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Mini-Review

Dendritic cell science: more than 40 years of history

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ABSTRACT

Over 40 years of research into the field of DCs has revolutionized our understanding into the activation and regulation of the immune system. This minireview discusses the major breakthroughs in DC science that have paved the way to the 2011 Nobel Prize in Physiology-Medicine awarded to Bruce A. Beutler and Jules A. Hoffmann (for their discoveries in innate immune recognition) and Ralph M. Steinman (for his discovery of the DC). *J. Leukoc. Biol.* 93: 33–38; 2013.

Introduction

DCs, although low in frequency, are highly specialized migratory leukocytes potent in antigen uptake, processing, and presentation to T cells. As a result of their capacity to activate naive T cells, DCs form the essential bridge between the innate and adaptive immune response. The history that has led to DCs as we know them today is quite distinct, from unknown irrelevant cells to central players in immunology.

IN THE BEGINNING

In 1868, the German physician Paul Langerhans described epidermal Langerhans cells for the first time [1]. Although the title of his publication suggested that these novel cells represented nerve cells, he noticed that these cells did not make contact with each other, and the precision of his observation of their dendritic morphology was remarkable. Although at the same time, the concept of phagocytosis by macrophages was introduced by Metchnikoff, for which he was awarded the Nobel Prize in 1908 [2], the field of cellular immunology was a largely unexplored area. It was not until the 1950s when immunologists started to study the initiation of the cellular immune response when antigen enters the body.

THE DISCOVERY OF THE DC

Frank Macfarlane Burnet—the father of the clonal selection theory—raised a major theoretical problem: what was the relationship between the macrophages that phagocytosed antigen and the lymphocytes that reacted to it? Nossal et al. [3] discovered that injection of labeled antigen in the footpath of rats accumulated in the B cell follicles of LNs and spleen. As the labeling was found between and not in lymphocytes, it was postulated that antigen was present in cytoplasmic extensions (dendritic processes) of specialized macrophages, pre-existent in lymphoid follicles. It was established that these macrophages were pivotal in the production of antibodies, possibly by their capacity to retain antigen for long periods of time [4]. Mosier and Coppleson [5] and Rowley and colleagues [6] described a splenic assessory cell (referred to as "a cell or third cell"), different from macrophages, which was required for antibody formation in vitro. In 1970, Steinman started as a postdoctoral researcher in the laboratory of Zanvil Cohn, studying how Burnet's selection of T cell clones was initiated [7, 8]. He discovered a novel cell type in murine spleen, which he named DCs; they did not look like macrophages and did not easily mediate endocytosis. At the same time, Veerman [9] proposed that the "interdigitating cells" in the thymus-dependent area of the rat spleen form a microenvironment, allowing T cells to differentiate and proliferate. In addition, retention of intact antigen and immune complexes was identified on the cell surface of "dendritic macrophages" (now called follicular DCs) [10, 11]. Later, it became apparent that follicular DCs represent a different cell type, as they are not derived from bone marrow hematopoietic stem cells but are of mesenchymal origin. Follicular DCs are involved in germinal center development and humoral immunity through their intimate interaction with B cells.

ANTIGEN PRESENTATION AND COSTIMULATION

It was not until the late 1970s that Steinman and coworkers [12, 13] found high levels of MHC molecules on DCs and demonstrated that DCs were potent inducers of the "mixed

Abbreviations: BDCA=blood DC antigen, CLR=C-type lectin receptor, pDC=plasmacytoid DC, Tc=cytotoxic T cell, Treg=regulatory T cell

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leukocyte reaction" in mice, which was the first functional assay performed with DCs. At the same time, Brigid Balfour and colleagues [14] pioneered contributions to the study of DCs by the characterization of "veiled cells" in afferent lymph derived from the skin, which were related to Langerhans cells, important in promoting lymphocyte activation. Earlier, Zinkernagel and Doherty [15] (Nobel Prize in 1996) had proposed that T cells see some form of complex between a MHC molecule and foreign antigen in their paradigm-shifting "altered-self" hypothesis [16]. In addition, Nussenzweig demonstrated that DCs present exogenous antigen to T cells in a MHC-restricted fashion and that DCs can induce specific cytolytic T cell responses ("cross-priming"), which were first described by Bevan [16]. It became clear that DCs were much more potent in inducing T cell responses than other APCs (such as B cells and macrophages), which was a breakthrough in understanding transplantation rejection [17]. The first human DCs were characterized in peripheral blood by Van Voorhis et al. in 1982 [18] (**Fig. 1**).

