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Dendritic Cells

Targets for Immune Modulation by Microbes and Immunologists

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INTRODUCTION

Since the original description of Th1 and Th2 T cells by Mosman and Coffman some 15 years ago *(1)*, there has been a profusion of knowledge about the cytokines that influence the type of Th response. Thus, interleukin 4 (IL)-4 is known to induce IL-4 production in T cells; conversely IL-12 and interferon (IFN)γ are known to induce IFNγ production by T cells. However, the original sources of these cytokines in vivo, and the mechanisms that initiate one or another response, are less clear. Recent developments from several labs point to a potential role for dendritic cells (DCs) in orchestrating this decision. Here, we present our current view of DC development in vivo and then review the literature that suggest that distinct DC subsets may direct Th responses differently. These ideas are discussed in the context that the Th polarizing potentials of DC subsets are not fixed, but are rather plastic. Given their pivotal roles in immunity, DCs represent prime targets for immune modulation by both microbes, and immunologists. Some examples of immune modulation by microbes, and prospects for clinical utility are briefly considered.

THE DC SYSTEM

Since its observation more than 25 years ago as an accessory cell of the immune system *(2)*, the dendritic cell (DC) has assumed center stage as the key initiator of adaptive immunity. DCs are scattered throughout the body, including the various portals of microbe entry, in which they reside in an immature form. Immature DCs are "immunological sensors" alert for potentially dangerous microbes and are capable of decoding and integrating such signals, and then

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ferrying this information to the T-cell areas of secondary lymphoid organs, in which naïve T cells are. Here, in a mature form they present this information to T lymphocytes, thus initiating an immune response. DCs can also tune the immune response, by modulating either the amplitude, or the type of the response *(2–5)*. We now know that there are several different types of DCs *(2–5)*. Recent evidence suggests that different subpopulations of DCs are capable of inducing distinct types of responses *(6–8)*. However, the function of DCs also appears to be modulated by microbes and the environment *(9–11)*.

DC SUBSETS

Like lymphocytes, DCs consist of multiple subsets that differ in phenotype, function, and microenvironmental localization *(1–5)*. It is not known whether this heterogeneity reflects distinct lineages or DCs at different stages of maturation, or both.

Mouse DCs that are characterized as "mature" express high levels of the integrin-α CD11c and class II major histocompatibility complex, and the costimulatory molecules CD80 and CD86. In the secondary lymphoid organs of mice, at least four subsets of "mature" DCs have been described: $CD8\alpha^+$ DCs, $CD8\alpha^-$ $CD4^+$ DCs, $CD8\alpha^-$ $CD4^-$ DCs, and Langerhans cell-derived DCs (LCDCs) *(1–5)*. $CD8\alpha^+$ DCs are located in the thymic cortex and T-cell areas of secondary lymphoid organs, although $CD8\alpha^-$ DCs occur in the marginal zones of the spleens, subcapsular sinuses of the lymph nodes, and the subepithelial dome of Peyer's patch *(1–5)*. LCs, which are the precursors of LCDCs are found in the epithelial layers of the skin and mucosa and contain unique structures called Birbeck granules, the development of which is dependent on expression of Langerin *(12)*. As LCs migrate to the T-cell areas of lymph nodes they mature into LCDCs.

More recently, a precursor DC subset with a plasmacytoid morphology, the ability to secrete large amounts of interferon-α in culture, and that can generate mature DCs in culture has been described *(13–15)*. This plasmacytoid precursor DC (pDC) subset is similar to its human counterparts (discussed below), and secrete copious amounts of interferon-α when stimulated with CpG DNA or certain viruses.

Early studies suggested that the $CD8\alpha^+$ DCs can develop from progenitor cell populations, which also yield T, B, and NK cells *(16)*, although whether the same progenitor cell yields DCs and lymphoid cells is not known. However recent evidence suggests that $CD8\alpha^+$ DCs can also develop from a myeloid precursor *(4)*, suggesting that lymphoid and myeloid precursors may have some plasticity in their developmental potentials. More recently, a common precursor population yielding $CD8^+$ and $CD8^-$ murine DCs, but devoid of myeloid or lymphoid differentiation potential has been characterized *(17)*. Given

this confusion, the developmental origins of DC subsets is at present a subject of intense debate.

