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Dendritic cells – why can they help and hurt us

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Abstract: Dendritic cells (DCs) show a Janus-like functional behavior. They help us by their orchestration of numerous immune responses to defend our body against invading pathogenic micro-organisms and also induce regulatory T cells to inhibit immune reactions against autoantigens as well as diverse harmless environmental antigens. However, DCs can also be of harm to us when misguided by their microenvironment as in allergic and autoimmune diseases or when DCs are targeted and exploited by microbes and cancer cells to evade the immune defense. This huge and diverse functional repertoire of DCs requires complex decision-making processes and the integration of multiple stimulatory and inhibitory signals. Although a given DC type has an extensive functionally plasticity, DCs are heterogeneous and individual DC subtypes are differentially distributed in tissues, express distinct sets of pattern recognition receptors and differ in their capacity to program naive T cells. With the help of transgenic mouse models and selective ablation of individual DC subtypes, we are just at the beginning of understanding the DC system in its complexity. Obtaining a more detailed knowledge of the DC system in mice and men holds strong promise for the successful induction of immunity and tolerance in therapeutic trials. This review presents the recent advances in the understanding of DC biology and discusses why and how DC can help and hurt us.

Key words: allergy – cancer – Dendritic cell – immune regulation – immunology – lupus – psoriasis – slanDC – T cell

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Introduction

Ralph Steinman was among the first who studied a rare subset of accessory cells that in contrast to macrophages displayed a rather stellate cytoplasmatic protrusions which made him call these cells dendritic cells (dendron the Greek word for tree) (DCs) (1,2). Although a specific marker to isolate these cells was lacking, they quickly realized the unique T-cell stimulatory capacity of these cells. This crucial observation changed the perspectives of many fields of immunology.

The physiology of DCs that ensures adequate immune responses is the subject of the first part of this article, followed by a discussion of how DCs can be misguided in autoimmunity as well as in allergy and exploited by pathogens and cancer cells.

Why can DCs help us

Innate defense mechanisms were acquired early in evolution and are already known in single-cell organisms (3). More complex immune defense systems made use of the family of toll-receptors which were first described in drosophila. Immune systems including specialized cells such as T cells and B cells developed in vertebrates with jaws (gnatostomes) where T cells required the presentation of antigens by DCs.

Different subtypes of DCs are distributed throughout the body which display specialized functions depending on their anatomical location. In steady state, DCs are found in lymphoid tissues and in a dense network at body surfaces like the skin (Fig. 1), pharynx, upper oesophagus, vagina, ectocervix and anus as well as at internal mucosal surfaces such as the respiratory and gastrointestinal systems (4). Together they ensure immunity against invading pathogens and maintain tolerance against autologous structures. In the gut, epithelial DCs were shown to actively extend their processes into the intestinal lumen which allows them to sample bacteria for the induction of protective immunity via secretory IgA (5). Characteristic for pulmonary DCs in mice is their steady-state production of IL-10 that enables them to program IL-10-producing regulatory T cells mediating tolerance to inhaled antigens (6). DCs also circulate in blood ready to migrate into tissues to enhance antimicrobial immunity (Fig. 1).

Pattern recognition receptors

Protective immunity to a plethora of microbial pathogens with different invasive strategies and live cycles require diverse and well-adapted immune effector mechanisms.

