

# Interplay of pathogens, cytokines and other stress signals in the regulation of dendritic cell function

Juan Sabatté, Julian Maggini, Karen Nahmod, María M. Amaral, Diego Martínez, Gabriela Salamone, Ana Ceballos, Mirta Giordano, Mónica Vermeulen, Jorge Geffner\*

*Institute of Haematological Research, National Academy of Medicine and National Reference Centre for AIDS,  
Department of Microbiology, Buenos Aires University School of Medicine, Buenos Aires, Argentina*

Available online 26 February 2007

## Abstract

Dendritic cells (DCs) are the only antigen-presenting cell capable of activating naïve T lymphocytes, and hence they play a crucial role in the induction of adaptive immunity. Immature DCs sample and process antigens, and efficiently sense a large variety of signals from the surrounding environment. Upon activation, they become capable to activate naïve T cells and to direct the differentiation and polarization of effector T lymphocytes. It is becoming increasingly clear that different signals are able to determine distinct programs of DC differentiation and different forms of immunity and tolerance. In the past few years many advances have been made in addressing the action exerted by pathogen-associated molecular patterns (PAMPs), cytokines, chemokines, and other less characterized stress molecules on the activity of DCs. In this review we focus on the multiplicity of innate signals able to modulate the functional profile of DCs.

© 2007 Elsevier Ltd. All rights reserved.

**Keywords:** Dendritic cell; Toll-like receptors; Maturation; Inflammation; Tolerance

## 1. Introduction

Dendritic cells (DCs) are highly specialized antigen-presenting cells with a unique ability to activate resting T lymphocytes owing to their efficiency to acquire and process antigens and their potential to express high levels of co-stimulatory molecules [1–4]. Although well recognized for their ability to activate T cells, accumulating evidence shows that they also play an important role in the induction and maintenance of self-tolerance, a response directed to purge the peripheral T-cell repertoire of autoreactive T cells [5–7].

DCs do not constitute a unique cell population, but rather they comprise a large collection of subpopulations, located in both lymphoid and non-lymphoid tissues, that can be distinguished by the expression of specific cell surface markers and functional properties, perhaps reflecting a

selective specialization in their response to infection [4,8–10]. Two main DC subsets have been identified: conventional (“myeloid”) DCs and plasmacytoid DCs (pDCs). pDCs play a crucial role in antiviral immunity. They selectively express toll-like receptors (TLRs) 7 and 9, which enable them to sense single stranded RNA and DNA viruses, respectively, producing vast amounts of type I interferons (IFNs) [11–13]. In the present review we focus on conventional non-plasmacytoid DCs (hereafter called simply DCs).

DCs arise from progenitors present in the bone marrow through yet non-fully characterized intermediates [8–10,14]. It is generally assumed that DC-precursors in the blood home to peripheral non-lymphoid tissues, particularly to sites of interface with the environment (skin and mucosa), where they reside as immature DCs. Immature DCs have a high capacity to sense, sample, and process incoming antigens, but a poor ability to stimulate naïve T cells. Upon maturation they become capable to trigger adaptive immunity by inducing the activation of naïve T cells and directing the differentiation of newly activated T lymphocytes into effector T cells [3,4].

\* Corresponding author at: Department of Immunology, IIHEMA, National Academy of Medicine, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina. Tel.: +54 11 48055695; fax: +54 11 48039475.

*E-mail address:* [geffnerj@fibertel.com.ar](mailto:geffnerj@fibertel.com.ar) (J. Geffner).

## 2. Sampling the surrounding environment by immature DCs

### 2.1. DCs capture antigens by macropinocytosis, receptor-mediated endocytosis and phagocytosis

Immature DCs have an extraordinary ability to sample the surrounding environment by macropinocytosis, receptor-mediated endocytosis and phagocytosis. They constitutively macropinocytose extracellular fluid, and also express a large variety of receptors mediating endocytosis and phagocytosis of antigens and pathogens [1,15–17]. Macropinocytosis refers to the formation of large (1–3  $\mu\text{m}$ ) primary endocytic vesicles by the closure of lamellipodia generated at ruffling membrane domains. Macropinosomes are heterogeneous in size but always much larger than the clathrin-coated vesicles [17–19]. Macropinocytosis is transiently induced in macrophages and epithelial cells after stimulation by cytokines, growth factors or phorbol esters [20,21]. By contrast, it is constitutive in immature DCs enabling them to take up a very large volume of extracellular fluid (40% of the cell volume every hour) in order to sample efficiently the antigens in the surrounding medium [1,16,17]. Macropinocytosis appears to play an important role, not only in the presentation of peptides from exogenous antigens by MHC class II molecules, but also in the cross-presentation of exogenous soluble antigens by MHC class I molecules [22,23]. Exposure of immature DCs to inflammatory cytokines such as TNF- $\alpha$  or microbial products such as LPS leads to an initial and transient stimulation of macropinocytosis favouring antigen capture for presentation on class I and class II MHC molecules [4,24]. This transient stimulation is followed by a dramatic inhibition of macropinocytosis concomitant with the up-regulation of maturation markers such as CD80, CD86 and MHC class II molecules [1–4,24].

Receptor-mediated endocytosis also plays an important role in the sampling of antigens by immature DCs. Soluble antigens recognized by DC receptors are usually internalized after clustering of receptors in clathrin-coated pits [25]. DCs express a large variety of endocytic receptors such as the receptors for the Fc portion of Ig (FcR): Fc $\gamma$ RI (CD64), Fc $\gamma$ RII (CD32), Fc $\gamma$ RIII (CD16) [26–28], Fc $\epsilon$ RI [29,30], Fc $\epsilon$ RII (CD23) [31], and Fc $\alpha$ RI (CD89) [32]. Interestingly, Amigorena and colleagues demonstrated that internalization of immune complexes by Fc $\gamma$ R not only triggers the maturation of DCs but also efficiently targets the antigen to the cytosol promoting presentation by MHC class I molecules (cross-presentation) [33,34]. This supports the notion that the B cell response may improve the generation of specific CTLs.