In human skin two subsets of immature DCs are found in distinct microenvironments; LCs in the epidermis and interstitial DCs in the dermis *(2–5)*. These two subsets also appear in culture of hematopoietic progenitor cells, driven by granulocyte-macrophage colony-stimulating factor (GM-CSF) plus tumor necrosis factor-α. In the blood, two subsets of DCs are identified, the $CD11c^+$ subset, which differentiates into mature $CD11c^+$ DCs in response to inflammatory stimuli, and the $CD11c^-$ subset, which differentiates into pDCs in response to IL-3 *(18)*. pDCs appear to be the principal source of type-1 interferons in response to viruses *(19,20)*. Cytokines such as Flt3-Ligand, GM-CSF, and granulocyte colony-stimulating factor, induce the development of these DC subsets in vivo *(21–26)*.

DCs AND IMMUNOLOGICAL TOLERANCE

Central Tolerance

The idea that certain DC subsets could induce self-tolerance was experimentally addressed by showing that splenic DCs, if introduced into fetal thymic organ culture, could induce negative selection *(27)*. However, subsequent studies have shown that other antigen-presenting cells such as thymic cortical epithelial cells can also induce thymic negative selection *(27)*. This suggests that the developmental stage of the thymocyte is crucial for negative selection, although it does not exclude some unique tolerogenic feature that thymic DCs may have. Indeed the transfer of thymic DCs has been shown to induce tolerance to myelin basic protein and limit experimental allergic encephalomyelitis *(28)*, and the role of thymic DCs in negative selection in vivo, has been confirmed by the targeted expression of class II myosin heavy chain molecules on $CD11c^+$ DCs *(29)*.

Peripheral Tolerance

The question of whether certain DC subsets can induce self-tolerance in the periphery (or at least downmodulate an ongoing T-cell response) has received much attention recently, and two broad scenarios have been envisioned. One concept is that all DCs have a the capacity to induce either immunity or tolerance, depending on the maturation or activation state of the DCs *(30)*. It was originally proposed that immature DCs *(31,32)*, or those exposed to cytokines such as IL-10, transforming growth factor -β, or prostaglandin E2 (PGE2), which maintain DCs in an immature state and can induce tolerance *(33–37)*. More recent evidence suggests that tolerance is induced by DCs that are mature but not activated, although immunity is induced by DCs that are fully activated *(38)*.

The second concept is that there is a specialized DC subset dedicated for peripheral tolerance induction. In mice, there is evidence that the $CD8\alpha^+$ DC

subset in mice can limit the proliferation of both $CD4^+$ and $CD8^+$ T cells in vitro *(39,40)*. Thus it has been suggested that the $CD8\alpha^+$ DCs play a role in inducing self-tolerance in the periphery *(41)*. Consistent with this notion, one study suggests that in DBA/2 mice, $CD8\alpha^+$ DCs are weaker than the $CD8\alpha^-$ DCs at eliciting DTH responses against a poorly immunogenic tumor peptide *(42)*. In these studies, the $CD8\alpha^-$ DCs were found to inhibit the function of $CD8\alpha^-$ DCs. The relevance of these observations to peripheral tolerance induction in vivo remains to be determined. However, recent studies suggest that steady state targeting of DC antigen receptors with low doses of antigen leads to deletion of corresponding T cells, and unresponsiveness to antigenic challenge with strong adjuvants *(43)*. There is also new evidence that DCs can contribute to the expansion of T cells that regulate or suppress other immune T cells *(44,45)*.

DCs AND THE CONTROL OF ADAPTIVE IMMUNITY

DC Subsets

There is evidence that distinct DC subsets can induce different Th responses. In mice, freshly isolated $CD8\alpha^+$ and $CD8\alpha^-$ DCs from spleens *(6–8)* or Peyer's patch *(46)* induce Th1 and Th2 responses, respectively. $CD8\alpha^+$ DCs can be induced to secrete IL-12 *(7,26,47,48)*, which is essential for their Th1 induction *(7)*. IL-10 appears to be important for optimal Th2 induction by $CD8\alpha^-$ DCs *(49)*. Consistent with this differential skewing, cytokines which differentially expand these DC subsets in vivo promote different responses. Thus, GM-CSF, which preferentially expands $CD8\alpha^-$ DCs in mice, elicits Th2 responses, although Flt3-L, which expands both DC subsets, elicits both Th1 and Th2 responses *(6)*. In humans, monocyte-derived $CD11c^+$ DCs and $CD11c^-$ pDCs can induce Th1 and Th2/Th0 responses in vitro, respectively *(8,26)*. However, the extent of polarization by these cells may differ according to their method of isolation and maturation *(20)* or the ratio of dendritic cells to T cells *(50)*. As with mice, IL-12 secretion by $CD11c^+$ DCs seem essential for their Th1 induction *(8)*, but the factors that induce Th2 responses are unknown.

