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Special Article

Dendritic Cells: A Link Between Innate and Adaptive Immunity

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Dendritic cells (DC) constitute a unique system of cells able to induce primary immune responses. As a component of the innate immune system, DC organize and transfer information from the outside world to the cells of the adaptive immune system. DC can induce such contrasting states as active immune responsiveness or immunological tolerance. Recent years have brought a wealth of information regarding DC biology and pathophysiology, that shows the complexity of this cell system. Although our understanding of DC biology is still in its infancy, we are now in a position to use DC-based immunotherapy protocols to treat cancer and infectious diseases.

KEY WORDS: Dendritic cell; innate immunity; adaptive immunity; tumor immunology; immunotherapy.

INTRODUCTION

Protective immunity results from the interplay of two cardinal systems: antigen (Ag)-nonspecific innate immunity and Ag-specific adaptive immunity (1). The innate immune system includes several immunoregulatory components, such as complement, natural killer (NK) cells, and phagocytic cells, that recognize pathogen and/or microenvironmental tissue damage and signal the presence of "danger" to cells of adaptive immunity (1–4). Localized at epithelial borders, cells of the innate system recognize nonprocessed Ag (mainly carbohydrates or nucleic acids of pathogens) using pattern recognition receptors that include CD14, mannose receptor, DEC 205, and molecules of the Toll family (1, 5, 6). Contrary to this nonclonal recognition pathways, B and T lymphocytes, that constitute the adaptive immune system, are able to create, by rearrangement of their immunoglobulin or T cell receptor genes, large numbers of clones expressing distinct Ag receptors recognizing Ag or peptides in a highly specific manner (1). However, these Ag-specific cells cannot distinguish structures that require an immune response from those that do not and thus need to be instructed by the cells of the innate system. An essential link between innate and adaptive immunity is provided by antigen presenting cells (APC), among which dendritic cells (DC) are the most capable inducers of both primary and secondary immune responses (1, 7). Distributed as sentinels throughout the body, DC are poised to capture Ag, migrate to draining lymphoid organs and, after a process of maturation, select Ag specific lymphocytes to which they present the processed Ag, thereby initiating clonal immunity (Fig. 1).

First observed in 1868 as Langerhans cells (LC) of the epidermis and then identified within the spleen again 25 years ago by Steinman and colleagues, DC remained enigmatic due to their scarcity and difficulties in isolation. Owing to the development of methods that allowed for *in vitro* DC generation, a wealth of information regarding their biology has recently been accumulated (reviewed in Refs. 7 and 8). The emerging picture is that of a complex system of cells encompassing multiple subsets with potentially distinct biologic functions (7–11) (Fig. 2). It is presently accepted that DC comprise three distinct subpopulations, including two within the myeloid lineage (LC and interstitial DC) and one within the lymphoid lineage. The DC complexity is enhanced by the fact that there is no single molecule known to be uniquely expressed by DC. Rather, the DC subsets as

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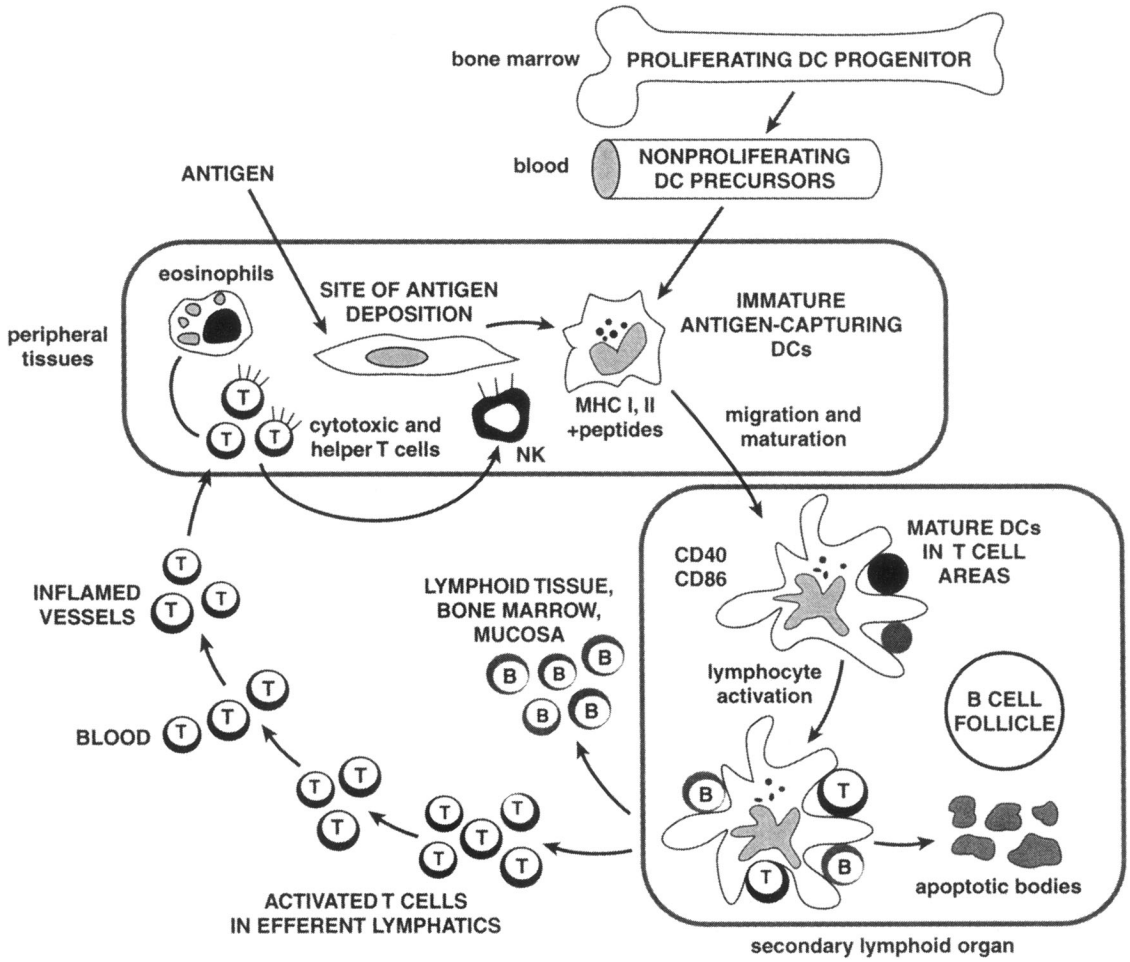