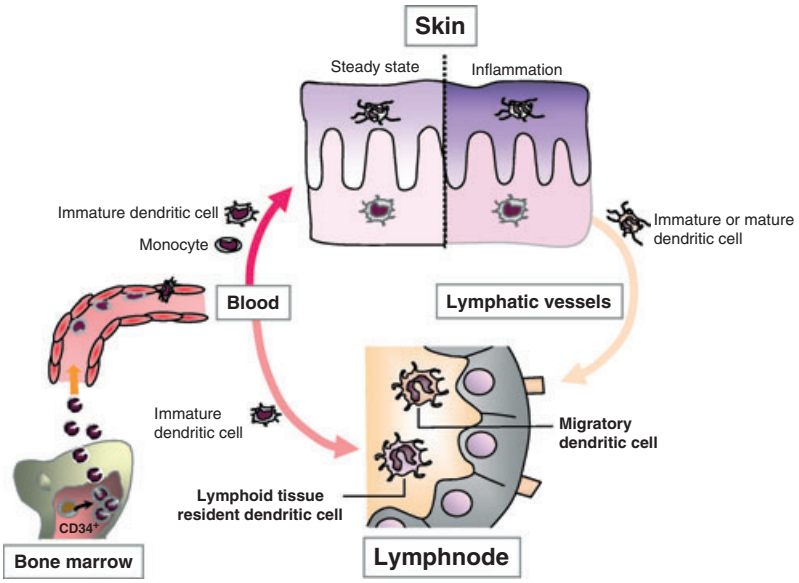


Figure 1. Migratory pathways of dendritic cells. Immature cDCs and pDCs circulate in blood at low numbers and home in into peripheral tissues like the skin. Blood monocytes in mice were shown to give rise to epidermal Langerhans cells and also to inflammatory dermal cDCs. Under steady-state conditions, DCs in tissues take up large quantities of antigens and were shown to constantly migrate through lymphatic vessels into the regionary lymphnode as immature, tolerogenic migratory DCs. When activate by pathogen encounter in tissues DCs rapidly mature and highly stimulatory DCs arrive in the lymphnodes and induce effector T cells. In addition, a substantial number of DCs enter the lymphnode directly via the blood circulation. These immature DCs can locally acquire antigen and induce effector T cells as well as tolerogenic T cells.

Ideally, the shape of the induced response assures efficient eradication of the pathogen (Fig. 2). The initial event is the sensing of a pathogen. Like many other cell types, DCs recognize pathogens by conserved pathogen-associated molecular patterns. At least four families of pathogen recognition receptors (PRRs) exist: Toll-like receptors (TLR), cell surface C-type lectin receptors (CLRs), intracytoplasmatic nucleotide oligomerization domain (NOD)-like receptors (NLRs) and intracellular retinoic acid inducible gene-I-like receptors (RLRs) (7). Depending on the contact site with the micro-organism, the PRR is located on the cell surface or within cells. Cell surface-expressed PRRs such as the CLR DC-SIGN (CD209), TLR4 and TLR2 bind products derived from extracellular pathogens such as candida or *Escherichia coli*. Whereas receptors for viral RNA like the RLRs or for cytoplasmatic Gram-positive bacteria like the NLRs are found intracellularly. Interestingly, receptors for double- or single-stranded RNA (TLR3, TLR7/TLR8) or DNA (TLR9) are confined to endosomes. The endosomal location prevents unwanted activation of DCs by free RNA or DNA derived from necrotic cells yet allows for activation of DC by ligands derived from phagocytosed microbial pathogens.

Antigen uptake

DCs have many uptake receptors that deliver antigens to processing compartments. Although poor in their phagocytic capacity, DCs efficiently take up antigens by pinocytosis and receptor-mediated endocytosis. An example of endocytotic receptors are receptors for the Fc part of immunoglobulins (Fc receptors, FcR), e.g. FcγRI, FcγRII, FcγRIII and FcεRI. They can increase the presentation of immunoglobulin-complexed antigens by at least 100-fold. In most instances, FcRs also induce DC activation, yet, triggering of the inhibitory FcγRIIb, containing a negative regulating motive (ITIM motive), blocks DC maturation and reduces IL-12 production (8). Furthermore, FcgRIIb was described to facilitate the reexpression of intact antigen on the surface of DCs which enables the stimulation of B cells by DCs (9). C-type lectins (DEC-205/CD205, mannose receptor/CD206, DC-SIGN/CD209, langerin/CD207, ASGPR, ORL1/LOX-1/CD91 and CLEC4A/DCIR) support the uptake of microbes. Many of these receptors have additional functions. For example, they can initiate intracellular signaling that inhibits DC maturation. This was demonstrated for DC-SIGN (CD209) which can reduce DC maturation and thereby can contribute to immune evasion of pathogens such as HIV, cytomegalovirus, mycobacteria and candida when they have bound to this receptor (10).

Antigen presentation

DCs are seen as mobile cells that bring antigens to lymph nodes where they activate naïve T cells. Extracellular antigens are taken up into endosomes that fuse with protease-containing lysosomes to generate immunogenic peptides. These peptides can bind to MHC class II molecules which are then transported to the cell surface. Cytoplasmatic protein antigens derived e.g. from viruses are presented as peptides bound to MHC class I molecules to cytotoxic $CD8^+$ T cells. These peptides are generated by ubiquitinylation and degradation by proteasomes before they are loaded onto MHC class I molecules. Cross-presentation describes an alternative way of antigen presentation where exogenous antigens are taken up and presented on MHC class I as

