacteroides fragilis* [28], have the capacity to activate pDC. The latter studies suggest that pDC can function as the enhancers of corresponding probiotic's activity.

5. DC in allergy

DC in lung tissue continuously sample exogenous Ags and make sure the immune system does not generate a harmful response to such generally un-harmful agents as pollens, dust mites, cockroaches, and others. Basically, instead of T cell activation, lung-resident DC were shown to induce T cell tolerance to those innocuous proteins in steady-state conditions. One of the potential mechanisms of T cell silencing by DC is based on ICOSL molecule, which has been shown to co-stimulate Treg cell development [24]. Local lung cytokines, such as TSLP [29] or VEGF [5], play critical nonredundant roles in making lung cDC immunogenic toward inducing Th2 responses to subsequent allergen exposures. The main direction in DC-based immunotherapy of asthma is targeting a pro-allergic lung cDC function and making cDC tolerogenic, Treg cell-inducing cells [24]. Targeted activation of Treg cell-inducing pDC represents another direction in DC-based asthma immunotherapy [24]. Similarly to the mechanisms of lung-associated allergies, in the diseases associated with intestinal allergic inflammatory reactions, such as food allergy and inflammatory bowel disease, gut lamina propria CD103+ cDC sample Ag and migrate into local lymph nodes, stimulate Treg cells from gut-associated lymphoid tissues to induce and maintain tolerance to food antigens [30]. The main two directions in DC-based therapy for food allergy are based on the induction of oral tolerance to a specific food allergen by: (1) directly activating Treg cell-stimulatory mucosal CD103+ cDC, and (2) gastrointestinal pDC-mediated tolerance through *de novo* generation of iTreg cells [31].

6. DC and cancer

Tumor Ag-loaded DC present a basis for DC vaccine in cancer. Currently, three ways to obtain such DC have been used in pre-clinical practice and clinical trials, namely: (1) The *in vitro* PBMC stimulation with Ag and GM-CSF (PBMC contain other cell types besides DC); (2) DC direct isolation from blood (approximately 1% of total PBMC) and their *in vitro* direct stimulation; (3) the *in vitro* expansion and activation of DC precursor cells (monocytes or CD34+ bone marrow-derived hematopoietic progenitor cells) followed by Ag loading, and the use of them as a vaccine [32]. The immunogenicity of such vaccines is highly dependent on DC subtype and activation level. Therefore, additional DC stimuli are currently being evaluated in order to potentiate DC activity and ability to induce the desired Th1 and/or CTL anti-tumor response. These stimuli include: (1) TLR agonists; (2) a combination of poly-IC with TNFα, IL-1β, IFNγ, and IFNα; and (3) a genetic engineering of DC by mRNA electrocorporation (such as TriMix) [32]. The discussed chapter here also describes in detail the *in vitro* culture conditions for an effective DC anti-cancer vaccine formulation.

7. DC and bone biology

Normally, DC are absent in bone tissues (reviewed in [33, 34]). However, numerous DC were found in synovial and periodontal tissues surrounding bone tissue during inflammation. Both, immature CD1α+ cells expressing RANK (receptor activator of NF-kB) and RANKL, and mature RANK-expressing DC-LAMP+ DC were identified in synovial tissues of patients with rheumatoid arthritis. RANKL is an absolutely necessary factor for osteoclasts (OC) differentiation and for their role in bone-absorption. Moreover, the *in vitro* studies using different DC culture conditions have shown that DC can also serve as octeoclast's precursor cells. When immature CD11c+CD11b-DC were exposed to an Ag stimulation as a maturation factor and interacted with CD4+T cells using RANK-RANKL ligation, they develop into so called "dendritic cell-derived osteoclasts (DDOC)", which were phenotypically CD11c+MHC-II+TRACP+(tartrate-resistant acid phosphatase) CT-R+(G protein-coupled receptor that binds the peptide hormone calcitonin) cells. This is rather an alternative pathway in OC differentiation in addition to a classical OC developmental pathway from monocyte precursors. It is well established now that OC are multi-nucleated bone-eating cells, and the excessive production of such cells can lead to a bone loss. DC can also participate in bone homeostasis through their secretion of multiple osteoblast's inhibitory (IL-27) or activating (RANK, IL-1, IL-6, and IL-23) factors, or through activation of certain arms of T cell immunity, which, in their turn, secrete cytokines directly or indirectly involved in bone formation process [34].

8. DC in autoimmunity

Genetic alteration occurring in several types of immune cells, including DC, could lead to the appearance and persistence of self-Ag reacting T and B lymphocytes, which is a hallmark of autoimmune diseases. Most studies on the role of DC in autoimmunity were

done in mice. It has been shown that autoimmune diabetes type 1 prone NOD (nonobese diabetic) mice have lower number of CD8α+ DC, which are dysfunctional in Ag cross-presentation (reviewed in [35]) that reduces the cross-tolerance. The Batf3$^{-/-}$ mice, which lack these cross-presenting DEC205+CD8α+ DC, do not develop diabetes. The other tolerogenic type of DC in mice is characterized by CD11b and DCIR2 (Clec4A4/DC immunoreceptor 2) expression. DC are tightly involved in pathogenesis of another autoimmune disease, multiple sclerosis. The study in mice have demonstrated a reduced EAE severity in functionally pDC-depleted mice (pIII+IV−/− mice, which lack MHCII expression on pDC cell surface). Thus, it is believed that pDC induce autoimmune inflammation through type I IFN production and tolerance through Treg cell activation. Indeed, there is a strong connection of type I IFN levels (or "signature"—elevated expression of type I IFN-stimulated genes) (reviewed in [15]). PBMC obtained from patients with systemic lupus erythematosus (SLE) can be distinguished from those in healthy volunteers by an overexpression of 18 genes, 12 of which were IFN type I-regulated. Similarly, IFN "signature" was detected in skin of patients with psoriasis, in PBMC and sera of patients with Wiskott-Aldrich syndrome (WAS), and in atherosclerotic lesions. However, as it is mentioned above, pDC can also induce tolerance, and those two distinct functions of pDC in autoimmunity are particularly dependent on Ag nature and timing of exposure (an Ag priming phase or a chronic Ag exposure/inflammation phase).

9. Summary

Ralph Steinman was awarded the highest honor for an outstanding scientific discovery, a Nobel Prize in Physiology or Medicine, in 2011 in recognition of DC discovery as well as the characterization of DC main functions. More recently, several DC-modulating technologies were developed for their use as vaccines for infectious diseases, cancer, allergy, and autoimmune diseases [9, 24, 36]. New insights into molecular characteristics of DC and their roles in human diseases continue to be researched, which will lead to a development of novel therapeutic strategies aimed at targeting specific DC subsets and/or their products. These strategies include the manufacturing of DC with an optimal immunocompetence, capable in enhancing the strength of immune effector cells and making the disease-causing cells susceptible to immune attacks [32]. Therefore, DC, according to Steinman and Banchereau, present an "unavoidable target" in the design of effective treatments for many human diseases [24].

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