Fig. 1. The life of a dendritic cell, the capture of antigens, and their presentation to selected antigen-specific lymphocytes. Circulating precursor DC enter peripheral tissues as immature DC where they are poised to capture antigens (e.g., microbial products). Following antigen capture immature DC leave the tissues and migrate to lymphoid organs, where, after maturation, they display antigen-derived peptides on their MHC molecules, which in turn select rare circulating antigen-specific lymphocytes. These reactive T cells become activated and further induce terminal DC maturation, which support lymphocyte expansion and differentiation. Activated T lymphocytes migrate back to the injured tissue, because they can selectively traverse inflamed epithelium. Helper T cells secrete lymphokines, and cytotoxic T cells eventually lyse the infected cells. Activated B cells differentiate into B lymphoblasts after contact with T cells and DC, then migrate into various areas where they mature into plasma cells and produce antibodies that will eventually neutralize the initial pathogen. Cytokines secreted by Th2-polarized T helper cells activate eosinophils, which then infiltrate the site of tissue injury. NK cells, one of the key components of the innate immunity, act at different stages of protective immune response by cytokine release and cytotoxic activity.

well as maturation stages are defined by a combination of markers as shown in Fig. 3. Finally, three stages of development have been delineated including precursor DC patrolling through blood and lymphatics, tissue-residing immature DC, and mature DC present within secondary lymphoid organs. The unique morphological appearance of DC suits well their key functions, i.e., uptake and presentation of Ag to cells of the adaptive immune system (Fig. 4).

PATHWAYS OF DENDRITIC CELLS DIFFERENTIATION

DC Development from CD34$^+$ Progenitors

The DC progenitors represent a small fraction of CD34$^+$ hematopoietic progenitor cells (HPC) in bone marrow or peripheral blood. GM-CSF and TNF stimulate growth and differentiation of DC progenitors into DC

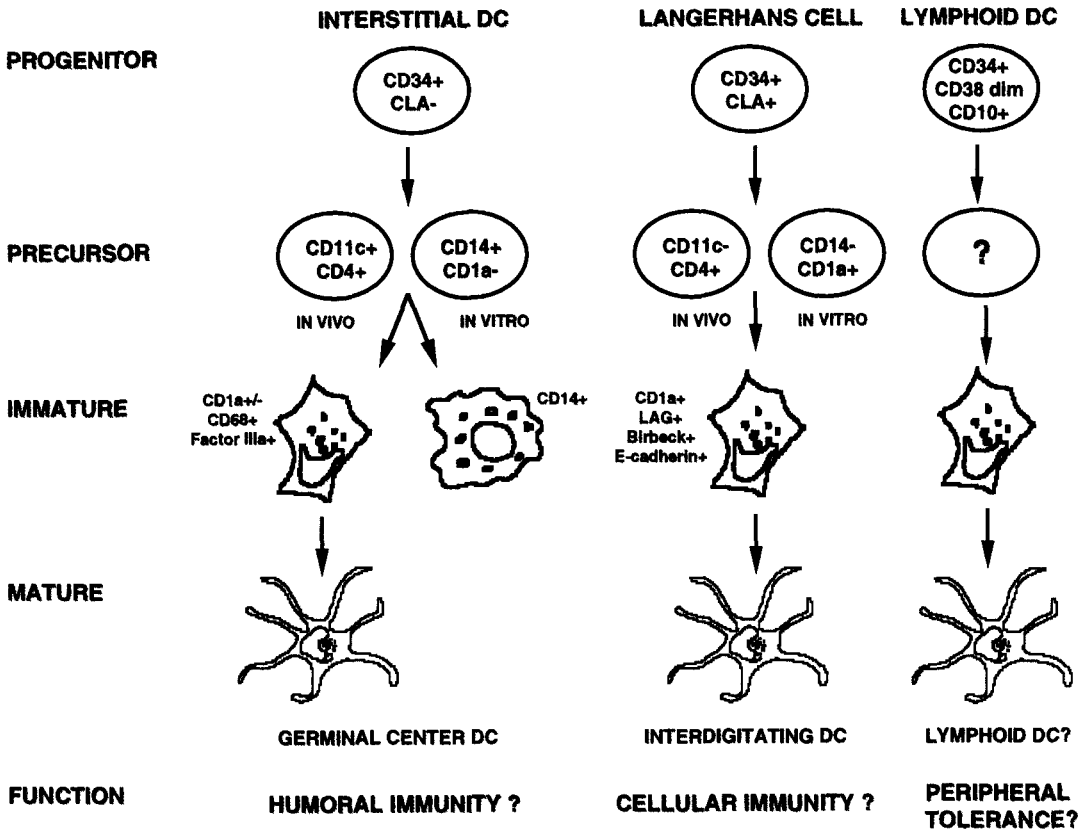

Fig. 2. Pathways of dendritic cell differentiation. CD34+ hematopoietic progenitor cells contain discrete subpopulations committed to DC differentiation. These progenitors grow and differentiate into precursors of at least three distinct DC subsets such as interstitial DC, Langerhans cells, and lymphoid DC. These subsets may have such distinct biological functions as induction of immunity or tolerance, polarization of T cell responses, and induction of humoral immunity.

precursors (reviewed in Ref. 8). Although this process can be enhanced and/or modulated by multiple cytokines (c-Kit ligand, Flt-3-ligand, IL-3, TGFβ, IL-4, and IL-13), TNF is a critical factor in DC development (8, 12). Whereas the intracellular signals mediating DC differentiation remain largely unknown, recent studies point to a central role for protein kinase C signaling (13) and NF-κB activation (14).