DCs express receptors for activated components of complement such as CR3 (CD11b/CD18) and CR4 (CD11c/CD18) which play a role, not only in the recognition of opsonized antigens and pathogens but also in the uptake of apoptotic cells, acting together with other receptors able to recognize apoptotic cells: LOX-1, CD36,  $\alpha\text{v}\beta 3$ , and  $\alpha\text{v}\beta 5$  [35–39]. DCs express a number of C-type lectin receptors

(CLRs) responsible for the recognition of carbohydrate structures on pathogens and the internalization of antigens for processing and presentation by DCs. Distinct subpopulations of DCs express different patterns of CLRs. DCs derived from peripheral blood monocytes express the macrophage mannose receptor (MR, CD206) [16], DEC-205 (CD205) [40], dendritic cell-specific ICAM3-grabbing nonintegrin (DC-SIGN, CD 209) [41], BCDA-2 [42], DECTIN-1 [43], DCIR [44], DCAL-1 [45], and C-LEC [46], while Langerhans cells express Langerin (CD 207) [47] and DEC-205. There is now ample experimental evidence that DC-SIGN plays a critical role in the recognition and internalization of different pathogens by DCs such as HIV, Dengue Virus, Cytomegalovirus, *Mycobacterium tuberculosis*, and *Leishmania* [48–53]. Of note, DC-SIGN can be coopted by pathogens to their own advantage to circumvent antigen processing, alter toll-like receptor (TLR) mediated signalling, and/or promote T cell infection [54,55]. DCs also express scavenger receptors (SRs), an expanding family of structurally diverse molecules that exhibit promiscuous binding to polyanionic ligands. As a result of their binding properties, SRs display a broad array of functions, including clearance of lipoproteins and uptake of pathogens. DCs express class-A scavenger receptors (SR-A) [56], CD36 (class B-SR) [37], and LOX-1 [39].

DCs share with macrophages a high phagocytic ability. Phagocytosis of opsonized microorganisms involves the participation of FcR and complement receptors, while phagocytosis of unopsonized microorganisms appears to involve different receptors such as the MR [57,58], DC-SIGN [52,53], CD36 [59], and the SR-PSOX/CXC chemokine ligand 16 [60].

### 2.2. DCs are strategically localized to improve antigen capture

The extraordinary ability of immature DCs to capture antigens is related, not only to their high endocytic capacity, but also to the fact that they are strategically localized at anatomic sites with high antigenic exposure such as skin, mucosal surfaces and spleen [1,61]. Even in the absence of inflammatory processes immature DCs or their precursors are constantly recruited from the blood into peripheral tissues [1,62]. This steady-state dynamic is markedly modified during the course of an ongoing infection. Observations made in the mucosa of the airways showed that immature DCs and/or committed bone marrow precursors are quickly recruited from the blood into the airways, peaking about 2 h after inflammatory challenge. Notably, this recruitment of DCs was as fast as the one observed for neutrophils during the course of acute inflammatory reactions. Stimuli responsible for the local recruitment of DCs included chemokines, complement cleavage products, defensins and bacterial peptides [62–65]. Similarly, observations made in the skin showed an increased recruitment of immature DCs from the blood at

inflammatory areas suggesting that this phenomenon may be an important element in determining the efficiency of primary immune responses [66].

### 2.3. DCs use an unique strategy to sample antigens through epithelial barriers on mucosal surfaces: the role of CX<sub>3</sub>CR1

Our body surfaces are defended against pathogens by the skin and epithelial barriers of gastrointestinal, respiratory and urogenital tracts. Host infection mainly occurs through these internal epithelial barriers, which have a combined surface area of at least 400 m<sup>2</sup> in the adult. In spite of this, little is known about the function and profiles of DCs at mucosal surfaces.

Epithelial barriers on mucosal surfaces differ dramatically in their cellular organization and antigen sampling strategies at different sites in the body (reviewed in [67]). In stratified and pseudostratified epithelia, such as those lining the oral cavity, pharynx, esophagus, urethra and vagina, which lack tight junctions, DCs appear to be able to migrate to the apical surface of the epithelium facing the environment, project dendrites outside the epithelium and directly sample antigens for subsequent presentation in secondary lymphoid tissues [68–71]. Rescigno and colleagues have shown that a similar strategy is employed by DCs in intestinal mucosa which is covered by only a single cell layer of epithelial cells. DCs open the tight junctions between epithelial cells, penetrate gut epithelial monolayers, extend dendrites outside the epithelium and directly sample bacteria. DCs express tight-junction proteins such as occludin, claudin 1 and zonula occludens 1, thus the integrity of the epithelial barrier is preserved along this process [72–74]. More recent observations made in the gut indicated that DCs form an extensive network in the lamina propria of the small and the large intestine. These DCs express CX<sub>3</sub>CR1 (the receptor for fractalkine/CX<sub>3</sub>CL1, a chemokine present on the surface of intestinal epithelial cells), and continuously sample luminal antigens by extending transepithelial dendrites into the epithelium by a CX<sub>3</sub>CR1-dependent mechanism [75]. This occurs at steady state in the terminal ileum, while after infection by Salmonella the extended dendritic formations are found throughout the small intestine [75,76]. Of note, CX<sub>3</sub>CR1-deficient mice show a delayed pathogen uptake by DCs from the lumen and, as a consequence, an intrinsic inability to develop an effective antibacterial immune response [75,76].

