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Microreview

# Dendritic cells and host resistance to infection

**Heidrun Moll**
*Institute for Molecular Biology of Infectious Diseases, University of Würzburg, Röntgenring 11, 97070 Würzburg, Germany.*

## Summary

**Host defence against infection requires an integrated response of both the innate and adaptive arms of the immune system. Emerging data indicate that dendritic cells contribute an essential part to the initiation and regulation of adaptive immunity. Dendritic cells guard the sites of pathogen entry to the host and are uniquely suited to detect and capture invading microbes. Upon recognition of microbial structures and appropriate activation, a maturation programme is triggered and dendritic cells migrate to lymphoid organs to stimulate a primary cell-mediated immune response. Moreover, dendritic cells play a critical role in shaping the emerging response, thereby controlling the course of infection. They can discriminate between various types of microorganisms and are capable of producing different cytokines in response to different microbial stimuli. On the other hand, pathogens developed numerous strategies to evade and subvert dendritic cell functions. Elucidating the interactions of dendritic cells with microbial pathogens may lead to novel strategies for combating infectious diseases by dendritic cell-based vaccination and immunotherapy. This review highlights recent advances in our knowledge of the unique role of dendritic cells in counteracting microbial infections.**

## Introduction

The body is constantly exposed to a remarkable variety of infectious agents, such as viruses, bacteria, fungi and parasites. The individual pathogens differ with regard to the way of transmission, the mode of replication, the mechanism of causing disease and the type of host response they elicit. As a physical and biochemical barrier to infection, epithelial surfaces prevent the entry of microorganisms. These epithelia comprise the skin and the mucosal linings of the gastrointestinal, respiratory and urogenital tract. They also secrete antimicrobial substances, including lysozyme and defensins. Only when a pathogen crosses the epithelial barrier, the host's immune system needs to initiate effector mechanisms to eliminate the infectious agent.

The first phase of host defence against invading microorganisms relies on the mechanisms of innate immunity, an evolutionary ancient and universal form of host protection. Innate immune recognition is based on a limited number of highly conserved receptors that detect common microbial components. It allows the immune system to discriminate between infectious non-self and non-infectious self and may be the major checkpoint in the decision to respond or not to respond to a particular antigen (Janeway and Medzhitov, 2002). The innate immune system is composed of a cellular arm, including macrophages, dendritic cells, neutrophils, eosinophils and natural killer (NK) cells, and soluble factors, such as complement components, cytokines and chemokines. In some cases, however, microorganisms overcome these early lines of defence and the initiation of an adaptive immune response is required to fight the infection. The adaptive immune response is associated with the activation of distinctive effector cells, B and T lymphocytes, that are capable of specific recognition of microbial antigens, and is accompanied by the generation of memory cells that prevent subsequent infections with the same pathogen. Together, the innate and adaptive immune systems form an integrated host defence machinery to confer optimal protection.

The signals resulting from detection of an invading pathogen by cells of the innate immune system must be conveyed to the lymphocytes of the adaptive immune system. This critical task is fulfilled by dendritic cells, specialized antigen-presenting cells, which provide T cells not only with microbial antigen but also with information about the features of the pathogen, thus conducting the development of an appropriate cell-mediated immune response.

Received 27 January, 2003; revised 25 March, 2003; accepted 26 March, 2003. *For correspondence. E-mail heidrun.moll@mail.uni-wuerzburg.de; Tel (+49) 931312627, Fax (+49) 931312578.

