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Erratum: Recent Advances in Dendritic Cell Biology [Journal of Clinical Immunology 25:87–98, 2005]

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When this review article was published in the previous issue (March 2005) of this journal, the figures were not published in color as intended due to a publication error. We regret this error and are republishing this article in its entirety with the color figures on the following pages of this issue.

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Recent Advances in Dendritic Cell Biology

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Dendritic cells are professional antigen presenting cells that are central to the induction and regulation of immunity. This review discusses recent advances in the understanding of dendritic cell biology.

KEY WORDS: dendritic cells; antigen-presenting cells; review.

DC DIFFERENTIATION AND SUBTYPES

Dendritic cells (DCs) are lineage-negative, MHC class II positive bone marrow-derived mononuclear cells that are found in tissues throughout the body (1), and are specialized for antigen presentation to cells of the adaptive immune system (Fig. 1). In human blood, DCs and DC precursors are commonly divided into two populations by staining with antibodies to CD11c and CD123. $CD11c^{+}CD123^{lo}$ blood DCs have a monocytoid appearance and are termed "myeloid DCs" (MDCs), whereas $CD11c^{-}CD123^{hi}$ DCs have morphological features similar to plasma cells and have thus been termed "plasmacytoid DCs" (PDCs), a designation that, while imprecise, has been useful. PDCs and MDCs differ in many ways, including their tissue distribution, cytokine production and growth requirements. PDCs are important cells in innate anti-viral immunity and autoimmunity and are found primarily in the blood and lymphoid organs. They are the major interferon α (IFNα) producing cells in the body and can as such induce anti-viral and in certain circumstances anti-tumor immune responses (2).

In the blood, MDCs—the main focus of this review—may be classified into two subsets that are distinguished by the expression of distinct carbohydrate moieties of P selectin glycoprotein ligand 1 (PSGL-1) (3). DCs with 6-sulfo LacNAc modifications of PSGL-1 have been termed "inflammatory DCs," as they produce large amounts of tumor necrosis factor α (TNFα) and respond to complement components C5a and C3a. In tissues, MDCs may also be divided into subtypes depending on their anatomic location—Langerhans cells of the epidermis (which express CD1a, langerin and E-cadherin) and interstitial or mucosal DCs, which express mannose receptor, DC-SIGN and, in the dermis, CD13 (4, 5).

Two models have been proposed for the differentiation of DCs from hematopoietic progenitor cells, one postulating a single committed DC lineage that has functional plasticity, the other postulating multiple DC lineages that are functionally distinct (4). Both models define three stages of differentiation—DC precursors, immature DCs and mature DCs. DC precursors and immature DCs are continuously produced in the bone marrow in response to fms-like tyrosine kinase-3 ligand (Flt-3L) and granulocyte-macrophage colony stimulating factor (GM-CSF).

Traditionally, MDCs have been thought to be of myeloid origin, and PDCs of lymphoid origin (4). Evidence supporting the lymphoid origin of PDCs includes recent observations that the gene encoding CIITA, a transcription factor essential for the activation of genes associated with MHC class II antigen presentation, is activated via its myeloid promoter, pI, in MDCs, but via its B cell promoter, pIII, in PDCs (6). However, other evidence indicates that the differentiation pathways for both types of DCs are more complex and may even interconnect. For example, experiments in mice indicate that both PDCs and MDCs can be derived from Flt3-expressing myeloid and lymphoid progenitors (7, 8), and that PDCs can differentiate into MDCs following viral infection (9).

DCs can display specialized functions dependent upon their anatomic location. For example, intestinal DCs play an important role in the induction of local immunity that ensures an adequate immune response to commensal bacteria, allowing their containment to the intestinal lumen

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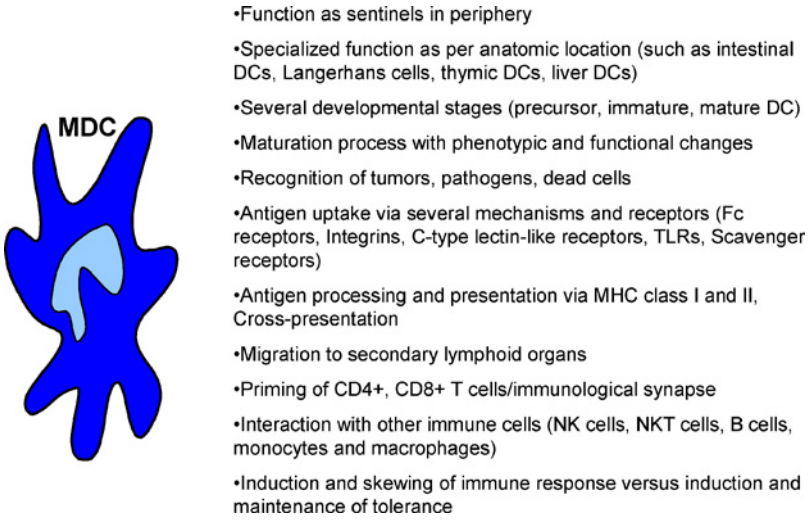

