Cell. Mol. Life Sci. 65 (2008) 1683 – 1697
1420-682X/08/111683-15
DOI 10.1007/s00018-008-8009-2


Cellular and Molecular Life Sciences

# Review

# Central role of dendritic cells in the regulation and deregulation of immune responses

**F. Granucci[a,*], I. Zanoni[a] and P. Ricciardi-Castagnoli[a,b]**

[a] Department of Biotechnology and Bioscience, University of Milano-Bicocca, Piazza della Scienza 2, 20126 Milan (Italy), Fax: +390264483553, e-mail: francesca.granucci@unimib.it
[b] Singapore Immunology Network (SIgN), Biomedical Sciences Institutes, Agency for Science, Technology and Research (A*STAR), 8A Biomedical Grove, IMMUNOS (Singapore 138648)

Received 7 January 2008; received after revision 18 January 2008; accepted 25 January 2008
Online First 10 March 2008

**Abstract.** Dendritic cells (DCs) play a critical role in orchestrating the innate and adaptive components of the immune system so that appropriate, coordinated responses are mounted against infectious agents. Tissue-resident DCs interact with microbes through germline-encoded pattern-recognition receptors (PRRs), which recognize molecular patterns expressed by various microorganisms. Antigens use PRR activation to instruct DCs for the appropriate priming of natural killer (NK) cells, followed by specific T-cell responses. Due to the central role of DCs in regulating the activation and progression of immune responses, minor imbalances in the feedback control of Toll-like receptor (TLR)-activated cells have been associated with autoimmunity in genetically prone individuals. We review here recent findings on the role of DCs in the priming of innate and adaptive immune responses and the possible involvement of DCs in inducing and maintaining autoimmune reactions.

**Keywords.** Dendritic cells, innate immunity, adaptive immunity, pattern recognition receptors, CD14, natural killer cells, autoimmunity.

## Introduction

Dendritic cells (DCs) were initially described as the 'natural adjuvants' inducing adaptive immune responses [1–3]. DCs are special leukocytes capable of alerting the immune system to the presence of infections and responsible for the activation and control of both innate and adaptive immune responses [4, 5]. DCs are particularly frequent in tissues forming an interface with the external environment, such as the skin, gut and lungs [6–8], where they perform a sentinel function – detecting incoming pathogens – and can recruit and activate cells of the innate immune system [9–11]. DCs take up antigens and efficiently process them for presentation in association with major histocompatibility complex (MHC) molecules. These cells must be sensitive to the amount of antigen present and the persistence of antigens if they are to fulfill their role as sentinels correctly. They use a repertoire of non-clonal receptors to signal downstream to the nucleus, conveying information about what is present in the environment (quality and quantity) and the duration of this signal. This complex activity is revealed by transcriptional responses involving the differential expression of thousands of genes and the integration of a number of signaling pathways. The active transcriptional response leads to

* Corresponding author.

the acquisition of diverse DC functional phenotypes, orchestrating the appropriate immune response [12, 13].

DCs are highly plastic. The signals determining a particular DC function and, consequently, the type of adaptive immune response therefore depend mostly on the local microenvironment and on the interaction between DCs and microbes. DCs are the critical link between innate and adaptive immune responses, and the deregulation of DC activation via Toll-like receptors (TLRs) has been associated with autoimmunity in susceptible individuals, particularly through the production of type I interferons (IFNs). In this review, we summarize recent findings on the role of DCs in priming innate and adaptive immune responses and the possible involvement of DCs in deregulated autoimmune reactions.

## DC heterogeneity

DCs are of hematopietic origin and have been found in many different organs and tissues, including heart, liver, thyroid, pancreas, bladder, kidney, ureter, gut, lungs and skin. Fully developed DCs have also been observed in the circulatory networks of the body, including blood and afferent lymphatic vessels. DCs display a high degree of plasticity within organs and lymphoid tissues, and DC effector functions are often regulated by tissue microenvironment [14].

As superbly described by Shortman [15, 16], DCs can be subdivided into conventional DCs, cells having phenotypic and functional characteristics of DCs, and pre-DCs, cells requiring a further step of development to acquire phenotypic and functional DC features. Conventional DCs can, in turn, be subdivided in migratory and lymphoid tissue-resident DCs. Migratory DCs are the sentinels of non-lympoid tissues and migrate to the draining lymph nodes after the encounter of inflammatory stimuli. Migration to lymph nodes can also occur at low rate in steady-state conditions. Lymphoid tissue-resident DCs do not reach the lymphoid organs through the lymphatics but capture the antigen directely inside the lymphoid organ. Most of thymic, spleen and around half of lymph node DCs are lymphoid tissue-resident cells.

Migratory and lymphoid tissue-resident DCs can be further divided into subtypes. For migratory DCs the division is based on the tissue origin, while for lymphoid tissue-resident DCs it is based on the expression of particular markers [17–20]. For instance, six different DC populations have been identified in skin-draining lymph nodes all expressing CD11c: $CD8^+DEC205^+$-resident DCs, $CD8^-DEC205^-$ (both $CD4^-$ and $CD4^+$)-resident DCs, $CD8^{low}CD205^{int}$ DCs (migratory dermal DCs) and $CD8^{low}DEC205^{high}$ DCs (migratory Langerhans cells, LCs) [20, 21]. In general, in mouse lymph nodes and spleen DCs are characterized by the expression of CD11c and are classified based on the expression of CD4, CD8 and the two uptake receptors DEC205 and DCIR2, recognized by the 33D1 antibody. Thus, $CD4^+CD8^-$, $CD4^-CD8^+$ and $CD4^-CD8^-$ have been identified. Moreover, a subpopulation of $CD8^+$ DCs expressing DEC205 and a subpopulation of $CD8^-$ DCs expressing DICR2 have also been described [22]. In the spleen, $CD8^-$ DCs are mostly found in the marginal zone, whereas $CD8^+$ DCs are mostly found in the T-cell area [19]. $CD8^-$ DCs migrate to the T-cell areas following stimulation with microbial stimuli [23].

In steady-state conditions, DCs resident in lymphoid and non-lymphoid tissues are phagocytic cells and express low levels of the costimulatory molecules CD80 and CD86, and low levels of MHC class II. Upon activation following microbial stimuli encounter, both migratory and lymphoid tissue-resident DCs downregulate phagocitic activity, increase processing capacity, and upregulate MHC and costimulatory molecules at the cell surface [21]. In addition, migratory DCs acquire the capacity to migrate to lymph nodes. When they reach the lymph nodes, they have a mature phenotype [15].

Finally, a DC population producing large amounts of type I interferons (IFNs) following microbial infections – IFN-producing plasmacytoid DCs (pDCs) – has been described in mouse blood and lymph nodes [24]. In steady-state conditions, these cells can be classified as preDCs [15]. Upon activation they acquire not only the capacity to produce large amounts of type I IFNs but also some DC antigen-processing and -presentation properties [25].

Human DC phenotypes have been less well typed. DCs expressing CD11b, CD11c and CD4 have been described in the spleen and tonsils [19]. No CD8-expressing DCs have been identified. Human IFN-producing pDCs are $CD45RA^+CD123^+$ and $CD11c^-$ [26].

Migratory and lymphoid tissue-resident DCs can sense the presence of a pathogen through a large innate receptor repertoire. The signal transmitted by these receptors is crucial for DC maturation and possible migration to secondary lymphoid tissues, leading to the initiation of adaptive immune responses.

## How do DCs sense pathogens?

DCs interact with microbes through germline-encoded pattern-recognition receptors (PRRs) [27], which recognize molecular patterns expressed by various micro-

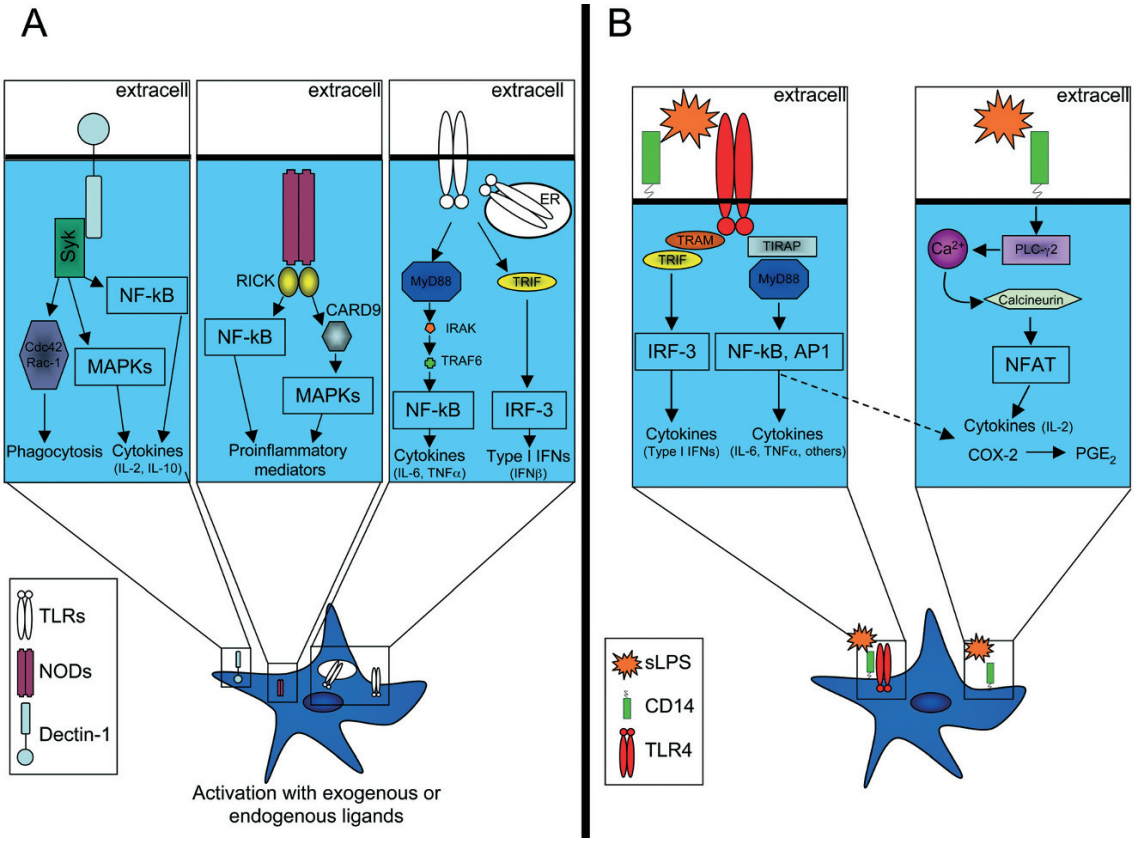


**Figure 1.** (*A*) Models of DC activation induced by exogenous or endogenous ligands detected by different classes of PRRs. (*B*) Model of CD14 functions. CD14, in addition to enhancing TLR4-dependent cellular responses to low doses of LPS and being required for the LPS-induced recruitment of TRIF and TRAM, is also involved in $Ca^{2+}$ mobilization and TLR4-independent NFAT activation following sLPS engagement. The activation of this pathway, together with that of the NF-κB pathway, leads to the efficient production of COX-2 and $PGE_2$ and other cytokines, such as IL-2.

organisms. PRRs comprise a large superfamily, including the C-type lectin family [28], the nucleotide binding and oligomerization domain (NOD)-like receptors (NLRs) [29], the retinoid acid-inducible gene I (RIG)-like receptors (RLRs) [30] and TLRs [31].