**Dendritic cell migration and maturation**

Dendritic cells are derived from haematopoietic stem cells in the bone marrow and form a network of heterogeneous cell populations. The movement of myeloid dendritic cell precursors into sites of infection in peripheral tissues has been suggested to be regulated sequentially by monocyte chemotactic protein (MCP), binding to the chemokine receptor CCR2 on dendritic cells, and macrophage inflammatory protein (MIP)-3α/CCL20, interacting with CCR6 (Vanbervliet *et al*., 2002). Immature dendritic cells also express the chemokine receptors CCR1, CCR5 and CXCR1, enabling them to respond to a number of inducible chemokines produced by tissue macrophages upon activation by microbial products, such as CCL3 (MIP-1α), CCL5 (RANTES) and CXCL8 (Interleukin 8, IL-8), and to accumulate at the site of infection (Dieu *et al*., 1998; Sallusto *et al*., 1998; Stumbles *et al*., 2001). Immature dendritic cells in peripheral tissues, such as Langerhans cells in the epidermal compartment of the skin, readily take up microbes and/or microbial antigens for degradation and peptide loading onto major histocompatibility complex (MHC) molecules (Blank *et al*., 1993; Guermonprez *et al*., 2002). The recognition and internalization of microbial structures induces the maturation of dendritic cells, a process that is accompanied by their migration from the peripheral tissues into the T cell areas of draining lymph nodes (Moll *et al*., 1993).

In the course of maturation, dendritic cells are subject to profound changes. The endocytic capacity is downregulated, while there is a marked up-regulation of MHC class II expression, from an already high constitutive level. The expression of inflammatory chemokine receptors, such as CCR1, CCR2, CCR5 and CCR6, and the responsiveness to their ligands decreases. At the same time, dendritic cells acquire surface expression of CCR7 and responsiveness to its ligands CCL19 (MIP-3β) and CCL21 (secondary lymphoid tissue chemokine, SLC) that are produced in the T cell areas of lymph nodes (Dieu *et al*., 1998; Saeki *et al*., 1999; Vecchi *et al*., 1999). As CCR7 also mediates the homing of T cells to secondary lymphoid organs (Willimann *et al*., 1998), it is a key receptor for the encounter of antigen-bearing mature dendritic cells and responder T cells. In addition, mature dendritic cells express enhanced surface levels of co-stimulatory and adhesion molecules such as CD80, CD86 and CD40 (Banchereau *et al*., 2000). As a result of these multiple modifications, mature dendritic cells acquire the distinct ability to trigger a primary T cell response. Moreover, dendritic cells play a critical role in shaping the emerging immune response. Their activation by microbial antigens induces the production of cytokines such as IL-12, IL-18 or IL-10, which may promote the development of either type 1 T helper (Th1) cells or type 2 T helper (Th2) cells (Reis e Sousa *et al*., 1997; Moser and Murphy, 2000). Th1 cells secrete interferon (IFN)-γ, which is effective against intracellular pathogens because it stimulates microbicidal activities in macrophages, whereas Th2 cells produce IL-4 and IL-5, which drive B cells to release IgG1 and IgE antibodies. IgE is involved in effector mechanisms protecting against worm infections.

**Pathogen recognition and induction of antimicrobial immunity by dendritic cells**

Different classes of microbial organisms are characterized by common chemical moieties which have been termed pathogen-associated molecular patterns. These microbial structures are recognized by members of the mammalian Toll-like receptor (TLR) family, homologues of *Drosophila* Toll, expressed on dendritic cells. TLR signalling induces the maturation of dendritic cells, thus leading to increased immunogenicity and T cell priming, as summarized above. In this way, TLRs are involved in the link between innate and adaptive immunity (Akira *et al*., 2001; Barton and Medzhitov, 2002). A number of TLRs have been identified to date that discriminate between distinct microbial features (Table 1). Flagellin from both Gram-positive and Gram-negative bacteria is recognized by TLR5 (Hayashi *et al*., 2001), and double-stranded RNA that is produced by most viruses triggers TLR3 (Alexopoulou *et al*., 2001). Interestingly, *Escherichia coli* lipopolysaccharide (LPS) is detected by TLR4, whereas the structurally different LPS molecules from the oral pathogen *Porphyromonas gingivalis* and the invasive spirochete *Leptospira interrogans* interact with TLR2 (Akira *et al*., 2001). This may correlate with the induction of strikingly different patterns of adaptive immune responses. It has been demonstrated that *E. coli* LPS induces a Th1-like response, whereas *P. gingivalis* LPS induces a Th2 profile, most likely by stimulating different cytokines in dendritic cell subsets (Pulendran *et al*., 2001). Similarly, the TLR2 agonists *Staphylococcus aureus* peptidoglycan and yeast zymosan were reported to favor the induction of Th2 development by dendritic cells (Re and Strominger, 2001). These findings support the conclusion that recognition of distinct microbial features by different TLRs on dendritic cells may contribute to the adjustment of the adaptive immune response; moreover, interaction of a given TLR with alternative stimuli may lead to the induction of different responses (Fig. 1). The discrimination of microbial signals may be mediated not only by the specific TLRs but may involve accessory receptors that participate in signalling and the shaping of the resulting responses (Perera *et al*., 2001).