Fig. 1. Overview of MDCs and their features/tasks as antigen-presenting cells.

without the generation of systemic immunity. In mice, intestinal DCs harbor live commensal bacteria, allowing them to induce protective immunity via secretory IgA to limit mucosal penetration. The restriction of these DCs to mucosal sites and draining mesenteric lymph nodes prevents unnecessary systemic immunity to the normal gut flora (10). In the lungs, a distinct subset of phenotypically mature pulmonary DCs have been found in mice that produce IL-10. These pulmonary DCs induce the differentiation of IL-10-secreting $CD4^+$ regulatory T cells (Tr), that in turn mediate tolerance to antigens acquired through the respiratory tract (11).

ANTIGEN UPTAKE, PROCESSING AND PRESENTATION

DCs process antigens acquired both endogenously (i.e., synthesized within the DC cytosol), or exogenously (acquired from the extracellular environment). Exogenous antigen sources include bacteria, viruses, apoptotic or necrotic cells, heat shock proteins, proteins and immune complexes. These are captured through phagocytosis, pinocytosis and endocytosis with the help of cell surface receptors on the DC. Examples include Fc receptors (12), integrins (13), C-type lectins (14)), and so-called "scavenger receptors" such as LOX-1 and CD91 (15–17). Many of these receptors have additional functions such as initiating intracellular signaling or mediating cell–cell interactions.

DCs process protein antigens into peptides which are loaded onto major histocompatibility complex classes I and II (MHC I and II) molecules and transported to the cell surface for recognition by antigen-specific T cells. Endogenous protein antigens, which are processed onto MHC I, are first ubiquitinated and degraded into peptides by the proteasome in the cytosol. These are transported via transporters for antigen presentation (TAP) molecules into the endoplasmic reticulum (ER), where they are loaded onto MHC I. The peptide-MHC I complexes (pMHC I) are then transported from the ER via the trans-Golgi network to the cell surface for presentation to $CD8^+$ T cells.

Exogenously acquired protein antigens, on the other hand, are engulfed and processed in endosomes. Endosomes containing ingested proteins mature and fuse with lysosomes, where proteases degrade the proteins into peptides that are loaded onto MHC II molecules. This requires proteolytic degradation of the MHC II-associated invariant chain (Ii) that normally blocks access to the peptide-binding pocket of MHC II (18). Peptide-MHC II complexes (pMHC II) are then transported to the cell surface within specialized tubules for presentation to $CD4^+$ T cells (19).

Exogenous antigens may also be processed by DCs onto MHC I (13). This phenomenon, called "cross-presentation" or "cross-priming," permits DCs to elicit $CD8^+$ as well as $CD4^+$ T cell responses to exogenously acquired antigens (20–22). Cross-presentation occurs in specialized, self-sufficient, ER-phagosome derived compartments that contain MHC I, Sec61 protein (presumably to translocate antigens into the cytosol for proteosomal processing), TAP (to transport processed peptides from the cytosol), and calreticulin and calnexin (which facilitate loading of peptide onto MHC I) (20, 22, 23). MHC class I molecules which lack endosomal signaling motifs in their cytoplasmic tail do not cross-present, suggesting that at

least for some antigens, the MHC I must come from the cell surface (24). Not all antigens are cross-presented efficiently, for example peptides located in signal sequences are efficiently processed through the endogenous pathway but cross-presentation is markedly impaired (25). This observation suggests either reduced accessibility to the exogenous pathway or rapid degradation not supplying efficient antigen expression levels.

Lipid antigens expressed on pathogens (e.g., mycobacterial mycolates) or self tissues (sphingolipids, phosphatidylinositols) are presented on DCs by CD1 molecules, which heterodimerize with β2-microglobulin and are structurally similar to MHC I (26, 27). Processing of lipid antigens onto the various CD1 molecules is carried out in specialized intracellular compartments, not unlike antigen processing onto MHC II. The CD1d-restricted repertoire includes T cells with substantial TCR diversity as well as relatively invariant NKT cells. The latter, which have the potential to secrete IFNγ, recognize galactosyl ceramides and tumor cell-derived gangliosides and are important mediators of T cell immunity (28).

