Dendritic cell subsets in health and disease

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Acknowledgements
This article is dedicated to all our patients and volunteers who have participated in our studies and clinical trials. We thank former and current members of the institute for their contributions to our progress. We thank Dr Carson Harrod for proofreading the manuscript and Cindy Samuelsen for continuous help. We thank Dr Michael Ramsay and Dr William Duncan for their continuous support. We thank the NIH (AI068842-01, AR054083-01, 5U19AI057234-02, CA84512, 2R01CA078846-06 and 5R01AR050770-02), the Alliance for Lupus Research, the Dana Foundation, the Baylor Health Care System, and the Baylor Health Care System Foundation for their support.

Immunological Reviews 2007
Vol. 219: 118–142

Immunological Reviews
0105-2896

Summary: The dendritic cell (DC) system of antigen-presenting cells controls immunity and tolerance. DCs initiate and regulate immune responses in a manner that depends on signals they receive from microbes and their cellular environment. They allow the immune system to make qualitatively distinct responses against different microbial infections. DCs are composed of subsets that express different microbial receptors and express different surface molecules and cytokines. Our studies lead us to propose that interstitial (dermal) DCs preferentially activate humoral immunity, whereas Langerhans cells preferentially induce cellular immunity. Alterations of the DC system result in diseases such as autoimmunity, allergy, and cancer. Conversely, DCs can be exploited for vaccination, and novel vaccines that directly target DCs *in vivo* are being designed.

Keywords: *dendritic cells, subsets, human, diseases, phagocyte*

Introduction

Immunologists had long focused on antigens and lymphocytes, which by themselves are insufficient to elicit protective immunity. A third party, the dendritic cell (DC) system of antigen-presenting cells (APCs), is needed to educate lymphocytes. DCs efficiently stimulate B and T cells, the components of adaptive immunity, thereby initiating immune responses (1). First visualized as Langerhans cells (LCs) in the skin some 140 years ago, DC characterization began less than 40 years ago (2). During the first 20 years, they were painstakingly isolated from the tissues and studied by few investigators. However, the discovery of techniques to generate DCs *in vitro* (3–6) allowed the identification of many of their biological and molecular properties.

Although our skin and mucosa are covered by considerable amounts of microbes, we stay remarkably healthy. However, when the microbes break the skin or mucosal barriers, the immune system faces a number of options. First, it needs to

decide whether or not to respond. Second, if a response is made, it must be tailored to fight that particular microbe. Generating the right class of immune response can be a matter of life and death itself. In leprosy, the tuberculoid form of the disease is characterized by a type 1 response that keeps the disease in check, but the lepromatous form induces an often fatal type 2 response (7, 8). Microbe-specific immunity must therefore limit the extension of the infection as well as remove the infected cells. This process requires the participation of different cells of the innate immune system as well as cells of the adaptive immune system, more specifically T and B lymphocytes that are educated and activated by DCs.

The initiation of T-cell immunity poses several challenges. First, the frequency of microbe-specific T cells is extremely low. Second, infected cells express very few peptide–major histocompatibility complex (MHC) complexes recognized by the specific T cells (100 or fewer per cell). Third, infected cells lack the costimulatory molecules needed to drive T-cell clonal expansion and the production of cytokines, therefore lacking capacity to generate cytotoxic/helper T cells. These challenges are overcome by DCs, which capture microbes, present their antigens, and provide signals necessary for T-cell expansion and differentiation. Upon recognition of microbial components or in response to inflammatory cytokines secreted by cells in the tissue microenvironment, DCs upregulate costimulatory molecules and migrate to secondary lymphoid organs, i.e. spleen and lymph nodes (LNs), where they activate antigen-specific T cells. Thus, DCs have traditionally been viewed as mobile sentinels that bring antigens to T cells and activate them. More recent studies indicate however that soluble antigen can directly diffuse into the draining LNs through lymphatics and conduits, thereby reaching the LN-resident DCs (9). Murine *in vivo* studies suggest that these two waves of antigen delivery to LNs yield different immune responses (9). DCs are also important in launching humoral immunity partly through their capacity to directly activate B cells (10, 11). DCs also activate innate immune cells, such as natural killer (NK) cells (12, 13) and natural killer T (NKT) cells (14).

In addition to the ability to recognize and eliminate what is foreign or aberrant, the immune system has built in tolerance mechanisms to ignore components of 'self' (15). DCs appear to be essential in maintenance of immunological tolerance both in the thymus and in the periphery (15). Thus, their alteration might contribute to the break of tolerance and thereby to the pathogenesis of autoimmune diseases.

Just like lymphocytes, DCs are composed of several subsets with distinct functions (16). There are many reasons for a specialized system of DC subsets. For example, the requirements for establishing protective responses against viral infections are likely different from those necessary to eliminate bacteria, fungi, and parasites. Similarly, the requirements for priming T cells likely differ from those for priming B cells, and the requirements for induction of immunity have to differ from those for induction of tolerance. Likewise, the polarization of T-cell types, such as T-helper 1 (Th1) versus Th2 or regulatory T cell (Treg) versus Th17, etc., which have been extensively studied at the T-cell levels in DC-independent systems, might reflect differences at the DC level. This review emphasizes the role of DC subsets in disease pathogenesis and how we can exploit them for therapy.

DC biology

Activation of DCs and launching of protective immunity

DCs play a key role in initiating and controlling the magnitude and the quality of adaptive immune responses. Immature DCs act as immunological sensors to alert for potentially dangerous microbes, either by directly recognizing microbial components or by receiving signals formulated by the innate immune system that is exposed to microbes. Immature DCs decode and integrate such signals and ferry this information to adaptive immune cells (17). Thus, the type of adaptive immune response is highly dependent on the nature of the activating stimuli that DCs receive from the innate immune system.

In the steady state, DCs reside in both peripheral tissues and lymphoid organs. DC subsets also circulate in the blood. To elicit anti-microbial immunity, DCs undergo a complex process of maturation, a 'metamorphosis' from an antigen-capturing cell into an APC. This process includes (i) changes in morphology such as the loss of adhesive structures, cytoskeleton reorganization, and the acquisition of high cellular motility (18); (ii) loss of endocytic/phagocytic receptors; (iii) secretion of chemokines in coordinated waves according to the type of immune cells that need to be attracted (19–23); (iv) upregulation of costimulatory molecules, such as CD40, CD80, and CD86 (24); (v) translocation of MHC class II compartments to the cell surface (25, 26); and (vi) secretion of cytokines that differentiate and polarize the attracted immune effectors (27). DCs are activated by numerous agents derived from microbes, dying cells, cells of the innate immune system, and cells of the adaptive immune system (*Fig.* 1).

Activation of DCs by microbial components

The immune system recognizes microbes through pattern recognition receptors (PRRs) (28, 29). The microbes are recognized by a limited set of conserved molecular patterns, referred

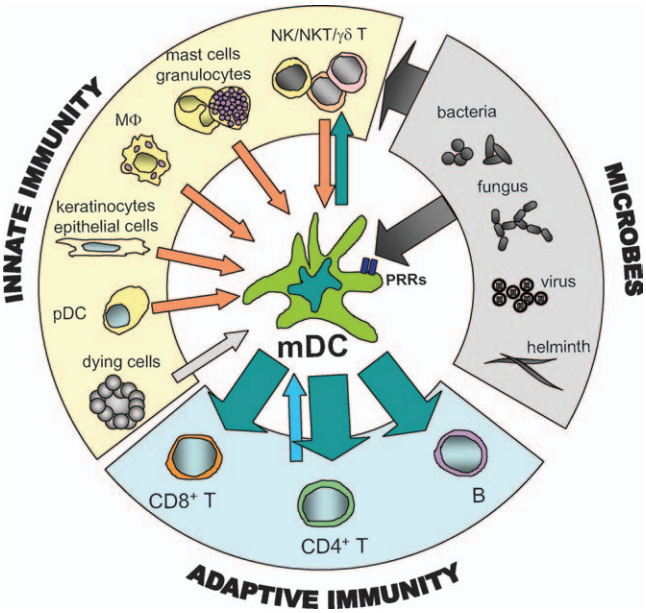

***Fig. 1.* Regulation of mDC activation.** Four major paths lead to the activation of mDCs: (i) microbes, (ii) dying cells, (iii) cells of the innate immune system, and (iv) cells of the adaptive immune system. The recognition of microbial PAMPs through PRRs delivers activation signals to mDCs. DAMPs secreted from dying cells can also lead to the activation of mDCs. Upon encounter with microbes, innate immune cells secrete cytokines and chemokines, which activate immature DCs and their precursors into mature cells with distinct phenotypes. Activated mDCs migrate to the draining LNs, where they encounter cells of the adaptive immune system (i.e. $CD4^+$and $CD8^+$T cells and B cells). MΦ, macrophage.

to as pathogen-associated molecular patterns (PAMPs) (30), which are invariant across pathogens. The combination of these PAMPs is unique to a microbial type. PAMPs are recognized through at least three PRR families of molecules: Toll-like receptors (TLRs), cell surface C-type lectin receptors (CLRs), and intracytoplasmic nucleotide oligomerization domain (NOD)-like receptors (NLRs). Microbes directly activate DCs through their PRRs or indirectly, for instance, by capture of apoptotic/necrotic products of other cells dying in response to microbial exposure. Microbes also induce a wide repertoire of cells, such as epithelial cells, fibroblasts, and cells of the innate immune system, to secrete cytokines capable of activating DCs.