Dectin-1 is a C-type lectin that plays an important role in anti-fungal defense [28, 32, 33]. Dectin-1 is a beta-glucan-specific receptor that mediates the phagocytosis of yeast and yeast-derived particles, such as zymosan. In mouse DCs, the dectin-1-mediated phagocytosis of zymosan depends at least partly on tyrosine kinase Syk activation, leading to activation of the Rho family GTPases Cdc42 and Rac-1. This, in turn, leads to actin polymerization and pseudopod protrusion around the particle [34, 35]. Dectin-1 engagement in DCs triggers the production of pro-inflammatory and anti-inflammatory cytokines, including interleukin (IL)-2 and IL-10 [35] (Fig. 1A).

NLRs comprise a large family of intracellular PRRs, all bearing a conserved NOD domain [36]. The binding of a ligand to the leucine-rich repeat (LRR) motif within this domain leads to a change in the conformation of the molecule and its activation. Unlike dectin-1 and TLRs, NLRs are cytosolic receptors. Their location suggests a possible role in the detection of microbes escaping the surveillance of extracellular or endosomal receptors. NOD1 and NOD2 are the best-characterized NLRs. They recognize molecules produced during the synthesis or degradation of peptidoglycan [37–39]. *In vitro* studies have shown that NOD1 can sense pathogens, such as *Shigella flexneri* [38], *Listeria monocytogenes* [39], *Campylobacter jejuni* [40] and enteroinvasive *Escherichia coli* [41]. NOD2 has also been implicated in the recognition of intracellular pathogens, such as *Listeria monocytogenes* [42], *Mycobacterium tuberculosis* [43] and *Streptococcus pneumoniae* [44]. The interaction of the LRR motif of NOD molecules with a ligand leads to recruitment of the adaptor molecules RICK and CARD9 [45], resulting in activation of the kinase TAK1, which is responsible for activating the IKK complex [46, 47]. This results in degradation of the nuclear factor (NF)-κBα inhibitor and translocation of NF-κB to the nucleus. NOD1 and NOD2 stimulation activates not only the NF-κB pathway but also MAP kinase p38, ERK and JNK

[48, 49]. The NF-κB and MAP kinase pathways cooperate in the induction of proinflammatory molecule expression [29] (Fig. 1A).

Like NLRs, RLRs are located in the cytoplasm and defend the host against viral infections within the cytoplasm [50]. Following dsRNA binding, RLRs recruit the adaptor molecule CARDIF (CARD adaptor-inducing IFN-β) through a caspase recruitment domain (CARD)-CARD interaction. Mitochondrial bound CARDIF recruits the appropriate molecules for the activation of NF-κB and IRF3 [51].

Although several receptors recognize microbial structures, TLRs are the only PRRs identified to date that directly mediate full DC maturation. Thirteen different TLRs have been identified in mammals [52]. Some of these receptors – TLRs 1–6 and 11 – are expressed at the cell surface and recognize different products of bacterial, fungal or protozoan origin, including lipopeptides, lipopolysaccharides (LPSs) and peptidoglycans. Others, such as TLRs 3, 7, 8 and 9, are located in the endoplasmic reticulum and recognize microbial nucleic acids [52]. TLRs can also bind to a large set of endogenous ligands, including heat shock proteins (HSPs), hyaluronate and heparan sulfate (extracellular matrix breakdown products), fibronectin, high mobility group box 1 protein (HMGB1) and modified low-density lipoproteins [53]. Moreover, myeloid-related protein-8 (Mrp8) and Mrp14 – two abundant cytoplasmic proteins of phagocytes, released after phagocyte activation [54] – have been also identified as endogenous ligands of TLR4.

By recruiting different combinations of adapter proteins, individual TLRs turn on signal transduction pathways leading to the activation of different transcription factors, such as NF-κB, activation protein (AP)-1 and IFN regulatory factors (IRFs) [55]. TLRs transduce the signal through two major pathways: the MyD88-dependent pathway and the Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF)-dependent pathway. The MyD88-dependent pathway leads to the production of proinflammatory cytokines, such as IL-6 and tumor necrosis factor (TNF)-α, via the recruitment of signaling molecules, including IRAK4 (IL-1R-associated kinase 4), IRAK1 and TRAF6 (TNF receptor-associated factor 6). The TRIF-dependent pathway may be activated by the engagement of TLR3 or TLR4, and leads to the production of type I IFNs, including IFN-β in particular [56] (Fig. 1A).

Coreceptors may assist TLRs in their functions. For example, CD14 amplifies the signals transduced by TLR4, TLR2 and TLR3 in the presence of particular ligands. CD14 may therefore serve as a coreceptor for TLRs both at the cell surface and in the endosomal compartment [57, 58]. CD14 may be expressed on the cell membrane as a glycosylphosphatidylinositol-anchored receptor (GPI-AR) [59] or secreted as a soluble recirculating serum protein. Cells of both hematopoietic and non-hematopoietic origins can express CD14 [60]. However, the precise role of this particular PRR remains unclear. Most of the information available concerns the role of CD14 as a coreceptor working with TLR4. Two functions have been attributed to CD14 in this context: i) recruitment of TRIF and TRAM for type I IFN production [61]; and ii) LPS presentation to TLR4, facilitating cellular responses to low doses of LPS [57, 62]. An absolute requirement for a full response to the smooth form of LPS (sLPS) has been demonstrated [63]. We recently showed that CD14 may have a third function [unpublished data]. Following LPS stimulation, CD14 activates the $Ca^{2+}$/calcineurin and NFAT pathway in DCs in a TLR4-independent manner. This function of CD14 is necessary to induce IL-2 and cyclooxigenase-2 (COX-2) production, leading to prostaglandin $E_2$ synthesis ($PGE_2$) (Fig. 1B).

$PGE_2$ is the most versatile prostanoid known, regulating many physiological and pathophysiological responses. In particular, it regulates or mediates various DC functions, including DC migration and the polarization of T-cell responses [64, 65] through autocrine or paracrine effects on different receptors [66]. DC-derived $PGE_2$ facilitates Th1 differentiation via the EP1 receptor expressed on naive T cells [66], whereas $PGE_2$-mediated activation of the EP2 and EP4 receptors promotes Th2 differentiation [67, 68]. Given the importance of $PGE_2$ for the regulation of DC function, this prostanoid is one of the components of the non-microbial stimulus cocktail used to activate DC for *in vivo* therapies. The definition of this new role for CD14 provides new insight into the molecular signaling occurring during the initial phases of host defense to bacterial infections. These initial events can then influence the development of the inflammatory process.

## DCs and innate immunity: DCs as a conductor of NK cell responses

DCs have clearly been demonstrated to play a role in NK cell activation in many different experimental systems [11, 69–76]. For instance, a key role for DCs in this priming process during herpes simplex virus (HSV)-1 as well as *Listeria monocytogenes* infections has recently been shown in experimental models in which DCs can be conditionally ablated [75, 76]. Starting from the pioneering work of Fernandez et al. [11], many groups have investigated the role of DC-derived cytokines and membrane-bound molecules in

the activation of NK cells. These studies have generally reported a major role for DC-derived type I IFN in NK cell cytotoxic activity [72, 77–79], but two main pathways have been identified as accounting for DC-mediated NK cell IFN-γ release in both humans and mice: i) DC-mediated NK cell activation is dependent on IL-12 and other DC-derived cytokines/molecules [69, 71, 80–93]; and ii) NK cell functions are strongly boosted by DC-derived IL-2 in association with other cytokines/molecules [72, 74, 94, 95].

IL-12 appears to be essential for the induction of IFN-γ by NK cells in different experimental settings [69, 80]. It is required for NK cell activation and is released after DC and NK cells come into contact [81], following the stimulation of DC derived from $CD34^+$ precursors with LPS [71], the priming of monocyte-derived DCs with *Actinobacillus, E. coli* or *Bacillus Calmette-Guèrin* (BCG) [82, 84], the activation of myeloid DCs with poly-I:C [77] or of PBMC-derived DC with LPS [92]. DC-derived IL-12 seems to be presented to NK through the formation of 'stimulatory synapses', ensuring the efficient presentation of low doses of IL-12 to both human and murine NK cells [86]. In some experimental settings, IL-12 has also been shown to be a key regulator of NK cell cytotoxicity [85]. In other studies based on peripheral blood DCs, IL-12 and cell-cell contacts were found to play only a marginal role, suggesting that other factors inducing NK cell cytotoxicity may be present [91]. Other cytokines released by DC, such as type I IFN, IL-15 and IL-18, may also affect NK cell functions such as IFN-γ production [87], migration [89], cytotoxic function [93] and proliferation [83]. In particular, IL-18 seems to play an important role in enabling NK cells to migrate to secondary lymphoid organs, where they can interact with DCs [89]. Human NK cells exposed to IL-18, but not IL-2, display rapid CCR7 induction and an increase in responsiveness to CCL21, with no increase in lytic activity. Once in the lymph nodes, these NK cells produce large amounts of IFN-γ in response to IL-12, TNF-α and IL-2. A membrane-bound form of DC-derived IL-15 seems to be required to trigger activation, or at least proliferation, of NK cells [83, 88]. Indeed, the presence of the IL-15 receptor on the surface of DCs is required to mediate the effects of IL-15. This suggests that DCs may present IL-15 *in trans* to NK cells. Finally, different human DCs display different patterns of cytokine secretion correlated with their ability to activate NK cells *in vitro* [90]. Monocyte-derived DCs produce IL-12p70, which induces NK cell activation in terms of NK cell proliferation, cytotoxicity and the upregulation of CD56. $CD34^+$ hematopoietic progenitor cell (HPC)-derived LCs do not produce sufficient IL-12p70 and have too few IL-15 receptors to induce NK cell activation. Nonetheless, once activated by recombinant IL-12, LCs provide additional factors (leading candidates include IL-15 and IL-18, which are produced in larger amounts by these cells) that promote NK cell proliferation and survival, sustaining IL-12-induced activation. Finally, $CD34^+$ HPC-derived dermal interstitial DCs show intermediate levels of cytokine production and NK cell activation.