DC MATURATION

Maturation is a complex process leading to terminal differentiation of DCs, transforming them from poorly immunostimulatory cells that function as sentinels in the periphery which capture antigens into cells potent for T cell stimulation. The process is accompanied by cytoskeletal reorganization, reduced phagocytic uptake, acquisition of cellular motility, migration to lymphoid tissues, enhanced T cell activation potential and the development of characteristic cytoplasmic extensions or "dendrites." Mature DCs express a number of specific markers that distinguish them from immature DCs such as CD83, a cell surface molecule involved in $CD4^+$ T cell development and cell–cell interactions (29, 30) and DC-LAMP, a DC-specific lysosomal protein.

Maturation Stimuli

Maturation is induced by stimuli, so called "danger signals" that alert the resting DC to the presence of pathogens, inflammation or tissue injury (31, 32). Maturation signals come from either host-derived inflammatory molecules such as CD40 ligand (CD40L), TNFα, IL-1, IL-6 and IFNα, or from microbial products and molecules released by damaged host tissues, which stimulate Toll-like receptors (TLRs) (33). The different TLRs have different expression patterns and recognize different sets of molecules (34). In humans, MDCs have been found to express TLRs 1 through 5 and, depending upon the subset, TLRs 7 or 8, whereas PDCs express TLRs 1, 7 and 9 (35–37). TLR7 was recently identified as a critical receptor for murine PDC responses to live and inactivated wild type influenza (38). All TLRs are transmembrane receptors, although not all may act at the cell surface—TLR9 is localized in the ER of resting human PDC and moves to the lysosomal compartment (presumably through ER-phagosome fusion) as its agonist CpG DNA is internalized into the cell (39). Other TLRs (7 and 8) are also found in the endosome where the agonist accesses them, but it is unclear if translocation occurs from the ER. Activation of TLRs transiently enhances endocytosis with simultaneous actin-rich podosome disassembly, suggesting mobilization of the DC actin cytoskeleton to enhance antigen capture and presentation (40).

Intracellular Signaling Events Associated with DC Maturation

TLRs link the recognition of danger signals to DC maturation by initiating complex signaling cascades (41). TLRs are members of the TLR-IL-1 receptor superfamily, all of which share an intracytoplasmic Toll-IL-1 receptor (TIR) domain that mediates the recruitment of TIR-containing adapter molecules such as MyD88, TIRAP, TRIF and TRAM. These adaptor molecules function to recruit other signaling molecules, notably the IL-1 receptor-associated kinase complex (IRAK). IRAK activates the TRAF6 protein, which is required for DC maturation in response to a number of different stimuli (42).

In mice, all TLRs can set off signaling through the MyD88-IRAK-TRAF6 pathway, which results in the activation of the transcription factor NF-κB and mitogen-activated protein (MAP) kinases, inducing the transcription of genes such as TNFα, IL-1 and IL-6. In addition, MyD88-independent differences in the signaling pathways initiated by the different TLRs are beginning to be described, and are associated with the induction of different patterns of gene expression. For example, TRIF controls a MyD88-independent pathway that is unique to TLR3 and TLR4 signaling and is important for the secretion of IFNβ (43, 44), and TRAM-deficient mice have defects in cytokine production in response to TLR4 ligand, but not to other TLR ligands (43).

Cytokine-induced maturation of DCs is under the feedback regulation of suppressor of cytokine signaling (SOCS) proteins (45). In an *in vitro* mouse model, IL-4 and GM-CSF induced activation of JAK/STAT signal transduction pathways in DCs is accompanied by upregulation of SOCS 1,2,3 and cytokine-induced SH2 protein (CIS). The STAT6 pathway is constitutively activated in

immature DCs, but declines with maturation; whereas STAT1 signaling is most prominent in mature DCs and required for upregulation of CD40, CD11c and SOCS expression. The SCOCS pathway may also block TLR-mediated activation of DCs.

DC Maturation Enhances Antigen Processing and Presentation

Antigen processing and loading onto MHC II is highly regulated by DC maturation. In the immature state, DCs efficiently capture antigens but their ability to stimulate T cells is limited, in part because their MHC II molecules are largely retained in lysosomes unable to form pMHC II. Upon maturation, DCs develop an enhanced ability to form pMHC II through the activation of lysosomal hydrolases, which degrade endocytosed proteins and MHC II-associated Ii. This effect is mediated by upregulation of the ATP-dependent vacuolar proton pump in mature DCs, which increases the acidification of lysosomes (46). Mature DCs develop tubules which enhance the transport of pMHC II from lysosomes to the cell surface (19).

Unlike pMHC II, pMHC I may be formed in immature DCs more efficiently. However, DC maturation also upregulates synthesis of TAP and components of the immunoproteasome, enhancing the processing of pMHC I (18).