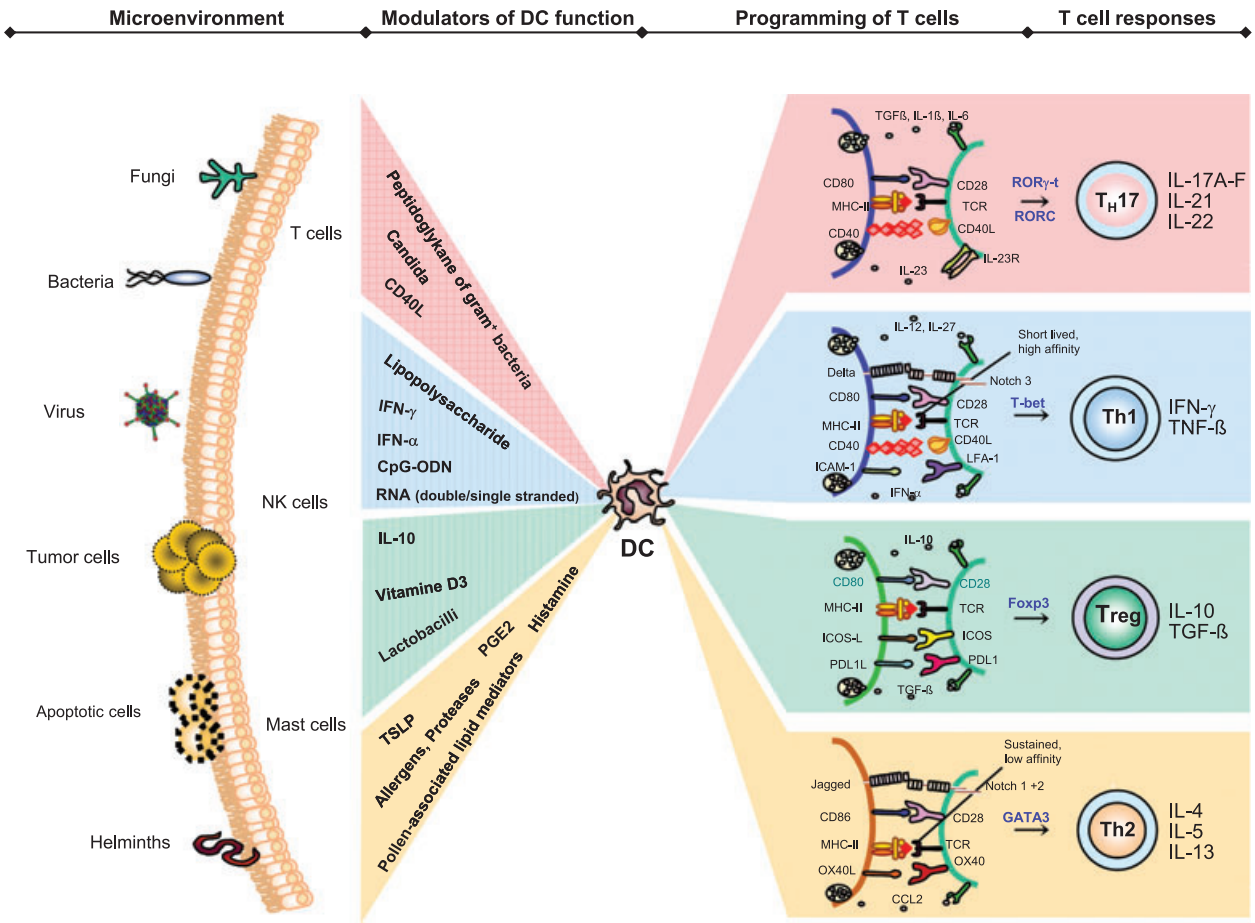


Figure 2. Environmental polarization of dendritic cell functions and programming of T cells. Resting DCs are under the control of the microenvironment which induces or restrains DC maturation. Important components creating this micromilieu are commensal or pathogenic microbes, epithelial cells and local resident or patrolling immune cells. Examples of well-known immune modulators are listed. Hereby, DCs are modulated and preferentially express cell surface molecules and cytokines that create distinct intracellular signals in naïve T cells leading to the expression of transcription factors that promote their differentiation into functionally specialized T-cell subsets.

well as MHC class II antigens (11). CD1 molecules that are quite similar to MHC class I are specialized to present lipid antigens (12).

The classical view of DCs is that they take up antigen in peripheral organs, migrate through lymphatic vessels to regionary lymphnodes where they present antigen and induce T-cell-dependent immune responses (Fig. 1). Alternatively, migratory DCs as well as newly described lymph node resident DCs can take up antigen from the lymph and induce primary immune responses specific for these antigens (Fig. 1) (13).

Maturation and T-cell programming

Maturation determines the functional diversity of DCs (Fig. 2), which on the one hand enables the induction of efficient immune responses against pathogens of all kinds and on the other hand induces tolerance to self-antigens and aid the resolution of inflammation by giving a negative feed back to effector cells (14,15).