The complexity of T cell activation by DCs became apparent when cell–cell clusters were investigated by Inaba and Steinman [19]. They discovered the importance of clusters of DCs, Th cells, and B cells, in which DCs activate naive T cells that subsequently interact with B cells to activate them to produce antibodies. At the same time, Witmer and Steinman [20] reported that the T cell areas in lymphoid organs are the main location where DCs are found, which suggested that activated T cells leave the LN and migrate to the site of inflammation. Furthermore, Schuler and Steinman [21] discovered the concept of DC maturation when they studied murine epidermal Langerhans cells, and Witmer-Pack et al. [22] documented the requirement of GM-CSF in DC maturation. The different features of immature DCs (potent in capturing antigen) and mature DCs (strong stimulator for T cells) also became evident in the late 1980s [23].

Another breakthrough came from Jenkins and Schwartz [24], who showed that T cell clones failed to proliferate in the absence of costimulatory signals and became unresponsive to further activation [25]. In the 1990s, the B7/CD28/CTLA-4 pathway was identified as a crucial regulator of T cell activation and tolerance induction, and later, additional costimulatory molecules (CD40, CD58, CD54, and others) were identified on DCs. In the search for specific DC markers, Georg Kraal et al. [26] generated a mAb, called NLDC-145 (later known as the DEC-205 antigen), which recognized murine Langerhans cells, veiled cells, and interdigitating cells. DEC-205 was later identified as a potent antigen-uptake receptor used for DC targeting in vivo.

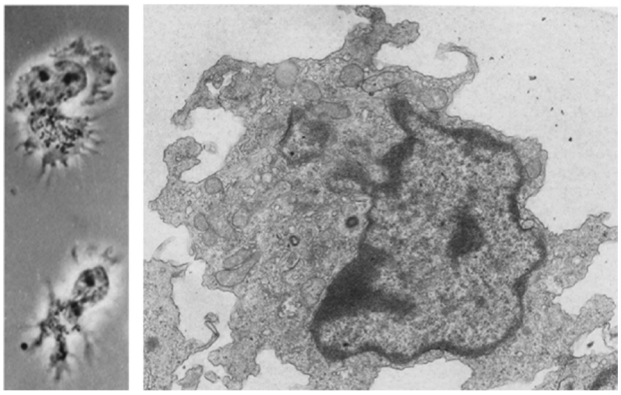

Figure 1. Human DCs purified from peripheral blood (0.3+0.2% of total PBMC) were analyzed by phase contrast and electron microscopy (adapted from ref. [18]). DCs extend smooth cytoplasmic processes in several directions, have irregularly shaped nuclei and many mitochondria, but exhibit few lysosomes or endocytic vacuoles.