In mice, cross-presentation of exogenous antigens on MHC I is tightly controlled by DC maturation induced by CD40 ligation and treatment with TLR agonists such as LPS, poly I:C or immunostimulatory CpG DNA (47, 48). MyD88 plays an important role in cross-presentation, lack of MyD88 resulting in decreased IFNγ production and reduced CTL-mediated killing (49).

Maturation Induces Adhesion Molecules, Costimulatory Molecules and Cytokine Production

Maturation is accompanied by increased expression of adhesion molecules and co-stimulatory molecules that are involved in the formation of the immunological synapse, an area encompassing sites of contact between T cells and DCs. Upregulated molecules include semaphorins, pMHC and members of the B7, TNF receptor and TNF families. These molecules are involved in bidirectional signaling between DCs and T cells, modulating both T cell activation and DC function. The complexity of these interactions can be illustrated by the B7 family of molecules, of which there are five members described to date. Signaling via pMHC and the T cell receptor (signal 1), and B7-1/B7-2 and CD28 (signal 2) is essential for T cell activation. B7-DC, a molecule primarily found on DCs, synergizes with B7-1 and B7-2 to stimulate $CD4^+$ T cells, enhance DC presentation of pMHC, promote DC survival and increase DC secretion of IL-12p70, a key Th1-promoting cytokine (50, 51). In contrast, related members of the B7 (B7-H3, B7x) and CD28 (CTLA-4, PD-1) families serve to downregulate T cell activation. B7-H3 and B7x are broadly expressed on many cell types and may be involved in attenuation of inflammatory responses in peripheral tissues (52, 53).

Maturation induces DCs to secrete cytokines that determine the type of ensuing immune response. The specific cytokine profile induced depends upon the type of maturation stimulus, the subtype of DC stimulated and the origin of the DC. For example, Listeria monocytogenes induces IL-12 production by MDCs (54), whereas cholera toxin generates mature MDCs that do not produce IL-12 (55). PDCs, but not MDCs, characteristically produce extremely high levels of type I IFN (IFNα/β) in response to bacterial CpG DNA as well as to a number of viruses. A recent report, however, indicates that mouse MDCs may have TLR independent pathways of type I IFN production (56).

Maturation Alters DC Expression of Chemokines and Chemokine Receptors

Immature blood DCs can enter inflamed tissue by virtue of interactions with ICAM-2 and P- and E-selectins expressed on activated endothelium (57), and through the expression of chemokine receptors such as CCR1, CCR2 and CCR5. Maturation imparts on peripheral DCs the ability to migrate from the tissues to T cell zones of lymph nodes. This is accomplished, at least in part, through downregulation of CCR1 and CCR5 and upregulation of CCR7, which targets DCs to lymphatic vessels and lymph nodes via chemokines CCL19 and CCL21. CCL19-mediated migration is enhanced by local secretion of leukotrienes, perhaps from the DCs themselves (58). Maturation also induces DCs to secrete chemokines such as TARC, MDC or IP-10 (which recruit various T cell subsets), and RANTES, MIP-1α and MIP-1β, which recruit monocytes and DCs into the local environment. Incomplete maturation (e.g. following uptake of apoptotic cells) may still upregulate CCR7, so partially matured DCs may be able to display enhanced lymph node homing (59). In addition, CCR7 has been identified as essential to the migration of dermal and epidermal DCs into afferent dermal lymphatics, both under inflammatory and steady-state conditions (60). This could be an important mechanism by which DCs convey peripheral self-antigens to lymph nodes for tolerance induction.

DC Survival

DC lifespan and immunogenicity depend on signals derived from the innate and adaptive immune systems, and are mediated through the activity of Bcl-2 family proteins (61). Ligands for TLRs and T cell-expressed costimulatory molecules (such as CD40L and TRANCE) stimulate the survival of activated DCs, dependent on Bcl-xL. However, TLRs can also trigger cell death by a pathway that is blocked by Bcl-2. Bcl-2 thus regulates the apoptosis pathway, setting the lifespan of the DC and thereby regulating the magnitude of the induced T cell response.

DC-T CELL INTERACTIONS

DCs prime T cell responses in secondary lymphoid organs such as lymph nodes, spleen or mucosal lymphoid tissues. Real-time imaging of murine DCs and naive T cells in intact explanted lymph nodes reveals that a DC interacts with as many as 500 T cells/h (29, 62, 63). In the presence of antigen, stable and durable DC-T cell contacts form, with antigen-bearing DCs engaging more than 10 T cells at a time. Intranodal *in vivo* imaging of the naive CD8+ T cell–DC interaction suggests three distinct phases: Initial short encounters of T cells with numerous DCs were followed by a phase of long-lasting T cell–DC interactions (up to several hours) leading to T cell cytokine secretion and upregulation of activation markers. Finally, after T cells dissociated from DCs, rapid migration and vigorous proliferation occurred, before exiting through efferent lymphatics (64). Rac1 and Rac2 (Rho family guanosine triphosphatases) in mature DCs have been implicated in controlling the formation of dendrites and directional membrane projections toward naïve T cell, as well as controlling DC migration toward T cells necessary for priming (65).