Microbes

The nature of the microbe also plays an important role in tuning the response, by modulating DC function. For example, viruses stimulate IFNα from the plasmacytoid $CD11c^-$ precursors *(19,20)* and induce their differentiation into DCs that induce IFNγ- and IL-10-producing T cells *(51)*; however IL-3 induces $CD11c^-$ precursors to differentiate into Th2-inducing DCs *(19,51)*. Different forms of the fungus *Candida albicans* instruct an immature, murine DC cell line to induce either Th1 or Th2 responses *(52)*. As stated above, the immune system can discriminate between different microbes through receptors, such as Toll-like receptors (TLRs). This is reminiscent of the situation in *Drosophila*, in which bacterial

and fungal infections signal through distinct TLRs to elicit different classes of antimicrobial peptides *(53–55)*. In mammals too, it is now clear that different microbial stimuli induce qualitatively distinct immune responses. For example, *Escherichia coli* lipopolysaccharide (LPS) induces a Th1 response, but LPS from the oral bacterium *Porphyromonas gingivalis*, which signals through TLR2 *(56)* skews toward a Th2 response *(57)*. Consistent with this, *E. coli* LPS, but not *P. gingivalis* LPS induces IL-12 in the splenic CD8α^+ DCs *(57)*. Similar results have been obtained with the synthetic TLR 2 ligand, Pam-3-cys *(58–60)*. Thus, Pam-3-cys, *E. coli* LPS, flagellin, and schistosome egg antigens (SEA) activate human DCs to secrete different cytokine profiles. *E. coli* LPS and flagellin induce IL-12(p70), but Pam-3-cys and SEA do not do so, but can induce the Th2-inducing or regulatory cytokine, IL-10. Although *E. coli* LPS and flagellin induce Th1 responses, Pam-3-cys and SEA favor a Th2 bias *(58)*. In the mouse system, almost identical results are evident; Pam-3-cys induces very little IL-12 (p70) in splenic CD8α^+ DCs compared to *E. coli* LPS *(59)*. Consistent with their differential cytokine induction in DCs, Pam-3-cys and *E. coli* LPS induced Th2- and Th1-biased responses, respectively *(58–60)*. These studies are supported by several other reports, which suggest that signaling via TLR2 may result in Th2 or T-regulatory responses *(61–64)*.

The Microenvironment

Cytokines secreted by activated T cells in the lymph node or in the periphery can also modulate DC function. Thus Th1-inducing DCs, when exposed to IL-10, transforming growth factor-β, induce Th2-like responses *(33–37)*. Conversely, IFNγ can instruct DCs to acquire some Th1-inducing capacity *(11)*. These results are consistent with observations that DCs in distinct microenvironments induce different Th responses. For example, Peyer's patch or respiratory tract DCs prime Th2 responses, although total spleen DCs prime Th1/Th0 responses *(43,65)*.

If one DC subset is capable of generating any type of response, depending on the microbial stimuli, then why evolve so many different subsets with different functions? One solution would be to have functionally different DC subsets capable of recognizing different microbial stimuli, because they express distinct, but overlapping repertoires of TLRs (Fig. 1). Indeed, consistent with this model recent studies suggest that in humans *(66,67)* and in mice (Pulendran, et al., unpublished data) different DC subsets express distinct but overlapping repertoire of TLRs. Thus, at the site of an infection, microbial stimuli 1 and 2 may preferentially activate immature DC1s and DC2s, which express quite different TLRs, and which have some genetic propensity to generate Th1 and Th2 responses respectively (Fig. 1). However, the DCs would have some plasticity in that stimulus 1 may prompt DC2s toward a Th1-inducing mode, and stimu-