Dendritic cells can be separated into subsets which differ in phenotype, function and localization (Shortman and Liu, 2002). In humans, myeloid dendritic cells, which include epidermal Langerhans cells, and plasmacytoid

**Table 1.** TLR recognition of microbial ligands.

| Receptors | Ligands |
|---|---|
| TLR2 + TLRX | Lipoproteins and lipopeptides (various bacteria) |
| | Peptidoglycan |
| | Zymosan |
| | LPS (*Porphyromonas gingivalis*, *Leptospira interrogans*) |
| | Lipoarabinomannan (*Mycobacterium tuberculosis*) |
| | Porins (*Neisseria meningitidis*) |
| | Glycophosphatidylinositol anchors and glycoinositolphospholipids (*Trypanosoma cruzi*) |
| TLR3 | Double-stranded RNA |
| TLR4 | LPS (*Escherichia coli*) |
| | Heat-shock protein 60 |
| | Fusion protein (respiratory syncytial virus) |
| TLR5 | Flagellin |
| TLR9 | Bacterial DNA (CpG DNA) |

TLRX, other TLRs forming heterodimers with TLR2 (TLR1, TLR6 and probably TLR10)

dendritic cells have been described. Murine dendritic cells express the CD11c integrin and can be subdivided on the basis of CD8α expression. A third population of murine CD11c$^+$ cells, also expressing B220 and Gr-1, is equivalent to human plasmacytoid dendritic cells (Colonna *et al.*, 2002). Notably, recent evidence suggests that CD8α is a marker for the maturation stage of dendritic cells rather than different lineages (Martinez del Hoyo *et al.*, 2002). Dendritic cell subtypes may differ in their expression of TLRs. In humans, only plasmacytoid dendritic cells, but not myeloid dendritic cells, express TLR9, the receptor for unmethylated CpG motifs that are abundant in bacterial DNA. Genetically determined differences in the composition of dendritic cell subsets may therefore be associated with resistance and susceptibility to infection with a given pathogen. In concordance with this suggestion, it has been shown that dendritic cells from mice that are resistant to infection with *Listeria monocytogenes* preferentially express TLR9, together with the dendritic cell maturation markers CD40 and CD86, and produce high levels of IL-12, whereas dendritic cells from susceptible mice strongly express TLR2, -4, -5, and -6, and produce larger amounts of MCP-1 (Liu *et al.*, 2002).

The intracellular signalling pathways activated by TLRs involve recruitment of the cytoplasmic adaptor molecule MyD88, activation of serine/threonine kinases of the IRAK family, and finally degradation of IκB and translocation of NF-κB to the nucleus (Akira *et al.*, 2001). Recently, a MyD88-independent pathway has been shown to be responsible for the induction of IFN-β and IFN-inducible genes (Akira, 2003). In mice lacking MyD88, host resistance to infection with the intracellular protozoan *Toxoplasma gondii* and parasite-induced IL-12 production by dendritic cells was shown to be dramatically reduced (Scanga *et al.*, 2002). Because dendritic cells from mice deficient in TLR2 or TLR4 mounted normal IL-12 responses to *T. gondii*