Immature DCs are not inactive, in fact, they are of critical importance for the maintenance of active immune tolerance for autologous proteins by programming $CD4^+$, $CD25^+$ regulatory T cells (Treg) (Fig. 2) (16,17). Treg produce the immunosuppressive cytokines IL-10 and/or TGF-β and in addition can inhibit targets such as T-effector cells upon direct contact by transfer of cAMP via gap-junctions (18). The formal proof for Treg induction by immature DCs *in vivo* was achieved by targeting antigen to DCs *in vivo* using the antigen receptor DEC-205 in mice (19–21). This anti-DEC targeting was very efficient and was shown to inhibit the development of autoimmune type I diabetes (22,23). Other means to modulated DC function to program Treg are IL-10 as well as 1α,25-dihydroxyvitamin D3 (24,24,25), also lactobacilli have been reported to

induce Treg via modulation of DC function (26). It is important to note that the previous view that only immature DCs can induce tolerance, has to be modified by the finding of several groups that also DCs displaying a mature phenotype can expand regulatory T cells and *de novo* induce tolerogenic T cells (27).

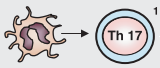
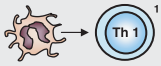
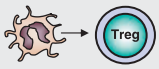
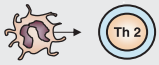
Th1 cells are important effector cells in the immune defense against intracellular bacteria and tumor cells and are of pathogenic relevance in autoimmune diseases (Table 1) (28,29). IL-4-, IL-5- and IL-13-producing Th2 cells are required for the induction of immune defense strategies against parasitic helminths by the induction of IgE and the activation and recruitment of mast cells and eosinophils. The programming of Th1 cells by DCs is well documented (Fig. 2). The key cytokine for the programming of Th1 cells is the heterodimeric cytokine IL-12p70 (p40 and p35). IL-12-production can be induced in DCs and macrophages by different microbial stimuli: the TLR4 ligand lipopolysaccharide, the TLR3 ligand Poli I:C, the TLR7 and TLR8 ligand R848, and also by activated T cells expressing CD40L (30).

In addition to IL-12 (31), also the quality of the of DC–T cell interaction is important. Short-lived interactions of peptide-loaded MHC molecules with the antigen receptor on T cells favours the programming of Th1 cells while long-lived DC–T cell interactions induces programming of Th2 cells (Fig. 2) (32–34). Recently, it was shown that the notch-pathway, well known for its crucial role in cell development, also influences the programming of T cells (35). Pathogen-induced upregulation of the delta-like ligand on DCs binding to notch molecules on T cells stimulated the programming of Th1 cells while jagged expression of DCs induced the programming of Th2 cells.

Many studies published in the past 2 years describe and discuss the characteristics of a third type of T-effector cell population called Th17 cells. This T-cell population preferentially produces IL-17, IL-21 and IL-22 (Fig. 2) (36) and is of importance in the pathogenesis of autoimmune diseases (37–43). Interestingly, many of these diseases were previously linked to the function of Th1 cells (44). The role of Th17 cells in immune defense against microbial pathogens is not clear (Table 1). It is assumed that Th17 cells are important for the clearance of certain pathogens such as candida or Gram-negative bacteria and at the same time promote the chronicity of the infection (45–48). Their programming is controlled by the transcription factor ROR-γt in mice and RORC variant 2 in humans (49). The cytokines IL-1β, TGF-β and IL-6 are important for the induction of the Th17 phenotype as shown by *in vitro* studies, while DC-derived IL-23 is critical for the expansion of Th17 cells *in vivo* (Fig. 2) (50). The exact requirements for efficient programming of Th17 by DCs are still incompletely understood.

It has to be kept in mind that T-cell programming is not only a one-step procedure induced by pathogens stimulating PRRs expressed by DCs. Rather, there appears to be a two-stage decision-making process and several feedback loops during the development of a polarized T-cell response (51). First, there is a primary polarization decision during the

Table 1. T cell programming by dendritic cells and its relevance for immunity and disease

	Physiologic relevance *'helps'*	**Pathophysiologic relevance *'hurts'***
Programming of T cells by DCs		
 [1]	Limits pathology in candida and pnemocystis carinii infection (34,35,46).	Psoriasis vulgaris (39) Chronic inflammatory bowl disease (41) Experimental allergic encephalitis (38) Collagen-induced arthritis (40) Experimental autoimmune uveitis (42)
 [1]	Enables immunity against intracellular bacteria and viruses (29). Permits efficient anti-tumor responses (29).	Aggravation of fungal infections at mucosal sites (47) Multiple sclerosis (44), rheumatoid arthritis (28) Experimental collagen-induced arthritis (28) Experimental allergic encephalitis (43)
	Enables tolerance of autologous proteins (16). Enables resolution of inflammatory immune responses (16).	Pathogenic relevance in autoimmune diseases often in combination with Th17 cells (37) Inhibits anti-tumor immune responses (112) Inhibits eradication of microbial pathogens in chronic infections (15)
	Protects against helminths (29).	Critical role in IgE-mediated allergic diseases (29)