Toll-like receptors

TLRs are expressed on a wide repertoire of cells including DCs. Ten TLRs have been identified in humans, and 13 TLRs have been identified in mice (29). TLRs can be divided into subfamilies, according to the ligands they recognize and to their cellular localization. Thus, the subfamily of TLR1, TLR2, TLR4, and TLR6 recognizes lipids, whereas TLR3, TLR7, TLR8, and TLR9 recognize nucleic acids (29). TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are expressed in intracellular compartments, typically late endosomes–lysosomes. Such restricted localization might provide the mechanism by which DCs avoid spontaneous activation by self nucleic acids (31, 32). Another level of regulation is provided by the differential expression of TLRs by distinct DC subsets. The distinct repertoire of TLRs allows DC subsets to respond differentially to microbes. In humans, blood plasmacytoid DCs (pDCs) express TLR1, TLR6, TLR7, TLR9, and TLR10, while blood myeloid DCs (mDCs) express TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, and TLR10 (33, 34). Epidermal LCs isolated from skin express TLR1, TLR2, TLR3, TLR6, and TLR10 but lack TLR4 and TLR5 expression. The expression of TLR7 and TLR8 remains unclear (35, 36). In contrast to LCs, dermal interstitial DCs (intDCs) express TLRs recognizing bacterial PAMPs, such as TLR2, TLR4, and TLR5 (36). Therefore, dermal intDCs may represent a DC subset specialized for bacterial recognition in the skin. As for many aspects of the immune system (37), significant differences are found between human and murine DC subsets. For instance, both mDCs and pDCs express TLR9 in the mouse (29, 38), while only pDCs express TLR9 in the human (33, 34).

Different TLRs recognize different PAMPs and deliver distinct molecular signals, thereby yielding distinct types of DC maturation and consequently distinct immune responses (39). For instance, *Escherichia coli* lipopolysaccharide (LPS) stimulates DCs through TLR4, inducing a Th1 response by interleukin-12 (IL-12) secretion, while *Porphyromonas gingivalis* LPS activates DCs through TLR2, inducing DCs to secrete IL-10, and eventually resulting in type 2 T-cell development (40). Similarly, while polyI:C, a TLR3 ligand, induce DCs to secrete tumor necrosis factor-α (TNF-α), peptidoglycan, a TLR2 ligand, and enhances their IL-10 secretion (35). Because microbes express different sets of TLR ligands, it is not surprising to find that some TLRs cooperate for increased DC activation, thereby ensuring generation of protective immunity. For example, DCs stimulated through TLR3/TLR4 and TLR7/TLR8 or TLR9 synergistically act on DCs for the production of IL-12p70 and induce very potent Th1 development (41).

C-type lectin receptors

DCs express a large collection of CLRs, molecules that bind the carbohydrate moiety of glycoproteins (42, 43). Similar to TLRs, distinct DC subsets express different CLRs, i.e. BDCA2 (blood DC antigen 2) is specific to pDCs (44), Langerin/CD207 is specific to LCs (45), and DC-SIGN [DC-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing non-integrin]/CD209 is specific to intDCs (46). Other CLRs, such as

DEC205/CD205 (47, 48) or asialoglycoprotein receptor (ASGPR) (49), are more broadly expressed.

C-type lectins act as anchors for a large number of microbes, including viruses, bacteria, parasites, and fungi, and allow their internalization. However, CLRs appear to carry multiple functions. C-type lectins also act as adhesion molecules between DCs and other cell types. Thus, DC-SIGN expressed on DCs interacts with multiple factors: (i) CD11b/CD18 heterodimer Mac-1 and carcinoembryonic antigen (CEA)-related cellular adhesion molecule 1 (CEACAM1) expressed by neutrophils, thereby contributing to neutrophil-mediated activation of DCs (50); (ii) ICAM-2 expressed on endothelial cells, which enables DCs to egress from blood or lymphatic vessels to the periphery through endothelium (51); and (iii) ICAM-3 expressed on T cells, facilitating T-cell priming (46). Natural ligands of several C-type lectins, such as DEC205 and ASGPR, are yet to be determined. Some C-type lectins have signaling motifs in their cytoplasmic regions and deliver activation/suppression signals (reviewed in 52). DC-SIGN (46), ASGPR (49), and Dectin-1 (53) show an immunoreceptor tyrosine-based activation motif (ITAM), which delivers activation signals to DCs. Dectin-1, a β-glucan-specific CLR mediating the phagocytosis of yeast, delivers signals to produce IL-2 and IL-10, or IL-12 and TNF-α through distinct pathways (54). The recent finding that the signaling through Dectin-1 and its downstream molecule Caspase recruitment domain-9 (CARD9) is critical for protection against *Candida* (55) exemplifies the significance of CLRs as signal-transmitting molecules. Dendritic cell immunoreceptor (DCIR) (56) and myeloid inhibitory C-type lectin receptor (MICL) (57) show an immunoreceptor tyrosine-based inhibitory motif (ITIM). Whether these ITIM-containing lectins deliver negative signals to DCs remains to be established. Similar to TLR expression, CLR expression differs between human and mouse. Multiple DCIRs (DCIR1-4) have been identified in the mouse (58), while only a single DCIR was found in humans. These differences complicate the extrapolation of the knowledge obtained in mouse studies to humans.

NOD-like receptors

NLRs are a family of receptors recognizing intracellular microbial components (reviewed in 59–62). The NLR family includes 22 members, the majority of which fall within two large protein subclasses: NODs (NOD1-5) and NALPs (NACHT, leucine-rich repeat, and pyrin-domain-containing proteins 1–14).

NLRs trigger signaling pathways that yield proinflammatory cytokines. Upon recognition of PAMPs, NLRs undergo a conformational rearrangement that activates them (61). Some NLRs are components of the inflammasome, a multiprotein complex that plays an important role in the activation of proinflammatory Caspases and subsequent processing and secretion of IL-1β and IL-18 (62). Of the three different known inflammasomes, the NALP3 inflammasome is the best characterized.

The list of NLR activators is growing, although much remains to be found. NOD1, NOD2, and NALP3, are activated by muropeptides, small bacterial peptidoglycan fragments derived from the Gram-positive and Gram-negative bacterial cell wall. NALP3 can also be activated by bacterial RNA and by endogenous danger signals released from dying cells like uric acid (63). Polymorphism or mutations in NLRs are associated with susceptibility to inflammatory disorders. For example, mutations in NOD2 are linked to the development of Crohn's disease (64) and familial sarcoidosis (Blau syndrome) (65), two autoinflammatory diseases. Mutations in the NACHT domain in NALP3 are involved in three autosomal dominant autoinflammatory diseases (familial cold-induced urticaria, Muckle–Wells syndrome, and neonatal onset multisystem inflammatory disease), which are characterized by recurrent episodes of fever and serosal inflammation as a result of increased production of IL-1 (66).

The expression of the majority of NLR members in human DCs is largely unknown. NOD1/2 are expressed in the cytosol of macrophages and DCs (67); NALP1 is absent in germinal center and intDCs, while highly expressed in LCs within mucosal surfaces and skin. A short DC-specific isoform of NALP3 has recently been identified (68); yet, its role in IL-1 production in DCs remains to be determined.

Activation of DCs by products of dying cells

The observation that lysates of dying cells induce the maturation of *in vitro*-generated DCs first indicated that components of dying cells can activate DCs (69). These components enhance antigen presentation by DCs, leading to T-cell immunity (69, 70). These endogenous activating molecules are collectively called damage-associated molecular pattern molecules (DAMPs) (71). DAMPs include heat shock proteins (HSPs) (72), high-mobility group box 1 protein (HMGB1) (73), β-defensin (74), and uric acid (75).

Many different HSPs, including HSP70, grp96, and HSP90, were reported to have the ability to induce DC maturation *in vitro* and act as adjuvants *in vivo* (72). The observation that DC maturation elicited by HSPs is dependent on the LPS receptor (TLR4/MD2/CD14) (76) and the demonstration that LPS-free HSP60 and HSP70 failed to activate DCs (77, 78) have raised doubts about the ability of HSPs to activate DCs. Other receptors for HSPs, such as CD40 and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), have been identified (79),

leaving the field unsettled. Other endogenous molecules, such as fibronectin (80), fibrinogen (81), and hyaluronic acid (82), have also been shown to activate DCs through TLR4.

HMGB1, a cytokine-like factor released from dying cells (73, 83), induces macrophages to secrete proinflammatory cytokines, such as TNF, IL-6, and HMGB1 itself (73). Thus, HMGB1 represents an endogenous DAMP that triggers a cascade of inflammatory responses in the absence of microbes. HMGB1 appears to bind to multiple receptors including TLR2, TLR4, and receptor for advanced glycation end products (RAGE), expressed on monocytes, macrophages, monocytes, and NK cells. β-Defensins are small anti-microbial peptides secreted from neutrophils and epithelial cells (84). β-Defensins were also shown to activate immature DCs through TLR4 (74).

While soluble uric acid, a degradation product from purines, does not induce DC maturation, crystals of monosodium urate (MSU) have a strong capacity to activate DCs in a TLR4-independent fashion (85). Recently, NALP3, an NLR receptor, has been identified as the receptor for MSU, triggering DCs to secrete proinflammatory cytokines, particularly IL-1β (63). Gout, an articular inflammatory disease, is dependent on MSU and is responsive to treatment with IL-1 receptor antagonist (86).

DCs orchestrate a ballet of cells of the innate and adaptive immune systems

DCs have long been known to secrete a variety of chemokines (87–89). However, it is remarkable that both pDCs and mDCs secrete sets of 'redundant' chemokines in three waves, corresponding to the three stages of the immune response to a microbe (23) (*Fig.* 2). The first chemokines that are produced within 2–4 h *in vitro* are CXCL1, CXCL2, and CXCL3, which attract innate effectors such as NK cells, and CXCL8, which attracts neutrophils. This set of cells might limit the spread of infection. The next wave produced within 4–8 h involves CXCL9–11 and CCL3–5, which attract activated memory T cells and monocytes that could replenish the pool of DCs or of tissue macrophages. Finally, at a late stage (>12 h) when mature DCs land in the draining secondary lymphoid organs, they secrete CXCL13 which attracts B cells and T cells specialized for humoral responses [follicular helper T cells (Tfh)], CCL19 and CCL21 which attract naive T cells, and CCL22 which attracts Tregs that might finally permit the termination of the immune response. This coordinated program of successive waves of chemokine production triggered by viral exposure has been observed on purified blood DCs and remains to be established with cells isolated from tissues.