## 3. Activation of DCs

### 3.1. Immature DCs express a variety of receptors to sense danger signals

Fig. 1 summarizes information about the families of receptors expressed by immature DCs which enable them to

sense their surrounding environment looking for ongoing dangerous processes. As a component of the innate immune system, DCs can recognize a limited but highly conserved set of molecular structures produced by pathogens (pathogen-associated molecular patterns, or PAMPs), which are directly recognized through a number of germ line encoded receptors called pattern-recognition receptors (PRRs) [77,78]. DCs express members of the two most important families of PRRs; Toll-like receptors (TLRs) and CLRs. TLRs usually recognize molecular patterns in microbial lipids, proteins, lipoproteins, LPS or nucleic acids leading to the activation of signalling cascades that result in the activation of DC and the production of inflammatory cytokines [79–81]. TLRs regulate gene expression in DCs via a conserved signalling pathway which involves activation of NF-κB, mitogen-activated protein kinases (MAPKs), and IFN regulatory factors (IRFs) [4,78,79]. By contrast, CLRs are mainly specialized in the recognition of carbohydrate structures on the pathogen surface and their major function is to internalize antigens for processing and presentation by DCs [82,83]. In addition to PRRs, DCs express receptors for a large number of cytokines and chemokines. Moreover, they also express numerous receptors designed to recognize a variety of agents produced in response to alteration in the internal milieu (Fig. 1).

The recognition of PAMPs, inflammatory cytokines and/or other stress signals may lead to the maturation of DCs [1–4]. The concept of DC maturation, first proposed by Steinman and co-workers 20 years ago, refers to a complex differentiation pathway mainly triggered by pathogens and inflammatory cytokines whereby DCs become capable to trigger the activation of naïve T cells. As we will discuss later, it is becoming clear that DCs can mature into different functional profiles according to the nature of the stimulus.

### 3.2. Maturation enables DCs to activate naïve T cells, to promote clonal expansion, and to direct the differentiation of newly activated T lymphocytes into effector cells

The maturation of DCs is usually associated with several coordinated events:

- (a) The novo expression of the main lymph-node-homing chemokine receptor, CCR7, that enables DCs to migrate to lymph node through peripheral lymphatic vessels. CCR7 recognizes the chemokines CCL19 and CCL21 that are highly expressed in the T cell-rich lymph node areas by interdigitating dendritic cells and stromal cells respectively [107–109]. The expression of CCR7, however, appears to be not sufficient for DC migration; inflammatory mediators such as PGE<sub>2</sub> and the ADP-ribosyl cyclase CD38 are required to sensitize CCR7 to CCL19 and CCL21 [108,109].
- (b) The downregulation of DC ability to capture and process antigens, which restricts the specificity of T-cell

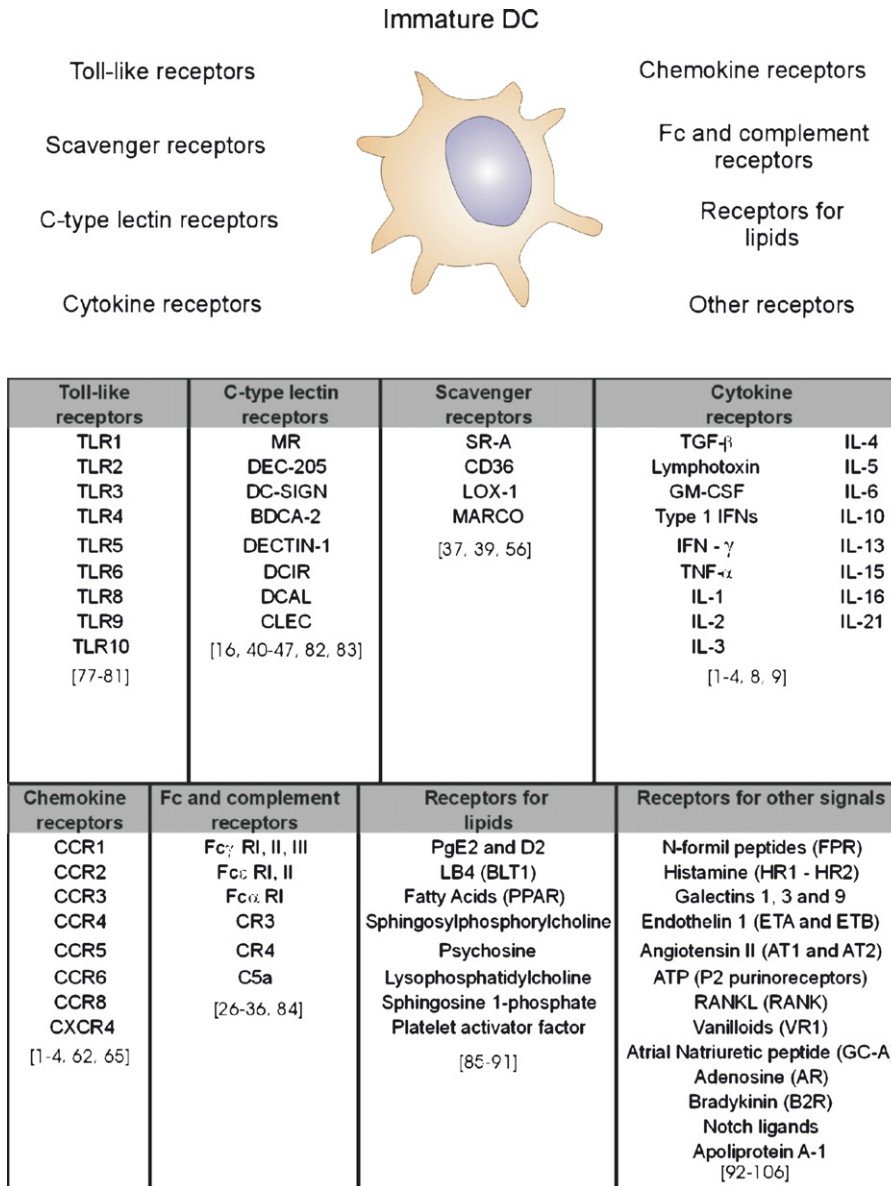


Fig. 1. Receptors expressed by immature DCs (see Refs. [84–103,105,106]).

stimulation to those antigens encountered in peripheral tissues [1–4].