Depending on the specificity of the T cells and the magnitude of the immune response, T-cell programming governed by dendritic cells can be helpful or can cause disease.
[1]Strong evidence for cross-regulation (37).

initiation of the primary response, which is induced by the pathogen. This polarization results from ligation of certain PRRs on the DCs and also includes cytokines such TNF-α, IL-1, IFNs or the newly described cytokine thymic stroma derived lymphopoietin (TSLP) originating from neighbouring cells. Thereby, these activated DCs undergo a complex maturation program modulating the expression of up to ~6000 genes (52). In stage two, the verification stage, an effective attack by already induced effector cells results in the preferential generation of pathogen-related antigenic materials. Th1-polarized cytotoxic T lymphocytes (CTL) lead to the apoptosis of pathogen-carrying cells. The resulting apoptotic bodies can boost CTL-mediated immunity by cross-presentation of the pathogen-derived material contained within the apoptotic bodies (53). Similarly, Th2 response-associated immune complexes will stabilize the 'successful' feedback loop of immunity by preferential presentation of the antigenic material via MHC class II. Most importantly, the cytokines and cell surface molecules expressed by T cells generated during the primary polarization can prime immature DCs to repetitively program the same quality of immune response.

We are one, but we are not the same

The DC system comprises several subsets of cells with distinct functions. The common feature of all DCs is that they take up antigen, process it and present antigen-derived peptides to naïve T cells. Subsets of DCs differ by their location and by their particular function in the immune system. The field of identifying DC subsets is rapidly progressing and the current plethora of DC subsets defined by multiple markers in mouse and man may be confusing. Although DCs in mice and man differ in many aspects we are constantly getting a much better understanding of the DC-system as a whole when studying mice. Particularly, the current strategies of inducible DC ablation in transgenic animals will rapidly increase our understanding of the contribution of each of the DC subsets to immunity or tolerance (52,54).

In general, we can differentiate between the classical text book DCs, the migratory DCs and DCs that primarily reside in the lymphoid tissue (Fig. 1). Furthermore, it seems necessary to differentiate between the distinct subtypes of DCs having different phenotypic and functional characteristics, and which in some instances also express specific markers (Table 2).

Migratory DCs act as sentinels in peripheral tissue and migrate to the lymph nodes through the lymphatic vessels, bearing antigens collected in peripheral tissue. A classical example of this type of DCs are Langerhans cells and interstitial DCs, which migrate from the skin to the lymph node, where they exhibit a mature phenotype and can induce a primary T-cell response (Fig. 2). However, this picture seems to be too simplistic and has been challenged by some recent studies. In mice, the observation was made that Langerhans cells are not involved in the presentation of pathogens that infect the skin, such as L. major (55,56), influenza virus, vaccinia virus or HSV (57,58). In addition, these studies provided evidence that rather the dermal DCs, another migratory DC type, and not Langerhans cells, play a crucial role in the presentation of antigens derived from these pathogens. These migratory DCs constitute approximately 50% of the lymph-node DCs in mice. They are hardly found in spleen and thymus as these organs do not receive afferent lymph. Lymphoid tissue-resident DCs include most of the DCs in the thymus and in spleen. They do not migrate into lymphoid organs from lymphatics and peripheral tissues, they rather collect and present antigens in the lymphoid organ itself. Lymphoid tissue-resident DCs have an

Table 2. Subpopulations of human blood dendritic cells

DC type	Conventional DCs			Plasmacytoid DCs
Name	$CD1c^+$ DCs	$CD141^+$ DCs	slanDCs	Plasmacytoid DCs
Marker	CD1c (MHC class I related)[1]	CD141 (BDCA3, Thrombomodulin)[1]	6-sulfoLacNAc (slan)	BDCA2 (CD303, C-type lectin) BDCA4 (CD304, Neuropilin 1)
Frequency[2]	~0.4%	~0.2%	~1.2%	~0.2%
Phenotype	$CD33^+$, $CD13^+$, $CD11b^+$ (Marker suggestiveof myeloid differentiation)			$CD33^-$, $CD13^-$, $CD11b^-$
	$CD1c^+$	$CD1c^-$	$CD1c^-$	$CD1c^-$
	$CD11c^+$	$CD11c^{low}$	$CD11C^+$	$CD11c^-$
	$CD16^-$	$CD16^-$	$CD16^+$	$CD16^-$
	$CD45RA^-$	$CD45RA^-$	$CD45RA^+$	$CD45RA^+$
	$CD88^-$ (C5aR)	$CD88^-$	$CD88^+$	$CD88^-$
	C3 aR^-	$C3aR^-$	$C3aR^+$	$C3aR^-$
	CD 123^{low}	$CD123^-$	$CD123^{low}$	$CD123^+$
Cytokine production	Low TNF-α Low IL-12p70		High TNF-α High IL-12p70	High IFNα