IL-2 has always been added to NK cell cultures *in vitro* to obtain hyperresponsive cells. However, this cytokine was not considered important for NK cell-mediated anti-tumor or antimicrobial responses *in vivo,* as IL-2 was thought to be produced exclusively by T cells during the late, antigen-specific phase of the immune response, after the peak of NK cell activation [96]. Following the first reports of IL-2 production by activated DCs in the first few hours after stimulation [12], we investigated the possible physiological role of this early production of IL-2 in NK cell activation. We found that *E. coli*-activated DCs were potent activators of NK cells both *in vitro* and *in vivo* and that this process was dependent on DC-derived IL-2 (necessary for NK cell IFN-γ production), type I IFN (required for optimal NK cell cytotoxicity) and other unknown factors [72]. It was subsequently shown that TLR-dependent, as opposed to TLR-independent full-maturation stimuli, render DCs able to elicit IFN-γ production by NK cells [74]. In particular, LPS, CpG and BCG have been shown to induce IFN-γ production *in vitro* and *in vivo* in an IL-2-dependent manner, whereas stimuli that did not induce the release of IL-2 by DCs, such as pertussis toxin (PT), cholera toxin (CT), *Leishmania mexicana*, and – in the C57/BL6 background but not in the BALB/c background – Pam-3-Cys, did not lead to the induction by DCs of IFN-γ production by NK cells. IL-2 was necessary for NK cell activation in all these experimental settings, but was unable to induce such activation if supplied alone as a recombinant molecule, highlighting the need for other soluble or membrane-bound DC-derived factors. These observations were recently called into question by the work of Schartz et al. [97], who suggested that IL-2 derived from LPS-activated DCs was not required for NK cell functions. However, these authors were unable to confirm this hypothesis experimentally, as they assessed only CD69 upregulation as to evaluate NK cell priming. CD69 upregulation, although associated with activation, does not actually indicate the acquisition of any real effector functions [98]. Monocyte/DC-derived IL-2 has also been shown to play a role in NK cell activation in humans. Newman et al. [94] demonstrated that the capacity of human NK cells to produce IFN-γ in response to stimulation with *Plasmodium falciparum*-infected red blood cells was strictly de-

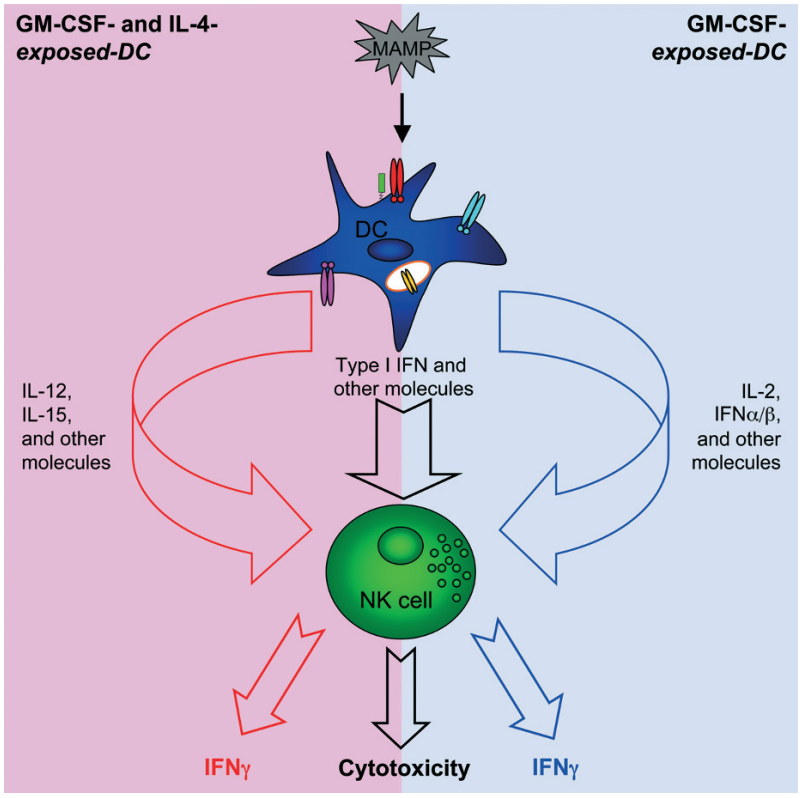


**Figure 2.** Mediators of NK cell activation produced by activated DCs differentiated in the presence of GM-CSF alone or GM-CSF and IL-4.

pendent upon cell contact-dependent and IL-2/type I IFN-mediated signals derived from monocytes and myeloid DCs. They excluded a major role for IL-12 and IL-15 in the activation of NK cells in their experimental setting, but could not totally exclude the possibility that contaminating cells that could produce IL-2 were present.

It is possible that the two different modes of NK cell activation by DCs described in published studies reflect different conditions for DC culture and the heterogeneity of DC populations differentiated *in vivo* (Fig. 2). Indeed, mouse and human DCs secrete bioactive IL-12 efficiently only if previously exposed to IL-4 [99]. DCs exposed to the semi-maturation stimulus IL-4 acquire the capacity to activate NK cells independent of microbial stimuli and IL-2, although microbial stimuli do enhance this process [82, 100]. IL-4 also inhibits microbe-induced IL-2 production by DCs ([101] and our personal observations). Thus, IL-12 may contribute to DC-mediated NK cell activation if DCs have previously been exposed to IL-4 *in vitro* or *in vivo*. Moreover, blockades of IL-2 activity *in vivo* [72] or *in vitro* with DCs derived *ex vivo* [74] result in strong inhibition of the activities of NK cells, but not in the complete inhibition of NK cell functions, suggesting that the heterogeneity of *in vivo* differentiated DCs may result in two different pathways of NK cell activation, as previously described.

Many studies have suggested that cell-cell contact, in addition to soluble factors, may play a role in the DC-mediated NK cell activation process [71, 72, 86, 102, 103]. On the one hand, cell-cell contact probably reflects a need for the formation of 'activating synapses' between DCs and NK cells, facilitating the local delivery of high concentrations of known or unknown cytokines. On the other hand, surface receptor-ligand interactions may be required for optimal NK cell activation. Xu et al. [95] recently found that DCs constitutively express a membrane-bound form of TNF that may bind TNFR2 on the surface of NK cells. Indeed, NK cells upregulate this receptor after long or short periods of culture with IL-2. This finding provides strong evidence supporting a role for DC-produced IL-2.

## DCs and adaptive immunity

### How do DCs internalize, process and present antigens?

Despite several early descriptions of the uptake of particulate material and cells by DCs, it was long thought that DCs had no phagocytic capacity. This view arose partly from the technical difficulties involved in the culture of immature DCs. Early procedures for DC purification and culture *in vitro*

tended to result in DC-enriched preparations containing mostly terminally differentiated cells with a mature phenotype and function. Once it became possible to grow and maintain immature mouse DCs *in vitro* [104, 105], these cells were found to have marked phagocytic activity that decreased with increasing DC differentiation. Indeed, immature DCs express a large array of phagocytic receptors, including lectins, scavenger receptors, Fc receptors and other PRRs. DCs have been shown to internalize latex and zymosan beads [106, 107], apoptotic bodies [108] and a number of microbes, including many bacteria and viruses, *in vitro* and *in vivo* [109]. *In vivo*, *Listeria monocytogenes* and *Salmonella typhimurium* have been colocalized with DCs in intestinal Peyer's patches after oral infection [110, 111], and *Listeria monocytogenes* has also been found in the DCs of the mesenteric lymph nodes 6 to 12 h after infection [111]. Splenic DCs have been found to be associated with *Salmonella typhimurium, Mycobacterium bovis* or BCG 4 h after intravenous infection [112, 113]. The phagocytic activity of DCs is designed to facilitate antigen processing and presentation. DCs have no bacterial scavenging function and are highly inefficient at bacterial clearance, but they do have unique mechanisms for antigen processing and for the antigen loading of MHC molecules. For instance, DCs produce various lysosomal proteases, but cannot recruit these enzymes efficiently to the phagosome. DC phagosomes therefore have a low protease concentration, accounting, at least partly, for a much lower efficiency of antigen degradation than observed for macrophages [114, 115]. DCs also produce several cystatin protease inhibitors, which inhibit proteolytic activity in lysosomes and phagosomes [116]. Thus, the proteolysis of antigens taken up by DCs is geared to antigen processing rather than to total destruction, whereas macrophages and neutrophils destroy antigens [117].

Stimuli inducing DC activation and maturation increase the efficiency of antigen processing, for both the class I and class II pathways, and the half-life of peptide-MHC complexes at the cell surface that would otherwise be rapidly internalized and recycled [9, 118, 119]. DC activation induces the *de novo* synthesis of class I molecules and increases the efficiency of preformed class II molecule transport at the cell surface. DCs have large numbers of multivesicular bodies (MVBs) containing a pool of MHC class II molecules. Following the activation of DCs by contact with a microbe, extensive MVB vesicle fusion occurs, resulting in the formation of long tubular compartments, in which MHC class II molecules and DM molecules are closely associated and directed towards the tips of the dendrites. This reorganization of the MVBs facilitates the efficient loading of class II molecules with exogenous peptides generated in the early endosomes and the presentation of complexes at the cell surface [120].

Another interesting feature of the specific processing machinery of DCs is the ability of these cells to delay the processing of internalized antigens by antigen retention in a mildly acidic storage compartment [121]. Antigens internalized in these vesicles are not immediately degraded, and fusion with the lysosomes is delayed. This mechanism seems to be coordinated with the generation of newly synthesized MHC class II molecules, 12–18 h after DC activation [9].

DCs also present exogenous antigens on MHC class I molecules, in a process known as cross-presentation [122]. It remains unclear how degraded antigens from the exogenous pathway are loaded onto MHC class I molecules, although it has been suggested that this loading may involve endoplasmic reticulum (ER)-phagosome fusion [123]. The recruitment of ER-resident proteins to the phagosome would allow the retrotranslocation of proteins from the phagosome to the cytosol, via the sec61 protein [124]. This molecule is known to mediate both the translocation of newly synthesized proteins into the ER and the retrotranslocation of misfolded proteins from the ER to the cytosol for proteasomal degradation [124]. The low efficiency of particle degradation in the phagosome of DCs would make this process optimal in these cells [124].

## DCs as conductors of adaptive T-cell responses

The requirement of DCs for T-cell activation in lymph nodes was initially demonstrated *in vivo* for $CD8^+$ T lymphocytes. Mice temporarily deprived of $CD11c^+$ DCs cannot mount efficient specific $CD8^+$ T-cell responses to infections with the intracellular bacterium *Listeria monocytogenes*, the parasite *Plasmodium yoelii*, LCMV or antigen immunization [125, 126]. It was subsequently shown that $CD11c^{high}$ conventional DCs are required for the priming of both $CD8^+$ and $CD4^+$ T cells in the spleen, whereas these cells are dispensable for $CD4^+$ T-cell priming in lymph nodes. Indeed, within lymph nodes, pDCs can replace conventional DCs for this function [127]. In the absence of conventional DCs, pDC-mediated $CD4^+$ T-cell priming occurs but is not associated with $CD8^+$ T-cell activation, indicating that pDCs prime $CD4^+$ T cell-dominated immune responses only [127].

There is indirect evidence to suggest that DCs are necessary for the activation of protective T-cell responses in humans. In particular, a lack of circulating DCs during dengue virus infections or bacterial sepsis is always associated with a poor prognosis [128, 129].

DCs can enter the lymph node via the blood or lymph [130]. If they arrive through the blood, they are initially found clustered together, close to high endothelial venules (HEVs). However, their distribution subsequently changes, such that, one day after reaching the lymph node, DCs are distributed throughout the T-cell area [131]. The process by which DCs reach the lymph node through the lymph and undergo redistribution has been well characterized in the skin compartment. Following skin inflammation, dermal DCs are the first cells to migrate to the draining cutaneous lymph node, where they are first detected after 24 h, their levels peaking after 2 days. LCs migrate to the lymph nodes slightly later, their numbers peaking in the draining lymph nodes 4 days after administration of the stimulus [132]. LCs and dermal-derived DCs localize to different areas of the lymph node. Within the T-cell area, dermal DCs localize to the outer paracortex just beneath the B-cell area, whereas LCs localize to the inner paracortex, suggesting that these two different DC populations may have different functions and encounter different T-cell subsets [132]. During cutaneous viral infections, such as herpes virus infections, the antigen is transported to the draining lymph node mostly by dermal-derived DCs, which transfer the antigen to resident $CD8^+$ DCs in the cortex, leading to the activation of $CD8^+$ T-cell responses through cross-presentation [133]. A continuous slow rate of LC migration to the draining lymph nodes is thought to occur in the absence of inflammation, in steady-state conditions. A few motile immature LCs loaded with tissue-specific antigens should continually reach the draining lymph node, conserving their immature or semi-mature state, probably maintaining T cell-mediated self-antigen tolerance [134–136].