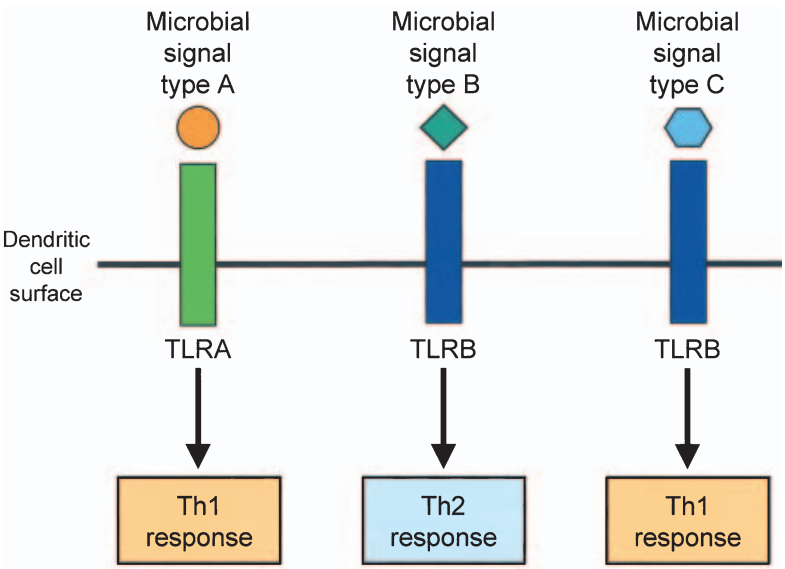


**Fig. 1.** Discrimination between microbial signals by dendritic cells. The recognition of distinct microbial features (e.g. microbial signals of type A or B) by different TLRs on dendritic cells (e.g. TLRA, TLRB) may lead to the development of polarized Th1 or Th2 immune responses. Moreover, interaction of a given TLR with alternative stimuli (e.g. here, TLRB recognizing microbial signals of type B and C) can result in the induction of different Th cell responses. For example, the TLR4 agonist *E. coli* LPS promotes the induction of a Th1 response, whereas signalling through TLR2, triggered by LPS from *Leptospira* or *P. gingivalis*, *S. aureus* peptidoglycan or yeast derivatives, stimulates a Th2 response. On the other hand, TLR2-mediated activation of dendritic cells by purified protein derivative of *M. tuberculosis* induces cytokines associated with Th1 responses.

antigen, these TLRs do not seem to be involved in the IL-12 response to this parasite. In contrast, TLR2 triggering has been demonstrated to play a role in the induction of cytokines by glycolipid antigens of *Trypanosoma cruzi* (Campos *et al*., 2001) and by purified protein derivative of *Mycobacterium tuberculosis* (Edwards *et al*., 2002).

Recent evidence indicates that TLRs may be less important for pathogen uptake by dendritic cells, as the internalization of Gram-negative bacteria was shown to be TLR4-independent (Rescigno *et al*., 2002). Thus, the major function of TLRs appears to be the discrimination of pathogens and the collection of information about the nature of a microorganism. Multiple TLRs may be used to recognize several structural features of a microbe simultaneously and to elicit slightly different immune responses tailored to the microbial threat (Underhill and Ozinsky, 2002).

Dendritic cells express a range of C-type lectins, including the mannose receptor (CD206) and DC-SIGN (CD209), which bind carbohydrate-containing structures of microorganisms and are involved in their internalization. Evidence is emerging that cytoplasmic sequences of C-type lectins determine the intracellular routing of pathogens in dendritic cells (Figdor *et al*., 2002). Although it has been demonstrated that microbial agents are transported to endosomal compartments (García-del Portillo *et al*., 2000; Bodnar *et al*., 2001), detailed knowledge of the intracellular fate of captured pathogens in dendritic cells is still lacking. The proportion of dendritic cells containing microorganisms as well as the number of microbes per infected dendritic cell are very low as compared to macrophages. Furthermore, it is important to note that dendritic cells were shown to be able to restrict the growth of internalized pathogens, but to be less efficient than macrophages at eliminating the infection (Blank *et al*., 1996; Bodnar *et al*., 2001). Thus, the functions of dendritic cells during infections appear to be aimed at alerting the immune system rather than the avid ingestion and clearance of pathogens.