- (c) An increased expression of MHC-peptide complexes at the cell surface [1–4].
- (d) The up-regulation of the expression of CD40, the integrin lymphocyte function-associated antigen 1 (LFA-1) and the co-stimulatory molecules CD80 and CD86 [1–4].
- (e) The novo synthesis and secretion of a number of cytokines and chemokines [1–4].

Mature DCs activate naïve T lymphocytes and direct their differentiation into effector cells by delivering three main signals. Signal 1 is induced by the cross-linking of T-cell receptor (TCR) triggered by the appropriate peptide-MHC

complex presented on DCs. Signal 2 (co-stimulation) is mainly induced through CD28 as a consequence of its interaction with the co-stimulatory molecules CD80 and CD86 expressed by DCs. Signal 3 enable the differentiation of T cells into effector cells: T<sub>H</sub>1, T<sub>H</sub>2 or cytotoxic T lymphocytes [4,3,110]. Fig. 2 illustrates the major functions of immature and mature DCs (Fig. 2).

DCs play a crucial role in adaptative immunity by virtue of their ability to activate naïve T cells as well as by directing the differentiation and polarization of effector T cells and the quality of the subsequent immune response. By producing IL-12, IL-18 and IFN- $\alpha$  (signal 3), mature DCs promote the differentiation of TCD4+ lymphocytes into T<sub>H</sub>1 cells, producing IFN- $\gamma$ , as well as the differentiation of T CD8+ lymphocytes into cytotoxic cells [1,4,3,110]. Alternatively,

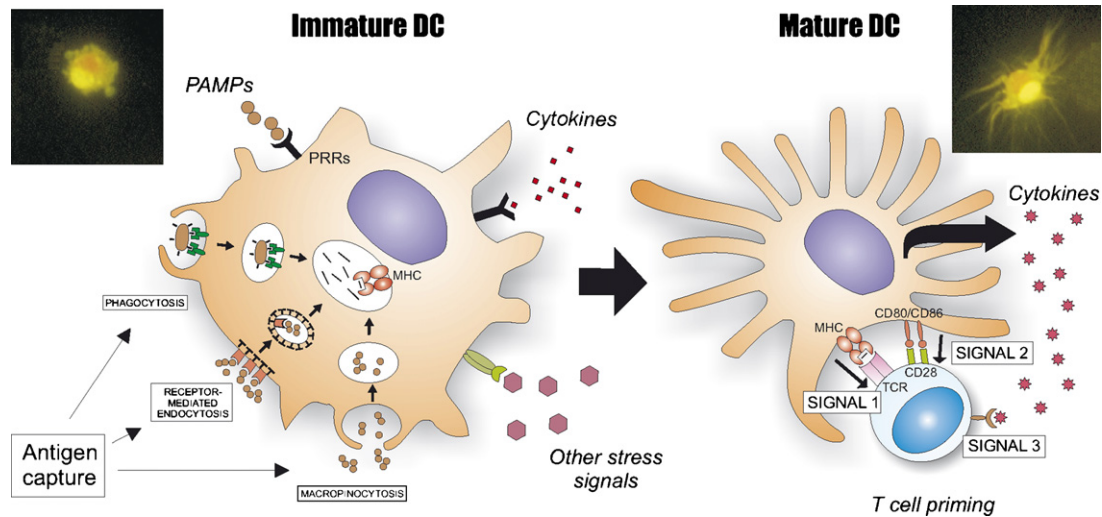


Fig. 2. Functional profile of immature and mature DCs. Immature DCs efficiently sample antigens from the surrounding environment by macropinocytosis, receptor-mediated endocytosis and phagocytosis. On the other hand, they express a high diversity of receptors which enable them to recognize PAMPs, cytokines, chemokines and other stress signals. Upon maturation, they become capable to activate naïve T cells (signals 1 and 2) promoting the differentiation of newly activated T lymphocytes into effector cells (signal 3).

by selectively expressing members of the Jagged family of Notch ligands, DCs seem to promote the differentiation of T CD4<sup>+</sup> lymphocytes into T<sub>H</sub>2 cells, producing IL-4, IL-5 and IL-13, cytokines which are silenced in the T<sub>H</sub>1 lineage [4,110–112]. T<sub>H</sub>1 cells are crucial for cellular immunity against intracellular pathogens while T<sub>H</sub>2 cells are essential in humoral immunity and in defence against nematode parasitic infections [1,4]. Moreover, DCs can also induce tolerance, rather than immune activation, by suppressing T-cell responses through mechanisms such as clonal deletion, clonal anergy or induction of regulatory T cells [5–7].

The existence of populations of DCs able to mediate distinct functions raises the question of whether they are related to specialized subsets of DCs which may have evolved to perform distinct roles in the immune response (reviewed in [113]). Evidence supporting this view comes from observations indicating that distinct subpopulations of DCs show some intrinsic biases in their ability to induce different types of immune responses. For example, either in murine and human models it has been described that distinct subsets of DCs differ in their ability to induce T<sub>H</sub>1 versus T<sub>H</sub>2 responses [4,113–115]. In spite of this, a large body of evidence support the notion that DCs show a high degree of plasticity and that a given population of DCs is able to show different functional profiles in response to distinct stimuli [4,110–113]. In fact, the acquisition of a specific profile by a given DC population appears to be dependent on the differentiation of immature DCs according to a specific program turned on by the recognition of multiple signals in the periphery. How these signals are integrated by DC remains largely unknown. Interestingly, the absence of signals in the periphery (absence of infection or injured self) appears to

lead to a “default” tolerogenic activity of DCs. In fact, a large body of evidence support that DCs in the steady state induce self-tolerance [4,6,7,113].