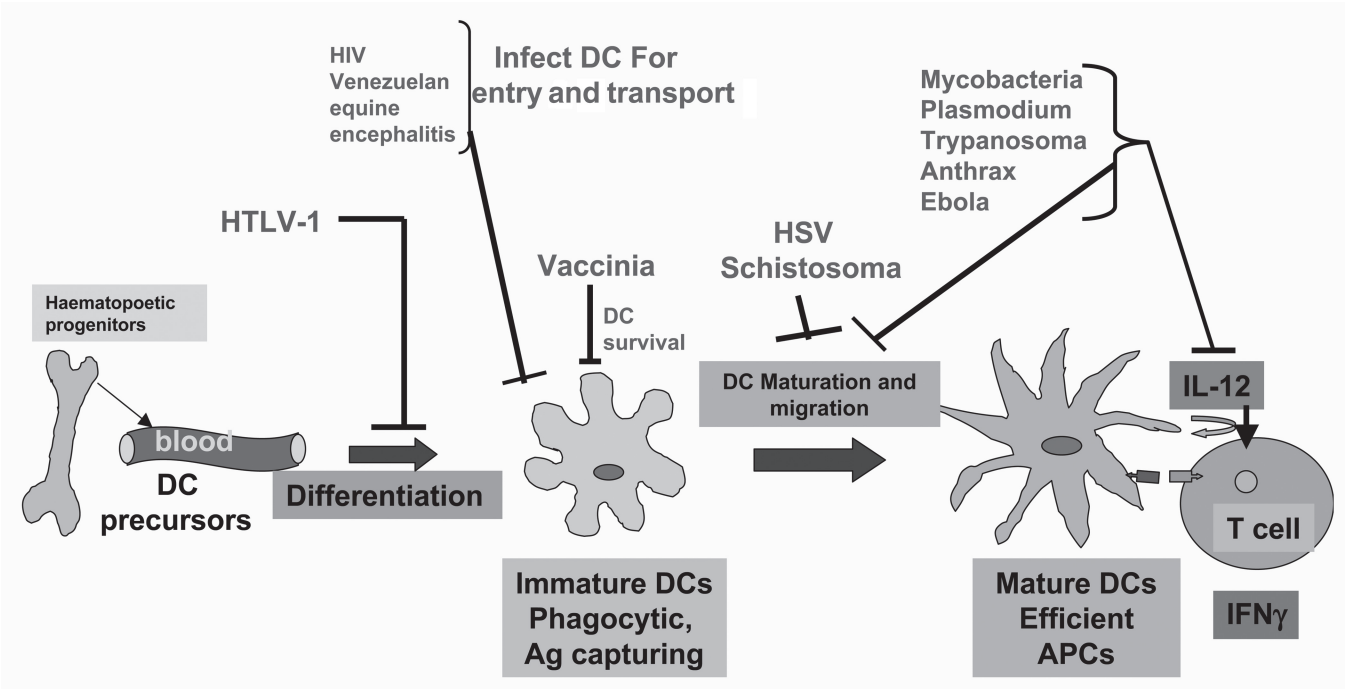

Fig. 1. The microbe's box of tricks. Pathogens have evolved several strategies to modulate various aspects of dendritic cell (DC) biology. For example, human immunodeficiency virus and Venezuelan equine encephalitis virus target DCs in the periphery and hitch a ride to the draining lymph nodes; vaccinia virus kills DCs (although the consequences of this for adaptive immunity is debatable); herpes simplex virus, schistosomes, mycobacteria, plasmodium parasites, anthrax, and ebola interfere with DC maturation and migration.

lus 2 may prompt DC1s toward a Th2-inducing mode (Fig. 1). A further level of regulation may occur in the draining lymph node, during the early stages of the response. Th1 and Th2 cytokines made by T cells could suppress DC2s and DC1s respectively, to amplify the response. Thus IL-10 and IFNγ suppress the function of DC1s and DC2s, respectively. However later in the response, Th2 cytokines may enhance the Th1-induction by DCs *(9)*, to prevent a runaway Th2 response. In this model therefore, the immune response is a multiparametric function of the microbe, microbe-recognition receptors, the genetic hardwiring of the DCs, and the environment and cytokines.

TURNING DOWN THE VOLUME

DCs may also play crucial roles in downregulating the immune responses. For instance, DCs may express molecules that inhibit T-cell expansion. B7 molecules on DCs engage CTLA-4 on activated T cells and inhibit their proliferation, and B7-H1 molecules on antigen-presenting cells engage inducible costimulator receptor on activated T cells and induce IL-10, which dampens T-cell activation *(68)*. In principle, these molecules may be upregulated on the same DCs that initially primed the T cells, or may be constitutively expressed on a specialized subset of DCs dedicated for switching off T cells *(39,40,42)*. Thus these regulatory DCs may capture and present antigens from stimulatory DCs to terminate an ongoing T-cell response. Indeed, as stated above, DCs that capture apoptotic cells do not stimulate T cells efficiently and presentation of antigens from apoptotic cells may result in immunological tolerance *(30,32, 62)*. A discrete population of DCs in the rat Peyer's patch have been shown to transport apoptotic cells from the intestinal epithelium to the lymph nodes, suggesting a possible mechanism through which oral tolerance may occur *(69)*.