DC RECOGNITION RECEPTORS

Possibly one of the major contributions to human DC biology was made in 1994 by Sallusto and Lanzavecchia [27] with the description of monocyte-derived DCs—a beautiful but artificial culture system to obtain large numbers of DC look-a-likes. This system allowed many researchers to study the basic function of DCs in humans. Around the same time, TLRs were described—first in the fruit fly, followed by the mouse—by the Nobel laureates Jules Hoffmann (and colleagues) [28] and Bruce Beutler (and colleagues) [29]. The concept of innate immune recognition was proposed by Charley Janeway Jr. and Ruslan Medzhitov several years prior to Hoffmann's and Beutler's work. As early as 1989, Janeway [30] wrote that "primitive effector cells" bear receptors, now known as TLRs, which allow recognition of certain PAMPs not found in the host, and that DCs are activated by TLR ligation. After pathogen encounter, DCs migrate to the draining LN, while processing the pathogen-derived antigen and presenting this in MHC I or II and up-regulating their costimulatory molecules to be able to properly activate naive T cells present in the LN. Depending on the type of pathogen or the TLR activated, DCs also express a set of molecules, membrane-bound or soluble, that determines the flavor of the T cell response (e.g., Th1, Th2, Th17, Treg, Tc1, Tc2), as has been demonstrated by Kapsenberg (reviewed in ref. [31]). Initial in vitro studies using artificial APCs demonstrated that cytokines (IL-12 and type I IFN) were critical for promoting development of CD8 T cell effector functions, including cytolytic activity and IFN-γ production [32]. It is now well-established that this so-called "third signal" is critical for the outcome of T cell polarization, thus commitment of naive T cells to differentiate toward Th1, Th2, or others [31]. Next to TLRs, another family of PRRs was identified: the CLR. An important discovery in this field was the demonstration by Theo Geijtenbeek, Yvette van Kooyk, Carl Figdor, and coworkers [33, 34] of a DC-specific C-type lectin, DC-specific ICAM-3-grabbing nonintegrin, which binds HIV-1 envelope glycoprotein gp120 and facilitates its transport to secondary lymphoid organs rich in T cells to enhance infection in trans of these target cells. In the years that followed, it became apparent that CLRs expressed by DCs are crucial for tailoring immune responses to pathogens and that targeting CLR is a powerful method to enhance antigen presentation (reviewed in ref. [35]).

DCs IN TOLERANCE AND IMMUNE REGULATION

Not only are DCs involved in the induction of T cell immunity but they also play an important role in the induction and maintenance of tolerance. Early on, Banchereau and Steinman [36] postulated that a controlled balance between these opposing functions of DCs ensures the homeostasis of the body. Lack of tolerance may result in unwanted immune responses to self or harmless antigens as observed in allergic or autoimmune disorders, whereas excessive tolerance may cause circumvention of tumor immunosurveillance or chronic infections as a result of lack of pathogen-specific immunity [37–39]. As discussed below, certain DC subsets are more specialized to support tolerogenic responses than other subsets, such as the gut mucosal $CD103^+$ DCs [40–42] or epidermal Langerhans cells [43]. These DC subsets induce de novo generation of Forkhead box $p3^+$ Tregs and depend on the ability of the DCs to produce or activate TGF-β [44, 45]. Alternatively, DCs may gain tolerogenic properties as a result of what they encounter. In particular, the work of Yasmine Belkaid [39] demonstrated that certain pathogenic stimulation of DCs promotes their capacity to induce immunity, which is accompanied by the induction of Tregs, involved in the re-establishment of homeostasis, and to prevent excessive tissue damage. In-depth research has been performed to identify the polarizing signal 3 molecules implicated in the induction of Tregs and demonstrated that IL-10, TGF-β, indoleamine-2,3,-dioxygenase, as well as negative costimulatory molecules, such as Ig-like transcript 3/4 [46–48], may be involved. On the other hand, pathogens may prevent the full activation of DCs, which may lead to tolerance through anergy, cell death, or the development of Tregs [49].

THE COMPLEXITY OF DC SUBSETS

Many researchers had noted the heterogeneity in DC surface molecules, which pointed to the existence of different DC subsets. Based on thorough DC surface characterization, Ken Shortman and colleagues [50] made an important contribution by confirming that DCs purified from mouse thymus, spleen, and LNs indeed consisted of different subpopulations. At the time, it was not clear whether these subsets arose from separate developmental pathways or whether developmental plasticity existed. However, it became apparent that certain subsets of DCs may be specialized in a specific function that determines the nature of the T cell response [51, 52]. Various groups demonstrated that murine $CD8a^+$ splenic DCs as well as human $BDCA3^+$ ($CD141^+$) DCs are superiorly equipped to cross-present antigens to $CD8^+$ Tc as compared with their $CD8a^-$ or $BDCA1^+$ counterparts [53–57]. Functional alignment of human and mouse DC subsets has been hampered by differences in cell surface marker expression [58]. However, recent comparative transcriptomic analysis of specific DC subsets will allow for better comparisons to be drawn between mouse and human [57, 59]. Cross-presentation is an important feature of DCs in the defense against viruses and tumors. During this process, dead cells (discussion is still going on whether these are necrotic and/or apoptotic cells), which express proteins derived from the virus that killed the cell, are taken up and transported from the endosome-MHC II route to the proteosome-MHC I route and presented to $CD8^+$ Tc.