$CD34^+$ HPC contain progenitors for two discrete myeloid DC populations: the epidermal LC and the interstitial DC (Fig. 2) (15, 16). The LC progenitors express cutaneous lymphocyte-associated antigen (CLA, a skin homing molecule which is also a ligand for E-selectin) (17). While LC precursors are committed in their differentiation potential, the precursors of interstitial DC can become macrophages in response to M-CSF (15). The mature DC derived from these two *in vitro* generated precursor subsets are equally potent in stimulating the proliferation of naive, allogeneic $CD45RA^+$ T cells or of autologous T cells in the presence of staphylococcal enterotoxin A (16). However, interstitial DC demonstrate a high efficiency of Ag capture, about 10-fold higher than that of LC, which correlates with the expression of nonspecific esterase, a marker of the lysosomal compartment (16). Nevertheless, the most striking functional difference between these subsets relates to B cells (discussed below). Finally, DC can also arise from a subset of $CD34^+$ HPC that coexpresses CD10, which is apparently committed to the lymphoid lineage (18).

DC Development from Blood Precursors

Three subsets of DC precursors circulate in the blood: $CD14^+$ monocytes, $CD11c^+$ precursor DC, and $CD11c^-$ precursor DC. Monocytes can differentiate into cells displaying features of immature DC or macrophages in response to GM-CSF and IL-4 (IL-13) or M-CSF, respectively (19–22). These immature monocyte-derived DC become mature DC upon CD40L and/or LPS signal-

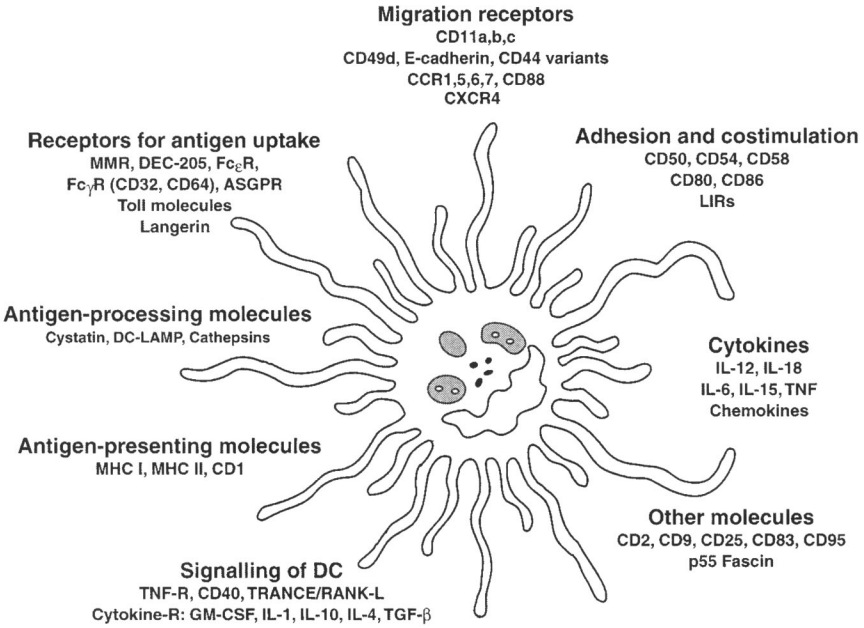

Fig. 3. Molecules expressed by dendritic cells. Illustrated are the key features used in combination to identify DC. At the present time there is not a single molecule that permits unambiguous assignment of a given cell to the DC family. The combination of several markers, however, defines a dendritic cell subpopulation and its stage of maturation.

ing or when cultured with either TNF + IL-1 or monocyte-conditioned medium (22–25). However, monocyte differentiation is reversible (22, 26, 27) and immature monocyte-derived DC or macrophages can interconvert into one another until late stages of their differentiation/maturation process (22).

Considerable advances have been made in the characterization of the nonmonocyte blood DC precursors (28–32). After depletion of T, B, and NK cells and monocytes from the blood mononuclear cell fraction, HLA-DR^{hi}/lineage-negative cells can be identified that are CD11c$^+$ or CD11c$^-$ with reciprocal expression of CD45RA. Cells of a similar phenotype can also be isolated from tonsils (33, 34) with CD11c$^+$ DC, which carry immune complexes, principally found within follicles. The germinal center CD11c$^+$ DC may represent the mature progeny of blood CD11c$^+$ precursors, as both uniquely express the metalloprotease decysin (35). CD11c$^-$ precursor DC are dependent for survival and differentiation of IL-3 and/or CD40-L (34, 36). These IL-3-dependent cells are CD68^{hi}, lack lysosomal lineage-related markers such as myeloperoxidase and lysozyme, and might be of nonmyeloid origin (32).

IMMUNOREGULATORY FUNCTION OF DENDRITIC CELLS

Antigen Capture

Consistent with their role in the induction of protective immunity, immature tissue-residing DC are very efficient in Ag capture and can utilize several pathways such as (a) macropinocytosis; (b) receptor-mediated endocytosis via C-type lectin receptors (mannose receptor; DEC-205) (37); and (c) receptor-mediated endocytosis through Fc receptors (20, 38); and d) engulfment of apoptotic bodies (39, 40).