The different DC subtypes present in the lymph nodes display considerable diversity in terms of specialization for antigen presentation. For instance, $CD8^-33D1^+$ DCs preferentially present antigens in association with the MHC class II molecules and, following activation, they increase the efficiency of the class II processing machinery. These cells are, therefore, specialized in $CD4^+$ T-cell activation [137]. By contrast, $CD8^+DEC205^+$ cells efficiently present antigens, leading to the clonal expansion and acquisition of effector functions by both $CD4^+$ and $CD8^+$ T cells [137]. These cells are the only cells able to prime $CD8^+$ T-cell responses in the lymph node [125].

There is at least one other important difference between the two DC subtypes. $CD8^+DEC205^+$ DCs primarily trigger Th1 responses, whereas $CD8^-33D1^+$ DCs induce the production of either IL-4 alone or both IFN-γ and IL-4 by T cells [138, 139]. IL-12 has been shown to be an essential cofactor for skewing toward Th1 responses in various experimental systems [140]. $CD8^+DEC205^+$ DCs produce much larger amounts of IL-12 than $CD8^-33D1^+$ cells [141]. However, these cells are thought to induce Th1 skewing by the membrane-bound cofactor CD70, a member of the tumor necrosis family [22], in the presence of TLR4 and TLR3 agonists, rather than through IL-12. This would explain why individuals with inherited IL-12 or IL-12 receptor deficiency respond to many different intracellular pathogens, displaying particularly strong susceptibility only to a limited range of microorganisms, including BCG and *Salmonella* [142].

## DCs and autoimmunity

DCs play a central role in regulating the activation and progression of immune responses. To limit self-tissue damages while maintaining the ability to respond to pathogens, the immune system has developed mechanisms for maintaining peripheral tissue tolerance. There is increasing evidence that DC and regulatory T cell (Tregs) cross-talk plays a crucial role in the equilibrium between tolerance and immunity [143]. Interaction between organ-specific Tregs and DCs presenting organ-derived antigens is fundamental in preventing autoimmune tissue destruction [144, 145]. Given the fundamental role of DC in controlling tolerance and immunity, a delicate imbalance in the feedback control of TLR-activated cells has been associated with autoimmunity in genetically prone individuals. An increasing number of reports have provided evidence that, in a susceptible genetic background, DC activation through TLRs can induce autoimmune tissue destruction, through the production of type I IFNs in particular.

The DC maturation process leads to DCs releasing various cytokines and chemokines [9] – including type I IFNs, key cytokines directing innate immune responses and favoring the subsequent development of adaptive responses to viruses and bacteria – within a few hours of microbial infection. Type I IFNs are encoded by 13 IFN-α genes and 1 IFN-β gene, clustered on chromosome 9, all with an unusual, intron-less structure. The products of all these genes signal via the IFN-α/βR pathway. Type I IFNs are produced by many cells in response to viral challenge. However, DCs, and pDCs in particular, produce large amounts of these cytokines [146, 147], which may also have an autocrine effect on DCs, promoting their activation [148].

TLRs 7 and 9 can induce type I IFN production and are expressed at high levels in both human and mouse pDCs, like TLRs 3, 4 and 9 in myeloid DCs [55]. TLR

stimulation may lead to the activation of two different signaling cascades leading to IFN production: the MyD88/IRAK-1 pathway downstream from TLR7, TLR8 and TLR9, and the Trif/IKKε pathway downstream from TLR3 and TLR4 [63, 149–151]. Activation of the Trif/IKKε pathway leads to the phosphorylation, dimerization and nuclear translocation of IRF-3, which is essential for IFN-β induction, and the activation of NF-κB and AP-1, which is also required to trigger the production of inflammatory cytokines. The pathways downstream from TLR7–9 are MyD88/IRF-7-dependent [55].

TLR-mediated tolerance breakdown and autoimmunity have been observed in various experimental disease models. For instance, autoimmune heart failure can be induced by injections of TLR-stimulated DCs loaded with a heart-specific self-peptide [152]. TLR activation and the stimulation of autoreactive $CD4^+$ T cells seem to be essential for this process. The pathogenesis of dilated cardiomyopathy depends on genetic susceptibility and microbial infections. The results obtained therefore suggest that the induction of autoimmunity does not necessarily require antigen mimicry, but does require tissue injury and the activation of innate immune cells through innate receptors in susceptible individuals [152].

TLR signaling also seems to be involved in the induction of experimental autoimmune encephalomylelitis (EAE) [153]. B10.S EAE-resistant mice expressing a transgenic TCR specific for the encephalitogenic myelin proteolipid protein do not develop EAE, despite having large numbers of self-reactive T cells. EAE resistance seems to depend on APC activation state. APC stimulation via TLR4 and TLR9 results in tolerance breakdown and the development of autoimmunity [153], suggesting an important role of the innate immune system in maintaining the equilibrium between tolerance and autoimmunity [153].

TLR activation is also required for the induction of autoimmunity in Alb-1 mice – a mouse model of hepatitis. These mice produce the LCMV (lymphocytic choriomeningitis virus) glycoprotein exclusively in the liver, under the control of the albumin promoter [154]. LCMV glycoprotein $peptide_{33-41}$ (gp-33) is processed and presented to $CD8^+$ T cells by the H-$2D^d$ molecule. The gp-33 peptide is not presented in the thymus, so gp33-specific T cells reach peripheral lymphoid organs. Nevertheless, they do not cause autoimmunity in steady-state conditions. However, the infection of these animals with LCMV induces the expansion and activation of self-reactive (anti-gp33) T cells and the development of hepatitis. Viral infection is essential for disease development, as the immunization of Alb-1 mice with the gp-33 peptide induced expansion of the autoreactive T-cell population but did not cause tissue damage [154]. TLR activation seems to be the key element of viral infection for this process. As a matter of fact LCMV infection induces autoimmunity via TLR3 engagement on macrophages and various DC subsets, leading to the consequent production of type I IFNs and TNFα, which, in turn, activate other DCs and bone marrow-derived cells. Moreover, type I IFNs and TNFα may also elicit the secretion of chemokines, such as CXCL9, from hepatocytes, attracting self-reactive T cells to the liver, leading to tissue destruction. CXCL9 has also been implicated in other autoimmune diseases. It is present in high concentration in the synovial fluids of patients with rheumatoid arthritis [155]. Studies in the Alb-1 mouse model have demonstrated a clear role for the TLR-mediated activation of DCs and other bone marrow-derived cells in tolerance breakdown and autoimmune precipitation in susceptible individuals. Loss of tolerance and autoimmunity has also been observed in an analogous mouse model in which the LCMV glycoprotein was produced exclusively in the pancreas β-cells, under control of the rat insulin promoter [156]. Autoimmune β-cell destruction may be induced by viral infection or the administration of viral proteins together with TLR3 or TLR7 agonists. As in the hepatitis model, disease development was strictly dependent on IFN-α production [156]. Various hypotheses have been put forward to explain the role of IFN-α in destructive insulitis. These hypotheses include the IFN-α-mediated overexpression of MHC class I on β cells, leading to an increase in β-cell susceptibility to $CD8^+$ T cell lysis [156], an IFN-α-mediated increase in the lytic functions of $CD8^+$ T cells and an IFN-α-mediated increase in the efficiency of LCMV glycoprotein cross-presentation by DCs [157].

Several lines of evidence suggest that type I IFNs may be involved in the pathogenesis of other autoimmune diseases, such as systemic lupus erythematosus (SLE). Patients with SLE have high levels of IFN-α in serum and affected tissues [158]. Moreover, a direct association has been observed between repeated administration of IFN-α in patients suffering from various cancers or chronic viral infections and the development of symptoms associated with SLE [159, 160]. Global gene expression studies on blood lymphoid cells and kidneys from SLE patients have shown that IFN-regulated genes (IFN-signature) are selectively upregulated in these patients [158, 161]. Some typical lupus symptoms have been described in individuals with trisomy of the type I IFN gene cluster [162] and with single nucleotide polymorphisms in the *IRF5* and tyrosine kinase 2 (*TYK2*) genes, the products of which are involved in regulating type I IFN production [163,

164]. Type I IFN has been shown to play a role in lupus in NZB lupus-prone mice, in which deletion of the common subunit of type I IFN receptors reduced the severity of disease and repeated injections of IFN-α accelerated lupus symptom manifestations [165].

Immune complexes isolated from the sera of SLE patients can efficiently induce the production of IFN-α by pDCs [166], and IgG (immunoglobulin) purified from lupus patients and mixed with apoptotic or necrotic cells constitutes a pDC activation stimulus sensitive to DNase and RNase [166]. Immune complexes from individuals with SLE do not stimulate pDCs previously treated with anti-FcγRIIa antibody. pDCs constitutively express TLR7 and TLR9 [167], which were originally identified as receptors for viral single-stranded RNAs and hypomethylated CpG motifs in bacterial DNAs, respectively. Based on these observations, a number of *in vitro* experiments have been carried out, and the results obtained suggest that the internalization of nucleic acid-containing immune complexes by pDCs, via FcγRs, delivers nucleic acid antigens to intracellular TLR7 or TLR9, triggering these receptors and resulting in cell activation and type I IFN production (reviewed in [168]. Autoreactive antibodies may be produced as a result of defects in B cell-mediated tolerance, such as defects in receptor editing in the bone marrow and spleen and other genetic factors in susceptible individuals [169, 170].

Two different models of disease development have been proposed [168, 171]. In both models, DC-derived type I IFNs are the central factors. However, in the first model, viral infections are considered to be the starting point, whereas, in the second model, the initiation phase is triggered by endogenous TLR ligands (apoptotic material) in the absence of infection. In the first model, viral infections induce pDCs to produce IFN-α, promoting cell death, the release of RNA-based autoantigens, TLR7 upregulation by B cells and the activation of pDCs, which subsequently respond more strongly to immune complexes. Autoreactive B cells can internalize RNA autoantigens through the B-cell receptor and deliver them to TLR7. This process induces B-cell activation, proliferation and differentiation. Differentiated B cells produce autoantibodies, which form immune complexes that are, in turn, internalized, via FcγRs, by pDCs and delivered to TLR7. This results in the production of more IFN-α by pDCs, perpetuating the feedback loop [168].

In the second model – the two-phase model – the initiation phase is induced by apoptotic cell material, which is taken up by a specialized subclass of lymphoid DCs, through TLRs. These DCs produce large amounts of type I IFNs, which induce the maturation of lymphoid and myeloid DCs. Mature myeloid DCs are potent APCs that activate autoreactive T helper cells that are otherwise quiescent. Primed T helper cells contribute to the activation of autoreactive B cells. Alternatively, mature DCs may activate autoreactive B cells that have interacted with the antigen via the B-cell receptor directly, by producing B lymphocyte stimulator protein (BlyS) and proliferation-inducing ligand (APRIL) [172]. Activated, autoreactive B cells proliferate and differentiate into autoantigen-producing plasma cells. Immune complexes are thus formed that, during the amplification phase, induce further type I IFN production by pDCs (with internalization via FcγRs) and enhance B-cell proliferation and autoantibody production [171].

