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Human dendritic cell subsets in vaccination

Karolina Palucka and **Jacques Banchereau**
Ralph M. Steinmann Center for Cancer Vaccines, Baylor Institute for Immunology Research, Baylor Research Institute, Dallas, TX, USA

Abstract

Owing to their properties, dendritic cells (DCs) are often called ‘nature's adjuvants’ and thus have become the natural targets for antigen delivery. DCs provide an essential link between the innate and the adaptive immune responses. DCs are at the center of the immune system owing to their ability to control both tolerance and immunity. DCs are thus key targets for both preventive and therapeutic vaccination. Herein, we will discuss recent progresses in our understanding of DC subsets physiology as it applies to vaccination.

Dendritic cells (DCs) are key regulators of innate and adaptive immune responses [1,2]. The plasticity of DCs in response to extrinsic signals and the existence of distinct DC subsets with distinct functions contribute to the mounting of highly diverse immune responses. DCs are essential in pathogen resistance including different viruses, bacteria and parasites as demonstrated using DC-depleted mice [3]. Vaccine adjuvants primarily act via activation of DCs. Preventive vaccines are designed to initiate protective humoral immune responses. Today, more than 70 preventive vaccines have been licensed for use against approximately 30 microbes, sparing countless lives [4••]. However, effective vaccines remain elusive for diseases such as human immunodeficiency virus (HIV)-induced acquired immune deficiency syndrome, plasmodium-induced malaria, virus-induced hepatitis C, and *Mycobacterium*-induced tuberculosis, to cite a few [4••]. Most of these are chronic diseases for which it is thought that strong cellular immunity, in particular cytotoxic T cells, is necessary to eliminate the cells that are infected with the causative agent. Therapeutic vaccines have been designed to eliminate existing diseases and cancer represents an important target for such therapeutic vaccines. Early studies also indicate that vaccines might also be developed in noninfectious settings for the treatment of allergy, and autoimmunity. Here we will discuss recent insights and current views on the biology of human DC subsets in the context of vaccination.

Human DC subsets

While there has been considerable progress in understanding the ontogeny of mouse DC subsets [5,6], less is known on the origin of human DCs and their differentiation program. This is due to their rarity in the blood, the poor accessibility of human tissues and the limited experimental approaches that can be applied to humans. Care should be taken, however, in extending the data generated from mouse DC subsets to human DC subsets. The knowledge of human DC subsets came from studies on blood and skin DC subsets. These studies have distinguished human-blood-circulating DC subsets based on three main cell surface markers: CD303 (BDCA-2) on plasmacytoid DCs (pDCs), CD1c (or BDCA-1) expressed on the majority of circulating DCs and CD141 (or BDCA-3) expressed on a minute population [7–9]. Human $CD141^{+}CD1c^{-}$ DCs uniquely express Toll like receptor 3; produce IL-12 and

Corresponding authors: Palucka, Karolina (karolinp@baylorhealth.edu) and Banchereau, Jacques (jacques.banchereau@gmail.com).

efficiently cross-prime $CD8^+$ T cells when activated with poly I:C [10–16]. However, other human DCs such as epidermal Langerhans cells (LCs) [17,18] and $CD1c^+$ DCs also cross-present antigens to $CD8^+$ T cells [12,14,15]. DCs express numerous nonclonal recognition receptors, including lectins, Toll-like receptors (TLRs), NOD-like receptors (NLRs) and helicases through which they can sense microbes and microbial products as, for example, nucleic acids thereby allowing the launching of protective type I interferon production [19•, 20]. Indeed the experimental adjuvants CpG and Imiquimod bind to TLR9 and TLR7/8 respectively [20]. Most recently biochemical approaches revealed novel sensors of nucleic acid function from the DExD/H-box helicase family molecules in DCs [21,22].