Strength of DC Priming Signal is Associated with T Cell "fitness"

Effective priming of naive T cells results in their clonal expansion and differentiation into cytokine-secreting effector cells and memory cells (Fig. 2). The ensuing T cell response is dependent on many factors, including the concentration of antigen on the DC, the affinity of the T cell receptor for the pMHC, the duration of the DC-T cell interaction, the state of DC maturation and the type of DC maturation stimulus (66). T cell stimulation by mature DCs is required for long-term T cell survival and

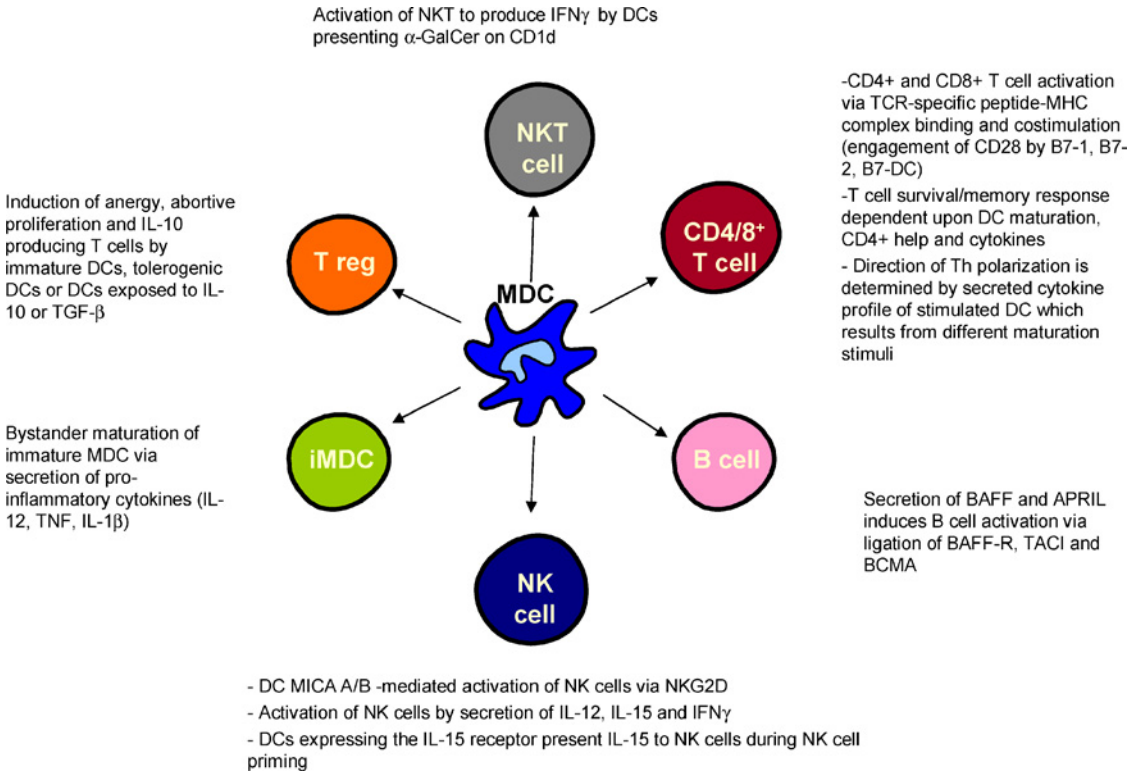

Fig. 2. Central role of MDCs—stimulation of cells of the innate and adaptive immune systems.

differentiation into memory and effector T cells, since T cell proliferation after stimulation by immature DCs is only short-lasting. The enhanced T cell survival capacity following priming by mature DCs is referred to as T cell "fitness," and is defined by resistance to cell death in the absence of cytokines, and by responsiveness to IL-7 and IL-15 which promote T cell survival in the absence of antigen stimulation (66, 67).

$CD4^+$ T Cell Polarization Depends on the Subtype of DC and Type of DC Maturation Stimulus

Following priming, $CD4^+$ T cells may differentiate towards T helper 1 (Th1) cells, which produce IFNγ and support $CD8^+$ cytotoxic T lymphocyte (CTL) responses, or towards T helper 2 (Th2) cells, which produce IL-4, IL-5 and IL-13, support humoral immunity and downregulate Th1 responses. The secreted cytokine profile of the stimulating DC determines the direction of this Th polarization (Fig. 2). IL-12, IL-18 and IL-27 polarize toward Th1, whereas CCL17, CCL22 or the absence of IL-12 skew the response toward Th2. The DC cytokine profile depends on the DC subtype, the local environment and anatomic location of the DC and the type of maturation stimulus (55). These factors control other characteristics of the T cell response as well, such as tolerance induction (11) or T cell homing (44, 68).