### 3.3. Maturation of DCs and polarization of T cell response: role of inflammatory cytokines and PAMPs

In vitro studies have shown that a variety of stimuli are able to trigger the activation of DCs and the subsequent priming of an adaptive immune response. However, little is known about the identity of the signals responsible for the activation of DCs under physiological conditions. Although the initiation of the innate immune response against pathogens is dependent on the recognition of PAMPs by TLRs, this recognition leads to a rapid production of inflammatory cytokines such as IFN- $\alpha$  and  $\beta$ , IL-1, IL-6, and TNF- $\alpha$  [1–4]. The relative contribution of PAMPs and inflammatory cytokines in the maturation of DCs was recently clarified by Sporri and Reis e Sousa [3,110,116], by comparing direct and indirect activation induced by microbial stimuli in mixtures of TLR-sufficient and TLR-deficient DCs. They demonstrate that inflammatory cytokines by themselves are able to upregulate the expression of MHC and costimulatory molecules on DCs supporting CD4<sup>+</sup> T cell clonal expansion, but failed to drive the differentiation of CD4<sup>+</sup> T cells into T<sub>H</sub>1 effectors, due to the inability of DCs to produce IL-12. By contrast, exposure to pathogen components resulted in fully activated DCs that promoted T<sub>H</sub>1 immunity. These observations support the notion that the main function of PRRs expressed by DCs is to gain information about the nature of the pathogen for priming an appropriate T cells response, and also suggest that

inflammatory cytokines amplify but not initiate an adaptative immune response.

Recently, it has become clear that T cell responses are suppressed by CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells (T<sub>R</sub> cells). These cells play a critical role for the maintenance of peripheral T cell tolerance by silencing peripheral autoreactive T lymphocytes. In addition, they also control the activation of naïve B and T cells in response to pathogens [117–119]. The mechanisms through which DCs modulate regulatory T cell responses are poorly understood. Recent observations published by Pasare and Medzhitov indicated that TLRs play a crucial role in the induction of T cell response, not only by virtue of their ability to trigger the maturation of DCs enabling them to support the clonal expansion and the differentiation of T lymphocytes into effector cells, but also by blocking the action of regulatory T cells [120,121]. Pasare and Medzhitov demonstrated that the activation of DCs through TLR4 and TLR9 ligands (LPS and CpG, respectively) blocks the suppressive effect of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells, allowing activation of pathogen-specific adaptive immune response. Blocking of suppressor activity was dependent, at least in part, on the production of IL-6 by DCs, which was induced through TLRs upon recognition of microbial stimuli [120,121].

The nature of the microbial stimulus exerts a potent influence on the ability of DCs to produce distinct cytokines and to induce T<sub>H</sub>1 versus T<sub>H</sub>2 responses. Exposure to helminth products usually induces the differentiation of DCs that drives the development of T<sub>H</sub>2-like responses, while the same DCs when exposed to LPS stimulate T<sub>H</sub>1 responses [76,122–125]. Moreover, Pulendran and colleagues demonstrated that TLR ligands instruct human DCs to induce distinct TH responses by differentially modulating MAPK (mitogen-activated protein kinase) signaling. LPS and flagellin, which trigger TLR4 and TLR5, respectively, instruct DCs to stimulate T<sub>H</sub>1 responses via IL-12p70 production, through a mechanism depending on the phosphorylation of p38MAPK and c-Jun. By contrast, the TLR2 agonist, Pam3cys, and the T<sub>H</sub>2 stimulus schistosoma egg stimulate T<sub>H</sub>2 responses by a mechanism dependent on a sustained activation of the MAPK ERK 1/2 which results in the stabilization of the transcription factor c-Fos, a suppressor of IL-12 production [126,127].

#### 4. Modulation of DC function by innate immune cells

Several reports have recently highlighted the relevance of the reciprocal interactions established among DCs and other innate cells during the early stages of innate immune responses. These interactions can take place in secondary lymphoid organs and/or inflamed peripheral tissues, and appear to play an important role in the control of the immune response.

##### 4.1. Cross-talk between DCs and NK cells

NK cells are specialized lymphocytes of the innate immune system, originally characterized by their ability to destroy tumour cells without prior activation, that provide a first line of defence against infections and tumours. NK cells are capable to induce the apoptosis of pathogen-infected or tumour cells recognized as targets. The identification of targets and the subsequent activation of NK cells involve the participation of a diverse array of inhibitory and activating cell-surface receptors, belonging to the Ig-like receptor and CLR families. These receptors recognize pathogen-encoded molecules, self proteins whose expression is increased in stressed cells, or self proteins expressed by normal cells that are down-regulated in infected or tumour cells. The activation of NK cells leads, not only to the apoptosis of target cells, but also to the release of large amounts of cytokines such as IFN- $\gamma$ , TNF- $\alpha$ , and GM-CSF, and chemokines including CCL3, MIP-1, CCL4 and CCL5 [128–130].