Activation of DCs by tissue environment and innate immune cells

Pathogen invasion leads to activation of innate immune cells including neutrophils, basophils, mast cells, and pDCs. Neutrophils are dedicated to phagocytosis and killing of bacteria, while eosinophils, basophils, and mast cells are dedicated to killing parasites. pDCs may have evolved to control viral infection (90). Neutrophils and macrophages secrete proinflammatory cytokines such as IL-1, IL-6, and TNF upon microbial recognition. Furthermore, neutrophils induce DC maturation through the interaction between DC-SIGN and Mac-1/CEACAM-1 (91) and through the secretion of β-defensins (74). Mast cells secrete granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-4, and TNF upon recognition of parasites (92, 93). pDCs secrete large amounts of type 1 interferon (IFN) in response to viral encounter (94). Epithelial cells including keratinocytes produce IL-15 and GM-CSF (95). In allergic inflammatory skin lesions, keratinocytes secrete large amounts of thymic stromal lymphopoietin

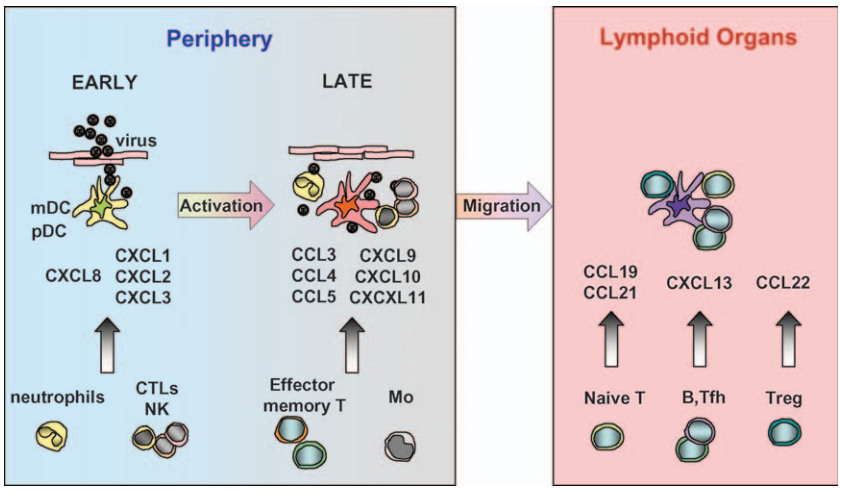

***Fig.* 2. DCs are choreographers of the immune system.** Both pDCs and mDCs secrete sets of redundant chemokines in three waves, which correspond to three stages of the immune response to a microbe. The first chemokines that are produced within 2–4 h attract innate effectors such as NK cells and neutrophils. This set of cells might limit the spread of infection. The next wave produced within 4–8 h attracts activated memory T cells and monocytes (Mo), which could replenish the pool of DCs or of tissue macrophages. At a late stage (>12 h) when mature DCs land in the draining secondary lymphoid organs, they attract B cells and Tfh cells for maturation of humoral responses and naive T cells to broaden the immune response. Tregs are also attracted to control the extent of the immune response.

(TSLP) (96). Furthermore, bioactive metabolites, such as prostaglandins, secreted by multiple types of cells are also involved in the modulation of DC functions (97).

DCs also have a reciprocal interaction with innate immune cells. The interaction of DCs with NK, NKT, and γδ T cells can occur in the periphery and the secondary lymphoid organs (reviewed in 98). A recent mouse study suggested that the activation of NK cells is totally dependent on the interaction with DCs at the secondary lymphoid organs (13). Activated NK cells enhance their cytotoxicity and capacity to secrete IFN-γ (99–101), which render DCs to induce type 1 responses (22). As described earlier, NK cells also secrete HMGB1, which promotes DC maturation (73). NK cells however might directly recognize viral proteins, for example influenza virus hemagglutinin, with its NKp46 receptor (102). Mature DCs also activate NKT and γδ T cells, inducing the secretion of IFN-γ and IL-4 from NKT cells (14, 103–105) and IFN-γ and TNF-α from γδ T cells (106, 107). In particular, activated NKT cells acquire the capacity to kill tumor cells (108). In return, CD40L expressed on NKT cells induces the strong activation of DCs (98).

These factors derived from innate immune cells activate immature DCs and their precursors to develop into mature cells with distinct phenotypes (*Fig.* 3). Thus, type I IFN, TSLP, TNF, IL-10, IFN-γ, or IL-15 yield DC differentiation into IFN–DCs (109–112), TSLP–DCs (96, 113), TNF–DCs (114), IL-10–DCs (115, 116), IFN-γ–DCs (22), or IL-15–DCs (117, 118), respectively. These distinct DCs induce distinct types of T-cell immunity. For example, TSLP–DCs skew T-cell development into inflammatory type 2 cells, which secrete large amounts of TNF as well as type 2 cytokines (96). IL-10–DCs promote IL-10-secreting Treg development (115, 116). IFN-γ–DCs promote potent type 1 T-cell responses through the upregulation of IL-12 secretion (22). IL-15–DCs, which express Langerin and share many characters with LCs (117, 118), are powerful activators of cytotoxic T lymphocytes (CTLs) (118). Thus, we propose a model whereby the innate immune system controls the adaptive immune system by modulating the type and function of mDCs. Much remains to be understood at this stage. In particular, it remains to be determined how DC conditioning by the innate effector cells affects humoral immunity.

DC interaction with adaptive immune cells

Once loaded with antigens and activated by the microbes and the innate immune cells, DCs migrate into the draining lymphoid organs. DCs act on lymphocytes through at least three families of molecules: cytokines, B7 family members, and TNF family members.

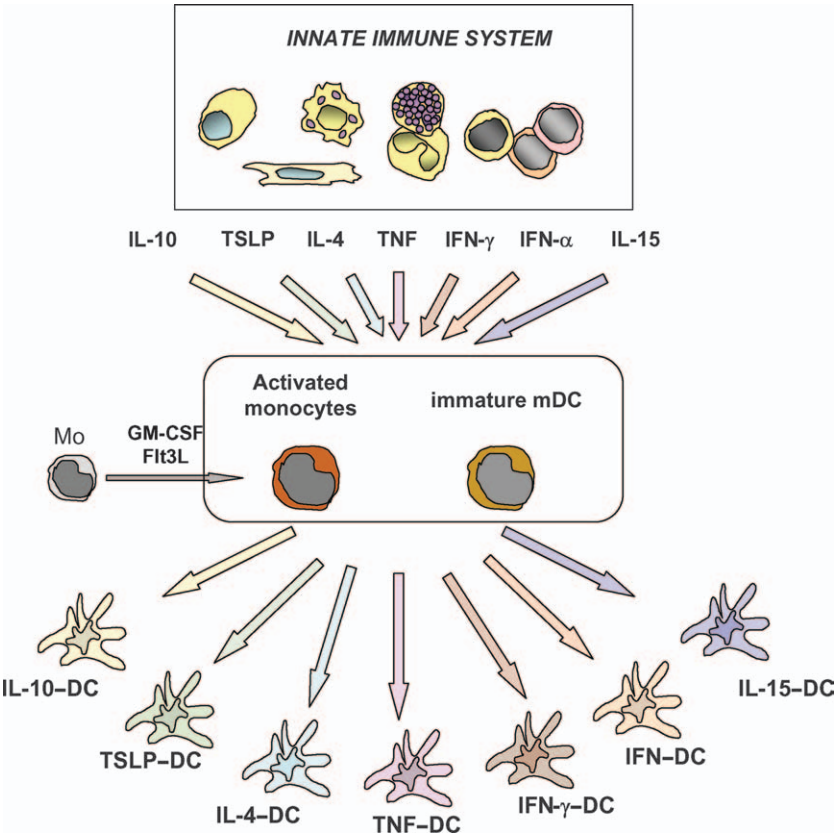

***Fig.* 3. The innate immune system controls the adaptive immune system by modulating the type and function of mDCs.** Innate immune cells secrete different sets of soluble factors in response to various stimuli. Granulocytes and macrophages secrete IL-1, IL-6, and TNF upon microbial recognition. NK cells secrete IFN-γ. Mast cells secrete GM-CSF, IL-4, and TNF. Keratinocytes secrete IL-15 and GM-CSF as well as TSLP in allergic lesions. pDCs secrete large amounts of type 1 IFN upon viral encounter. Immature DCs and monocytes (Mo) activated by GM-CSF and/or Flt3L during extravasation are exposed to these factors, resulting in the differentiation into mature DCs with distinct phenotypes. These distinct DCs promote distinct types of T-cell immunity. Thus, mDCs are the key player to convey information from the innate immune cells to the adaptive immune cells.

Cytokines

IL-12 is a product of activated DCs and promotes the differentiation of T cells into type 1 cells (27, 119). Other IL-12 family molecules, IL-23 (120–122) and IL-27 (123, 124), are also secreted from DCs but differentially regulate immune responses. IL-23, which shares IL-12p40 with IL-12, promotes the differentiation of T cells into Th17 cells, secreting IL-17 (125, 126), which is associated with inflammation (127, 128). The development of Th17 cells also depends on IL-6 and transforming growth factor-β (TGF-β) in mice (129) and IL-1 and IL-6 in humans (Federica Sallusto at Keystone symposium 2007: Immunological Intervention in Human Diseases). IL-27, in contrast, appears to act as an anti-inflammatory agent *in vivo*. Experimental autoimmune encephalitis models suggested that IL-27 actually inhibits the differentiation of Th17 cells (130, 131). Upon activation, immature DCs also secrete IL-2 in the mouse (132) and IL-15 in both the mouse and human (133), which might be involved in the proliferation of naive T cells and/or in modifying their differentiation.