Several intracellular events within the DC that determine Th polarization have been described. Distinct TLR ligands differentially modulate MAP kinase signaling to instruct human MDCs to induce distinct Th cell responses (69). LPS and flagellin, which trigger TLR4 and TLR5, respectively, instruct murine DCs to phosphorylate p38 and JNK1/2 kinases, which stimulate Th1 responses via IL-12 production. In contrast, a TLR2 agonist, (Pam3cys) and a classic Th2 stimulus (schistosome egg antigens) stimulate ERK1/2 phosphorylation, which results in stabilization of the transcription factor c-Fos (a suppressor of IL-12) and Th2 polarization. DCs can also express T-bet, the transcription factor which is associated with IFNγ production in T cells. T-bet induced production of IFNγ in DCs can in turn skew Th polarization towards Th1 responses (70).

Generation of $CD8^+$ T Cell Memory

$CD4^+$ T cell help at the time of priming is required to generate $CD8^+$ T cell memory (7, 44, 71). It is believed that this T cell help is mediated by CD40–CD40L interactions with DCs, which in turn fully prime the $CD8^+$ T cell response (72). One study, however, suggests that $CD4^+$ Th cells may interact directly with CD40 on $CD8^+$ T cells to mediate this effect, although this is still controversial (73).

Other T cell surface molecules are also involved in the generation of memory. Members of the immunoglobulin-related CD28 family of molecules are clearly important, but cannot fully account for the co-stimulatory activity that is necessary for the induction of long-lived T cell responses and T cell memory (74). Members of the tumor necrosis factor receptor (TNFR) superfamily, including OX40 (CD134) and 4-1BB (CD137) are critical for both initiating and sustaining long-lived T cell immunity. The ligands for OX40 and 4-1BB (OX40L and 4-1BBL) are expressed on activated, but not immature, DCs (74). Ligation of OX40 promotes Bcl-xL and Bcl-2 expression in CD4+ T cells and is essential for their long-term survival (75).

A recent observation in mice showed that memory and/or effector T cells induced by oral administration of antigens can educate DCs via IL-4 and IL-10 to induce naïve T cells to produce the same cytokines. *In vitro* data suggest that 'educating' and naïve T cells do not need to encounter the DC at the same time. Therefore, a small number of memory and/or effector T helper cells is able to educate a significant number of DCs and influence a large pool of naïve T cells (76).

DC Induction of Tolerance

Antigen presentation by immature DCs *in vivo* is considered to be an important pathway by which tolerance to self antigens is maintained. This occurs through induction of abortive proliferation and anergy of antigen-reactive T cells, and by the induction of immunosuppressive (regulatory) T cells (77) (Fig. 2). In mice, antigen uptake (e.g. cross-presentation of self antigens in the form of autologous apoptotic cells) by resting ("steady-state") DCs *in vivo* leads to initial antigen-specific T cell activation and expansion, but the T cell response is not sustained. This abortive proliferation results in residual T cells that are unresponsive to systemic challenge with antigen (14, 78). Similar observations have been reported using mice engineered to have inducible expression of antigenic peptides in steady state $CD11c^+$ cells (79). In these studies, antigen-specific $CD8^+$ T cell expansion and protective immunity was only seen with co-administration of anti-CD40 agonistic antibody.

There is increasing evidence that naturally occurring regulatory T cells (Tr)—are critically important in the maintenance of peripheral immune tolerance (80, 81). Both $CD4^+$ and $CD8^+$ Tr populations apparently exist (80). $CD4^+$ Tr can be grouped into two subsets. Naturally occurring Tr produced in the thymus constitutively express CD25 (IL-2Rα), CTLA-4 and the transcription factor Foxp3, and exert their immunosuppressive effect

in a cell contact-dependent manner. $CD25^+CD4^+$ T cells constitute 5–10% of peripheral $CD4^+$ T cells, and removal of this T cell population in mice triggers excessive inflammatory responses and autoimmunity (82). The second type of $CD4^+$ Tr, referred to as Th3 or Tr1 cells, are induced peripherally and suppress immune responses via secretion of cytokines such as IL-10 and TGFβ (81). Immature DCs have been shown to induce both $CD4^+$ and $CD8^+$ IL-10-producing Tr (79, 83, 84) but even mature autologous DC in the absence of exogenous antigen can induce a fraction of CD4+ T cells to proliferate and acquire regulatory properties, such as secretion of IL-10 and TGF-β, induction of Foxp3 mRNA expression and suppression of T cell proliferation in an allogeneic mixed lymphocyte reaction (85).