Human DC subsets and humoral immune responses

T helper (Th) subsets, specialized for promoting particular types of immune responses and eventually inflammations, function through their secretion of a restricted set of cytokines enabling unique immune responses (reviewed in [23]). Among those, T follicular helper (Tfh) cells help B cells to differentiate into antibody-secreting cells and govern the germinal center reaction, the main site of Immunoglobulin somatic mutation and isotype switching [24,25]. Human blood CXCR5+ CD4+ T cells represent circulating memory Tfh cells. Blood CXCR5+ CD4+ T cells comprise three subsets: T helper 1 (Tfh1), Tfh2, and Tfh17 cells. Tfh2 and Tfh17 cells efficiently induced naive B cells to produce immunoglobulins via interleukin-21 (IL-21) [26]. In contrast, Tfh1 cells lacked the capacity to help naïve B cells [26]. *In vitro* studies, permitted us to conclude that Tfh development is regulated by a specific dermal DC subset, interstitial CD14+ DCs [17] and requires IL-12 both *in vitro* [27] and *in vivo* as IL-12Rb1 deficient humans displayed substantially less circulating memory Tfh and memory B cells than control subjects [28]. Importantly in the context of vaccination, expansion of Tfh1 cells at day 7 correlates with protective antibody titers at day 28 after influenza vaccination in healthy adults and children [29]. Whether the induction of Tfh differentiation depends on the same mechanisms in mice remains to be established. *In vivo* DC targeting tools will facilitate delineation of specific subset function in antigen responses as discussed later.

Human DC subsets and cellular immune responses

$CD8^+$ T cells recognize peptide-MHC (pMHC) class I molecules expressed by DC and develop into cytotoxic T lymphocytes (CTLs) able to kill cells presenting a specific pMHC complex [30]. As such $CD8^+$ T cells represent the goal of therapeutic vaccination in cancer and chronic infections. The ideal properties of vaccine-elicited $CD8^+$ T cells include: (i) high avidity for pMHC on tumor cells; (ii) high levels of granzyme and perforin, molecules essential for cytotoxic activity against cancer/infected cells; (iii) expression of surface molecules allowing trafficking into the tumor; and (iv) resistance to regulatory mechanisms present in the tumor [17,31]. At least four components of the immune response are necessary for that ideal response to happen: (1) the presence of antigen presenting DCs; (2) the quality of induced $CD4^+$ helper T cells; (3) the elimination of Tregs; and (4) the breakdown of the immunosuppressive tumor microenvironment. Earlier studies of human cutaneous DCs have demonstrated their phenotypic and functional heterogeneity with regards to cellular immunity and priming of highly efficient CTLs [32]. Our studies with human Langerhans cells and interstitial DCs, showed their specialization in priming CD8+ T cell immunity and humoral immunity, respectively [17,33]. Skin LC efficiency in priming naïve $CD8^+$ T can be at least partially explained by their surface expression of IL-15 [34,35] and/or upregulation of CD70 upon viral exposure [36]. Furthermore, interstitial DCs play a major role in generation of suppressor CD8+ T cells [37]. Here again the mouse and the human seem to differ under some circumstances as suggested by murine studies using a Candida albicans skin infection model. There, direct presentation of antigen by LC is

necessary for Th17 responses whereas Langerin-expressing dermal DCs are required for the generation of antigen specific CTLs [38]. Recent studies have further analyzed lymph-node-resident and skin-migratory DC subsets in the human [16,39]. Both $CD1c^+$ and CLEC9A-expressing $CD141^+$ DCs isolated from human lymph nodes were able to cross-present long peptides (requiring processing) of melanoma-tissue-derived antigen (MART-1) to T cell lines [39] whereas blood DCs can cross-present when activated via Toll-like receptor ligands [11,12] (see Figure 1).

T cell immunity has long been described in terms of two circulating memory populations. Central memory T cells migrate between the secondary lymphoid organs and are capable of mounting a recall proliferative response on pathogen re-encounter, whereas effector memory T cells traffic between blood and extralymphoid compartments for effective peripheral immune surveillance. A third category of memory cells, that is, tissue-resident memory T cells are phenotypically distinct from other T cells [40••,41]. Studies in mice [42,43] and humans [44] have revealed that these tissue-resident memory T cells can be superior to circulating central memory T cells at providing rapid long-term protection against re-infection. Therefore, an active mechanism of T cell retention in the periphery likely exists not only to facilitate the clearance of infected cells but also to promote the accumulation noted at sites that have cleared an infectious virus. Among relevant molecules is CD103/β7 integrin that endows peripheral $CD8^+$ T cells with a unique capacity to access the epithelial compartments [45,46]. The expression of CD103 on CTLs that mediates adherence to E-cadherin appears to be an important factor in the final cancer lysis and rejection [47]. The role of DC subsets residing in the tissue in the regulation and maintenance of tissue residing T cells remains to be characterized [48]. Studies using humanized mice and human lung tissues revealed that lung $CD1c^+$ DCs were uniquely able to drive the differentiation of $CD103^+CD8^+$ mucosal T cells while both lung $CD1c^+$ and $CD141^+$ DC subsets DC subsets could acquire viral antigens and drive anti-viral effector $CD8^+$ T cell responses (Yu *et al.*, in press). These findings have important implications for our understanding of protective immune memory at epithelial interfaces with the environment, and suggest novel strategies for vaccines that protect against tissue tropic organisms. They are also important for cancer vaccines as recently demonstrated in the context of mucosal cancers in the mouse [49••].