The captured Ag is directed toward the MHC class II-rich compartments (MIICs), late-endosomal structures, containing the HLA-DM products that are able to enhance and edit peptide binding to MHC class II molecules (reviewed in Ref. 41). Immature DC constantly degrade MHC class II molecules in their MIICs (42, 43). The complexes of Ag and class II molecules relocalize subsequently to the cell surface, where they remain stable for days and are available for recognition by CD4$^+$ T cells (42–44). The delivery of class II

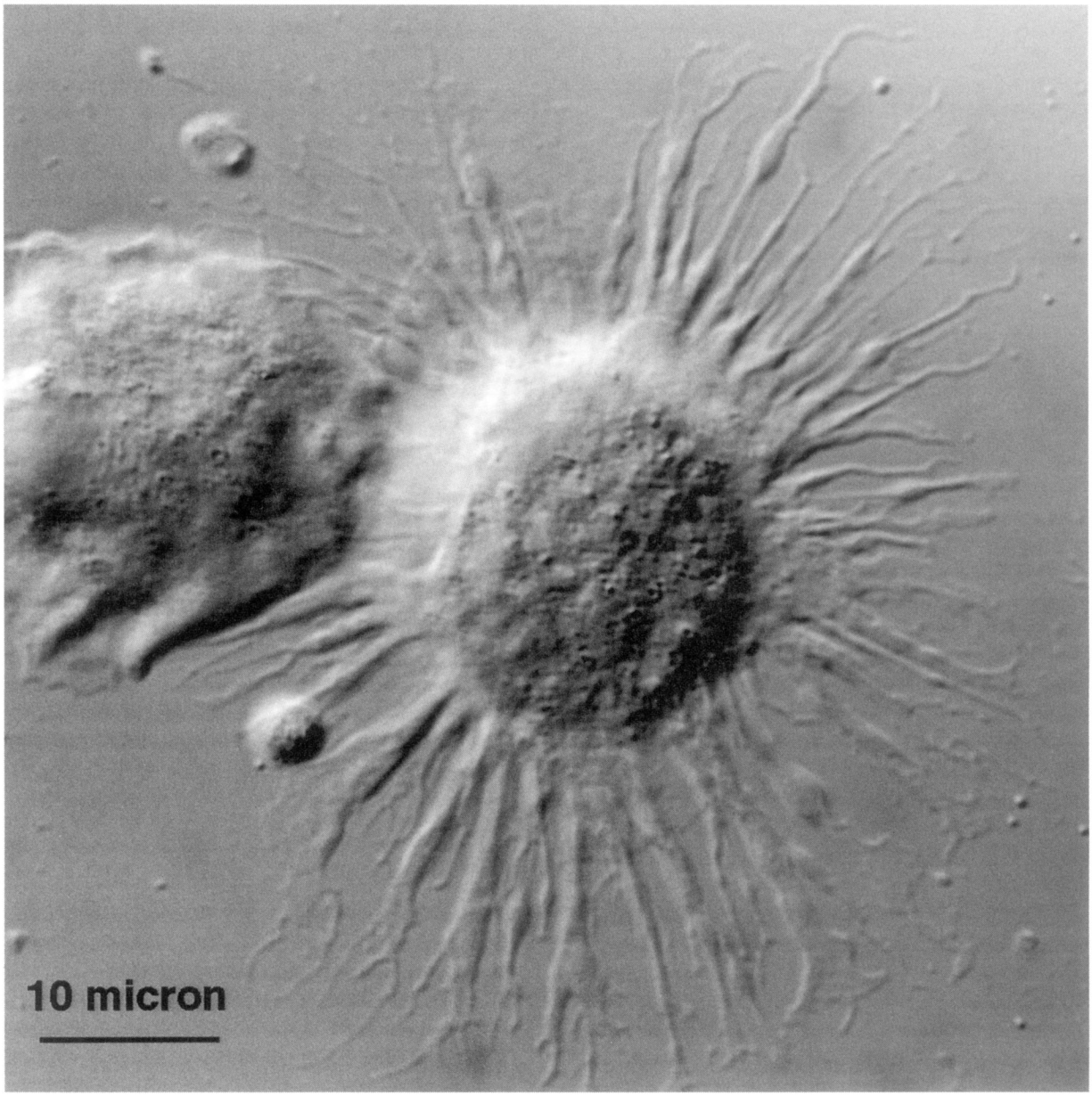

Fig. 4. Dendritic cell morphology. Differential interference contrast (DIC) of a fully mature dendritic cell. Monocyte-derived dendritic cells were cultured for 9 days with GM-CSF and IL-4 and induced to maturation by CD40 ligand. The cells were allowed to adhere to polylysine-coated glass coverslips for 1 hr, fixed, and mounted for observation on Leica TCS-NT confocal microscope equipped for DIC measurement through a 100× objective. Dendrites of the cell flatten on the solid support and extend for 20 μm around the cell.

molecules to cell membrane is controlled by cathepsin S, particularly by the ratio between cathepsin S and its endogenous inhibitor cystatin C (43). To generate $CD8^+$ cytotoxic killer cells, DC have to present antigenic peptides in the context of MHC class I molecules (41). This is relatively straightforward if the DC is infected itself, with, for instance, influenza virus. The virus uses the cell's machinery to synthesize viral proteins, which like cellular proteins, are degraded into peptides by the proteasome and then translocated from the cytosol to the endoplasmic reticulum, where they bind to class I molecules (41). These Ag–MHC class I complexes are then sent to the cell surface, where they are available for recognition by $CD8^+$ T cells. It is less clear, however, how DC process and present Ag that have no access to the cytosol in an MHC class-I-restricted manner (for

instance transplant- and tumor-derived Ag, or Ag from viruses that cannot infect DC). The engulfment and processing of apoptotic bodies by DC represent a probable pathway for the loading of MHC class I (40). Indeed, monocyte-derived DC loaded with apoptotic bodies obtained from either macrophages or HeLa cells infected with influenza virus stimulate the proliferation of influenza specific T cells and the generation of class I-restricted influenza-specific $CD8^+$ CTL (40). The capture of apoptotic bodies by DC is likely to account for the *in vivo* phenomenon of "cross-priming," whereby Ag from tumors or transplanted organs are presented by host APC. Tolerance to tissue-restricted self Ag (peripheral tolerance) may actually be initiated by the tissue DC that capture the cells undergoing apoptosis as occurs during normal cell turnover.