In mice, both immature and mature DCs can maintain the expansion of $CD25^+CD4^+$ Tr (86), although mature DCs can also inhibit $CD25^+CD4^+$ Tr-mediated immune suppression through the production of IL-6 (87). DC expression of CD40 is an important factor determining whether priming will result in immunity or Tr-mediated immune suppression. Antigen-exposed DCs which lack CD40 prevent T cell priming, suppress previously primed immune responses and induce IL-10-secreting $CD4^+$ Tr that can transfer antigen-specific tolerance to primed recipients (88).

A novel mechanism for peripheral T cell tolerance induced by steady state DC was recently discovered and involves increased expression of CD5. Induced CD5 expression on peripheral T cells leads to proliferative unresponsiveness to antigenic re-challenges, however these self-reactive T cells remained highly responsive to TCR crosslinking *in vitro* (89).

Specific subtypes of DCs appear to be tolerogenic *in situ*. In humans, a subset of monocyte-derived DCs has been described that expresses indoleamine 2,3-dioxygenase (IDO), an enzyme that catabolizes tryptophan. DC IDO activity is associated with inhibition of T cell proliferation and induction of T cell death *in vitro* (90). IDO can be induced in DCs by ligation of DC B7 molecules with CTLA-4 (91, 92) (Fig. 3). The presence of "IDO DCs" in tumor-draining lymph nodes might contribute to the immunologic unresponsiveness in cancer patients (90, 93).

MDCs can be rendered tolerogenic in culture. Culture of mouse bone marrow cells in the presence of IL-10 induces the differentiation of a distinct subset of $CD11c^{lo}$ DCs that specifically express CD45RB (94). These DCs have a plasmacytoid morphology, are present in the spleen and lymph nodes of normal mice, are enriched in the spleen of IL-10 transgenic mice, and secrete high levels of IL-10 after activation. When pulsed with antigenic

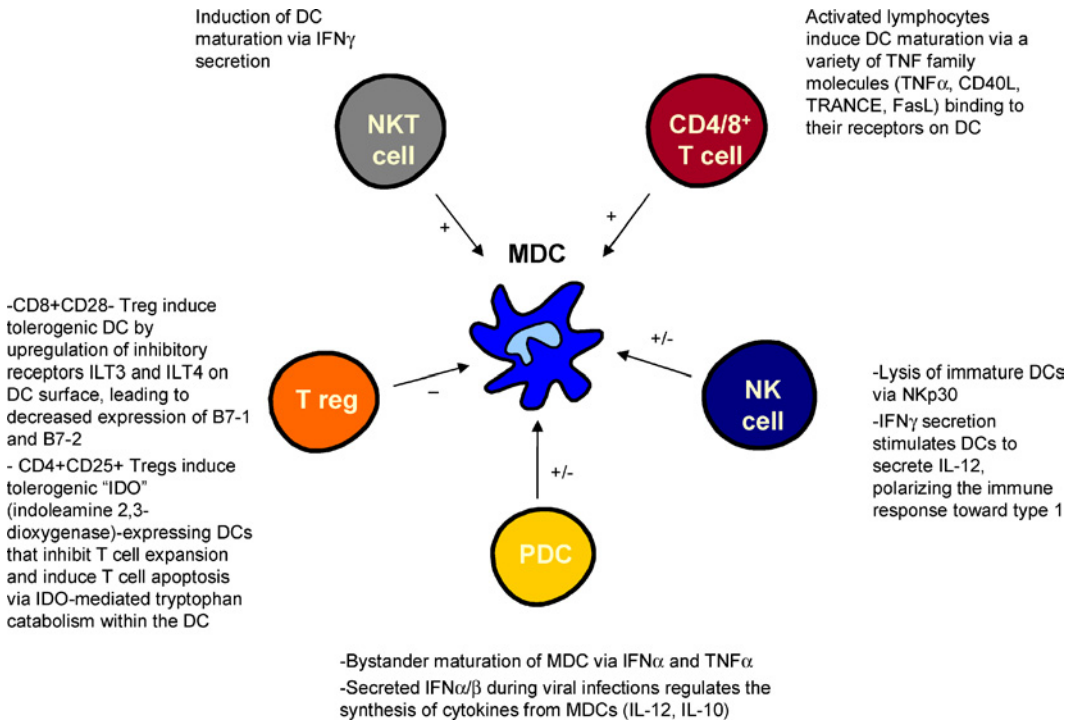

Fig. 3. Inhibition and activation of MDCs by cells of the innate and adaptive immune systems.

peptide, CD45RB DCs induce antigen-specific tolerance through the induction of Tr cells. The presence of TGFβ, Vitamin D3, IL-10 and corticosteroids in culture also confer tolerogenic properties upon DCs (94). DCs may also be rendered tolerogenic by naturally-occurring CD8+CD28- Tr, which upregulate inhibitory receptors (ILT3 and ILT4) on the DC surface and disrupt CD40-mediated stimulation of B7-1 and B7-2 expression on the DC (95).