Vaccination via DCs: cell-based therapy

Therapeutic vaccines in humans have been mostly developed in the context of cancer. DCs can be engaged indirectly as for example with GVAX [50] or Listeria-based vaccines [51] to name a few. DC can also be used directly following their generation ex vivo and injection to patients [52]. These studies concluded that DC-based vaccines are safe and can induce the expansion of circulating CD4+ and CD8+ T cells that are specific for tumor antigens [52–55]. Objective clinical responses have been observed in some patients. A recent study focused on optimizing vaccine immunogenicity and demonstrated in phase I/II clinical trials that provision of MHC class II epitopes from defined melanoma tumor antigens results in improved immunogenicity [56]. Furthermore, novel approaches are being developed including the preoperative vaccination of patients with her2+ breast cancer [57] as well as combination therapies in ovarian cancer utilizing autologous DC vaccines and adoptive T cell transfer to enhance vaccine efficacy [58]. More recent studies have utilized another DC subset, plasmacytoid DCs, which are the main source of type I interferon upon viral infection [59•]. Patients with metastatic melanoma received intranodal injections of pDCs activated and loaded with tumor antigen-associated peptides ex vivo. Several patients mounted vaccine antigen-specific $CD4^+$ and $CD8^+$ T cell responses. Despite the limited number of administered pDCs, an IFN signature was observed after each vaccination [59•]. Whereas the clinical efficacy of elicited immunity will need to be determined in larger cohorts and long-term follow up, type IFN response is highly desirable in melanoma

[60,61]. All in all, the field is active as evidenced by 122 open and ongoing trials with known status, identified by searching the clinical trial database (clinicaltrials.gov) with the term ‘dendritic cells’.

Vaccination with DCs has also been used for other medical conditions including HIV infection and autoimmune diseases. Numerous approaches have been taken to vaccinate HIV infected individuals, including peptides, inactivated virus, viral vectors, and ex vivo generated DCs [62–64]. The latter represents an approach to optimize the induction of immune responses in patients. Different DC preparations loaded with different HIV antigens have been tested [65]. Two studies, where DCs have been loaded with a high dose of chemically inactivated autologous virus, have reported a decrease in viral load. One study reported a decrease by 90% in eight out of 18 untreated patients lasting at least one year [66] and the other study reported a decrease of plasma viral load set point ≥1 log in 12 of 22 (55%) at 12 weeks after analytical treatment interruption [67•]. Another approach to load HIV antigens onto DCs is to transfect them with RNA isolated from the autologous virus [68]. This approach has yielded some immune response in patients but has not clearly been associated with a control of viral replication. Whereas further studies are needed to achieve the functional cure, DC-based vaccines represent an essential component of modern therapeutic strategies in HIV.

Autoimmune diseases are the result of an imbalanced immune regulatory network [69]. Tolerogenic DCs are key players of this network by inducing and maintaining both central and peripheral tolerance [70]. Therefore, ex vivo generated tolerogenic DCs are considered as therapeutic vaccines to re-establish antigen-specific tolerance in autoimmune disorders such as rheumatoid arthritis [71] or multiple sclerosis [72]. Studies in the mouse using antigen targeting approach demonstrated that migratory DCs have a superior ability to generate antigen-specific Tregs *in vivo*, leading to improved outcomes in experimental autoimmune encephalomyelitis [73••]. Furthermore, targeting of DCs via DEC-25 with beta cell antigens led to deletion of autoreactive CD8+ T cells even in the context of ongoing autoimmunity in NOD mice [74••]. These results provide support for the development of DC targeting of self antigens for treatment of chronic T cell-mediated autoimmune diseases.