Besides the classical presentation of processed Ag in the context of MHC class I and class II, DC can also employ the CD1 pathway to present microbial lipid-containing Ag and induce an immune response to infectious agents, particularly *Mycobacteria* (45). CD1 molecules, a hallmark of the DC phenotype, constitute a family of β_2-microglobulin-associated nonpolymorphic glycoproteins which assemble with a nonprocessed Ag in the endosomal/lysosomal compartments and present Ag in a TAP-independent manner (41, 45). Presentation of mycobacterial lipoglycan via CD1b requires pathogen uptake through the mannose receptor (45).

Homing and Migration

During their life span, DC migrate from the blood to peripheral tissues and from peripheral tissues to lymphoid organs. The homing of DC to a given tissue as well as their migratory capacity following antigen capture is tightly regulated by chemotactic factors released by the target tissue and by modulation of surface adhesion molecules. For example, IL1 and TNF activate and mobilize LC by downregulating the surface expression of E-cadherin, thereby loosening their interactions with keratinocytes (46). Interstitial DC likewise migrate from the kidney and heart in response to IL1 and TNF (47). DC express several chemokine receptors such as CCR1 (receptor for RANTES), CCR2 (receptor shared by MCP-1 and MCP-3), CCR3 (receptor for eotaxin), CCR5 (receptor for MIP-1α and -β and RANTES), CCR6 (receptor for MIP-3α), and CCR7, a receptor for MIP-3β (48–52). CCR1, CCR5, and CCR6, expressed on immature DC, are downregulated during maturation (51, 52). Conversely, CCR7 is lacking on immature DC but is induced upon activation (51, 52). Importantly, MIP-3α is preferentially produced at sites enriched with immature DC while MIP-3β is preferentially expressed within the paracortex of secondary lymphoid organs where mature DC home (51). Thus the coordinated expression of distinct chemokine receptors may play a critical role in the migration of DC at various stages of maturation.

The isoforms of CD44, a receptor for the extracellular matrix-component hyaluronate involved in lymphocyte homing and activation (53), may also play a role in LC and DC trafficking and functions. During their migration to peripheral lymph nodes, LC and DC upregulate pan-CD44 epitopes and sequences encoded by CD44 variant exons CD44v4, v5, v6, and v7 (53).

Antigen Presentation and T Cell Activation

The ability to prime naive T cells constitutes a unique and critical function of DC. Following Ag uptake DC migrate to the lymph nodes and, meanwhile, mature from Ag-capturing cells into Ag-presenting/activating cells (Fig. 5) (reviewed in Refs. 7 and 54). *In vitro*, DC induce the mixed leukocyte reaction (MLR), a model for graft rejection, where only one DC is necessary to activate 100–3000 T cells. Molecules mediating efficient T cell binding and activation by DC have yet to be identified and the unique ability of DC to affect these processes may essentially be related to the persistent expression of high levels of antigens and costimulatory molecules (Fig. 6). For example, MHC products and MHC–peptide complexes are 10–100 times higher on DC than on other APC like B cells and monocytes. Recognition of MHC–peptide complexes on DC by antigen-specific T cell receptor (TCR) constitutes "signal one" in DC–T cell interaction (7, 54). This initial phase is strengthened by high expression of several adhesion molecules, like integrins β1 and β2 and members of the immunoglobulin superfamily (CD2, CD50, CD54, CD58). Several accessory molecules, expressed on DC (B7.1/CD80, B7.2/CD86, CD40), interact with ligands and counterreceptors on T cells, constituting "signal two," which is required to sustain T cell activation. CD86 on DC is so far the most critical molecule for amplification of T cell responses (55, 56).

The interaction between CTLA-4/CD28 on T cells and CD80/CD86 on DC may play a role in the regulation of type 1 vs. type 2 T cell development (Th1 vs. Th2). In particular, B7.1/CD80 may promote Th1 responses, whereas B7.2/CD86 ligation may skew toward Th2 responses (57, 58). An emerging pattern is that of distinct DC subsets, lymphoid vs. myeloid, inducing different class of immune response [Th1 vs. Th2 (B. Pulendran, personal communication)]. That can be explained partly by heterogeneous IL-12 release by these DC subsets with

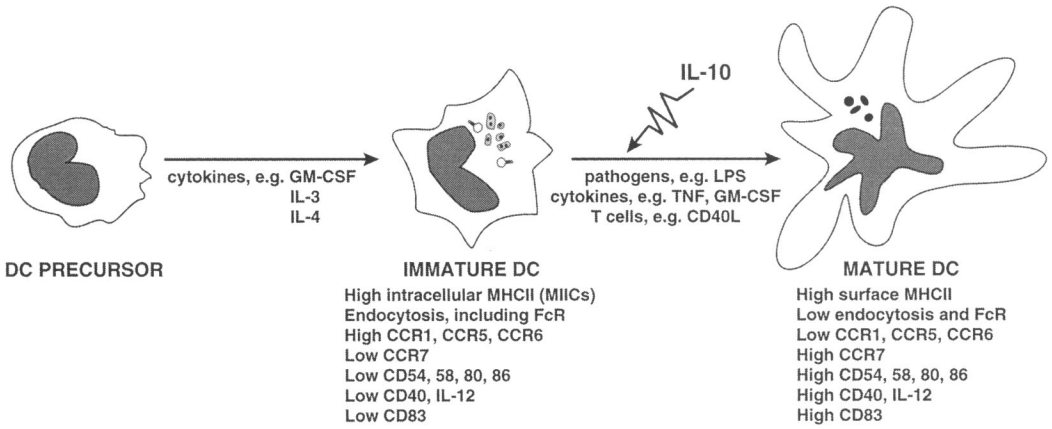

Fig. 5. Stages of dendritic cell maturation and transformation from antigen capture to antigen presentation. Circulating DC precursors, which originate from $CD34^+$ bone marrow progenitors, can be identified as monocytes as well as class II MHC-positive $CD11c^+$ or $CD11c^-$ cells. These precursors migrate into tissues to become resident immature DC, and this may increase in response to inflammatory cytokines. After antigen capture, immature DC undergo maturation during migration to secondary lymphoid organs. Maturation is completed after the selection, activation, and interaction with antigen-specific T cells.