## Concluding remarks

DCs are key regulators of immune responses. They react to infectious agents with a complex innate receptor repertoire, which, by transducing the appropriate intracellular signal, indicates the type of functional reprogramming DCs should undergo. Thus, DCs show a functional plasticity in their maturation process that depends on the nature of the perturbation and makes it possible to develop a particular, efficient immune response to each pathogen. The various functions of DCs are segregated in time and space, allowing these cells to control immune responses. As DCs play a key role in priming innate and adaptive immune responses, the establishment of a self-renewing inflammatory environment leading to DC activation may lead to the generation of autoimmune reactions and autoimmune symptoms in genetically susceptible individuals. Understanding the biology of DCs should help us make progress toward the successful manipulation of immune responses, enhancing or attenuating these responses depending on pathophysiological conditions.

*Acknowledgments.* This work was supported by grants from the CARIPLO Foundation, The European Commission 6th Framework Program (Mugen and DC-Thera projects), The Italian Association Against Cancer (AIRC), The European Commission 7th Framework Program (Tolerage and Encite projects).

1 Steinman, R. M. (1991) The dendritic cell system and its role in immunogenicity. Annu. Rev. Immunol. 9, 271–296.
2 Ibrahim, M. A., Chain, B. M. and Katz, D. R. (1995) The injured cell: the role of the dendritic cell system as a sentinel receptor pathway. Immunol. Today. 16, 181–186.
3 Banchereau, J. and Steinman, R. M. (1998) Dendritic cells and the control of immunity. Nature 392, 245–252.
4 Zitvogel, L. (2002) Dendritic and natural killer cells cooperate in the control/switch of innate immunity. J. Exp. Med. 195, F9–14.

5 Steinman, R. M. (2001) Dendritic cells and the control of immunity: enhancing the efficiency of antigen presentation. Mt Sinai J. Med. 68, 106–166.
6 Nelson, D. J., McMenamin, C., McWilliam, A. S., Brenan, M. and Holt, P. G. (1994) Development of the airway intraepithelial dendritic cell network in the rat from class II major histocompatibility (Ia)-negative precursors: differential regulation of Ia expression at different levels of the respiratory tract. J. Exp. Med. 179, 203–212.
7 Nestle, F. O., Zheng, X. G., Thompson, C. B., Turka, L. A. and Nickoloff, B. J. (1993) Characterization of dermal dendritic cells obtained from normal human skin reveals phenotypic and functionally distinctive subsets. J. Immunol. 151, 6535–6545.
8 Sertl, K., Takemura, T., Tschachler, E., Ferrans, V. J., Kaliner, M. A. and Shevach, E. M. (1986) Dendritic cells with antigen-presenting capability reside in airway epithelium, lung parenchyma, and visceral pleura. J. Exp. Med. 163, 436–451.
9 Rescigno, M., Citterio, S., Thery, C., Rittig, M., Medaglini, D., Pozzi, G., Amigorena, S. and Ricciardi-Castagnoli, P. (1998) Bacteria-induced neo-biosynthesis, stabilization, and surface expression of functional class I molecules in mouse dendritic cells. Proc. Natl. Acad. Sci. USA 95, 5229–5234.
10 Foti, M., Granucci, F., Aggujaro, D., Liboi, E., Luini, W., Minardi, S., Mantovani, A., Sozzani, S. and Ricciardi-Castagnoli, P. (1999) Upon dendritic cell (DC) activation chemokines and chemokine receptor expression are rapidly regulated for recruitment and maintenance of DC at the inflammatory site. Int. Immunol. 11, 979–986.
11 Fernandez, N. C., Lozier, A., Flament, C., Ricciardi-Castagnoli, P., Bellet, D., Suter, M., Perricaudet, M., Tursz, T., Maraskovsky, E. and Zitvogel, L. (1999) Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo. Nat. Med. 5, 405–411.
12 Granucci, F., Vizzardelli, C., Pavelka, N., Feau, S., Persico, M., Virzi, E., Rescigno, M., Moro, G. and Ricciardi-Castagnoli, P. (2001) Inducible IL-2 production by dendritic cells revealed by global gene expression analysis. Nat. Immunol. 2, 882–888.
13 Granucci, F., Vizzardelli, C., Virzi, E., Rescigno, M. and Ricciardi-Castagnoli, P. (2001) Transcriptional reprogramming of dendritic cells by differentiation stimuli. Eur. J. Immunol. 31, 2539–2546.
14 Everson, M. P., McDuffie, D. S., Lemak, D. G., Koopman, W. J., McGhee, J. R. and Beagley, K. W. (1996) Dendritic cells from different tissues induce production of different T cell cytokine profiles. J. Leukoc. Biol. 59, 494–498.
15 Shortman, K. and Naik, S. H. (2007) Steady-state and inflammatory dendritic-cell development. Nat. Rev. Immunol. 7, 19–30.
16 Naik, S. H., Sathe, P., Park, H. Y., Metcalf, D., Proietto, A. I., Dakic, A., Carotta, S., O'Keeffe, M., Bahlo, M., Papenfuss et al. (2007) Development of plasmacytoid and conventional dendritic cell subtypes from single precursor cells derived in vitro and in vivo. Nat. Immunol. 8, 1217–1226.
17 Ardavin, C. (2003) Origin, precursors and differentiation of mouse dendritic cells. Nat. Rev. Immunol. 3, 582–590.
18 Ardavin, C., Martinez del Hoyo, G., Martin, P., Anjuere, F., Arias, C. F., Marin, A. R., Ruiz, S., Parrillas, V. and Hernandez, H. (2001) Origin and differentiation of dendritic cells. Trends Immunol. 22, 691–700.
19 Shortman, K. and Liu, Y. J. (2002) Mouse and human dendritic cell subtypes. Nat. Rev. Immunol. 2, 151–161.
20 Henri, S., Siret, C., Machy, P., Kissenpfennig, A., Malissen, B. and Leserman, L. (2007) Mature DC from skin and skin-draining LN retain the ability to acquire and efficiently present targeted antigen. Eur. J. Immunol. 37, 1184–1193.
21 Henri, S., Vremec, D., Kamath, A., Waithman, J., Williams, S., Benoist, C., Burnham, K., Saeland, S., Handman, E. and Shortman, K. (2001) The dendritic cell populations of mouse lymph nodes. J. Immunol. 167, 741–748.
22 Soares, H., Waechter, H., Glaichenhaus, N., Mougneau, E., Yagita, H., Mizenina, O., Dudziak, D., Nussenzweig, M. C. and Steinman, R. M. (2007) A subset of dendritic cells induces CD4+ T cells to produce IFN-gamma by an IL-12-independent but CD70-dependent mechanism in vivo. J. Exp. Med. 204, 1095–1106.
23 De Smedt, T., Pajak, B., Klaus, G. G., Noelle, R. J., Urbain, J., Leo, O. and Moser, M. (1998) Antigen-specific T lymphocytes regulate lipopolysaccharide-induced apoptosis of dendritic cells in vivo. J. Immunol. 161, 4476–4479.
24 Asselin-Paturel, C., Boonstra, A., Dalod, M., Durand, I., Yessaad, N., Dezutter-Dambuyant, C., Vicari, A., O'Garra, A., Biron, C., Briere et al. (2001) Mouse type I IFN-producing cells are immature APCs with plasmacytoid morphology. Nat. Immunol. 2, 1144–1150.
25 Liu, Y. J. (2005) IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu. Rev. Immunol. 23, 275–306.
26 Kadowaki, N. and Liu, Y. J. (2002) Natural type I interferon-producing cells as a link between innate and adaptive immunity. Hum. Immunol. 63, 1126–1132.
27 Janeway, C. A., Jr. and Medzhitov, R. (2002) Innate immune recognition. Annu. Rev. Immunol. 20, 197–216.
28 Robinson, M. J., Sancho, D., Slack, E. C., LeibundGut-Landmann, S. and Reis e Sousa, C. (2006) Myeloid C-type lectins in innate immunity. Nat. Immunol. 7, 1258–1265.
29 Kanneganti, T. D., Lamkanfi, M. and Nunez, G. (2007) Intracellular NOD-like receptors in host defense and disease. Immunity 27, 549–559.
30 Meylan, E. and Tschopp, J. (2006) Toll-like receptors and RNA helicases: two parallel ways to trigger antiviral responses. Mol. Cell 22, 561–569.
31 Takeda, K., Kaisho, T. and Akira, S. (2003) Toll-like receptors. Annu. Rev. Immunol. 21, 335–376.
32 Saijo, S., Fujikado, N., Furuta, T., Chung, S. H., Kotaki, H., Seki, K., Sudo, K., Akira, S., Adachi, Y., Ohno, N. et al. (2007) Dectin-1 is required for host defense against Pneumocystis carinii but not against Candida albicans. Nat. Immunol. 8, 39–46.
33 Taylor, P. R., Tsoni, S. V., Willment, J. A., Dennehy, K. M., Rosas, M., Findon, H., Haynes, K., Steele, C., Botto, M., Gordon, S. et al. (2007) Dectin-1 is required for beta-glucan recognition and control of fungal infection. Nat. Immunol. 8, 31–38.
34 Herre, J., Marshall, A. S., Caron, E., Edwards, A. D., Williams, D. L., Schweighoffer, E., Tybulewicz, V., Reis e Sousa, C., Gordon, S. and Brown, G. D. (2004) Dectin-1 uses novel mechanisms for yeast phagocytosis in macrophages. Blood 104, 4038–4045.
35 Rogers, N. C., Slack, E. C., Edwards, A. D., Nolte, M. A., Schulz, O., Schweighoffer, E., Williams, D. L., Gordon, S., Tybulewicz, V. L., Brown, G. D. et al. (2005) Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity 22, 507–517.
36 Meylan, E., Tschopp, J. and Karin, M. (2006) Intracellular pattern recognition receptors in the host response. Nature 442, 39–44.
37 Chamaillard, M., Hashimoto, M., Horie, Y., Masumoto, J., Qiu, S., Saab, L., Ogura, Y., Kawasaki, A., Fukase, K., Kusumoto, S. et al. (2003) An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. Nat. Immunol. 4, 702–707.
38 Girardin, S. E., Boneca, I. G., Carneiro, L. A., Antignac, A., Jehanno, M., Viala, J., Tedin, K., Taha, M. K., Labigne, A., Zahringer, U. et al. (2003) Nod1 detects a unique muropeptide from gram-negative bacterial peptidoglycan. Science 300, 1584–1587.
39 Hasegawa, M., Yang, K., Hashimoto, M., Park, J. H., Kim, Y. G., Fujimoto, Y., Nunez, G., Fukase, K. and Inohara, N. (2006) Differential release and distribution of Nod1 and Nod2