B7 family

Molecules of the B7 family are essential in the regulation of T-cell-mediated immunity and tolerance. This family consists of seven molecules: CD80 (B7-1), CD86 (B7-2), inducible costimulator ligand (ICOSL), programmed death ligand 1 (PD-L1) (B7-H1), PD-L2 (B7-DC), B7-H3, and B7-H4, all of which can be expressed on DCs and macrophages (134). CD80 and CD86 are commonly used as DC 'maturation markers' (1). However, their upregulation does not necessarily indicate the capacity of DCs to induce immunity, as we discuss later for DCs infected by respiratory syncytial virus (RSV). Both CD80 and CD86 bind to CD28 and cytotoxic T-lymphocyte antigen-4 (CTLA-4). While CD28 delivers signals for T cells to become functional effector cells, CTLA-4 delivers inhibitory signals that suppress their functions. We have observed that DC subsets differentially express these molecules. Human LCs generated *in vitro* express more CD80 than CD86, while intDCs express more CD86 than CD80 (135). The biological consequences remain unclear.

DCs express ICOSL, which is a homolog of CD28 and which is also expressed on activated T cells (136). The expression of ICOSL is differentially regulated from CD80 or CD86, as CD40 and LPS stimulation do not upregulate ICOSL expression on DCs (137). Although ICOSL is widely expressed on APCs including B cells, monocytes, DCs, and macrophages, high levels of ICOSL appear to be limited to DC subsets specialized in the induction of Tregs. For instance, mouse bronchial mDCs at steady state (138) and human pDCs stimulated with virus or TLR-9 ligand (139) express high levels of ICOSL and induce IL-10-producing Tregs.

PD-L1 and PD-L2 appear to be specifically involved in the induction and maintenance of tolerance (134). Both molecules bind to PD-1 and deliver potent inhibitory signals (140). While PD-L1 is broadly and constitutively expressed on immune cells, PD-L2 expression is limited to DCs and macrophages, suggesting a unique function of PD-L2 for immune regulation. 'Exhausted' T cells in chronic infections, such as lymphocytic choriomeningitis virus in mice (141) and human immunodeficiency virus (HIV) in humans (142), were found to express high levels of PD-1. Blockade of the PD-1/PD-L1 pathway reverses the exhausted status of T cells *in vitro* and *in vivo*, resulting in recovery of their expansion and cytokine secretion (141–143). Thus, the PD-1/PD-L1 pathway is involved in the control of T-cell anergy in chronic viral infection and probably cancer. Much remains to be established to understand how T cells acquire constitutive PD-1 expression.

TNF family

TNF (3) and CD40 ligation (24) were found early to act as activators of DCs. CD40/CD40L interaction promotes DCs to upregulate CD80 and CD86 and to secrete IL-12. Importantly, CD40 ligation also induces DCs to express other TNF family molecules such as CD70, 4-1BBL, and OX40L. TSLP can also induce DCs to express OX40L (96). OX40L on DCs polarizes T-cell differentiation into type 2 (144) and shuts down IL-10 secretion from Tregs (145). CD70 is critical for the priming of naive $CD8^+$ T cells (146, 147) and for the differentiation into IFN-γ-secreting CTLs (148) or memory T cells (149). 4-1BBL expression (150, 151) is also important in the priming of naive $CD8^+$ T cells and the survival of memory $CD8^+$ T cells. DCs also express TNF family molecules associated with B-cell priming and/or differentiation. BAFF (B-cell activating factor belonging to the TNF family)/BLyS (B-lymphocyte stimulator) (152, 153) is upregulated on DCs in response to type I and II IFNs and LPS (154) and interacts with its receptors expressed on B cells, such as BAFF-R, TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), and BCMA (B-cell maturation antigen) (155). The stimulation with BAFF and its closely related APRIL (a proliferation-inducing ligand) promote B-cell survival and differentiation into antibody-secreting plasma cells and their class switching (154).

Maintenance of tolerance by DCs

DCs play a pivotal role in the control of both central and peripheral tolerance (15). The thymus steadily produces thymocytes expressing newly assembled T-cell receptors, some

of which are reactive with components of self. High-affinity autoreactive thymocytes are eliminated upon encountering self-MHC peptide (central tolerance). There is evidence that both thymic epithelial cells as well as mature DCs in the thymus are involved in this process (156). However, this step is imperfect, and autoreactive T cells are still released in the periphery. Thus, well-organized mechanisms have been established in the periphery to prevent the development of autoimmunity (peripheral tolerance). An important crossroad of central and peripheral tolerance can be found in the human thymic structures called Hassall's corpuscles. In these structures, resident mDCs stimulated by TSLP drive the positive selection of self-reactive $CD4^+CD25^+$ Tregs (157). These thymus-derived Tregs are critical for the maintenance of self-tolerance in the periphery.

Peripheral DCs are also involved in the maintenance of peripheral tolerance. Non-activated immature DCs are thought to continuously present self-antigens to autoreactive T cells and, in the absence of costimulation, induce the anergy or deletion of these potentially harmful T cells (158). Indeed, targeting of non-activated DCs *in vivo* with fusion proteins composed of anti-DC antibodies and antigens results in induction of antigen-specific tolerance through the deletion of antigen-specific T cells (159) or the induction of forkhead box protein 3 $(FOXP3)^+$ antigen-specific Tregs (160). However, mature DCs also appear to be involved in the maintenance of peripheral tolerance. Mature mDCs can expand functional Tregs both *in vitro* and *in vivo* (160–163). This role may be best explained by the existence of various stages of DC maturation.

Peripheral tolerance may possibly be actively maintained by 'tolerogenic' DCs (164). In addition to deleting T cells, tolerogenic DCs induce the differentiation and proliferation of T cells with regulatory/suppressor functions (165, 166). Some pathogens have a capacity to actively render DCs tolerogenic. Filamentous hemagglutinin in *Bordetella pertussis* stimulates DCs to secrete IL-10, leading to the development of IL-10-secreting T regulatory type 1 cells (167). Although the specific markers of tolerogenic DCs are to be determined, expression of inhibitory immunoglobulin-like transcript (ILT) receptors might be their feature (168). Indeed, *in vitro*-generated DCs exposed to IL-10 express ILT3, which is associated with their tolerogenic functions (169). RSV-infected DCs upregulate the expression of ILT4 and ILT5 as well as PD-L1 and render the DCs unable to induce the proliferation of allogeneic naive $CD4^+$ T cells. Furthermore, very few of these RSV-infected DCs potently suppress allogeneic $CD4^+$ T-cell proliferation induced by activated DCs (Connolly *et al.*, unpublished observations). This finding might explain the pathophysiology of RSV infections, which are often recurrent because of the inefficient induction of specific adaptive immunity. RSV-infected DCs express high levels of CD80, CD86, and CD83 (170). Thus, the mere expression of CD80, CD83, and CD86 is insufficient to characterize the functional status of DCs. The identification of the different states of DC activation is barely started and will be a fertile area of research in the coming years.

A few studies indicate that pDCs might be involved in tolerance induction as well. pDCs stimulated through CD40 induce IL-10-secreting $CD4^+$ Tregs (139) as well as $CD8^+$ T cells (171). Furthermore, *in vivo* depletion of pDCs resulted in the exacerbation of airway hypersensitivity in mouse (172).

DC subsets

There are two main pathways of DC ontogeny from hematopoietic progenitor cells (HPCs). One pathway generates mDCs, while another generates pDCs, a subset capable of secreting large amounts of type I IFN in response to viral stimulation (94, 173). Flt3-ligand (Flt3L) appears as a major factor governing DC homeostasis in the steady state. Flt3L enhances the generation of both mDCs and pDCs *in vivo* (174–176) and *in vitro* (177, 178). Administration of Flt3L to healthy human volunteers increases the frequencies of blood mDCs by 48-fold and pDCs by 13-fold (176). Conversely, Flt3L-deficient mice show a considerable decrease in numbers of DCs in both peripheral and lymphoid tissues (179), indicating that Flt3L is a critical factor for DC ontogeny in both humans and mice.

mDC subsets

In vivo mDCs exist in at least three compartments: peripheral-tissue-resident DCs, secondary lymphoid-organ-resident DCs, and circulating blood mDCs. In the skin, two distinct types of mDCs are found in two distinct layers. LCs reside in the epidermis, while intDCs are present in the dermis (180). Skin DC subsets express different sets of molecules (*Fig.* 4). Early studies have shown that epidermal LCs express CD1a, Langerin, and E-cadherin, while dermal intDCs express DC-SIGN, CD11b, factor XIIIa, and CD14 (181).