PDCs can also be tolerogenic—PDCs can induce $CD8^+$ Tr *in vitro* (78), and ligation of specific PDC receptors such as BDCA-2 confers inhibition of T cell activation (55).

Two recent reports indicate that STAT3 activity in DCs is critical for the induction of antigen-specific T cell tolerance. If activated by tyrosine phosphorylation following exposure to IL-10, impaired antigen-specific T cell responses result. Targeted disruption of STAT3 in DCs results in their ability to prime antigen-specific T cells in response to a normally tolerogenic dose of antigen. This enhanced T cell priming is largely mediated by DC secretion of IL-12 and RANTES (33). IL-6 is a dominant cytokine for regulating the DC and T cell state in lymph nodes and spleen. In mice, IL-6 signaling increases numbers of resting/immature DCs and decreases numbers of activated/mature DCs, suggesting IL-6 acts a immunosuppressive cytokine through STAT3 activation (96). STAT3 hyperactivation might be one mechanism for abnormal DC differentiation and impaired functional activity in cancer. In mice, tumor-derived factors (tumor cell conditioned medium) prevented the differentiation of DCs and led to an increased production of immature myeloid cells via constitutive activation of Jak2/STAT3 in myeloid cells (97).

DC INTERACTIONS WITH OTHER LYMPHOCYTES

Dendritic cells play a central role in the regulation of innate and adaptive immunity and directly interact with natural killer (NK) cells, natural killer T (NKT) cells and B lymphocytes (Figs. 2 and 3).

Both immature and mature DCs can activate and induce the expansion of resting NK cells (98). The mechanisms underlying NK activation are not well understood Requirements for direct cell contact, soluble factors, or inducible expression of MHC class I-related chains A and B (MICA/B), which are ligands for the NKG2D activating receptor on NK cells, have been described (99, 100). In mice infected with murine cytomegalovirus, cytokines released by DCs via the TLR9/MyD88 pathway such as type 1 IFN and IL-12 are critical for the activation of NK cells (101). IL-15 Rα expression by DCs has been shown to be critical for NK cell activation. DCs present bound IL-15 to NK cells via the IL-15 receptor; this activation route might explain the need for direct cell contacts (102). In contrast, NK cells are able to edit DCs in the periphery at sites of inflammation and in lymph nodes (100). Activated NK cells can lyse immature, but not mature, DCs. This has been shown to be dependent on TNF-related apoptosis-inducing ligand (TRAIL) (103). IFNγ-secreting NK cells have also been shown to polarize immune responses toward type 1, stimulate DCs to produce IL-12 and to induce protective $CD8^+$ T cell responses to cross-presented antigens (100, 104, 105).

DCs presenting the synthetic glycolipid α-galactosyl ceramide (αGalCer) on CD1d can activate NKT cells to produce IFNγ and promote resistance to tumors (28). Activated NKT cells can rapidly induce the full maturation of DCs and can enhance both $CD4^+$ and $CD8^+$ T cell responses *in vivo* through direct interaction with DCs (77, 106).

Activated MDCs can directly induce B cell proliferation, isotype switching and plasma cell differentiation to T independent antigens through the production of B cell activation and survival molecules, BAFF and APRIL, which interact with three receptors on B cells (BAFF-R, TACI and BCMA) (107–109). In culture, human PDCs induce the differentiation of CD40-activated B cells into IgG-secreting plasma cells in response to influenza virus (110). This is mediated through the sequential action of type I IFN (which induces B cell differentiation into non-immunoglobulin-secreting plasmablasts), and IL-6 (which promotes differentiation into immunoglobulin-secreting plasma cells). Human PDCs can also enhance plasma cell differentiation and immunoglobulin production in a T cell-independent manner, when B-cells are stimulated by B cell receptor ligation and CpG DNA *in vitro* (111).

CONCLUDING REMARKS

Recent advances in DC biology and knowledge about bidirectional interactions with other immunocompetent cells make the exploitation of DCs for immunotherapies possible and exciting. We refer the reader to recent reviews on modulation of DCs for therapeutic antitumor vaccines (112, 113).

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