immunostimulatory molecules among bacterial species and environments. J. Biol. Chem. 281, 29054–29063.
40 Zilbauer, M., Dorrell, N., Elmi, A., Lindley, K. J., Schuller, S., Jones, H. E., Klein, N. J., Nunez, G., Wren, B. W. and Bajaj-Elliott, M. (2007) A major role for intestinal epithelial nucleotide oligomerization domain 1 (NOD1) in eliciting host bactericidal immune responses to Campylobacter jejuni. Cell. Microbiol. 9, 2541.
41 Kim, J. G., Lee, S. J. and Kagnoff, M. F. (2004) Nod1 is an essential signal transducer in intestinal epithelial cells infected with bacteria that avoid recognition by toll-like receptors. Infect Immun. 72, 1487–1495.
42 Kobayashi, K. S., Chamaillard, M., Ogura, Y., Henegariu, O., Inohara, N., Nunez, G. and Flavell, R. A. (2005) Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science 307, 731–734.
43 Ferwerda, G., Girardin, S. E., Kullberg, B. J., Le Bourhis, L., de Jong, D. J., Langenberg, D. M., van Crevel, R., Adema, G. J., Ottenhoff, T. H., Van der Meer, J. W. et al. (2005) NOD2 and toll-like receptors are nonredundant recognition systems of Mycobacterium tuberculosis. PLoS Pathog. 1, 279–285.
44 Opitz, B., Puschel, A., Schmeck, B., Hocke, A. C., Rosseau, S., Hammerschmidt, S., Schumann, R. R., Suttorp, N. and Hippenstiel, S. (2004) Nucleotide-binding oligomerization domain proteins are innate immune receptors for internalized Streptococcus pneumoniae. J. Biol. Chem. 279, 36426–36432.
45 Ogura, Y., Inohara, N., Benito, A., Chen, F. F., Yamaoka, S. and Nunez, G. (2001) Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. J. Biol. Chem. 276, 4812–4818.
46 Abbott, D. W., Wilkins, A., Asara, J. M. and Cantley, L. C. (2004) The Crohn's disease protein, NOD2, requires RIP2 in order to induce ubiquitinylation of a novel site on NEMO. Curr. Biol. 14, 2217–2227.
47 Windheim, M., Lang, C., Peggie, M., Plater, L. A. and Cohen, P. (2007) Molecular mechanisms involved in the regulation of cytokine production by muramyl dipeptide. Biochem. J. 404, 179–190.
48 Girardin, S. E., Tournebize, R., Mavris, M., Page, A. L., Li, X., Stark, G. R., Bertin, J., DiStefano, P. S., Yaniv, M., Sansonetti, P. J. et al. (2001) CARD4/Nod1 mediates NF-kappaB and JNK activation by invasive Shigella flexneri. EMBO Rep. 2, 736–742.
49 Park, J. H., Kim, Y. G., McDonald, C., Kanneganti, T. D., Hasegawa, M., Body-Malapel, M., Inohara, N. and Nunez, G. (2007) RICK/RIP2 mediates innate immune responses induced through Nod1 and Nod2 but not TLRs. J. Immunol. 178, 2380–2386.
50 Kato, H., Sato, S., Yoneyama, M., Yamamoto, M., Uematsu, S., Matsui, K., Tsujimura, T., Takeda, K., Fujita, T., Takeuchi, O. and Akira, S. (2005) Cell type-specific involvement of RIG-I in antiviral response. Immunity 23, 19–28.
51 Meylan, E., Curran, J., Hofmann, K., Moradpour, D., Binder, M., Bartenschlager, R. and Tschopp, J. (2005) Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature 437, 1167–1172.
52 Kawai, T. and Akira, S. (2007) TLR signaling. Semin. Immunol. 19, 24–32.
53 Miyake, K. (2007) Innate immune sensing of pathogens and danger signals by cell surface Toll-like receptors. Semin. Immunol. 19, 3–10.
54 Vogl, T., Tenbrock, K., Ludwig, S., Leukert, N., Ehrhardt, C., van Zoelen, M. A., Nacken, W., Foell, D., van der Poll, T., Sorg, C. et al. (2007) Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. Nat. Med. 13, 1042–1049.
55 Kaisho, T. and Akira, S. (2006) Toll-like receptor function and signaling. J. Allergy Clin. Immunol. 117, 979–987; quiz 988.
56 Takeda, K. and Akira, S. (2004) TLR signaling pathways. Semin. Immunol. 16, 3–9.
57 Haziot, A., Ferrero, E., Kontgen, F., Hijiya, N., Yamamoto, S., Silver, J., Stewart, C. L. and Goyert, S. M. (1996) Resistance to endotoxin shock and reduced dissemination of gram-negative bacteria in CD14-deficient mice. Immunity 4, 407–414.
58 Lee, H. K., Dunzendorfer, S., Soldau, K. and Tobias, P. S. (2006) Double-stranded RNA-mediated TLR3 activation is enhanced by CD14. Immunity 24, 153–163.
59 Ulevitch, R. J. and Tobias, P. S. (1995) Receptor-dependent mechanisms of cell stimulation by bacterial endotoxin. Annu. Rev. Immunol. 13, 437–457.
60 Jersmann, H. P. (2005) Time to abandon dogma: CD14 is expressed by non-myeloid lineage cells. Immunol. Cell Biol. 83, 462–467.
61 Jiang, Z., Georgel, P., Du, X., Shamel, L., Sovath, S., Mudd, S., Huber, M., Kalis, C., Keck, S., Galanos, C. et al. (2005) CD14 is required for MyD88-independent LPS signaling. Nat. Immunol. 6, 565–570.
62 Moore, K. J., Andersson, L. P., Ingalls, R. R., Monks, B. G., Li, R., Arnaout, M. A., Golenbock, D. T. and Freeman, M. W. (2000) Divergent response to LPS and bacteria in CD14-deficient murine macrophages. J. Immunol. 165, 4272–4280.
63 Beutler, B., Jiang, Z., Georgel, P., Crozat, K., Croker, B., Rutschmann, S., Du, X. and Hoebe, K. (2006) Genetic analysis of host resistance: Toll-like receptor signaling and immunity at large. Annu. Rev. Immunol. 24, 353–389.
64 Harizi, H. and Gualde, N. (2005) The impact of eicosanoids on the crosstalk between innate and adaptive immunity: the key roles of dendritic cells. Tissue Antigens 65, 507–514.
65 Randolph, G. J., Sanchez-Schmitz, G. and Angeli, V. (2005) Factors and signals that govern the migration of dendritic cells via lymphatics: recent advances. Springer Semin. Immunopathol. 26, 273–287.
66 Nagamachi, M., Sakata, D., Kabashima, K., Furuyashiki, T., Murata, T., Segi-Nishida, E., Soontrapa, K., Matsuoka, T., Miyachi, Y. and Narumiya, S. (2008) Facilitation of Th1-mediated immune response by prostaglandin E receptor EP1. J. Exp. Med. Epub 29 Oct 2007.
67 Betz, M. and Fox, B. S. (1991) Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. J. Immunol. 146, 108–113.
68 Sugimoto, Y. and Narumiya, S. (2007) Prostaglandin E receptors. J. Biol. Chem. 282, 11613–11617.
69 Andrews, D. M., Scalzo, A. A., Yokoyama, W. M., Smyth, M. J. and Degli-Esposti, M. A. (2003) Functional interactions between dendritic cells and NK cells during viral infection. Nat. Immunol. 4, 175–181.
70 Ferlazzo, G., Tsang, M. L., Moretta, L., Melioli, G., Steinman, R. M. and Munz, C. (2002) Human dendritic cells activate resting natural killer (NK) cells and are recognized via the NKp30 receptor by activated NK cells. J. Exp. Med. 195, 343–351.
71 Gerosa, F., Baldani-Guerra, B., Nisii, C., Marchesini, V., Carra, G. and Trinchieri, G. (2002) Reciprocal activating interaction between natural killer cells and dendritic cells. J. Exp. Med. 195, 327–333.
72 Granucci, F., Zanoni, I., Pavelka, N., Van Dommelen, S. L., Andoniou, C. E., Belardelli, F., Degli Esposti, M. A. and Ricciardi-Castagnoli, P. (2004) A contribution of mouse dendritic cell-derived IL-2 for NK cell activation. J. Exp. Med. 200, 287–295.
73 Moretta, A. (2002) Natural killer cells and dendritic cells: rendezvous in abused tissues. Nat. Rev. Immunol. 2, 957–964.
74 Zanoni, I., Foti, M., Ricciardi-Castagnoli, P. and Granucci, F. (2005) TLR-dependent activation stimuli associated with Th1 responses confer NK cell stimulatory capacity to mouse dendritic cells. J. Immunol. 175, 286–292.
75 Kassim, S. H., Rajasagi, N. K., Zhao, X., Chervenak, R. and Jennings, S. R. (2006) In vivo ablation of CD11c-positive dendritic cells increases susceptibility to herpes simplex virus type 1 infection and diminishes NK and T-cell responses. J. Virol. 80, 3985–3993.

76 Lucas, M., Schachterle, W., Oberle, K., Aichele, P. and Diefenbach, A. (2007) Dendritic cells prime natural killer cells by trans-presenting interleukin 15. Immunity 26, 503–517.

77 Gerosa, F., Gobbi, A., Zorzi, P., Burg, S., Briere, F., Carra, G. and Trinchieri, G. (2005) The reciprocal interaction of NK cells with plasmacytoid or myeloid dendritic cells profoundly affects innate resistance functions. J. Immunol. 174, 727–734.

78 Dalod, M., Hamilton, T., Salomon, R., Salazar-Mather, T. P., Henry, S. C., Hamilton, J. D. and Biron, C. A. (2003) Dendritic cell responses to early murine cytomegalovirus infection: subset functional specialization and differential regulation by interferon alpha/beta. J. Exp. Med. 197, 885–898.

79 Nguyen, K. B., Salazar-Mather, T. P., Dalod, M. Y., Van Deusen, J. B., Wei, X. Q., Liew, F. Y., Caligiuri, M. A., Durbin, J. E. and Biron, C. A. (2002) Coordinated and distinct roles for IFN-alpha beta, IL-12, and IL-15 regulation of NK cell responses to viral infection. J. Immunol. 169, 4279–4287.

80 Moretta, L., Ferlazzo, G., Bottino, C., Vitale, M., Pende, D., Mingari, M. C. and Moretta, A. (2006) Effector and regulatory events during natural killer-dendritic cell interactions. Immunol Rev. 214, 219–228.

81 Amakata, Y., Fujiyama, Y., Andoh, A., Hodohara, K. and Bamba, T. (2001) Mechanism of NK cell activation induced by coculture with dendritic cells derived from peripheral blood monocytes. Clin. Exp. Immunol. 124, 214–222.

82 Ferlazzo, G., Morandi, B., D'Agostino, A., Meazza, R., Melioli, G., Moretta, A. and Moretta, L. (2003) The interaction between NK cells and dendritic cells in bacterial infections results in rapid induction of NK cell activation and in the lysis of uninfected dendritic cells. Eur. J. Immunol. 33, 306–313.

83 Ferlazzo, G., Pack, M., Thomas, D., Paludan, C., Schmid, D., Strowig, T., Bougras, G., Muller, W. A., Moretta, L. and Munz, C. (2004) Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. Proc. Natl. Acad. Sci. USA 101, 16606–16611.

84 Kikuchi, T., Hahn, C. L., Tanaka, S., Barbour, S. E., Schenkein, H. A. and Tew, J. G. (2004) Dendritic cells stimulated with Actinobacillus actinomycetemcomitans elicit rapid gamma interferon responses by natural killer cells. Infect. Immun. 72, 5089–5096.

85 Alli, R. S. and Khar, A. (2004) Interleukin-12 secreted by mature dendritic cells mediates activation of NK cell function. FEBS Lett. 559, 71–76.

86 Borg, C., Jalil, A., Laderach, D., Maruyama, K., Wakasugi, H., Charrier, S., Ryffel, B., Cambi, A., Figdor, C., Vainchenker, W. et al. (2004) NK cell activation by dendritic cells (DCs) requires the formation of a synapse leading to IL-12 polarization in DCs. Blood 104, 3267–3275.