lymphoid $CD8^+$ DC secreting high levels of IL-12, while myeloid $CD8^-$ DC secrete low levels of IL-12 (9). Human studies also reflect heterogeneity in the production of IL-12 by DC. In particular, monocyte-derived DC secrete large amounts of IL-12 (>10 ng/ml) that skews the T cell response toward Th1 (59), while $CD34^+$ HPC-derived DC show only a relatively low secretion of IL-12 (10–100 pg/ml) in response to CD40 ligation.

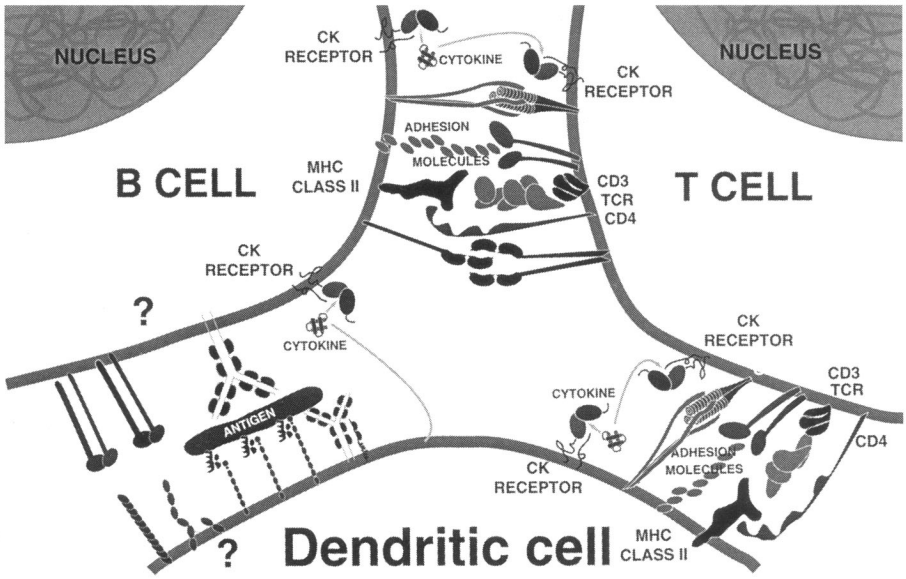

Fig. 6. Ménage à trois: the conversation among dendritic cells, T cells, and B cells. $CD4^+$ T cells recognize peptide presented by class II MHC on dendritic cells and the interaction is strengthened by adhesion molecules. This results in upregulation of CD40 ligand on T cells. Triggering of CD40 on DC permits cytokine production and upregulation of CD80/CD86 (B7). The secreted cytokines further activate T cells and support their proliferation. The increased CD80/CD86 expression on DC triggers CD28 and/or CTLA-4 on T cells. The T cells then secrete cytokines in turn, which will either further activate the DCs or act as autocrine T cell growth factors. B cells may utilize similar pathways for interaction with T cells, however, the levels of class II and costimulatory molecule expression are lower than that of DC. Except for IL-12, the molecules regulating direct B cell–DC dialogue remain unknown.

In the DC–T cell interaction, T cells play an important role in activating DC, in particular, via CD40 ligand (CD40L)-CD40 signaling. Ligation of CD40 enhances T cell stimulatory capacity of DC by inducing their maturation (manifested by increased expression of CD80, CD83, and CD86) and cytokine release (IL1, TNF, chemokines, and IL-12) (7, 20, 59). The CD40-activated DC can trigger T killer responses in the absence of helper T cells and thus act as a temporal bridge between a $CD4^+$ T helper and a $CD8^+$ killer T cell (60–62). However, CD40 activation of DC can be bypassed by inflammatory agents, as provided by an adjuvant, or by viral infection (60, 61).

Regulation of B Lymphocytes

Recent studies established the role of DC in regulation of B cell growth and immunoglobulin secretion. DC can elicit their regulatory function toward B cells in an indirect way by activation and expansion of T helper cells, which in turn induce B cell growth and antibody production (reviewed in Refs. 7 and 54). There is evidence however, for a direct DC–B cell dialogue as well (Fig. 6). Naive B cells respond uniquely to the interstitial, non-LC type of DC (16). By secretion of soluble factors (including IL-12) DC directly stimulate the production of antibodies and the proliferation of CD40L-activated B cells (63). DC also orchestrate immunoglobulin class-switching of T cell-activated B cells: whereas soluble factors like IL-10 and TGFβ can induce secretion of IgA1, expression of IgA2 appears to be strictly dependent on a direct DC–B cell interaction (64). This indicates that DC are in control of mucosal immunity, and, in fact, DC can be found in mucosal lymphoid tissues beneath antigen-transporting M cells and in T-cell areas.