Another important aspect is the ability of dendritic cells to present microbial non-protein antigens to T cells via CD1 molecules. The best-characterized antigens for CD1-mediated presentation are mycobacterial cell wall components, such as mycolic acids and lipoarabinomannan (Matsuda and Kronenberg, 2001). These antigens have been shown to be recognized by conventional T cells, a subset of $\gamma\delta$ T cells and NKT cells. Thus, dendritic cells are well equipped to stimulate a cellular immune response to microbial proteins as well as glycolipid and lipid antigens.

## Modulation of the antimicrobial immune response by dendritic cells

Host resistance against an infectious organism requires the development of an immune response of the appropriate class. Dendritic cells play a key role in determining the type of induced response. An important aspect of the capacity of dendritic cells to tailor the emerging T cell response is their potential to produce different cytokines in response to different stimuli. It has been demonstrated that the choice of cytokine production by dendritic cells is dictated by microbial signals; components from *Toxoplasma* and *Mycobacterium* were shown to induce IL-12 production by different dendritic cell subsets, whereas heat-killed yeasts or yeast derivatives lead to production of IL-10 (Edwards *et al*., 2002). The level of cytokine production is enhanced by T cell feedback signals mediated by CD40 ligation. Different forms of the same pathogen may also condition dendritic cells to induce different T cell responses. The yeast form of *Candida albicans* elicits a protective Th1 response via stimulation of IL-12 production by dendritic cells, whereas the hyphal form inhibits IL-12 formation and triggers a non-protective Th2 response (d'Ostiani *et al*., 2000). A similar principle has been reported for conidia and hyphae of *Aspergillus fumigatus* (Bozza *et al*., 2002). Antigen-bearing dendritic cells can be long-lived and therefore may also be critical for the maintenance of the induced type of immune response. It has been demonstrated that low numbers of *Leishmania* parasites persist in lymph node dendritic cells of mice that have recovered from infection, thereby maintaining parasite-specific T cell responses and protecting the host from reinfection (Moll *et al*., 1995). Furthermore, the continuous activation of Th2 cells with specificity for the *Leishmania* antigen LACK, used as an inducer of allergic airway inflammation, was shown to be associated with a subset of long-lived LACK-bearing dendritic cells (Julia *et al*., 2002).

The molecular basis of the induction of polarized Th immune responses by dendritic cells appears to be diverse. For example, engagement of CD40 on dendritic cells has been shown to play a fundamental role in the development of dendritic cell-driven Th2, but not Th1, responses *in vivo* (MacDonald *et al*., 2002). On the other hand, both soluble egg antigen from *Schistosoma mansoni* and cholera toxin stimulate dendritic cells promoting Th2 responses, albeit via different mechanisms involved in the cross-talk between these microbial agents and dendritic cells (de Jong *et al*., 2002). Interestingly, analysis of the cytokine production upon dendritic cell encounter with *Salmonella typhimurium* revealed that bacterial contact, but not internalization, was required to stimulate the release of IL-12p40 and tumor necrosis factor-$\alpha$ (Yrlid and Wick, 2002). After administration of *S. typhimurium* to mice, dendritic cells collected from the spleen, a site of *Salmonella* replication and T cell activation, could stimulate both $CD4^+$ Th cells and $CD8^+$ cytotoxic T cells specific for bacteria-encoded antigens.

Type I IFN and IL-12 play critical roles in the host defence against viruses. Recently, a specialized subset of dendritic cell with plasmacytoid morphology has been identified as the major producer of type I IFN and IL-12 during infection with selected viruses, and was designated IFN-producing cell, or IPC. Via the production of these cytokines, IPC activate macrophages and NK cells, induce the Th1 polarization of T cell responses and also control myeloid dendritic cells to prevent excess production of IL-12 (Colonna *et al*., 2002).