87 Kamath, A. T., Sheasby, C. E. and Tough, D. F. (2005) Dendritic cells and NK cells stimulate bystander T cell activation in response to TLR agonists through secretion of IFN-alpha beta and IFN-gamma. J. Immunol. 174, 767–776.

88 Koka, R., Burkett, P., Chien, M., Chai, S., Boone, D. L. and Ma, A. (2004) Cutting edge: murine dendritic cells require IL-15R alpha to prime NK cells. J. Immunol. 173, 3594–3598.

89 Mailliard, R. B., Alber, S. M., Shen, H., Watkins, S. C., Kirkwood, J. M., Herberman, R. B. and Kalinski, P. (2005) IL-18-induced CD83+CCR7+ NK helper cells. J. Exp. Med. 202, 941–953.

90 Munz, C., Dao, T., Ferlazzo, G., de Cos, M. A., Goodman, K. and Young, J. W. (2005) Mature myeloid dendritic cell subsets have distinct roles for activation and viability of circulating human natural killer cells. Blood 105, 266–273.

91 Osada, T., Nagawa, H., Kitayama, J., Tsuno, N. H., Ishihara, S., Takamizawa, M. and Shibata, Y. (2001) Peripheral blood dendritic cells, but not monocyte-derived dendritic cells, can augment human NK cell function. Cell. Immunol. 213, 14–23.

92 Vitale, M., Della Chiesa, M., Carlomagno, S., Romagnani, C., Thiel, A., Moretta, L. and Moretta, A. (2004) The small subset of CD56brightCD16- natural killer cells is selectively responsible for both cell proliferation and interferon-gamma production upon interaction with dendritic cells. Eur. J. Immunol. 34, 1715–1722.

93 Yu, Y., Hagihara, M., Ando, K., Gansuvd, B., Matsuzawa, H., Tsuchiya, T., Ueda, Y., Inoue, H., Hotta, T. and Kato, S. (2001) Enhancement of human cord blood CD34+ cell-derived NK cell cytotoxicity by dendritic cells. J. Immunol. 166, 1590–1600.

94 Newman, K. C., Korbel, D. S., Hafalla, J. C. and Riley, E. M. (2006) Cross-talk with myeloid accessory cells regulates human natural killer cell Iiterferon-gamma responses to malaria. PLoS Pathog. 2, e118.

95 Xu, J., Chakrabarti, A. K., Tan, J. L., Ge, L., Gambotto, A. and Vujanovic, N. L. (2006) Essential role of the TNF-TNFR2 cognate interaction in mouse dendritic cell-natural killer cell cross-talk. Blood 109, 3333–3345.

96 Biron, C. A., Nguyen, K. B., Pien, G. C., Cousens, L. P. and Salazar-Mather, T. P. (1999) Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu. Rev. Immunol. 17, 189–220.

97 Schartz, N. E., Chaput, N., Taieb, J., Bonnaventure, P., Trebeden-Negre, H., Terme, M., Menard, C., Lebbe, C., Schimpl, A., Ardouin, P. et al. (2005) IL-2 production by dendritic cells is not critical for the activation of cognate and innate effectors in draining lymph nodes. Eur. J. Immunol. 35, 2840–2850.

98 Granucci, F., Zanoni, I. and Ricciardi-Castagnoli, P. (2006) Natural killer (NK) cell functions can be strongly boosted by activated dendritic cells (DC). Eur. J. Immunol. 36, 2819–2820.

99 Hochrein, H., O'Keeffe, M., Luft, T., Vandenabeele, S., Grumont, R. J., Maraskovsky, E. and Shortman, K. (2000) Interleukin (IL)-4 is a major regulatory cytokine governing bioactive IL-12 production by mouse and human dendritic cells. J. Exp. Med. 192, 823–833.

100 Terme, M., Tomasello, E., Maruyama, K., Crepineau, F., Chaput, N., Flament, C., Marolleau, J. P., Angevin, E., Wagner, E. F., Salomon, B. et al. (2004) IL-4 confers NK stimulatory capacity to murine dendritic cells: a signaling pathway involving KARAP/DAP12-triggering receptor expressed on myeloid cell 2 molecules. J. Immunol. 172, 5957–5966.

101 Guiducci, C., Valzasina, B., Dislich, H. and Colombo, M. P. (2005) CD40/CD40L interaction regulates CD4(+)CD25(+) T reg homeostasis through dendritic cell-produced IL-2. Eur. J. Immunol. 35, 557–567.

102 Zitvogel, L., Fernandez, N., Lozier, A., Wolfers, J., Regnault, A., Raposo, G. and Amigorena, S. (1999) Dendritic cells or their exosomes are effective biotherapies of cancer. Eur. J. Cancer. 35 Suppl. 3, S36–38.

103 Van Den Broeke, L. T., Daschbach, E., Thomas, E. K., Andringa, G. and Berzofsky, J. A. (2003) Dendritic cell-induced activation of adaptive and innate antitumor immunity. J. Immunol. 171, 5842–5852.

104 Sallusto, F. and Lanzavecchia, A. (1994) Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. J. Exp. Med. 179, 1109–1118.

105 Winzler, C., Rovere, P., Rescigno, M., Granucci, F., Penna, G., Adorini, L., Zimmermann, V. S., Davoust, J. and Ricciardi-Castagnoli, P. (1997) Maturation stages of mouse dendritic cells in growth factor-dependent long-term cultures. J. Exp. Med. 185, 317–328.

106 Inaba, K., Inaba, M., Naito, M. and Steinman, R. M. (1993) Dendritic cell progenitors phagocytose particulates, including bacillus Calmette-Guerin organisms, and sensitize mice to mycobacterial antigens in vivo. J. Exp. Med. 178, 479–488.

107 Reis e Sousa, C., Stahl, P. D. and Austyn, J. M. (1993) Phagocytosis of antigens by Langerhans cells in vitro. J. Exp. Med. 178, 509–519.

108 Parr, M. B., Kepple, L. and Parr, E. L. (1991) Langerhans cells phagocytose vaginal epithelial cells undergoing apoptosis during the murine estrous cycle. Biol. Reprod. 45, 252–260.
109 Rescigno, M., Granucci, F. and Ricciardi-Castagnoli, P. (2000) Molecular events of bacterial-induced maturation of dendritic cells. J. Clin. Immunol. 20, 161–166.
110 Hopkins, S. A., Niedergang, F., Corthesy-Theulaz, I. E. and Kraehenbuhl, J. P. (2000) A recombinant Salmonella typhimurium vaccine strain is taken up and survives within murine Peyer's patch dendritic cells. Cell. Microbiol. 2, 59–68.
111 Pron, B., Boumaila, C., Jaubert, F., Berche, P., Milon, G., Geissmann, F. and Gaillard, J. L. (2001) Dendritic cells are early cellular targets of Listeria monocytogenes after intestinal delivery and are involved in bacterial spread in the host. Cell. Microbiol. 3, 331–340.
112 Yrlid, U., Svensson, M., Hakansson, A., Chambers, B. J., Ljunggren, H. G. and Wick, M. J. (2001) In vivo activation of dendritic cells and T cells during Salmonella enterica serovar Typhimurium infection. Infect. Immun. 69, 5726–5735.
113 Jiao, X., Lo-Man, R., Guermonprez, P., Fiette, L., Deriaud, E., Burgaud, S., Gicquel, B., Winter, N. and Leclerc, C. (2002) Dendritic cells are host cells for mycobacteria in vivo that trigger innate and acquired immunity. J. Immunol. 168, 1294–1301.
114 Lennon-Dumenil, A. M., Bakker, A. H., Maehr, R., Fiebiger, E., Overkleeft, H. S., Rosemblatt, M., Ploegh, H. L. and Lagaudriere-Gesbert, C. (2002) Analysis of protease activity in live antigen-presenting cells shows regulation of the phagosomal proteolytic contents during dendritic cell activation. J. Exp. Med. 196, 529–540.
115 Delamarre, L., Pack, M., Chang, H., Mellman, I. and Trombetta, E. S. (2005) Differential lysosomal proteolysis in antigen-presenting cells determines antigen fate. Science 307, 1630–1634.
116 El-Sukkari, D., Wilson, N. S., Hakansson, K., Steptoe, R. J., Grubb, A., Shortman, K. and Villadangos, J. A. (2003) The protease inhibitor cystatin C is differentially expressed among dendritic cell populations, but does not control antigen presentation. J. Immunol. 171, 5003–5011.
117 Savina, A. and Amigorena, S. (2007) Phagocytosis and antigen presentation in dendritic cells. Immunol. Rev. 219, 143–156.
118 Cella, M., Engering, A., Pinet, V., Pieters, J. and Lanzavecchia, A. (1997) Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature 388, 782–787.
119 Pierre, P., Turley, S. J., Meltzer, J., Mirza, A., Steinman, R. and Mellman, I. (1997) Localization and intracellular transport of MHC class II molecules in bone marrow-derived dendritic cells. Adv. Exp. Med. Biol. 417, 179–182.
120 Kleijmeer, M., Ramm, G., Schuurhuis, D., Griffith, J., Rescigno, M., Ricciardi-Castagnoli, P., Rudensky, A. Y., Ossendorp, F., Melief, C. J., Stoorvogel, W. et al. (2001) Reorganization of multivesicular bodies regulates MHC class II antigen presentation by dendritic cells. J. Cell Biol. 155, 53–63.
121 Lutz, M. B., Rovere, P., Kleijmeer, M. J., Rescigno, M., Assmann, C. U., Oorschot, V. M., Geuze, H. J., Trucy, J., Demandolx, D., Davoust, J. et al. (1997) Intracellular routes and selective retention of antigens in mildly acidic cathepsin D/lysosome-associated membrane protein-1/MHC class II-positive vesicles in immature dendritic cells. J. Immunol. 159, 3707–3716.
122 Rock, K. L., Gamble, S. and Rothstein, L. (1990) Presentation of exogenous antigen with class I major histocompatibility complex molecules. Science 249, 918–921.
123 Guermonprez, P., Saveanu, L., Kleijmeer, M., Davoust, J., Van Endert, P. and Amigorena, S. (2003) ER-phagosome fusion defines an MHC class I cross-presentation compartment in dendritic cells. Nature 425, 397–402.
124 Ackerman, A. L., Giodini, A. and Cresswell, P. (2006) A role for the endoplasmic reticulum protein retrotranslocation machinery during crosspresentation by dendritic cells. Immunity 25, 607–617.
125 Jung, S., Unutmaz, D., Wong, P., Sano, G., De los Santos, K., Sparwasser, T., Wu, S., Vuthoori, S., Ko, K., Zavala, F. et al. (2002) In vivo depletion of CD11c(+) dendritic cells abrogates priming of CD8(+) T cells by exogenous cell-associated antigens. Immunity 17, 211–220.
126 Probst, H. C. and van den Broek, M. (2005) Priming of CTLs by lymphocytic choriomeningitis virus depends on dendritic cells. J. Immunol. 174, 3920–3924.
127 Sapoznikov, A., Fischer, J. A., Zaft, T., Krauthgamer, R., Dzionek, A. and Jung, S. (2007) Organ-dependent in vivo priming of naive CD4+, but not CD8+, T cells by plasmacytoid dendritic cells. J. Exp. Med. 204, 1923–1933.
128 Green, S. and Rothman, A. (2006) Immunopathological mechanisms in dengue and dengue hemorrhagic fever. Curr. Opin. Infect. Dis. 19, 429–436.
129 Huang, X., Venet, F., Chung, C. S., Lomas-Neira, J. and Ayala, A. (2007) Changes in dendritic cell function in the immune response to sepsis. Cell- & tissue-based therapy. Expert Opin. Biol. Ther. 7, 929–938.
130 Cavanagh, L. L. and Von Andrian, U. H. (2002) Travellers in many guises: the origins and destinations of dendritic cells. Immunol. Cell Biol. 80, 448–462.
131 Mempel, T. R., Henrickson, S. E. and Von Andrian, U. H. (2004) T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. Nature 427, 154–159.
132 Kissenpfennig, A., Henri, S., Dubois, B., Laplace-Builhe, C., Perrin, P., Romani, N., Tripp, C. H., Douillard, P., Leserman, L., Kaiserlian, D. et al. (2005) Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells. Immunity 22, 643–654.
133 Allan, R. S., Waithman, J., Bedoui, S., Jones, C. M., Villadangos, J. A., Zhan, Y., Lew, A. M., Shortman, K., Heath, W. R. and Carbone, F. R. (2006) Migratory dendritic cells transfer antigen to a lymph node-resident dendritic cell population for efficient CTL priming. Immunity 25, 153–162.
134 Nishibu, A., Ward, B. R., Jester, J. V., Ploegh, H. L., Boes, M. and Takashima, A. (2006) Behavioral responses of epidermal Langerhans cells in situ to local pathological stimuli. J. Invest. Dermatol. 126, 787–796.
135 Kamath, A. T., Henri, S., Battye, F., Tough, D. F. and Shortman, K. (2002) Developmental kinetics and lifespan of dendritic cells in mouse lymphoid organs. Blood 100, 1734–1741.
136 Merad, M., Manz, M. G., Karsunky, H., Wagers, A., Peters, W., Charo, I., Weissman, I. L., Cyster, J. G. and Engleman, E. G. (2002) Langerhans cells renew in the skin throughout life under steady-state conditions. Nat. Immunol. 3, 1135–1141.
137 Dudziak, D., Kamphorst, A. O., Heidkamp, G. F., Buchholz, V. R., Trumpfheller, C., Yamazaki, S., Cheong, C., Liu, K., Lee, H. W., Park, C. G. et al. (2007) Differential antigen processing by dendritic cell subsets in vivo. Science 315, 107–111.
138 Maldonado-Lopez, R., De Smedt, T., Michel, P., Godfroid, J., Pajak, B., Heirman, C., Thielemans, K., Leo, O., Urbain, J. and Moser, M. (1999) CD8alpha+ and CD8alpha- subclasses of dendritic cells direct the development of distinct T helper cells in vivo. J. Exp. Med. 189, 587–592.
139 Pulendran, B., Smith, J. L., Caspary, G., Brasel, K., Pettit, D., Maraskovsky, E. and Maliszewski, C. R. (1999) Distinct dendritic cell subsets differentially regulate the class of immune response in vivo. Proc. Natl. Acad. Sci. USA 96, 1036–1041.
140 Trinchieri, G. and Scott, P. (1995) Interleukin-12: a proinflammatory cytokine with immunoregulatory functions. Res. Immunol. 146, 423–431.
141 Hochrein, H., Shortman, K., Vremec, D., Scott, B., Hertzog, P. and O'Keeffe, M. (2001) Differential production of IL-12,