Most studies with human mDC subsets have been performed with *in vitro*-generated DCs. $CD34^+$-HPCs, when cultured with GM-CSF and TNF-α (3), give rise to $CD1a^+CD14^-$ LCs and $CD1a^-CD14^+$ intDCs (135). These two human mDC subsets show different phenotypes and biological functions. For example, intDCs but not LCs produce IL-10 in response to CD40L stimulation (182) and express non-specific esterases (183). These two mDC subsets differentially respond to chemokines. intDCs migrate in response to both monocyte chemotactic protein/CCL2 and macrophage inflammatory

	Epidermal Langerhans cells	Dermal Interstitial DCs	Blood Myeloid DCs	Blood Plasmacytoid DCs
C-type lectin	Langerin	DC-SIGN Mannose Receptor	(DC-SIGN) (Mannose Receptor)	BDCA-2
Specific molecules	CD11c CD1a E-cadherin	CD11c CD1a/CD14 CD11b CD36 Factor XIIIa	CD11c	CD123 ILT7
TLRs	1, 2, 3, 6, (7), (10)	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 3, 4, 5, 6, (7), 8, 10	1, 6, 7, 9, 10

Fig. 4. Human DC subsets in vivo. In the skin, two mDC subsets, LCs and intDCs, reside in two distinct layers. Blood contains two major DC subsets, mDCs and pDCs. These DC subsets express different sets of molecules, including CLRs and TLRs.

protein-3α (MIP-3α)/CCL20, while LCs respond only to MIP-3α (184). These responses might explain the differential migration kinetics to inflammatory site between LCs and intDCs. intDCs induce the differentiation of naive B cells into immunoglobulin M (IgM)-secreting plasma cells through the secretion of IL-6 and IL-12 (183, 185) but are not very efficient at priming naive $CD8^+$ T cells. In contrast, LCs are particularly efficient at inducing cytotoxic high-avidity $CD8^+$ T cells (Klechevsky *et al.*, unpublished observation), while they are not able to promote the development of naive B cells into IgM-secreting plasma cells (183). LCs are also strong activators of naive $CD4^+$ T cells, inducing their polarization into T cells secreting IFN-γ (Th1) as well as cells secreting IL-4, IL-5, and IL-13 (Th2). In contrast, intDCs preferentially induce $CD4^+$ T cells, which help immunoglobulin production from B cells (Tfh) (Klechevsky *et al.*, unpublished observation). LCs and intDCs appear to be equally potent at activating the proliferation and differentiation of memory T and B lymphocytes. These recent findings led us to propose that intDCs (dermal DCs) preferentially induce humoral immunity, while LCs induce cellular immunity (*Fig.* 5). These findings made *in vitro* with human DC subsets isolated from skin tissues or generated from $CD34^+$ HPC cultures are in concordance with *in vivo* data in mouse. Mouse dermal DCs and LCs migrate into distinct areas of the paracortex of draining LNs (186). More specifically, dermal DCs migrate into the outer paracortex, just beneath the B-cell follicles (9, 186), whereas LCs migrate into the T-cell-rich inner paracortex (186). This concept may be particularly important in vaccine design to activate humoral responses or cellular responses or both (discussed later). The concept of differential regulation of T-cell immunity by distinct DC subsets was elegantly proven in a recent mouse study. Antigens were selectively loaded *in vivo* onto distinct DC subsets, $CD8\alpha^+$ mDCs expressing DEC205 or $CD8\alpha^-$ mDCs expressing DCIR2, using specific antibodies conjugated with ovalbumin (187). $CD8\alpha^+$ mDCs preferentially induce $CD8^+$ T-cell immunity, while $CD8\alpha^-$ mDCs preferentially induce $CD4^+$ T-cell immunity (187). Accordingly, $CD8\alpha^-$ mDCs and $CD8\alpha^+$ mDCs preferentially express distinct sets of genes involved in MHC class II and class I presentation, respectively (187).

Peripheral lymphoid organ-resident DCs are also involved in both immunity and tolerance. LN-resident DCs capture microbial antigens rapidly delivered through lymphatics and conduits, and upon stimulation through PRRs, these DCs induce the proliferation and IL-2 secretion of antigen-specific T cells (9). In the steady state, LN-resident DCs captured self-antigens and induce tolerance. Another mDC subset in secondary lymphoid organs has been found in the germinal center, named germinal center DCs (188). However, their function is yet to be established.

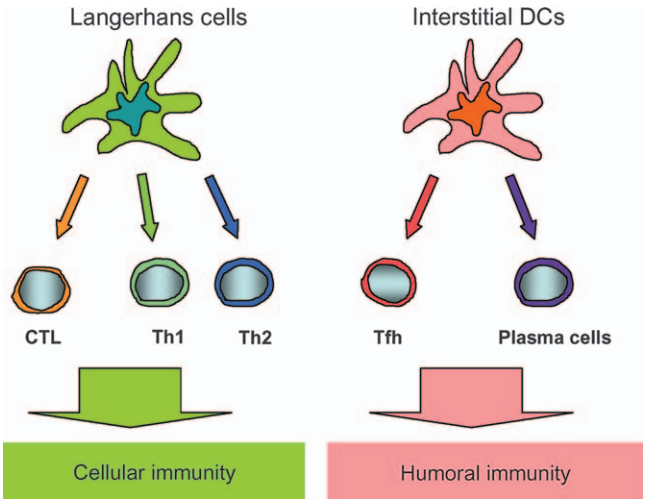

Fig. 5. intDCs preferentially induce humoral immunity, while LCs induce cellular immunity. LCs are particularly efficient at inducing high-avidity cytotoxic $CD8^+$T cells and are also strong activators of naive $CD4^+$T cells, inducing their polarization into T cells secreting IFN-γ(Th1) as well as cells secreting IL-4, IL-5, and IL-13 (Th2). In contrast, intDCs are particularly efficient at inducing the differentiation of naive B cells into IgM-secreting plasma cells and $CD4^+$T cells that help immunoglobulin production from B cells (Tfh).

Blood DC subsets

Blood contains both mDCs and pDCs (*Fig.* 4). Blood DCs are characterized as Lin^- human leukocyte antigen (HLA)-DR^+ cells with reciprocal expression of CD11c (mDCs) and IL-3Rα chain (CD123, pDCs) (94, 173, 189–191) (*Fig.* 4). TLRs are differentially expressed by these DC subsets, as discussed earlier, showing the specialization of the DC system for the recognition of microbes. The route to enter secondary lymphoid organs appears different between pDCs and mDCs (90). pDCs appear to directly migrate into the inflamed secondary lymphoid tissues through high endothelial venules (192), while mDCs first migrate to the inflammatory site and then migrate into the secondary lymphoid tissues through afferent lymph (90).

The physiological role of circulating blood mDCs is unclear. They may represent either a reservoir of precursor cells that migrate into the tissues to replenish the DC population, a sensor of blood borne pathogens, or both. Circulating mDCs might be subdivided further according to the expression of CD1a (193), CD16, or CD34 (194).

pDCs secrete large amounts of type I IFN (94, 173) as well as other cytokines upon viral exposure. pDCs also differentiate into cells with the typical morphology and functions of DCs. Autocrine TNF is involved in the maturation of pDCs into APCs and in the downregulation of type I IFN secretion (195). pDCs act as APCs *in vitro*, although their role in priming T-cell responses *in vivo* is not yet fully established. We recently found that pDCs show unique MHC class I compartments, which permits direct vesicular loading of MHC class I ligands, thereby allowing prompt activation of cytotoxic $CD8^+$ T cells (DiPucchio *et al.*, unpublished observation). pDCs activated with IL-3 and CD40L have been shown to secrete negligible amounts of IL-12 and prime Th2 responses (196) and $CD8^+$ T cells with regulatory/suppressor function (171). However, pDCs also induce Th1 responses *in vitro* when stimulated with both viral antigens and CD40L (38, 197). In humans, CD2 distinguishes two pDCs subsets. Both $CD2^-$ and $CD2^+$ pDC subsets are able to secrete type I IFN in response to viral exposure; however, $CD2^+$ pDCs, which represent 20–30% of blood pDCs, efficiently kill target cells in a TNF-related apoptosis-inducing ligand (TRAIL)-dependent fashion. Furthermore, $CD2^+$ pDCs are more potent than $CD2^-$ pDCs in inducing the proliferation of allogeneic naive $CD4^+$ T cells (Matsui *et al.*, unpublished observation). Recently, IFN-producing killer DCs (IKDCs) have been identified as a novel mouse pDC subset that is endowed with the capacity to secrete large amounts of type I and II IFNs as well as to kill target cells (198, 199). Whether $CD2^+$ pDCs represent a counterpart of mouse IKDCs is yet to be established.

DC subsets regulate B-cell responses

The possibility that DCs may present antigens to B cells has been mostly ignored, although early studies have shown that DCs loaded with proteins were able to induce humoral responses once administered to animals (200). DCs can retain unprocessed antigens (201) and transfer them to B cells (202). Immune complexes captured by DCs through the inhibitory Fc receptor FcγRIIB are retained in a non-degradative intracellular vesicular compartment for up to 48 h and are presented as a native antigen to B cells (203). Two-photon intravital imaging further showed the direct interaction of DCs and B cells in the extrafollicular region in LNs. This interaction is required for B cells to recognize antigens, indicating the significance of DCs for the induction of humoral immunity (11).

Distinct subsets of *in vitro*-generated DCs differentially regulate B-cell responses. Both LCs and intDCs derived from $CD34^+$ HPCs promote the proliferation of CD40-activated B cells as well as the differentiation of memory B cells into plasma cells secreting IgG and IgA (183, 204). However, only intDCs are able to induce the differentiation of CD40-activated naive B cells into IgM-secreting plasma cells. IL-12 secreted from intDCs plays a critical role in the first step for the differentiation into plasmablast (185), and IL-6 together with IL-12 are essential for the differentiation into Ig-secreting plasma cells in the second step. Isotype switching of plasma cells promoted by the interaction with DCs appears to be dependent on several factors. BAFF and APRIL, molecules of TNF family, expressed by DCs appear to be involved in plasma cell differentiation (154, 205). Addition of IL-10 and TGF-β to DC–B cell coculture skews the differentiation of naive B cells toward IgA1- and IgA2-secreting plasma cells, which are most important for mucosal immunity (206).

Induction of B-cell differentiation is not a unique property of mDCs. pDCs stimulated with influenza virus promote B-cell differentiation into Ig-secreting plasma cells (207). As for mDCs, B-cell differentiation by pDCs requires two steps. Rather than IL-12 as is the case with mDCs, type I IFN plays a critical role at the first step in memory B-cell differentiation into plasmablast, followed by the second differentiation step into Ig-secreting plasma cells by IL-6. Therefore, IL-6 secreted from DCs appears to be a critical element for the generation of Ig-secreting plasma cells.