## Pathogen evasion of dendritic cell function

Infectious agents evolved a multitude of strategies to interfere with the development of host immunity at several levels. As dendritic cells have a key function in connecting innate and adaptive immune responses, the suppression of dendritic cell maturation, migration and antigen presentation as well as the inhibition of dendritic cell-mediated T cell activation provide means to facilitate the survival of pathogens (Table 2). The maturation of dendritic cells may be inhibited either directly or indirectly. Soluble factors released by *T. cruzi* have been shown to reduce the upregulation of MHC class I and co-stimulatory molecules normally associated with dendritic cell activation, resulting in an impairment of the ability of dendritic cells to present MHC class I-restricted antigens to specific $CD8^+$ T cells (Van Overtvelt *et al*., 2002). This mechanism may allow the parasite to avoid immune recognition and to persist in the mammalian host. *Plasmodium falciparum* exerts its effect on dendritic cells via infected erythrocytes which adhere to dendritic cells and profoundly reduce their maturation and their ability to stimulate antigen-specific T cell responses (Urban and Roberts, 2002). Interestingly, this inhibitory effect was shown to be mediated by CD36 and CD51 on dendritic cells, molecules that are also involved in the recognition of apoptotic cells. Thus, the malaria parasite-infected erythrocyte may mimic some of the adhesive ligands of apoptotic cells which also inhibit the maturation and functional activities of dendritic cells. This effect may have an impact on the disease, as the percentage of mature dendritic cells expressing HLA-DR was found to be significantly reduced in children with acute *P. falciparum* malaria (Urban and Roberts, 2002).

The production of IL-12 by dendritic cells in the early phase of an immune response is essential for the development of Th1 cells that mediate host resistance to intracellular pathogens. Autocrine IL-10 has been shown to down-regulate the IL-12 response of dendritic cells after mycobacterial infection (Demangel *et al*., 2002). In addition, mannosylated lipoarabinomannans from *Mycobacterium bovis* bacillus Calmette-Guérin and *M. tuberculosis* are able to inhibit IL-12 production by dendritic cells, and the mannooligosaccharide caps appear to play a critical role in this inhibitory activity (Nigou *et al*., 2001). Dendritic cells exposed to *Bordetella pertussis* filamentous hemagglutinin are also impaired in their ability to produce IL-12, but release IL-10 and induce antigen-specific regulatory T cells that suppress protective Th1 responses (McGuirk *et al*., 2002). Similarly, dendritic cells stimulated with schistosome-derived phosphatidylserine induce the development of IL-10-producing regulatory T cells, which might account for the T cell hyporesponsiveness during chronic schistosomiasis (van der Kleij *et al*., 2002). For *Leishmania* parasites, species-restricted differences determine the effect on dendritic cell cytokine production. Infection with *Leishmania major*, but not *L. tropica* or *L. donovani*, triggers IL-12 secretion by human myeloid dendritic cells (McDowell *et al*., 2002). Recently, a potent mechanism for the inhibition of IL-12 production by dendritic cells has been elucidated. The induction of lipoxin $A_4$, an arachidonate-derived inhibitor of acute inflammation, after stimulation with an extract of *T. gondii* was shown to be associated with a profound suppression of the IL-12 response of dendritic cells *in vivo* (Aliberti *et al*., 2002). Moreover, it is accompanied by reduced expres-