IFN-alpha, and IFN-gamma by mouse dendritic cell subsets. J. Immunol. 166, 5448–5455.
142 Fieschi, C. and Casanova, J. L. (2003) The role of interleukin-12 in human infectious diseases: only a faint signature. Eur. J. Immunol. 33, 1461–1464.
143 Tarbell, K. V., Yamazaki, S. and Steinman, R. M. (2006) The interactions of dendritic cells with antigen-specific, regulatory T cells that suppress autoimmunity. Semin. Immunol. 18, 93–102.
144 Luo, X., Tarbell, K. V., Yang, H., Pothoven, K., Bailey, S. L., Ding, R., Steinman, R. M. and Suthanthiran, M. (2007) Dendritic cells with TGF-beta1 differentiate naive CD4+CD25- T cells into islet-protective Foxp3+ regulatory T cells. Proc. Natl. Acad. Sci. USA 104, 2821–2826.
145 Yang, H., Ding, R., Sharma, V. K., Hilaire, F. S., Lagman, M., Li, B., Thomas, D. A., Luo, X., Song, P., Stauffer, C. et al. (2007) Hyperexpression of Foxp3 and IDO during acute rejection of islet allografts. Transplantation 83, 1643–1647.
146 Diebold, S. S., Montoya, M., Unger, H., Alexopoulou, L., Roy, P., Haswell, L. E., Al-Shamkhani, A., Flavell, R., Borrow, P. and Reis e Sousa, C. (2003) Viral infection switches non-plasmacytoid dendritic cells into high interferon producers. Nature 424, 324–328.
147 Trottein, F., Pavelka, N., Vizzardelli, C., Angeli, V., Zouain, C. S., Pelizzola, M., Capozzoli, M., Urbano, M., Capron, M., Belardelli, F. et al. (2004) A type I IFN-dependent pathway induced by Schistosoma mansoni eggs in mouse myeloid dendritic cells generates an inflammatory signature. J. Immunol. 172, 3011–3017.
148 Gallucci, S., Lolkema, M. and Matzinger, P. (1999) Natural adjuvants: endogenous activators of dendritic cells. Nat. Med. 5, 1249–1255.
149 Yang, K., Puel, A., Zhang, S., Eidenschenk, C., Ku, C. L., Casrouge, A., Picard, C., von Bernuth, H., Senechal, B., Plancoulaine, S. et al. (2005) Human TLR-7-, -8-, and -9-mediated induction of IFN-alpha/beta and -lambda Is IRAK-4 dependent and redundant for protective immunity to viruses. Immunity 23, 465–478.
150 Kawai, T. and Akira, S. (2006) Innate immune recognition of viral infection. Nat. Immunol. 7, 131–137.
151 Stetson, D. B. and Medzhitov, R. (2006) Type I interferons in host defense. Immunity 25, 373–381.
152 Eriksson, U., Ricci, R., Hunziker, L., Kurrer, M. O., Oudit, G. Y., Watts, T. H., Sonderegger, I., Bachmaier, K., Kopf, M. and Penninger, J. M. (2003) Dendritic cell-induced autoimmune heart failure requires cooperation between adaptive and innate immunity. Nat. Med. 9, 1484–1490.
153 Waldner, H., Collins, M. and Kuchroo, V. K. (2004) Activation of antigen-presenting cells by microbial products breaks self tolerance and induces autoimmune disease. J. Clin. Invest. 113, 990–997.
154 Lang, K. S., Georgiev, P., Recher, M., Navarini, A. A., Bergthaler, A., Heikenwalder, M., Harris, N. L., Junt, T., Odermatt, B., Clavien, P. A. et al. (2006) Immunoprivileged status of the liver is controlled by Toll-like receptor 3 signaling. J. Clin. Invest. 116, 2456–2463.
155 Loos, T., Dekeyzer, L., Struyf, S., Schutyser, E., Gijsbers, K., Gouwy, M., Fraeyman, A., Put, W., Ronsse, I., Grillet, B., Opdenakker, G. et al. (2006) TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis. Lab. Invest. 86, 902–916.
156 Lang, K. S., Recher, M., Junt, T., Navarini, A. A., Harris, N. L., Freigang, S., Odermatt, B., Conrad, C., Ittner, L. M., Bauer, S., Luther, S. A., Uematsu, S., Akira, S., Hengartner, H. and Zinkernagel, R. M. (2005) Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. Nat. Med. 11, 138–145.
157 Bach, J. F. (2005) A Toll-like trigger for autoimmune disease. Nat. Med. 11, 120–121.
158 Baechler, E. C., Gregersen, P. K. and Behrens, T. W. (2004) The emerging role of interferon in human systemic lupus erythematosus. Curr. Opin. Immunol. 16, 801–807.
159 Ronnblom, L. E., Alm, G. V. and Oberg, K. E. (1990) Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. J. Intern. Med. 227, 207–210.
160 Gota, C. and Calabrese, L. (2003) Induction of clinical autoimmune disease by therapeutic interferon-alpha. Autoimmunity 36, 511–518.
161 Baechler, E. C., Batliwalla, F. M., Karypis, G., Gaffney, P. M., Ortmann, W. A., Espe, K. J., Shark, K. B., Grande, W. J., Hughes, K. M., Kapur, V. et al (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc. Natl. Acad. Sci. USA 100, 2610–2615.
162 Zhuang, H., Kosboth, M., Lee, P., Rice, A., Driscoll, D. J., Zori, R., Narain, S., Lyons, R., Satoh, M., Sobel, E. et al. (2006) Lupus-like disease and high interferon levels corresponding to trisomy of the type I interferon cluster on chromosome 9p. Arthritis Rheum. 54, 1573–1579.
163 Sigurdsson, S., Nordmark, G., Goring, H. H., Lindroos, K., Wiman, A. C., Sturfelt, G., Jonsen, A., Rantapaa-Dahlqvist, S., Moller, B., Kere, J. et al. (2005) Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. Am. J. Hum. Genet. 76, 528–537.
164 Graham, R. R., Kozyrev, S. V., Baechler, E. C., Reddy, M. V., Plenge, R. M., Bauer, J. W., Ortmann, W. A., Koeuth, T., Gonzalez Escribano, M. F., Pons-Estel, B. et al. (2006) A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nat. Genet. 38, 550–555.
165 Santiago-Raber, M. L., Baccala, R., Haraldsson, K. M., Choubey, D., Stewart, T. A., Kono, D. H. and Theofilopoulos, A. N. (2003) Type-I interferon receptor deficiency reduces lupus-like disease in NZB mice. J. Exp. Med. 197, 777–788.
166 Ronnblom, L., Eloranta, M. L. and Alm, G. V. (2006) The type I interferon system in systemic lupus erythematosus. Arthritis Rheum. 54, 408–420.
167 Kadowaki, N., Ho, S., Antonenko, S., Malefyt, R. W., Kastelein, R. A., Bazan, F. and Liu, Y. J. (2001) Subsets of human dendritic cell precursors express different toll-like receptors and respond to different microbial antigens. J. Exp. Med. 194, 863–869.
168 Marshak-Rothstein, A. (2006) Toll-like receptors in systemic autoimmune disease. Nat. Rev. Immunol. 6, 823–835.
169 Lamoureux, J. L., Watson, L. C., Cherrier, M., Skog, P., Nemazee, D. and Feeney, A. J. (2007) Reduced receptor editing in lupus-prone MRL/lpr mice. J. Exp. Med. 2004, 2853–2864.
170 Yurasov, S., Wardemann, H., Hammersen, J., Tsuiji, M., Meffre, E., Pascual, V. and Nussenzweig, M. C. (2005) Defective B cell tolerance checkpoints in systemic lupus erythematosus. J. Exp. Med. 201, 703–711.
171 Baccala, R., Hoebe, K., Kono, D. H., Beutler, B. and Theofilopoulos, A. N. (2007) TLR-dependent and TLR-independent pathways of type I interferon induction in systemic autoimmunity. Nat. Med. 13, 543–551.
172 Litinskiy, M. B., Nardelli, B., Hilbert, D. M., He, B., Schaffer, A., Casali, P. and Cerutti, A. (2002) DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat. Immunol. 3, 822–829.