Another important development in DC biology was the identification of a rare cell type specialized in the secretion of high levels of type I IFNs [60]. Almost simultaneously, pathologists characterized a unique cell population that was abundant in LNs of patients with infectious diseases [61]. These cells were named "plasmacytoid T cells/monocytes" based on their plasma cell morphology and expression of a distinct set of myeloid-lymphoid surface antigens ($CD4^+$, $IL\text{-}3R^+$, $CD11c^-$, negative for most lineage markers) [62]. As these cells had characteristics of precursor DCs, they were renamed to pDCs, and pDC biology differs from conventional DC biology in many aspects (cell morphology, phenotype, and function). pDCs display a potent capacity to produce large amounts of type I IFNs in response to viruses, CD40 ligand, and bacterial CpG [63, 64]. pDCs are rare cells (~0.4% of human peripheral blood or of murine lymphoid organs) that originate from the bone marrow (presumably from a lymphoid precursor) and reside primarily in the lymphoid organs under steady-state conditions. Mature pDCs can efficiently induce $CD4^+$ T cell responses and cross-prime $CD8^+$ T cells in the LNs. In addition, pDCs have been found to display tolerogenic and/or Treg-inducing properties, indicating plasticity of pDC function.

DC DEVELOPMENT AND THE TISSUE ENVIRONMENT

The precise origin of DCs and their differentiation program has puzzled scientists for many years. The current dogma is that DCs, like other leukocytes, develop from hematopoietic stem cells in the bone marrow [65]. Myeloid-derived progenitors produce monocytes and committed DC progenitors. These latter progenitors give rise to pre-DCs that leave the bone marrow and migrate through the blood to peripheral tissues. The next step is differentiation of pre-DCs into various different subsets, including $CD8^+DEC205^+$ and $CD8^-33D1^+$ in the spleen and $CD103^+$ DCs in nonlymphoid tissues. This differentiation program is under tight control of specific transcription factors and cytokines. From the Langerhans cell studies, it was believed initially that antigen presentation of tissue-derived antigens within LNs was restricted to DCs that had migrated from peripheral tissues. However, the characterization of lymphoid-resident DCs in thymus, spleen, and LNs revealed that antigen presentation can extend to DCs that permanently reside within lymphoid tissues [66]. An example of such a lymphoid-resident DC population includes the $CD8^+$ DCs, capable of presenting MHC I-restricted antigen in the case of skin infection [67].

More recently, another layer of complexity has been added by the observation that progenitors of DCs may develop into specific subsets under the stringent control of tissue-derived factors. In this respect, the production of TGF-β by the epithelial cells of the skin, keratinocytes, controls the development of Langerhans cells [68, 69]. Another example of such tight