DCs dictate the tissue tropism of T cells

DCs originating from a specific tissue have the unique capacity to instruct T cells to home back to that tissue. Thus, DCs obtained from Peyer's patches or mesenteric LNs elicit $CD8^+$ T cells able to migrate to gut (208). These $CD8^+$ T cells express the integrin

α4β7 and the chemokine receptor CCR9, the receptor for the gut-associated chemokine TECK/CCL25, both of which represent essential receptors for intestinal homing (208). This gut tropism of T cells is dependent on retinoic acid, a vitamin A metabolite expressed in DCs at Peyer's patches or mesenteric LNs (209). In contrast, DCs obtained from peripheral LNs endow naive $CD8^+$ T cells with the ability to migrate to inflamed skin (210). Vitamin D 1,25(OH)(2)D(3), the active form of vitamin D3 that is expressed in the epidermis exposed to ultraviolet B radiation, turns on CCR10 expression on T cells, a skin-homing chemokine receptor for CCL27, a product of keratinocytes (211). The concept of T-cell tissue tropism governed by distinct DC subsets is important for the design of vaccines, where the migration of activated T cells into the appropriate sites is desired. Indeed, the route of vaccination with antigen-loaded DCs in tumor-bearing mice affects the development of metastasis (212). Subcutaneous DC administration activates tumor-specific T cells in the peripheral LNs as well as spleen, resulting in the control of subcutaneous and lung metastasis. In contrast, intravenous DC administration activates spleen T cells, which cannot control subcutaneous metastases (212).

DCs in disease

It comes as no surprise that a system as complex as the DC system might suffer dysregulation leading to the development of distinct types of diseases. Intrinsic dysregulation might lead to autoimmunity and allergy. Furthermore, the critical role of DCs in the launching of protective anti-microbial immune responses make them primary targets for microbes who want to survive and eventually thrive.

DCs in autoimmunity

Autoimmune diseases are chronic inflammatory conditions that depend on inappropriate responses to self-antigens in persons with certain genetic backgrounds. DCs bearing self-antigens are able to induce autoimmunity in mouse models of autoimmune cardiomyopathy (213) and systemic lupus erythematosus (SLE), a systemic disease in which antibodies are formed against several self-antigens, especially nucleoproteins (214).

A pivotal step in a specific autoimmune disease is an imbalance in the production of a particular cytokine (215). For instance, a large body of *in vitro* studies in humans and *in vivo* studies in mice concluded that TNF-α plays an essential role in rheumatoid arthritis (RA) (216). Indeed, the best demonstration of the role of TNF is the beneficial effect of TNF antagonists in patients with RA (216) as well as several other diseases including psoriasis. Thus, an excessive production of TNF might result in ectopic maturation of DCs that would otherwise control peripheral tolerance. DCs themselves might represent a major source of TNF. In psoriasis, large amounts of TNF-α are secreted by mDCs infiltrating the inflamed skin lesions (217). Thus, it is to be determined whether the beneficial effect of TNF antagonist is at the level of DC activation or at the level of effector cells.

Type I IFN in SLE and other autoimmune diseases

SLE appears to be associated with an increased production of type I IFNs (112). Blood monocytes from patients with SLE behave like DCs, as they induce the robust proliferation of allogeneic naive $CD4^+$ T cells. Exposure of normal monocytes to SLE serum results in the generation of functional DCs. This functional effect of SLE serum can be blocked by anti-type I IFN antibody, suggesting a critical role of type I IFN in the generation of SLE-DCs. Indeed, the combination of type I IFN and GM-CSF results in the differentiation of monocytes into mature DCs. These mature DCs can present antigens from dying cells in an immunogenic rather than tolerogenic manner (112). Genomic studies on blood cells indicated that most if not all patients with SLE overexpress IFN-induced genes (218, 219). In addition to this IFN signature, blood cells from patients with SLE express genes from immature neutrophils including defensins, short anti-microbial peptides that activate DCs (74). The clinical relevance of the IFN signature in SLE is indicated by its loss upon treatment of patients with high-dose glucocorticoids (219), a standard treatment of disease flares, which results in a total disappearance of pDCs from the circulation (220). The involvement of IFN in lupus pathogenesis is also supported by several mouse studies. In particular, the progeny from mice with a null mutation of type I IFN receptor bred with lupus-prone mice exhibited decreased morbidity and prolonged survival (221, 222). IFN considerably accelerates the development of autoimmune symptoms in lupus-prone NZB/NZW mice (223). Elucidating the mechanisms leading to the increased production of type I IFN remains the object of intense studies and debate (215, 224). A genetic alteration, such as the overexpression of TLR-7 (225) or alteration in SOCS (suppressor of cytokine signaling) expression (226), could result in an extended production of IFN by pDCs in response to viral encounter. This primary mechanism might be further enhanced by the stimulatory effects of nucleic-acid-containing immune complexes, which further activate pDCs through TLR-7 (for RNP-containing immune complexes) (227) or TLR-9 (for DNA-containing immune complexes) (228–230). Viral nucleic acids as well as self-nucleoproteins internalized in the form of immune complexes trigger TLR7 and TLR9, leading to

type I IFN production from pDCs (231). In patients with SLE, the secretion of type I IFN does not appear to happen in the blood, as no IFN transcription could be detected by microarray analysis (219). Rather, it might happen in the secondary lymphoid organs or in the skin lesions, which are infiltrated by pDCs (232). However, microarray studies indicate that IFN alone does not reconstitute the full SLE monocyte phenotype (Patel *et al.*, unpublished observations). It is possible that immune complexes present in the serum of SLE and/or TLR activation also contribute to the DC maturation (233, 234). DCs generated in the presence of SLE sera also drive the differentiation of $CD8^+$ T cells toward fully active cytotoxic effector T lymphocytes (112, 235), which might be actively involved in the generation of autoantigen fragments through the destruction of target tissues. These autoantigens could be captured and presented by mDCs, thereby further broadening the autoimmune process.

SLE cannot however only be viewed as a disease with dysregulation of type I IFN secretion. Only a fraction of patients who received type I IFN as a treatment for chronic hepatitis C or cancer develops SLE (236). An alteration of the B-cell pathway leading to breakdown of tolerance to nuclear antigens is also likely to play a key role (237, 238). Indeed, B-cell depletion is emerging as a useful therapeutic alternative in SLE (239).

Type I IFN and pDCs are also proposed to be pathogenic in other autoimmune diseases, including psoriasis, insulin-dependent diabetes mellitus, dermatomyositis, and Sjögren's syndrome. In psoriasis, pDCs accumulate in the inflamed skin at an early stage of the disease, and these cells secrete type I IFN (240). Blocking type I IFN inhibits the development of the disease (240). In insulin-dependent diabetes mellitus, elevated expression of IFN was found in the pancreas of recently diagnosed patients (241). In dermatomyositis, a disease targeting the skin and proximal muscle groups, muscle biopsies show infiltration with pDCs as well as IFN-inducible gene and protein expression (242, 243). In Sjögren's syndrome, an autoimmune disease affecting mainly salivary and lacrimal glands, pDCs infiltrate salivary glands, where IFN-inducible genes are overexpressed (244).

Although TNF antagonists bring considerable relief to patients, their administration is associated with some clinical complications, such as reactivation of tuberculosis and induction of SLE (216). Our *in vitro* studies showed that TNF antagonists enhance the production of type I IFN by pDCs exposed to viruses, while addition of TNF inhibits it, suggesting that secretion of TNF by pDCs represents an endogenous mechanism to control IFN production (195). Treatment of patients suffering from arthritis with anti-TNF induces overexpression of type I-IFN-regulated genes in blood leukocytes (195). The high amounts of soluble TNF receptors found in patients with SLE (245) may block endogenous TNF. TNF-mediated downregulation of IFN could explain earlier observations in the mouse lupus model NZB/W, in which mice bear a genetic deficiency in TNF and benefit from TNF replacement therapy (246).

Conversely, there is evidence that IFN may regulate TNF. For example, in multiple sclerosis, IFN-β inhibits *in vitro* TNF production by microglia, a finding that might explain the beneficial effect of IFN-β therapy in this disease (247). Furthermore, peripheral blood mononuclear cells from healthy volunteers injected with IFN-β show markedly decreased secretion of TNF and lymphotoxin as compared with placebo-treated volunteers (248).

We have thus proposed an extension of the Th1–Th2 paradigm (249), to integrate cells that contribute to inflammatory responses. We view immunity as a dynamic system controlled by several sets of opposite vectors, i.e. TNF–IFN-α/β and IL-4–IFN-γ (*Fig.* 6). Furthermore, mouse studies suggested that IL-17-secreting proinflammatory $CD4^+$ T cells (Th17) may represent a subset opposite to Tregs, both requiring TGF-β but IL-6 skewing the development toward Th17 (129). The sum of the vectors yields an equilibrium point, which allows protective immunity when vectors are equal. This dynamic system allows the prevalence of either vector, therefore yielding a given type of immune responses. However, when one of the vectors prevails beyond a certain threshold, the equilibrium point moves into a zone of immunopathology, i.e. autoimmunity, inflammation, or allergy.

Autoimmunity and tolerogenic DCs

A series of studies in mice suggest that DCs might be used in the treatment of autoimmunity through their ability to induce Tregs. In particular, repetitive injections of 'semimature' DCs induce antigen-specific protection of mice from experimental autoimmune encephalomyelitis and thyroiditis (250, 251). In NOD mice, which spontaneously develop diabetes, DCs can induce the generation of Tregs *in vitro* that provide a therapeutic benefit even after onset of disease (252). Indeed, Tregs appear to suppress DCs that can induce autoimmunity by presenting autoantigens (162, 252). Animals that have been depleted of Tregs show autoimmunity that is associated with expansion of activated DCs (253, 254). Thus, tolerogenic DCs, such as those generated with IL-10 (116, 255) or those infected with RSV, might be considered for the treatment of autoimmunity or the induction of specific tolerance in transplantion, such as pancreatic islet cell grafts.