**Table 2.** Pathogen evasion of dendritic cell (DC) function.

| Pathogen | Effect | Mechanism | Reference |
|---|---|---|---|
| *P. falciparum* | Inhibition of DC maturation and T cell-stimulatory function | Adherence of infected erythrocytes to DC | Urban and Roberts (2002) |
| *T. cruzi* | Inhibition of DC maturation and T cell-stimulatory function | Soluble factors released by the parasites | Van Overtvelt *et al*. (2002) |
| Mycobacteria | Inhibition of IL-12 production by DC | Induction of autocrine IL-10<br>Binding of bacterial lipoarabinomannans to DC mannose receptor | Demangel *et al*. (2002)<br>Nigou *et al*. (2001) |
| *T. gondii* | Inhibition of IL-12 production by DC | Induction of lipoxin $A_4$ | Aliberti *et al*. (2002) |
| *B. pertussis* | Induction of regulatory T cells | IL-10 production by DC | McGuirk *et al*. (2002) |
| *S. mansoni* | Induction of regulatory T cells<br>Inhibition of DC migration | Parasite-derived phosphatidylserine<br>Prostaglandin $D_2$ released by parasite larvae | van der Kleij *et al*. (2002)<br>Angeli *et al*. (2001) |
| *Leishmania* | Inhibition of DC migration | Secreted parasite products<br>*Leishmania* lipophosphoglycan | Jebbari *et al*., 2002<br>Ponte-Sucre *et al*. (2001) |

sion of the chemokine receptor CCR5 by dendritic cells and a marked inhibition of dendritic cell migration into T cell areas of the spleen.

Alteration of the migratory activities of dendritic cells is another convenient strategy for a pathogen to affect the host's immune response. The motility of splenic dendritic cells is inhibited by secreted products of *L. major* (Jebbari *et al*., 2002), and the emigration of Langerhans cells from skin is significantly reduced by purified *L. major* lipophosphoglycan (Ponte-Sucre *et al*., 2001), suggesting that *Leishmania* parasites interfere with the ability of dendritic cells to transport antigen to or within lymphoid tissues. Percutaneous infection with *S. mansoni* was also reported to impede the emigration of Langerhans cells from the epidermis and their subsequent accumulation as dendritic cells in the draining lymph node (Angeli *et al*., 2001). This inhibitory effect is mediated by lipophilic factors released by parasite larvae, particularly prostaglandin $D_2$.

## Conclusions

In the past few years, dendritic cells have been in the forefront of research on innate immunity and immunoregulation, owing to their exquisite efficiency in processing and presenting antigens, and activating the adaptive arm of the immune system. Dendritic cells recognize common structures of pathogens, but they also detect distinct features of different microorganisms and different stages of their life cycle, and convey this information to T cells, thereby tailoring the 'best fit' immune response. The increasing knowledge of the interaction of dendritic cells with microbes, on the one hand, and with T cells, on the other, provides new insights into the nature of Th1/Th2 regulation and suggests approaches for its manipulation. Vaccination strategies and therapeutic immune interventions based on dendritic cells may be particularly useful in cases of infectious diseases that are associated with specific types of immune responses. In leishmaniasis, for example, susceptibility to infection correlates with the development of Th2 cells, whereas protective immunity is based on the activation of Th1 cells. It has been demonstrated that dendritic cells loaded *ex vivo* with *Leishmania* antigen have the capacity to induce protection in otherwise susceptible mice against challenges with the parasites (Flohé *et al*., 1998; Berberich *et al*., 2003). The dendritic cell-mediated protection is long-lasting and is associated with a shift of the *Leishmania*-specific immune response towards a Th1-type response. Induction of protective immunity with microbial antigen-pulsed dendritic cells has also been reported for a variety of other infections, including those caused by *C. albicans* (d'Ostiani *et al*., 2000), *Chlamydia trachomatis*, *Borrelia burgdorferi*, *M. tuberculosis* and lymphocytic choriomeningitis virus (reviewed by Moll and Berberich, 2001). These findings underline the potent immunomodulatory functions of dendritic cells and demonstrate that they can serve as vaccine carriers. The ultimate aim is the design of vaccines and immune intervention strategies that induce protective immunity by specific targeting and activation of appropriate dendritic cells in tissues and modulation of their functions *in vivo*. This knowledge could be of great value not only for vaccination and immunotherapy to combat infectious diseases, but also for the treatment of cancer and other disorders where enhancing or biasing the immune response has a beneficial effect.

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