NK cells have recently shown an important role in the process of DC maturation. This function is mainly mediated through two different mechanisms, by killing those DCs that do not properly acquire a mature phenotype or, alternatively, by stimulating the maturation of DCs [131,132]. Killing of immature DCs appears to be dependent on signals delivered by NK activating receptors, mainly the NK-cell protein 30 (NKp30). Of note, mature DCs are resistant to NK-cell cytotoxicity, a phenomenon which appears to be due to the up-regulation of MHC class I molecules, specifically of HLA-E, during the process of DC maturation. Unlike the usual mechanism employed by NK cells to lyse tumour targets, the destruction of immature DCs by NK cells seems to be mainly mediated through death receptors rather than by granule exocytosis. It has been proposed that this mechanism may improve the activation of adaptative immunity by favouring antigen presentation only by mature DCs [131–135].

Alternatively, activated NK cells can directly stimulate the maturation of DCs. This response is mediated both by the production of TNF- $\alpha$  and IFN- $\gamma$ , and by cell–cell contact-dependent mechanisms, which appears to involve the triggering of NKp30 on NK cells [131,132,136,137]. Promotion of DC maturation by NK cells through TLR-independent mechanisms may be relevant in the development of the immune response against pathogens and tumour cells that induce poor inflammatory responses. On the other hand, it is becoming clear that mature DC produce large amounts of cytokines able to trigger NK cell-functions, such as IL-2, IL-12, IL-18, IL-15 and type I IFNs. Even immature DCs have been shown to induce the activation of NK cells. They constitutively express CD48 and CD70, which are ligands for two activating receptors of NK cells 2B4 and CD27, respectively [131,132,136,137].

The outcome of the actions exerted by NK cells on DCs (induction of apoptosis versus promotion of maturation)

appears to be dependent on a complex array of factors. Among them, the ratio of the interacting partners appears to play a major role. Low NK cell to DC ratios favour the maturation, while high NK cell to DC ratios induce the elimination of immature DC [132,138].

#### 4.2. Cross-talk of DCs and other innate leukocytes

It is becoming clear that other cells of the innate immunity are also able to trigger the maturation of DC. The stimulation of NKT cells by the synthetic glycolipid  $\alpha$ -galactosylceramide presented by CD1d molecules on DCs results in the maturation of DCs, evidenced by increased expression of costimulatory molecules and IL-12 production through a mechanism dependent on the interaction between CD40 expressed by DCs and CD40L expressed by NKT cells [131,139,140]. Similarly, the activation of CD1-restricted  $\gamma\delta$  T cells can also induce the maturation of DCs through a pathway which requires both, the direct interaction of both cell types and the production of TNF- $\alpha$  by  $\gamma\delta$  T cells [131,141,142].

Neutrophils, which provide a first line of defence against pathogens, have also shown to trigger the maturation of DCs. Neutrophils strongly cluster with immature DCs and, upon activation, induces the maturation of DCs enabling them to support not only the expansion of T cells, but also the differentiation of CD4<sup>+</sup> T cells into T<sub>H</sub>1 effectors. Neutrophil-DC interaction is mediated by the binding of DC-SIGN on DCs to the  $\beta$ 2 integrin Mac-1 on neutrophils. This interaction induces the maturation of DCs through a mechanism completely dependent on the production of TNF- $\alpha$  by activated neutrophils [143,144].

Recently, it has been shown that distinct subsets of DCs effectively collaborate during the course of the immune response. Ohteki and co-workers characterized a novel mechanism which enables the collaboration between conventional DCs (DCs) and plasmacytoid DCs [145,146]. They showed that immunization with CpG DNA results in the production of IL-15 by DCs. IL-15, in turns, stimulates DCs enhancing the expression of CD40. Immunization with CpG DNA also results in the activation of plasmacytoid DCs inducing the expression of CD40L. The interaction of DCs and pDCs through the CD40/CD40L system not only stimulates the production of IL-12 by DCs but also confer resistance against *Listeria monocytogenes* challenge [145,146].

Fig. 3 illustrates the mechanisms through which NK cells, neutrophils and plasmacytoid DCs modulate the function of conventional DCs (DCs) (Fig. 3).

#### 4.3. Modulation of the function of mucosal DCs by epithelial cells: role of the cytokine TSLP

As previously mentioned in this review, mucosal DCs are able to recognize and sample both, pathogens and commensal bacteria, directly from the lumen, by opening the tight junctions between adjacent epithelial cells and

sending dendrites into the lumen [72,76,147]. Since both, commensal and pathogenic bacteria share similar TLR ligands, including LPS and bacterial DNA, and also considering the high ability of these PAMPs to trigger the activation of DCs in a proinflammatory profile and the high numbers of bacteria found in the intestinal content (up to 10<sup>12</sup> organisms per gram), it is generally assumed that mucosal surfaces have specific mechanisms able to impair the development of a chronic inflammatory status [76,147].

A large body of observations suggest that mucosal DCs preferentially promote the differentiation of T CD4<sup>+</sup> cells into T<sub>H</sub>2 cells, and also induce B cells to produce IgA [148,149]. This suggests that mucosal DCs are committed to promote a noninflammatory environment. Whether this profile represents an intrinsic property of mucosal DCs or whether it is conferred by the mucosal microenvironment is not clear. Rescigno and colleagues have recently shown that epithelial cells constitutively release thymic stromal lymphopoietin (TSLP) and other mediators resulting in the induction of noninflammatory DCs [150]. These DCs promote the differentiation of TCD4<sup>+</sup> lymphocytes into T<sub>H</sub>2 cells, even after exposure to a T<sub>H</sub>1 inducing pathogen. Interestingly, the authors presented evidence indicating that this control mechanism appears to be lost in patients suffering Crohn disease, an inflammatory bowel disease involving a T<sub>H</sub>1-mediated response [150]. Thus, TSLP released constitutively by epithelial cells appears to play a critical role in the homeostasis of the gut by preventing the development of T<sub>H</sub>1 responses, favouring the differentiation of CD4<sup>+</sup> T lymphocytes into T<sub>H</sub>2 cells. Interestingly, TSLP is also produced under homeostatic conditions at high amounts in skin affected by atopic dermatitis, and in bronchial epithelium and submucosa in allergic asthma, two pathologies strongly associated with a T<sub>H</sub>2 profile [151–153].