THE MICROBE'S BOX OF TRICKS

Cells that play such crucial roles in the immune response must also be the prime targets of many a conspirator wishing to manipulate the immune system. This appears to be the case with many pathogens, and at least a few immunologists. Pathogens have evolved a remarkably wide array of strategies to subvert DC function, (and adaptive immunity), in almost every conceivable way.

Trick 1: Impairment of DC Recruitment, Maturation, and Survival

One mechanism of subversion is impairment of DC maturation or survival, as observed with erythrocytes infected with the malaria parasite *Plasmodium falciparum (70)*, or with human T cell leukemia virus 1 (HTLV-1), or with *Trypanoma cruzi (71)*, or with herpes simplex virus *(72)*, or measles virus *(73–75)*, or canarypox or vaccinia viruses, which eventually kill DCs *(76,77)*. Furthermore, poxviruses and herpesviruses encode secreted homologues of chemokine

receptors that act as chemokine antagonists to prevent the recruitment of additional DCs to infection sites *(78,79)*, and *Schistosoma mansoni* suppresses Langerhans cell migration from the epidermis via a parasite-derived homologue of PGD2 *(80)*. Our recent work suggests that *Bacillus anthracis* lethal toxin inhibits mitrogen-activated protein kinase signaling in DCs to impair DC function and adaptive immunity *(81)*, and that infection of DCs with Ebola or Lassa viruses results in an inhibition of DC maturation and function *(82)*.

Trick 2: Highjacking DCs

Pathogens may also highjack DCs to control to immune system. Thus human immunodeficiency virus (HIV)-1 gp-120 uses the "Trojan Horse" strategy by binding to DC-specific adhesion molecule-3-grabbing nonintegrin, a lectin expressed on DCs, facilitating transport of the virus to the lymph nodes, in which it infects $CD4^+$ T cells *(83)*. Interaction of HIV-infected DCs with memory or activated T cells favors HIV replication. Furthermore, Venezuelan equine encephalitis virus targets LCs, which serve as replication sites and transport the virus into the draining lymph node *(84)*.

Trick 3: Messing With T-Cell Activation

Microbes have devised several ways to impair T-cell activation. As mentioned above, several microbes can inhibit DC maturation, thus preventing efficient T-cell priming. This effect may be because of inhibition of factors contributing to T-cell proliferation and differentiation. Another mechanism of impeding T-cell immunity is via the apoptosis of T cells by virally infected DCs. For instance, measles virus and human cytomegalovirus render DCs cytotoxic through the upregulation of both FasL/CD95L and tumor necrosis factor-related apoptosis-inducing ligand on DCs *(85,86)*. The virus sensitizes the activated T cells, which are otherwise resistant to these molecules. The bacterium *Bordetella pertussis*, which is the causative agent of whooping cough, has crafted a strategy to generate antigen-specific T regulatory cells (Tr cells) to suppress protective Th1 responses *(87)*. During acute infection with *B. pertussis*, Tr cells specific for *B. pertussis* filamentous hemagglutinin (FHA) and pertactin, which are generated at the mucosal surfaces, secrete IL-10 but neither IL-4 nor IFN-, and suppress the Th1 responses against *B. pertussis*, and unrelated pathogens. The generation of Tr cells is mediated by FHA, which inhibits DC IL-12 secretion but promotes their secretion of IL-10.

THE IMMUNOLOGIST'S QUEST

The microbes offer us valuable lessons in our quest for immune modulation in the clinic. The growing list of strategies used by microbes offer us many insights into the untapped potential that lie within these cells. Already, much

progress has been made in eliciting tumor immunity in humans using adoptive therapy of DCs loaded with tumor antigens *(88)*. The ultimate challenge is to design vaccines that induce optimally effective immunities in different clinical settings by modulating DC function in vivo. Microbes have taken evolutionary time scales to learn the art of immune modulation. Immunologists of the 21st century will surely take a much shorter time to master this art!

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