[1]Marker not specific for DCs.
[2]Among peripheral blood mononuclear cells.

immature phenotype and are active in antigen uptake (13). Furthermore, the subset of $CD8^+$ lymphoid resident DCs in mice can take up antigens directly from migratory DCs, perhaps in the form of endosomal vesicles or apoptotic bodies, and cross present these antigens on MHC class I molecules. These $CD8^+$ DCs also express CD205 and are concentrated in the T-cell areas (59). $CD8^-$ DCs are the major population of DCs in spleen where they are primarily located in the marginal zones and migrate into the T-cell zones on stimulation by microbial products (59). A third population of lymphoid resident DCs in mice are $CD4^-$, $CD8^-$ DCs. Apparently, lymphoid resident DCs exist in the human immune system as well (60). In human spleen, immature marginal zone DCs could be identified, which in some donors may have moved to the T-cell zones (white pulp) after their activation.

DCs have previously been categorized into myeloid and lymphoid DCs subsets. However, as studies in mice show that different types of DCs can be generated from lymphoid as well as from myeloid progenitor cells, it is proposed not to categorize DCs in lymphoid and myeloid any more (61). They should be rather regarded as conventional DCs (cDCs) and plasmacytoid DCs (pDCs) (Table 2).

Because of their accessibility in humans, many studies concentrated on the characterization of blood DC subtypes. Human pDCs produce high levels of IFN-α after viral stimulation (62,63) and can be found in peripheral tissues ($BDCA2^+$ or CD45RA and CD123 double positive) (61,64) as well as lymphnodes (61,62). Among the cDCs, we can differentiate between $CD1c^+$ DC and $BDCA3^+$ DCs. In addition $CD16^+$ $CD14^{low\ or\ negative}$ cells can be found in human blood termed inflammatory monocytes (65). Among the heterogeneous population of $CD16^+$ $CD14^{low\ or\ negative}$ cells, our group identified a homogenous subset selectively expressing the carbohydrate modification 6-sulfo LacNAc (slan) on PSGL-1, called slanDC (Table 2) (66,67). These cells show all functional characteristic of DCs, they efficiently prime keyhole limped hemocyanin (KLH)-specific T cells, stimulate naïve cord-blood T cells and expand tetanus-toxoid specific T cells. Furthermore, slanDC primed cytotoxic T cells, stimulated NK cells and were efficient inducers of antibody dependent cytotoxicity (68,69). In contrast to $CD1c^+$ DC and pDC, slanDCs produce very high levels of TNF-α and turned out to be the leucocyte subset that readily produces high levels of IL-12p70 in the absence of a priming signal such as IFN-γ (67,70). Given their presence in the inflammatory infiltrate in psoriasis, rheumatoid arthritis (70) as well as Crohn's disease (71) and their high proinflammatory capacity it may be suggested that slanDCs are relevant for stimulating the local inflammation.

Also monocytes can give rise to DCs. This was first shown *in vitro* when blood monocytes were stimulated with GM-CSF and IL-4 (72,73); however, these cytokines may not be the critical signals in tissue to allow for DC development. Monocyte-derived DCs cannot be found in peripheral tissues under steady-state conditions, they rather emerge during inflammatory responses. Large numbers of monocyte-derived DCs were found in the skin of mice infected with Leishmania major (74) or Listeria monocytogenes (53) and in skin of patients suffering from leprosy (75). These monocyte-derived DCs may serve the function of an 'emergency' source of DCs.

DCs as tools in immunotherapy

The progress in understanding the regulatory function of DCs has stimulated much research on DC-based vaccination strategies. The good news is, that DC can be harnessed to efficiently induce immune responses in humans. This prove of principal was first shown in healthy subjects by Steinman and co-workers (76,77) when they studied the induction of KLH-specific $CD4^+$ T cells as well as the expansion of TT-specific $CD4^+$ T cells and influenza-matrix-specific $CD8^+$ T cells. However, in clinical trials a limited success has been achieved in terms of inducing partial or complete remission in patients with advanced stages of cancer (78). In many trials, *in vitro*-generated DCs pulsed with tumor antigens or peptides were used. An alternative approach is the direct *in vivo* targeting of DCs with tumor antigens conjugated to antibodies that enable more or less specific binding to the cell surface of DCs (79). Much was learned about these strategies in mice where DCs were targeted by their expression of CD205 (80,81). Targeting of DCs may also be possible in humans as many types of DCs express more or less restricted marker molecules such as langerin by Langerhans cells, DC-SIGN by dermal DCs, BDCA2 by pDCs or 6-sulfoLacNAc (slan) by slanDCs (Table 2). DCs targeted with antigens also require an activation signal, such as TLR-ligation, that should induce antigen processing, antigen presentation via MHC class I molecules and enable the translocation of the DCs into lymphnodes where effector T cells are primed (82). Mere targeting of antigen to DC receptors without providing an activation signal can result in tolerance, which may serve as an attractive strategy in the treatment of allergy, autoimmunity and transplant rejection. As it seems at the moment, there is still much to be learned until we develop efficient targeting strategies to modulate the function of DCs to reliably induce clinical benefit. This research field is currently developing rapidly and in light of the wide applicability of such 'of the shelf product' the future development appears promising.