### 5. Modulation of DC function by other stress stimuli

Studies of the mechanisms involved in the regulation of DC activity are mostly restricted to the action of cytokines, chemokines and microbial products. However, other stress signals generated during the course of dangerous processes have also shown to stimulate the activation of DCs. Considering that the development of acidic microenvironments is a hallmark of inflammatory processes we have analyzed the influence of extracellular acidosis on the function of DCs. Our results indicated that DCs are able to sense extracellular acidosis as a danger signal thus enhancing endocytosis, the acquisition of extracellular antigens for MHC class I-restricted presentation (cross-presentation) and the ability of antigen-pulsed DCs to prime CD8<sup>+</sup> CTL responses [154,155]. Aliberti and colleagues, on the other hand, reported that kinins stimulate the production of IL-12 by DCs through the activation of the B(2) bradykinin receptor subtype and that bradykinin-induced IL-12 responses are

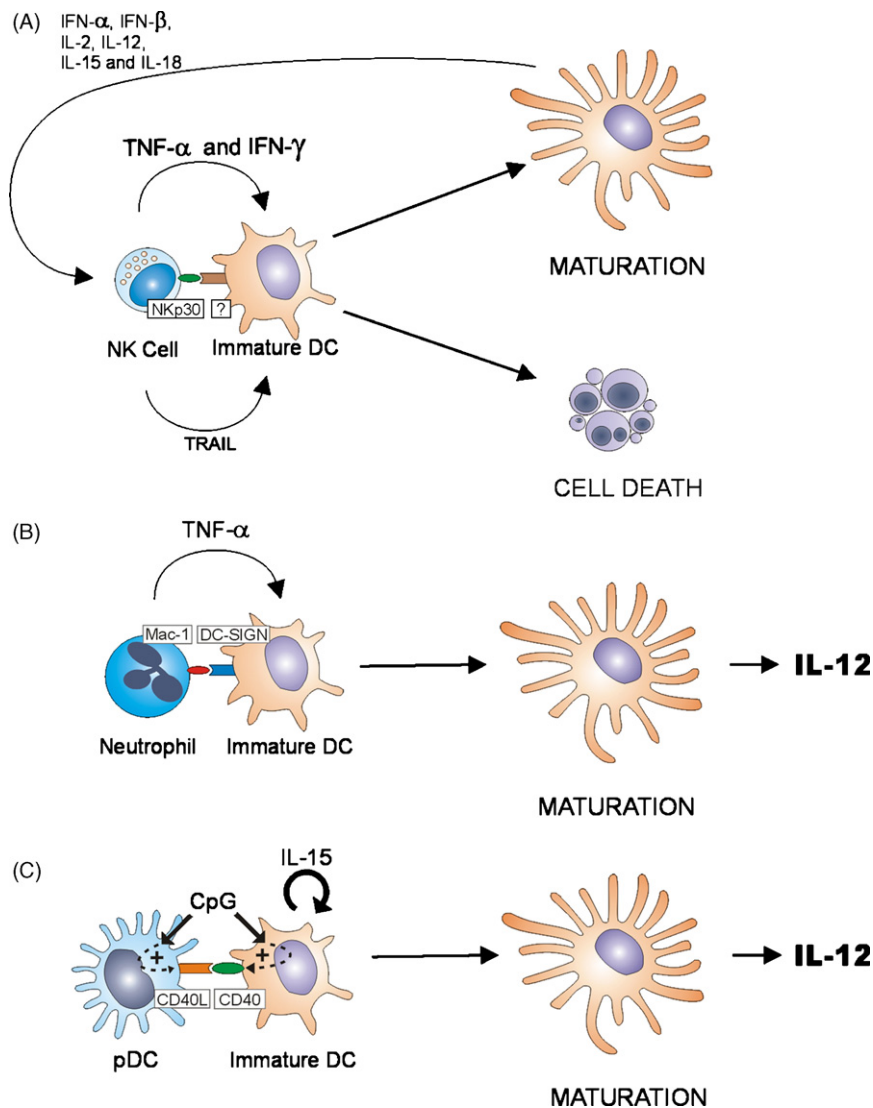


Fig. 3. Modulation of DC function by innate immune cells. (A) NK cells modulate the function of DCs by two alternative mechanisms. They can kill immature DCs through a TRAIL-mediated mechanism or, alternatively, they can stimulate the maturation of DCs by both, cell–cell contact-dependent mechanisms and the production of  $\text{TNF-}\alpha$  and  $\text{IFN-}\gamma$ . Both processes require the participation of the NK activating receptor  $\text{Nkp30}$ . (B) Neutrophils can stimulate the maturation of DCs and the production of  $\text{IL-12}$ . This process is mediated by the interaction of  $\text{DC-SIGN}$  on DCs and the  $\beta 2$  integrin  $\text{Mac-1}$  on neutrophils. This interaction leads to the maturation of DCs through a mechanism dependent on the production of  $\text{TNF-}\alpha$  by activated neutrophils. (C) Cooperation between plasmacytoid DCs and conventional DCs (DCs). Immunization with CpG DNA induces the activation of DCs (through a TLR9-dependent mechanism), the production of  $\text{IL-15}$ , and also a modest synthesis of  $\text{IL-12}$ . In turns,  $\text{IL-15}$  stimulates DCs in an autocrine way through the  $\text{IL-15}$  receptor, enhancing the expression of  $\text{CD40}$  on DCs. CpG DNA also stimulates plasmacytoid DCs via TLR9 inducing the expression of  $\text{CD40L}$  on a subset of these cells. These  $\text{CD40L}^+$  plasmacytoid DCs stimulate  $\text{CD40}$ -expressing DCs augmenting the production of  $\text{IL-12}$  and conferring resistance to *Listeria monocytogenes* infection.