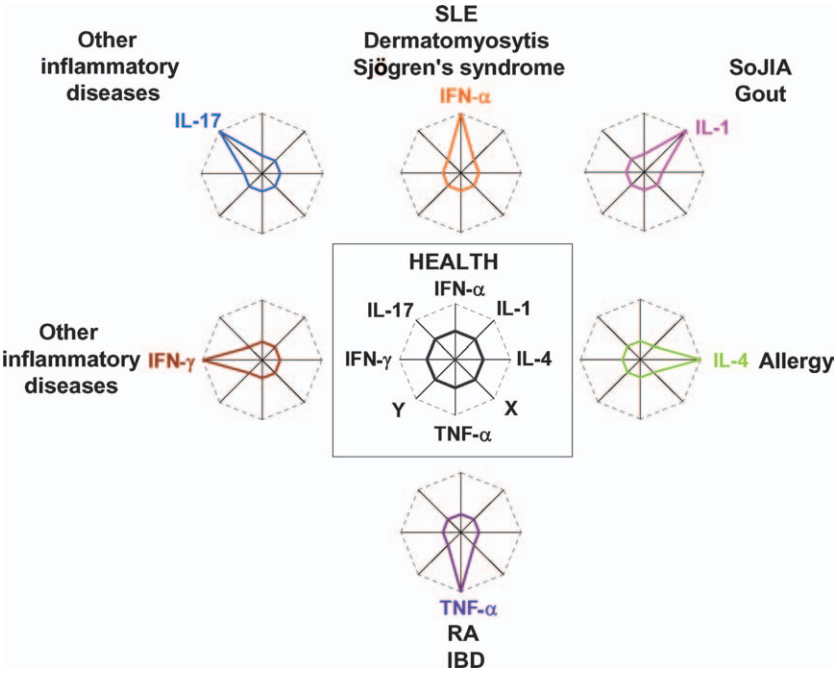

***Fig. 6.* Immunological compass determines the type of disease.** Immunity is a dynamic system controlled by several sets of opposite vectors driven by cytokines. The sum of the equal vectors yields protective immunity. When one of the vectors prevails beyond a certain threshold, the equilibrium point moves into a zone of immunopathology and causes various autoimmune diseases, autoinflammatory diseases, or allergy. SoJIA, systemic-onset juvenile idiopathic arthritis; IBD, inflammatory bowel disease.

DCs and allergy

Many elements of the allergic reaction, including the production of IgE antibodies and the development of eosinophils, depend on type 2 T cells that produce IL-4, IL-5, and IL-13. In normal mice, mDCs at mucosal surfaces capture harmless environmental antigens, such as pollens and dust mites, and silence the corresponding T cells by inducing IL-10-producing Tregs through the interaction between ICOS/ICOSL (138). pDCs also appear to be involved in the induction and maintenance of tolerance. ICOSL is expressed on activated pDCs at higher levels than on activated mDCs *in vitro*, and it promotes the differentiation toward IL-10-producing Tregs (139). *In vivo* depletion of pDCs in a mouse model for airway hypersensitivity resulted in the exacerbation of the development of asthmatic symptoms (172), supporting this hypothesis. In allergy, instead of this immune tolerance, T-cell development is skewed toward the Th2 pathway. mDCs are critical both for the differentiation of type 2 cells at the secondary lymphoid organs and for the activation of differentiated type 2 cells at the inflammatory sites (256–258). TSLP, which is secreted by epithelial cells such as keratinocytes at the allergic inflammatory sites, skews the T-cell response toward inflammatory type 2, characterized by the secretion of not only IL-4, IL-5, and IL-13 but also high levels of TNF-α (96, 259). TSLP induces DCs to express high levels of OX40L, without secreting IL-12 family molecules (260), or type I IFNs, which both promote type 1 T-cell development (260). TSLP also allows the expansion of circulating memory Th2 cells (261). This newly recognized TSLP-based pathway has been implicated in atopic dermatitis in mice and humans (96, 262) as well as murine models for asthma (263). Proinflammatory cytokines, such as TNF and IL-1, and type 2 cytokines, such as IL-4 and IL-13, promote TSLP secretion from skin keratinocytes (264). As skin and airways are always exposed to external stimuli, the dysregulation of inflammatory responses against microbial components may generate the first phase of allergic inflammation in individuals with some genetic background by enhancing the secretion of TSLP from epithelial cells. It remains to be determined why TSLP is overproduced by the keratinocytes or epithelial cells of patients suffering from atopic dermatitis and asthma, respectively. Here again, the novel tools of genetics might help to elucidate the key defects. Understanding the role of DCs in the development of the atopic reaction might lead to the discovery of novel drugs that will directly target them. The local application of the sphingosine 1-phosphate receptor agonist (FTY720) (265) or iloprost, a prostacyclin analog (266), abrogates experimental asthma by affecting DC function. Furthermore, activation of the D prostanoid-1 receptor suppresses asthma by modulating lung function and induction of Tregs (267).

DCs and infection

Pathogens have multiple approaches to alter DCs at each level of their physiology (268). Certain bacteria, such as *Yersinia pestis*, deliver toxins into phagocytes including DCs (269). Many

viruses, such as measles virus and herpes simplex virus 2, induce apoptotic cell death in DCs (270, 271). Some viruses have evolved to selectively block antigen presentation on MHC class I and II in virally infected cells (272). Human cytomegalovirus (HCMV)-infected DCs (273) and RSV-infected DCs (Connolly *et al.*, unpublished observations) show a partial downregulation of their MHC, leading to reduced antigen presentation. HCMV-infected DCs express Fas-L and TRAIL, which allows them to delete activated T lymphocytes (273). Herpes simplex virus-1 inhibits DC migration from the periphery to lymphoid organs by blocking CCR7 expression (274). Many pathogens including herpes simplex (275), HIV (276), and anthrax lethal factor protein (277) actively block DC maturation. An alternative strategy for pathogens is to alter the T-cell polarizing function of DCs, for example switching responses from protective Th1 to non-protective Th2 in infections with *Candida albicans* (278). Exposure of DCs to *Bordetella pertussis* (167) and RSV (Connolly *et al.*, unpublished observations) results in IL-10 production, leading to immunological tolerance. DCs exposed to RSV were found to be the most potent inhibitors of mixed lymphocyte reaction when compared with tolerogenic DCs prepared by exposing monocytes to cytokines such as IL-10 (115) and TGF-β or pharmacological reagents such as vitamin D3 (279) and steroids (280). In addition to the alteration of mDC functions, microbes may have mechanisms to evade pDCs as these cells are diminished in the blood of patients with several infections including HIV (281, 282) and RSV (283).

Some pathogens also use DCs for their own replication and spreading in the infected host. HIV-1, cytomegalo virus (CMV), and Ebola virus bind to the antigen uptake receptor DC-SIGN and use it to enter into the endocytic system of DCs, which later transmit infectious virus to other targets like T cells (284–287). In stark contrast to DC-SIGN, which mediates HIV transmission, Langerin appears as a natural barrier to HIV transmission (288), as it binds HIV and directs it to Birbeck granules where HIV is degraded.

DCs and cancer

The cancer immunoediting hypothesis (289), which integrates tumor-immune escape and tumor immunosurveillance, identifies three phases of tumor development. The first phase, elimination, refers to cancer immunosurveillance, where cells of both the innate and adaptive immune systems recognize and eliminate developing tumors. The second phase, equilibrium, sees equilibrium between the tumor and the immune cells. In the third phase, escape, tumor variants emerge by an immune selection process. We contend that DCs represent major player in cancer immunoediting. Evidence of naturally occurring effective immune responses to tumors in humans comes from studies on paraneoplastic neurologic diseases that develop as remote effects of systemic malignancies (290, 291). Paraneoplastic neurologic diseases result from the presence of onconeuronal antigens, shared between tumors (e.g. breast cancer and small cell lung cancer) and the central nervous system, to which specific CTLs are present *in vivo* (292).

Tumors use several approaches to subvert the immune system (reviewed in 293) with three major consequences: prevention of specific immunity, induction of specific tolerance, and triggering of suppressive pathways. The common denominator of these three mechanisms is altered DC functions in their differentiation, maturation, and antigen presentation.

Signal transducer and activator of transcription 3 (Stat3), a molecule that is constitutively activated in diverse cancers of both hematopoietic and epithelial origin, has been shown to be a critical regulator of inflammation (294). Constitutive Stat3 activity in tumors inhibits the production of proinflammatory cytokines, while promoting the release of soluble factors that suppress DC functions (295). Furthermore, these factors upregulate Stat3 expression in DCs, resulting in the induction of anti-tumor tolerance rather than immunity (296). Several cytokines also have been implicated in suppression of DCs in the tumor beds. For example, vascular endothelial growth factor (VEGF) interferes with DC differentiation and maturation (297, 298). Tumor derived IL-10, as in melanoma, interferes with DC differentiation and maturation, yielding tolerogenic DCs that induce tumor antigen-specific anergy (115, 299–301). IL-6 secreted by breast cancer cells can skew monocyte differentiation into macrophages at the expense of DCs (302). Metabolites of arachidonic acid, including prostaglandins and thromboxanes synthesized by cyclooxygenases-1 and -2, might also contribute to tumor progression through enhanced angiogenesis and/or through direct inhibitory effects on tumor-infiltrating DCs (303).

Tumor cells can interfere with the DC antigen-capture and antigen-presenting pathways. For example, tumor glycoproteins such as CEA and mucin-1 (MUC-1) interact with DC-SIGN (304). MUC-1, overexpressed and secreted by breast cancer cells, is endocytosed by DCs but mostly retained in early endosomes, leading to its inefficient processing and presentation to T cells and thus lower frequency of MUC-1-specific effector cells (305–307). Furthermore, MUC-1 inhibits the capacity of DCs to secrete IL-12, thereby skewing the development of T-cell responses toward type 2 (308).

At the early stages of disease, the immune response can simply be misled and used to promote cancer development. For example, in breast cancer, immature DCs are attracted into

the tumor bed, while mature DCs are confined to peritumoral areas (309). DCs at tumor sites skew $CD4^+$ T-cell differentiation toward T cells secreting high levels of Th2 (IL-4 and IL-13) cytokines, which promote early tumor progression. IL-13 secreted from such T cells appears to be responsible for the tumor growth, as blocking of IL-13 partially inhibits the tumor growth in a humanized mouse model of breast cancer (310). In myeloma, DCs directly interact with myeloma cells, enhancing the tumor clonogenicity and survival (311).