Why do DCs hurt us?

DCs present two faces: on the one hand, they protect us by inducing adaptive immune responses against invading

microbial pathogens; on the other hand, they can be the driving force stimulating autoimmunity or inhibiting immune responses against cancer cells. In addition, their central importance in immune regulation makes DCs an attractive target for immune modulation by microbial pathogens which developed many ways to destroy and disable DCs for their own benefit.

Autoimmunity

Autoimmune diseases are characterized by the loss of immune tolerance to self-antigens and stimulation of inflammatory immune responses against a large number of tissues. Dysregulated DCs in a genetically predisposed host appear to be crucial for the programming of autoreactive effector T cells and B cells, and it is well documented in different mouse models that DCs loaded with self-antigens are able to break immune tolerance (83,84).

Lupus erythematosus

Systemic lupus erythematodes (SLE) presents with widespread immunologic abnormalities and multiorgan involvement. A hallmark is the loss of tolerance to nuclear antigens resulting in complement fixing immune complexes that deposit in tissues and cause widespread inflammation. Altered T cell–B cell interactions have been proposed to represent the common mechanism leading to the establishment of SLE. Although SLE typically presents with many different clinical manifestations, one cytokine appears to be of particular importance for its pathogenesis. It was shown that serum levels of type I IFN correlate with disease activity and severity (85,86), and genomic studies on blood cells of patients with SLE indicated that many patients over express IFN-induced genes (54,87). In addition, polymorphisms of IFN-related genes were found to be associated with an increased susceptibility for the development of SLE (54,88). In mice, a null mutation of type I interferon bred with lupus prone mice exhibited decreased morbidity and prolonged survival (89,90), and IFN accelerates the development of autoimmune symptoms in lupus-prone NZB/NZW mice (91). As pDCs are the major IFN-α producing cell type (Table 2), much effort was put into studies revealing the mechanisms of how resting pDCs can be turned into high level IFNα-producing pDCs. It is assumed that UV-light induces apoptosis of skin keratinocytes, whereby nuclear antigens are released that can form stimulatory immune complexes with respective autoantibodies. These immune complexes can be taken up via Fcγ-receptors into many different cells types. In endosomes of pDCs, immuncomplexes containing ssRNA or DNA ligate TLR, and thereby stimulate the production of large amounts of IFN-α. These immune complexes are formed of DNA-specific autoantibodies and autologous DNA that can bind to TLR9. Alternatively, immuncomplexes are formed of autoantibodies specific for U1RNP, SM-Antigen, Ro-SSB or La-SSA (RNA-binding proteins) and attached single stranded RNA that can stimulate TLR7 (92). It is interesting to note, that chloroquine which is successfully used in the treatment of LE, may exert its therapeutic action by blocking the acidification of the endosomes and thereby inhibiting signaling via TLR7, TLR8 and TLR9 (22,93,94).

The type I interferon-producing pDCs may also be involved in the pathogenesis of other autoimmune diseases such as dermatomyositis as well as Sjögren's syndrome (95,96). This is in contrast to multiple sclerosis, that benefits from type I interferon therapy.

How type I IFNs induce disease is not completely clear. IFN-α enhances the cytotoxicity of lymphocytes (97) and induces the production of the antiviral proteins MxA and IFI27. IFN-α was also shown to enhance the production of the chemokines CXCL9 und 10 which induce the recruitment of lymphocytes and pDCs (22). In addition, IFN-α stimulates monocytes to express the NK cell marker CD56 and to increase their cytotoxic potential (98).