Vaccination via DCs: *in vivo* DC targeting

Following the pioneering studies from Ralph Steinman and Michel Nussenzweig labs with anti-DEC 205 antibodies [75–77], numerous studies performed in mouse models and in human *in vitro* systems demonstrated the efficacy of targeting DCs [2]. Most particularly, targeting antigens through the DC surface lectins DCIR [18,78], DC-SIGN [79], Dectin [80], Clec9A [81], and Langerin [82], results in humoral and/or cellular $CD4^+$ and/or $CD8^+$ T-cell responses. In the absence of adjuvants, targeting $DEC205^+$ DCs *in vivo* can induce tolerance [75]. Provision of adjuvants such as TLR3 or TLR7/8 agonists or DC activation signal via CD40 enables the concomitant maturation of vaccine engulfing DCs [83]. Furthermore, targeting different DC receptors generate quantitatively and qualitatively different immune responses [84••,85••]. Injection of antigens coupled to antibodies against DC surface molecule Clec9A results in production of strong antibody responses even without co-administration of adjuvants [86]. That happens via antigen presentation by DC on MHC class II and consequent Tfh expansion [87]. These results in the mouse are in line with prior studies showing the essential role of DCs in the generation of antibody responses and show that these can be amplified by targeting antigen to DC surface receptors *in vivo*. Importantly CLEC9a is also a receptor for necrotic cells and has been shown to facilitate cross-presentation [88]. As opposed to antibody response, CLEC9A dependent generation of CD8+ T cell responses requires adjuvant. Generation of different responses by targeting distinct DC receptors is further exemplified by recent studies targeting DC-

asialoglycoprotein receptor (DC-ASGPR), a lectin-like receptor, which is a known scavenger receptor. Targeting antigens to human DCs via DC-ASGPR *in vitro* but not lectin-like oxidized-LDL receptor, Dectin-1, or DC-specific ICAM-3-grabbing nonintegrin favored the generation of antigen-specific suppressive CD4+ T cells that produce interleukin 10 (IL-10) [89]. These findings apply to both self-antigens and foreign antigens, as well as memory and naive CD4+ T cells both *in vitro* in the human system and *in vivo* in nonhuman primates [89]. Furthermore, comparing the cross presentation of identical antigens conjugated with antibodies against different DC receptors that are targeted to early or late endosomes at distinct efficiencies revealed remarkable differences [90]. Thus, in human BDCA1+ and monocyte-derived DCs, CD40 and mannose receptor targeted antibody conjugates to early endosomes, whereas DEC205 targeted antigen primarily to late compartments. Surprisingly, the receptor least efficient at internalization, CD40, was the most efficient at cross presentation. This did not reflect DC activation by CD40, but rather its relatively poor uptake or intraendosomal degradation compared with mannose receptor or DEC205 [90]. DC targeting-based vaccination studies in nonhuman primates demonstrated robust T cell immunity in prime-boost design with HIV gag-DEC205 targeting vaccine [91]. Early clinical trials in the human analyzed the delivery of gonadotropin [hCG-b] to APCs by antibody-mediated targeting of a mannose receptor [92]. Delivery of this product with GM-CSF and TLR3/TLR7/8 agonists induced consistent humoral and cellular immune responses to hCG-b [92]. Several studies are ongoing testing the immune efficacy of HIV antigens or NY-ESO1 cancer antigen targeted via DEC-205 in healthy individuals and in cancer patients (clinicaltrials.gov).

Conclusions

DCs are composed of subsets that differ in their localization, phenotype, and functions. DCs regulate cell types critical to generation of protective and therapeutic immunity including Tfh cells which dictate the quality of humoral immunity and CD8+ T cells that give rise to CTLs able to eliminate infected/transformed cells. Targeting antigens and adjuvants to distinct DC subsets *in vivo* can be used to generate specific type of immune response. Thus, ever increasing understanding of DC biology along with the generation of tools allowing their direct manipulation *in vivo* will enable the development of next generation improved vaccines.