However, DCs can fight back. Under certain circumstances, different DC subsets express cytotoxic molecules. pDCs express granzymes but no perforin (312, Matsui *et al.*, unpublished observations). Type I IFN enables mDCs to kill tumor cells by coexpressing TRAIL (313). Furthermore, immature DCs can induce tumor apoptosis (313–315). More recently, murine IKDCs with cytotoxic activity have been identified, thus extending the armamentarium of DCs in their fight against tumors (199). These cells are able to prevent tumor outgrowth upon adoptive transfer and use TRAIL for cytotoxic activity. Another subset of killer DCs in the mouse is capable of tumor lysis using NK-activating receptors (198). The existence and function of IKDCs in human tumors remains to be determined.

Design of vaccines through DC biology

Given their capacity to modulate immune responses, DCs are an attractive target for the development of both preventative and therapeutic vaccines. Two approaches to DC-based vaccines are being developed: antigen-loaded *ex vivo*-generated DCs and *in vivo* DC targeting.

Ex vivo DC-based vaccines

Ex vivo DC vaccines were tested initially in a few healthy volunteers (316, 317) and more extensively in patients with different forms of cancer (reviewed in 318). Studies in healthy volunteers by Steinman, Bhardwaj, and Dhodapkar were performed with DCs generated by culturing monocytes with GM-CSF and IL-4 (IL-4–DCs) (316, 317). These studies concluded that when matured with a cocktail of proinflammatory cytokines, DCs can induce broad T-cell immunity including priming of keyhole limpet hemocyanin (KLH)-specific $CD4^+$ T cells, as well as boosting of tetanus toxin (TT)-specific $CD4^+$ T cells and influenza-matrix-specific $CD8^+$ T cells (316, 319). Maturation appeared to be important, as the injection of immature DCs resulted in specific inhibition of influenza-matrix-specific $CD8^+$ T-cell effector function and the appearance of peptide-specific IL-10-producing cells (317), which show regulatory functions in a cell contact-dependent manner (320).

Most trials in cancer-bearing patients have used IL-4–DCs (4, 6, 321–325). However, monocytes are not the only source of DC precursors/progenitors that have been used in clinical studies. Blood DCs loaded with specific idiotype protein have been used as vaccines in patients with follicular B-cell lymphoma (326), where immune and clinical responses were observed. Similarly, blood DCs loaded *ex vivo* with a recombinant fusion protein consisting of prostatic acid phosphatase linked to GM-CSF have been used in patients with prostate cancer (327). Furthermore, blood DCs mobilized by Flt3L were shown to induce immune responses as well as some clinical responses (328). We have vaccinated patients with metastatic melanoma with antigen-loaded DCs derived from $CD34^+$ HPCs (CD34–DCs) (329). CD34–DC vaccination elicited melanoma-specific immunity, and patients who survived longer were those who mounted immunity to more than two melanoma antigens. These results justify the design of larger follow-up studies with a range of different DC vaccines to assess their immunological and clinical efficacy.

These early phase I studies have concluded that DC vaccines are safe and can induce immune responses as well as some clinical responses. However, many parameters need to be considered to reach a greater rate of clinical responses. The definition of clinical endpoints and hence the measures that are used to assess vaccine efficacy may need to be revisited. Indeed, DC vaccination might bring about improved survival, particularly in patients with specific HLA type (HLA-A*0201^+ and $B44^-$), as indicated recently in phase III study comparing vaccination with DCs and decarbazine (DTIC) (325).

A major parameter may actually be the DCs themselves. In cancer-bearing patients, IL-4–DCs matured with a cocktail of proinflammatory cytokines (IL-1β, TNF, IL-6, and prostaglandin E2) (330) can induce functional $CD8^+$ T cells and polarize $CD4^+$ T cells toward IFN-γ production (323), although these DCs also expand the Treg population (163). Yet, a combination of IL-1β and TNF with type I (IFN-α) and II (IFN-γ) IFNs seems to yield more potent DCs in terms of IL-12 secretion and induction of tumor-specific CTLs *in vitro* (331). It will therefore be important to identify stimuli that trigger a desired DC maturation program, leading to induction of tumor-specific CTLs but limited or no induction of suppressor T cells, in the various human DC subsets.

For cancer vaccines, the desired DCs would preferentially induce high-avidity CTLs (332) together with strong helper activity to provide long-term memory. Humoral immunity and induction of Tregs are not desired outcomes. Therefore, additional studies are necessary to select the most appropriate

DC platform. IL-4–DCs, comprising intDC-like DCs, might not represent the optimal platform for induction of high-avidity CTL responses. As discussed earlier, when combined with GM-CSF, other cytokines, such as IFN-α (109, 112, 333–335), TNF-α (114), or IL-15 (117, 118), induce monocytes to differentiate into DCs, each of which carries unique biological features. IFN–DCs acquire the expression TLR7, through which IL-12 production can be triggered (333). Furthermore, IFN–DCs appear to be more efficient than IL-4–DCs to prime antigen-specific naive $CD8^+$ T cells through cross-presentation (Saito *et al.*, unpublished observations). IL-15–DCs are remarkably more efficient than IL-4–DCs at priming and maturation of rare antigen-specific $CD8^+$ CTLs (118, 336).

An important area of DC-based cancer vaccine development will be combination with therapies that block the suppressive environment created by the tumor. Early clinical trials performed without DCs are testing the value of blocking molecules such as CTLA-4 (337) or PD-1 (142) or activating CD137 to enhance costimulation of effector T cells (338). Also, DC-based vaccines will be used in combination with cytostatic drugs. Mouse studies in the late 1970s and early 1980s showed that cytostatic drugs, i.e. cyclophosphamide, facilitate adoptive immunotherapy for tumors, possibly through elimination of suppressor T cells (339). Recent studies showing improved outcomes of vaccination with DCs in myeloablated animals (340, 341) reinforce this concept. Furthermore, cytostatic drugs such as anthracyclins (342) or proteasome inhibitors (bortezomib) (343) can generate effective anti-tumor immunity by inducing 'immunogenic' tumor cell death. Thus, chemotherapy combined with intratumoral DC injection might prove an efficient vaccination strategy (344–346), which might circumvent the need for *ex vivo* loading of tumor antigens.

Several other combination therapies are considered to enhance vaccine efficacy (347). Studies in mice show that preinjection of TNF at the site of the DC vaccination greatly improves the migration of DCs to the draining lymphoid tissue and the magnitude of induced immunity (348). Concomitant administration of other cytokines, for example IFN-α, could improve the performance of the DC vaccine (109–112) and possibly protect it from tumor-derived inhibitory factors, such as VEGF or IL-10 (349), and also support induced T cells.

Targeting DCs *in vivo*

The *ex vivo*-generated DC vaccines discussed above will permit us to acquire useful knowledge about DC biology *in vivo* in humans and eventually permit us to treat patients. However, novel strategies have been proposed to directly target the antigens to DCs *in vivo*. Multiple DC surface molecules have been considered as targets, as they need to allow internalization of the antigen cargo and its processing for presentation on both MHC class I and class II molecules. Studies in mice have shown that targeting the antigens in the absence of DC activation results in tolerance induction (159, 160). In contrast, targeting the antigen in the presence of DC activation (CD40 and TLR-3 agonists) results in the generation of immunity against a variety of antigens (159, 350). This approach may lead eventually to the eradication of the infectious agents, i.e. HIV (48, 351) and the *Plasmodium* circumsporozoite protein (352). Different targets are expressed on different murine DC subsets, yielding different functional outcomes. In particular, the mouse $CD8^+DEC205^+$ DC subset is specialized in MHC class I presentation, whereas the $CD8^-DCIR2^+$ DC subset is specialized in MHC class II presentation (187). Furthermore, these subsets use different mechanisms for $CD4^+$ T-cell priming. The $DEC205^+DCIR2^-CD8^+$ DCs prime T cells to make IFN-γ in an IL-12-independent CD70-dependent fashion, while the $DEC205^-DCIR2^+CD8^-$ DCs prime T cells in an IL-12-dependent fashion (353). Mouse DC molecules also have been efficiently targeted through other surface molecules, including LOX-1 (a type II CLR that binds to HSP70) (354), mannose receptor (355), CD40 (356), as well as Gb3 (a receptor for Shiga toxin) (357). Much less is known regarding human DCs. Conjugates of anti-DC-SIGN with KLH (358), anti-DEC205 with gag (48), and anti-mannose receptor with human chorionic gonadotropin hormone (359) have been shown to be cross-presented in peripheral blood cell cultures or in cultures of DCs with relevant T-cell clones. We found that conjugates of influenza hemagglutinin or matrix protein with anti-Langerin, ASGPR, Dectin-1, or LOX-1, can be cross-presented to peripheral blood $CD4^+$ and $CD8^+$ T cells (unpublished observations). We are expecting considerable activity in the field of DC targeting, as it has the potential of yielding a wealth of vaccines, possibly the first vaccines generated by immunologists.

Concluding remarks

Ten years have passed since the writing of Dendritic Cells and the Control of Immunity (1). Considerable progress has been made in the understanding of the basic biology of DCs both *in vitro* as well as *in vivo* in mice. As we emphasize in this review, significant progress has also been made in the study of DCs in the context of human diseases. Yet, much remains to be done. We are however optimistic that the translation of this new knowledge on how DCs regulate the immune system into clinical medicine will result in a wealth of new treatments that target DCs to improve the quality

of life of many patients. We foresee that the improved vaccines targeting DCs will permit us to treat and prevent many chronic infectious diseases caused by viruses (HIV, hepatitis C), bacteria (*Mycobacteria*), and parasites (*Plasmodium*), as well as cancer. We also foresee that the manipulation of DCs will permit dampening immune responses possibly by turning on Tregs, therefore helping patients suffering from allergy and autoimmunity and those in need of organ transplantation.

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