Psoriasis

In psoriasis as well as in rheumatoid arthritis and Crohn's disease, dysregulated DCs appear to produce large quantities of TNF-α and IL-23 that induce IL-17-, IL-21 and IL-22-producing effector T cells, called Th17 cells (Fig. 2, Table 1) (92,99,100). The substantial clinical benefit of therapies targeting TNF-α and IL-23/IL-12p40 are in support of this pathogenetic concept (39). The type of DC that is the source of these cytokines in not clearly defined. Lowes et al. identified dermal $CD11c^+$ DCs in psoriasis that produce large quantities of TNF-α and that are $iNOS^+$ (101). In humans, CD11c is expressed on different cell types including macrophages, therefore a more detailed analysis may be needed to define the TNF-α-producing cell types. With the better characterization of these DCs, we may be able to develop strategies to target them for therapeutic needs. pDCs, that can produce 1000 times more IFN-α than any other cell type, were linked with the initiation of psoriasis (102). It appears, that pDCs specifically accumulate in psoriasis at an early stage of the disease. Furthermore, in a human skin graft model it could be demonstrated that the production of IFN-α by pDCs is associated with the development of a psoriatic skin lesion. Previously, it was already observed that treatment of psoriasis patients with IFN-α for unrelated reasons can exacerbate the inflammatory skin reaction (103). Lande et al. recently gave an answer to the question of how the pDCs are activated in psoriasis (104). They found out that the microbial peptide LL37, which is overexpressed in psoriatic skin can form complexes with autologous DNA. These DNA/LL37 complexes are taken up by pDCs and induces IFN-α production by ligating TLR9 in endocytotic vesicles.

However, the stimulus that turns cDCs in psoriasis into high level producers of TNF-α and other proinflammatory cytokines is still to be identified.

DCs in allergy

The immune system normally tolerates harmless environmental antigens such as pollen, house dust mites and food. It is clear from many studies that immature or partially mature DCs in the respiratory tract as well as in the gut mucosa are prone to induce immune tolerance when sampling antigenic material in the absence of microbial stimulation. In fact, in mice experimental application of antigens by the inhalative route efficiently induces IL-10- and/or TGF-β-producing regulatory T cells, which depends on IL-10 and/or inducible T-cell co-stimulatory ligand (6,105).

It appears that the usual outcome of antigen contact via inhalation or the oral route induces tolerance by partially mature DCs. There are many ways of breaking tolerance and inducing Th2 responses. One possibility, already mentioned above, are low antigen loads, long lived and low affinity antigen-specific interactions of T cells and DCs. Other means of inducing Th2 cells are protease-active allergens as nicely documented for the house dust mite allergen Der p1 and the fungal protease 4 derived from Aspergillus spp. (Fig. 2) (32,32,106). Similarly, pollen-derived phytoprostanes were shown to promote a pro-allergic phenotype in DCs (107,108). An important cytokine that skews DC function towards the promotion of Th2 cells is TSLP. This cytokine is produced by epithelial cells such as keratinocytes and its capacity to promote the development of allergy was implicated in atopic dermatitis and allergic asthma (109–111).

DCs in cancer, induction of tolerance

Tumor cells have efficient strategies to prevent the induction of tumor-specific immunity and to induce tumor-specific immune tolerance (112). Diverse tumors and tumor cell lines show a constitutive expression of the transcription factor STAT3 which supports tumor growth and spread (113,114). In addition, STAT3 also inhibits the expression of proinflammatory mediators within the tumors cells, while promoting their expression of immune-suppressing factors, which in turn activates STAT3 signaling in DCs leading to immune tolerance (114). A well-known example is the production of IL-10 by melanoma cells. Tumor-derived IL-10 was shown to efficiently modulate DCs so that they induce tumor-specific anergy (115,116). Furthermore, IL-6 produced by breast cancer cells can inhibit DC differentiation and rather promotes the differentiation of macrophages than DC (117). Breast cancer cells produce the tumor antigen MUC-1 that was shown to efficiently inhibit the production of IL-12 by DCs. MUC-1 also interferes with antigen-capture and antigen presentation resulting in low frequencies of MUC-1-specific effector cells (118,119). Tumor-derived prostaglandin has similar effects. In concert, these tumor-derived mediators have a strong capacity to condition local DC to stimulate suppressive T cells (120).

In the near future, we will learn much more about the contribution of individual subtypes of DCs during the sensitization and effector phase of many immune responses. Different DC-specific transgenic mouse models which allow the temporal ablation of langerin-positive DCs are currently under study and the results already stimulate fruitful discussions. Using the model of contact allergy, it became obvious that Langerhans cells are not strictly required during the sensitization phase. Furthermore, it appeared that rather a newly identified population of highly migratory population of langerin$^+$ dermal DCs were responsible for the induction of contact allergy (121).

This is a good example that we need to get a detailed view of the DC system as a whole. DCs are key targets for immunotherapy, exploiting their function for therapeutic use requires a deep understanding of the functional relevance that different DC subsets have *in vivo*.

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