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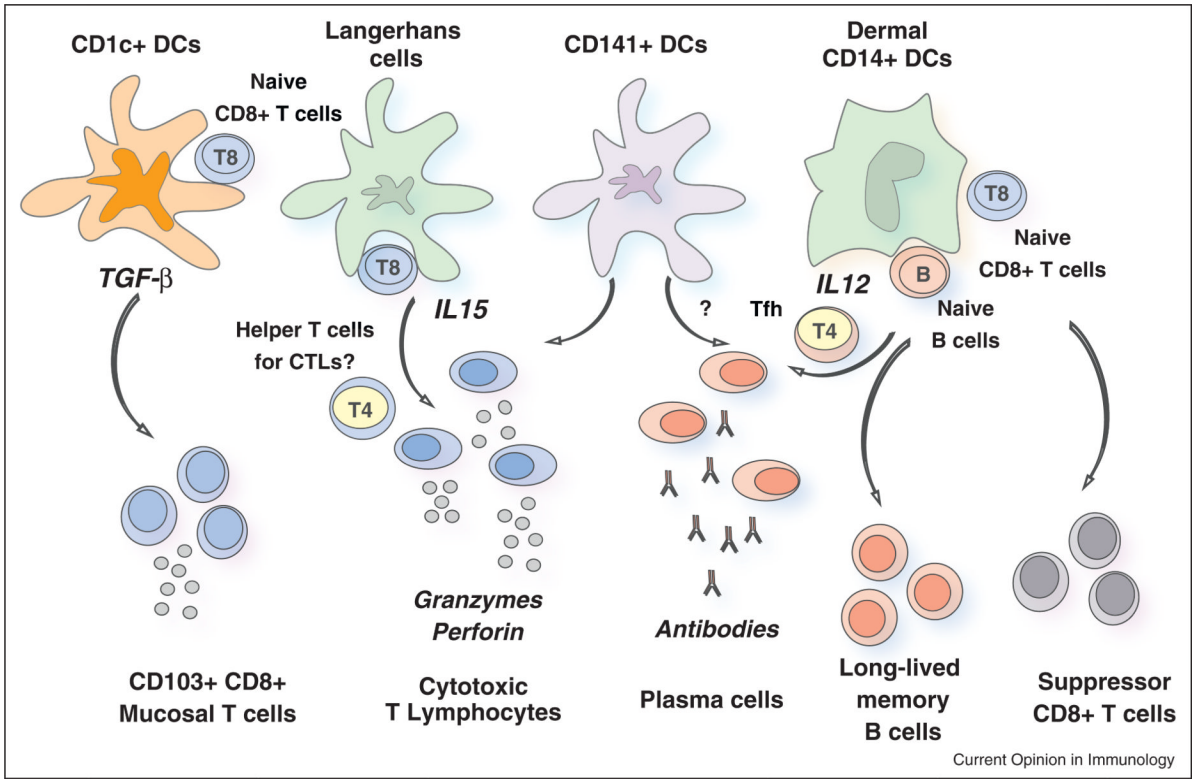

Figure 1.

The two arms of the adaptive immune response — humoral and cellular — are regulated by different subsets of dendritic cells (DCs) in humans. Humoral immunity is preferentially regulated by $CD14^+$ dermal DCs, which produce interleukin-12 (IL-12). IL-12, in turn, acts directly on B cells and promotes the development of T follicular helper (T_{FH}) cells. In the mouse, $CD141^+$ DCs seem to be able to promote humoral immunity upon CLEC9A engagement. In the human this function remains to be established. $CD141^+$ DCs might also be involved in the development of humoral responses through IL-12 secretion. Cellular immune responses in the blood, skin and peripheral tissues are differentially regulated by human DC subsets. Thus, Langerhans cells prime highly efficient cytotoxic T lymphocytes (CTLs), possibly via IL-15. It is also possible that Langerhans cells can preferentially activate a dedicated subset of $CD4^+$ T cells that are specialized to help $CD8^+$ CTLs, though this remains to be established. Given their capacity to cross-present antigens to $CD8^+$ T cells, $CD141^+$ DCs are also involved in the development of CTL-mediated responses. $CD1c^+$ DCs can cross-present antigens as well and can equip the primed $CD8^+$ T cells with the expression of CD103 which allows them to reside in mucosa. Finally, $CD14^+$ dermal DCs generate suppressor $CD8^+$ T cells with ILT-2 and ILT-4 among possible mediators. Much remains to be learned about other immune phenotypes that these DC subsets can elicit.