Dendritic Cells and NK Cells

As discussed above, IL-12 is one of the major DC-derived factors regulating T and B cell function. NK cells constitute another IL-12-responding cell type and IL-12 activation of NK cells triggers CD28-dependent and independent cytotoxic pathways, allowing for elimination of B7-expressing cells including autologous DC (65, 66). Thus, by releasing IL-12, DC not only polarize T cell responses but also may bring about their own demise. Besides negative regulatory effects, it is possible that activated NK cells may also elicit positive regulatory signals, particularly toward immature DC, for instance, by promoting DC maturation at marginal zones in the spleen via release of cytokines or cell–cell contact (65, 66).

Interestingly, DC themselves can acquire an NK phenotype. Thus, rat spleen and thymus DC express low levels of the natural killer cell receptor protein 1 (NKR-P1; C-type lectin superfamily), which is an activation receptor that leads to stimulation of granule exocytosis (67). The expression of NKR-P1 on DC is strongly upregulated after overnight culture. In addition to expressing this typical NK cell marker, rat spleen DC, but not thymus DC, are able to kill the NK cell-sensitive target YAC-1. Human monocyte- or $CD34^+$ HPC-derived DC also express NKR-P1, ligation of which results in calcium fluxes and IL-12 secretion (68). It is not presently known whether human DC express any functional NK activity.

DENDRITIC CELLS AND PATHOGENS

In accordance with their function as a link between innate and adaptive immunity, DC interact with multiple pathogens, express pattern recognition receptors as well as phagocytose pathogens, and present their Ag via class I and class II MHC molecules or CD1. Bacterial LPS is one of the major molecules recognized by the innate immune system (69, 70). Ligation of membrane CD14 by complexes of LPS and soluble LPS-binding protein leads to proinflammatory signals including TNF and IL1 secretion, which, when released at the site of tissue damage, increase the turnover of local APC as well as recruitment of precursor cells (47). Recently, Toll-like receptor-2 (TLR2) has been shown to be a signaling receptor that is activated by LPS in a response that is dependent on LPS-binding protein and is enhanced by CD14 (70). TLR2 contains a region in the intracellular domain which is homologous to a part of the IL-1 receptor and which is involved in the activation of IL-1-receptor-associated kinase (70). Following *in vitro* or *in vivo* exposure to LPS or other bacterial products, DC undergo maturation characterized by increased expression of costimulatory and MHC-class II molecules, high T cell stimulatory capacity, and IL-12 release (42, 71) which all together lead to the induction of protective immune responses.

DC are also involved in the induction of immune response against parasites. Perhaps the best-studied parasite is *Leishmania*. Immature DC can phagocytose the organism *in vitro*, and LC infected by *Leishmania major* are present in the dermal infiltrate of skin lesions (72). Leishmania-infected LC can migrate into the draining lymph nodes, where they mature and activate Leishmania-specific T cells. Another parasite of considerable

clinical interest is *Toxoplasma gondii*, which can be fatal in immunocompromised patients. *Toxoplasma* Ag induce the redistribution of DC to T cell areas and activate the secretion of IL-12 by DC but not by macrophages (73). It remains to be determined whether the *Toxoplasma* parasites that invade the gut are directly taken up by DC or whether macrophages capture and process them (74).

Finally, due to their pivotal role in the initiation of immune responses, DC represent a target of choice for viruses (reviewed in Refs. 7 and 54). Sequestration within the DC themselves may provide a very efficient strategy for viruses to hide from the immune system. Moreover, due to the distribution of DC throughout body surfaces like skin and mucosa, DC provide a means for virus to access other cells like T cells. DC also contribute to the development of an early (nonclonal) as well as an Ag-specific antiviral response. Indeed, utilizing their mannose receptor, peripheral blood DC interact with enveloped viruses, such as HIV or herpes viruses, which leads to IFN-α release (75). Moreover, DC can acquire virus antigens, for example, influenza antigens, from virus-infected apoptotic cells and subsequently stimulate class I MHC-restricted $CD8^+$ CTL.

DC are infected upon exposure to influenza virus but remain viable and produce little infectious virus (61, 76). Infected DC, but not infected monocytes/macrophages or B cells, can induce recall CTL responses by $CD8^+$ T cells (61, 76). On the contrary, DC infected with wild-type measles virus as well as the vaccine strains eventually undergo apoptosis and are unable to stimulate proliferation of alloreactive T cells (77–79). While this can explain the profound immunosuppression caused by measles, it becomes unclear how immunity against measles is ever established. One possibility is that noninfected DC may capture measles virus-induced apoptotic bodies, as occurs with influenza virus, and subsequently initiate CTL responses. Alternatively measles virus may differentially affect the various DC subsets or maturational stages, as evidenced by the fact that measles virus-infected immature DC induce T cell death, whereas T cell viability is not altered by infected mature DC (77–79).

DC express CD4, the receptor for HIV, as well as chemokine receptors that act as coreceptors for HIV (80). Early studies analyzed whether DC would act as transporters of the virus, initially deposited on the mucosa, to activated T cells in secondary lymphoid organs, or as permissive sites for virus replication (81–83). These studies eventually led to the finding that explosive HIV replication occurs when DC and resting T cells are cocultured (81–84). Most of the viral production from DC–T cell cocultures occurs within syncytia that are heterokaryons of DC and T cells. Each cell type brings a specific transcription factor allowing viral genome expression. In accordance with these *in vitro* studies, HIV-expressing syncytia have been found *in vivo* at the surfaces of mucosal lymphoid tissues like tonsils and adenoids (85, 86). A deficit of circulating DC may explain the early loss of $CD4^+$ memory T cells.

DENDRITIC CELLS AND TUMOR IMMUNOLOGY

The immune system has the potential to eliminate neoplastic cells as evidenced by occasional spontaneous remissions in renal cell carcinomas and melanomas (87, 88). Tumor regression occurs through various pathways, one of which is mediated by CTL recognizing class I MHC peptide complexes on the tumor cell surface. For this to happen, DC should first home to the tumor, capture tumor antigens, and then migrate to secondary lymphoid organs to initiate T lymphocyte responses against the tumor associated antigens (TAA). The final or efferent step of the antitumor immune response occurs when the primed TAA specific CTL leave the secondary lymphoid organs and return to the tumor to kill the malignant cells.