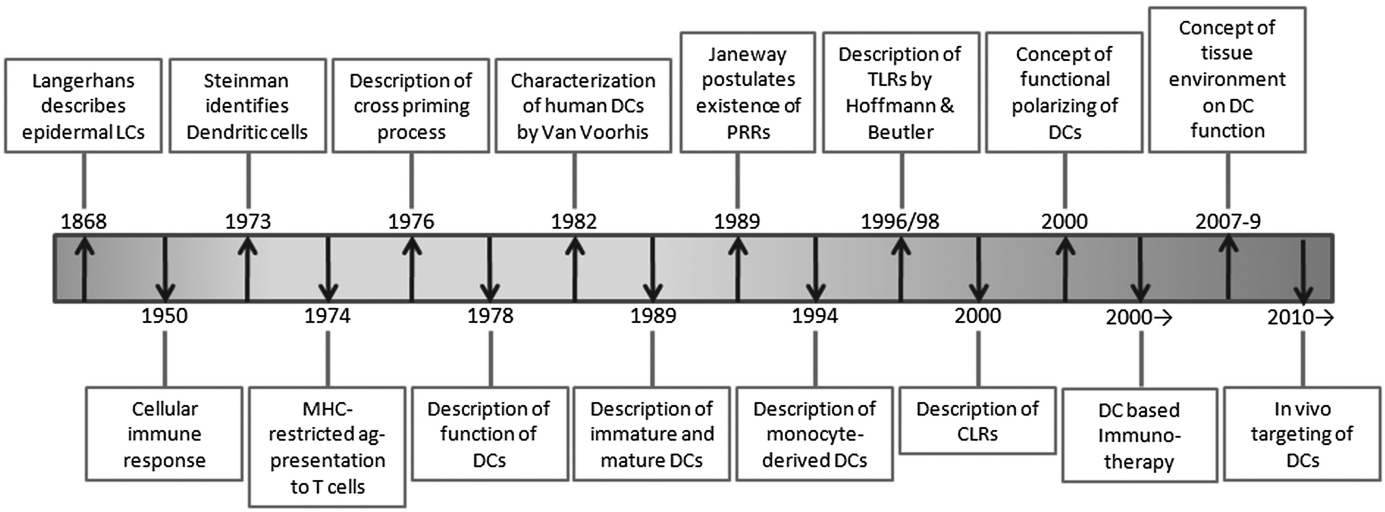

Figure 2. Time-line of major events in DC biology.

regulation of DC subset development has been demonstrated by Fiona Powrie, Yasmin Belkaid, and Maria Rescignio and their coworkers [40–42] in the gastrointestinal tract, where epithelial cell-derived retinoic acid promotes the development of $CD103^+$ DCs. These $CD103^+$ DCs drive specifically the development of Tregs, which play an important role in the maintenance of homeostasis in the intestines, continuously exposed to large amounts of microbes. These studies suggest that select tissues generate their DCs locally, possibly from a pool of DC precursors, rather than depending on influx of DCs from the bone marrow [58]. In the lungs, Bart Lambrecht and Hamida Hammad [70] have demonstrated the relative contributions of different DC subsets to viral infections and inflammatory disorders, such as asthma. Thus, the DC lineage, the tissue environment, and the pathogen encounter shape the outcome of the initiated immune response.

DCs IN THE FUTURE

All of the efforts to unravel the function of DCs, as well as the knowledge about features of specific subsets, have led to the use of these cells for the treatment of various diseases. Different groups (Jolanda de Vries, Jacques Banchereau, Karolina Palucka, Gerold Schuler, and their colleagues [71–74] and others [75]) have embraced the idea of harnessing DCs for cancer immunotherapy. Although this therapy is far from perfect yet, major advances have been made. The first experimental procedures involved the application of tumor antigens to monocyte-derived DCs ex vivo and subsequent administration to the patient. This approach has resulted in the first DC vaccine (Sipuleucel-T or Provenge), which was approved by the U.S. Food and Drug Administration in May 2010 for prostate cancer. This vaccine is composed of autologous mononuclear cells that have been activated ex vivo with a recombinant fusion protein that consists of a prostate antigen (prostatic acid phosphatase) fused to GM-CSF.

Treatment with this DC vaccine demonstrated a 4-month improvement in overall survival of patients with metastatic prostate cancer compared with placebo-treated patients [76].

Recently, in vivo targeting of tumor antigens to DCs is being applied, for instance, using the aforementioned uptake receptor DEC-205 [72, 77]. Coadministration of activating agents (adjuvants or DC maturation stimuli) will be required to induce robust cellular immune responses. Targeting antigens to DC in vivo are not only under development for cancer immunotherapy but also for immunotherapy against infectious diseases, such as HIV or autoimmune disorders [78]. The challenge will be to identify the optimal targeting receptor(s), molecular pathways, and the most effective route of administration that results in potent therapeutic vaccines.

CONCLUDING REMARKS

The cells that we now call DCs have a long history of key observations made more than 40 years ago. Although some original publications were disregarded at first, the importance of DCs has been widely appreciated by immunologists since the 1980s. The 2011 Nobel Prize for the discovery of recognition receptors that activate the innate immune system, including DCs, reflects the advances that have been made in understanding our immune system. Still, the diversity of DC subsets, their function, and the potential use in immunotherapy are the focus of intense research today. Taken together, during the last 40 years, ample knowledge has gathered about this illustrious cell (**Fig. 2**), although we are only just beginning to understand how and why this important cell develops as it does.

AUTHORSHIP

A.B.v.S. initiated the minireview. A.B.v.S. and E.C.d.J. wrote the review together.

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KEY WORDS:
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