Immunohistological analysis of carcinomas, using S100 staining as a marker for DC, demonstrated the association of DC infiltration with a better prognosis (reviewed in Ref. 54). Nevertheless, tumor-associated DC are usually of a low allostimulatory capacity, particularly if isolated from the progressing metastatic lesions (89). The alteration of DC functions in cancer appears to extend beyond the tumor site, as blood DC from patients suffering from stage III and IV breast cancer show decreased allostimulatory capacity (90). Tumor cells may actively inhibit DC development and function, for example, by release of IL-10, M-CSF, or vascular endothelial cell growth factor (91).

DC-Based Immunotherapy Protocols

Transfer of TAA-loaded DC results in eradication of experimental tumors. Several Ag-delivery systems have been employed including pulsing with synthetic or tumor-derived peptides or by using recombinant retroviral or adenoviral vectors. In all instances, the induction of MHC-restricted CTL responses and considerable antitumor effects have been observed in mice (92, 93). Most recently, tumor peptide pulsed DC-derived exosomes (subcellular structures containing high levels of MHC molecules and peptides) have been successfully used to prime specific CTL *in vivo* and eradicate or suppress growth of established murine tumors (94).

Clinical responses have been observed in preliminary human trials with various DC subpopulations pulsed with lymphoma idiotype, prostate-specific membrane antigen peptide, or melanoma peptides (95–97). These encouraging preliminary results further warrant the clarification of several issues for optimal design of DC-based immunotherapy protocols. The complexity of the DC lineage, with diverse subsets, stages of maturation, and methods of generation, necessitates that each variable be tested independently. Furthermore, the nature of the tumor antigens and the optimal method for loading DC with those tumor antigens represent additional parameters for careful analyses. Strategies that introduce antigen into DC, but allow the DC to select and tailor peptides for presentation on available MHC molecules, would circumvent the need to identify tumor specific peptides with known MHC restrictions a priori. Such approaches would also offer the theoretical advantage of introducing both helper and cytolytic antigenic epitopes for the generation of effective CTL. Route of administration, dose of DC and frequency of injections, patient selection, and tumor selection also need to be established.

Assuming successful induction of strong antitumor CTL activity in patients after DC immunization, other obstacles need to be addressed to ensure success of DC-based immunotherapy of cancer. CTL may not readily migrate to the tumor site. Tumor cells may escape CTL recognition/killing by losing the MHC class I expression required for CTL recognition (98), by losing the expression of critical tumor antigens, or by expressing FasL (99) or IL-10 (100) that inactivate CTL. Patients may also experience tumor-related or drug-induced immune suppression that would render CTL priming inefficient *in vivo*, in which case CTL priming may best be accomplished *in vitro*, followed by adoptive transfer. An alternative approach may be to increase, directly, the levels of DC *in vivo* that are capable of capturing tumor antigens and turning in specific immune responses. Accordingly, administration of FLT3-L to mice challenged with fibrosarcoma has been shown to induce complete tumor regression in a significant proportion of mice and decreased tumor growth in the remaining mice (101).

DC IN TRANSPLANTATION AND HYPERIMMUNE RESPONSES

Immunostimulatory potential of DC may contribute to disease pathogenesis. This can be particularly relevant in the context of organ transplantation, allergy, and autoimmunity. Indeed, DC migrate from cardiac or liver allografts to the T cell areas of recipient spleens, where they effectively prime Ag-specific immune responses leading to graft rejection (102–103). Graft survival could be prolonged by DC depletion (104). Although little is known about the role of DC in graft-versus-host disease, they are likely to be involved, as all sites involved in GVHD are populated by DC. DC, which are radioresistant, theoretically contribute to direct donor T lymphocyte allosensitization and prime for the donor immune reactivity that results in the clinical syndrome of graft-versus-host disease.

DC may play a significant role in allergic asthma (105). Following capture of inhaled Ag, DC that are abundant in the lung migrate to the draining lymph nodes and induce primary immune responses (106, 107). DC are also important for presenting inhaled Ag to previously primed Th2 cells, leading to chronic eosinophilic airway inflammation (108). The number of DC is significantly higher in the airways of asthmatics compared with control subjects, as is the proportion of DC expressing FcE R I-a (109).

Finally, LC contribute to the contact sensitivity by processing and presentation of hapten-modified proteins. Unlike classical delayed-type hypersensitivity (DTH) to proteins or cellular antigens, mediated primarily by class II MHC-restricted $CD4^+$ T cells, the T cell response to haptens appears to be more complex and may be elicited by $CD8^+$ T cells and downregulated by $CD4^+$ T cells as observed in C57 BL/6 mice (110, 111). *In vivo* application of IL-10, a potent inhibitor of T cell and DC function, before allergen exposure induces antigen-specific tolerance in mice (112).

CONCLUDING REMARKS

Despite considerable achievements in our understanding of how DC induce and regulate immune responses, much remains to be learned about this complex system of cells. Little is known about the interplay between DC and other components of the innate immune system like NK cells and TCR$\gamma\delta$ cells. Furthermore, the mechanisms by which DC can induce immunological tolerance need to be elucidated. Resolving these issues will permit the therapeutic manipulation of the DC system. Initially, defined DC populations generated *in vitro* will be administered to patients to induce either immunity (as required in cancer and infectious diseases) or tolerance (as required in allergy, autoimmunity, and transplantation). Finally, DC could be targeted *in vivo* with specific pharmacological agents. While single agents like steroids or FLT-3L exert effects on DC in experimental models, more sophisticated strategies targeting various DC subpopulations and various stages of maturation will prob-

ably be necessary to enhance or inhibit specific immune responses with precise control.

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