tightly regulated both by angiotensin-converting enzyme, a kinin-degrading peptidase, and by endogenous  $\text{IL-10}$  [104]. Soruri and colleagues have shown that the complement anaphylatoxin  $\text{C5a}$  induce “in vivo” the differentiation of human monocytes into mature DCs by  $\text{TNF-}\alpha$  and prostaglandin  $\text{E2}$ -dependent mechanisms [156]. Oxidative stress has also been shown to induce the activation and the production of cytokines by DCs [157,158], while fever-like temperature stimulated the maturation of DCs through the induction of  $\text{hsp90}$  [159]. Together, these observations suggest the existence of multiple pathways by which the activation of

DCs can be induced, supporting the view that this multiplicity of pathways enable immature DCs to efficiently sense a variety of danger signals at the onset of infection.

## 6. Concluding remarks

Emerging concepts about innate immunity indicate that DCs play a crucial role in sensing environment signals and integrating this information to determine the profile of the adaptive immunity. A variety of signals including



cytokines, chemokines, PAMPs, and other less characterized stress molecules have shown to be able to modulate the function of immature DCs and to determine distinct programs of DC differentiation and different forms of immunity. Further studies are needed to define how DCs integrate information from pathogens, tissues, and other innate leukocytes required for effective immunity against pathogens.

## Acknowledgements

This work was supported by grants from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), University of Buenos Aires School of Medicine, and Agencia Nacional de Promoción Científica y Tecnológica, Argentina. We thank Dr. Analía Trevani for critical review of the manuscript.

## References

- [1] Guermonprez P, Valladeau J, Zitvogel L, Théry C, Amigorena S. Antigen presentation and T cell stimulation by dendritic cells. *Annu Rev Immunol* 2002;20:621–67.
- [2] Steinman RM. Some interfaces of dendritic cell biology. *APMIS* 2003;111:675–97.
- [3] Ardavin C, Amigorena S, Reis e Sousa C. Dendritic cells: immunobiology and cancer immunotherapy. *Immunity* 2004;20:17–23.
- [4] Reis e Sousa C. Dendritic cells in a mature age. *Nature* 2006;6:476–83.
- [5] Mahnke K, Knop J, Enk AH. Induction of tolerogenic DCs: “you are what you eat”. *Trends Immunol* 2003;24:646–51.
- [6] Steinman RM, Hawiger D, Nussenzweig C. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003;21:685–711.
- [7] Hugues S, Boissonnas A, Amigorena S, Fétler L. The dynamics of dendritic cell–T cell interactions in priming and tolerance. *Curr Opin Immunol* 2006;18:491–5.
- [8] Shortman K, Liu Y. Mouse and human dendritic cell subtypes. *Nat Rev Immunol* 2002;2:151–61.
- [9] Ardavin C. Origin, precursors and differentiation of mouse dendritic cells. *Nat Rev Immunol* 2003;3:582–90.
- [10] Ardavin C. Dendritic cell heterogeneity: developmental plasticity and functional diversity. *Semin Immunol* 2005;17:251–2.
- [11] Liu YJ. IPC: professional type I interferon-producing cells and plasmacytoid dendritic cell precursors. *Annu Rev Immunol* 2005;23:275–306.
- [12] Asselin-Paturel C, Trinchieri G. Production of type I interferons: plasmacytoid dendritic cells and beyond. *J Exp Med* 2005;202:461–5.
- [13] Blasius AL, Colonna M. Sampling and signaling in plasmacytoid dendritic cells: the potential roles of Siglec-H. *Trends Immunol* 2006;27:255–60.
- [14] Zenke M, Hieronymus T. Towards an understanding of the transcription factor network of dendritic cell development. *Trends Immunol* 2006;27:140–5.
- [15] Théry C, Amigorena S. The cell biology of antigen presentation in dendritic cells. *Curr Opin Immunol* 2001;13:45–51.
- [16] Sallusto F, Cella M, Danieli C, Lanzavecchia A. Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products. *J Exp Med* 1995;182:389–400.
- [17] Norbury CC. Drinking a lot is good for dendritic cells. *Immunology* 2006;117:443–51.
- [18] Hewlett LJ, Prescott AR, Watts C. The coated pit and macropinocytosis pathways serve distinct endosome populations. *J Cell Biol* 1994;124:689–703.
- [19] Swanson JA, Watts C. Macropinocytosis. *Trends Cell Biol* 1995;5:424–8.
- [20] West MA, Bretscher MS, Watts C. Distinct endocytic pathways in EGF-stimulated human carcinoma A431 cells. *J Cell Biol* 1989;109:2731–9.
- [21] Racoosin EL, Swanson JA. M-CSF-induced macropinocytosis increases solute endocytosis but not receptor-mediated endocytosis in mouse macrophages. *J Cell Sci* 1992;102:867–80.
- [22] Norbury CC, Chambers BJ, Ljunggren H, Watts C. Constitutive macropinocytosis allows TAP-dependent major histocompatibility complex class I presentation of exogenous soluble antigen by bone marrow-derived dendritic cells. *Eur J Immunol* 1997;27:280–8.
- [23] Ackerman AL, Kritsis C, Tampe R, Cresswell P. Early phagosomes in dendritic cells form a cellular compartment sufficient for cross presentation of exogenous antigens. *Proc Natl Acad Sci USA* 2003;100:12889–94.
- [24] West MA, Wallin RP, Matthews SP, Svensson HG, Zaru R, Ljunggren HG, et al. Enhanced dendritic cell antigen capture via toll-like receptor induced actin remodeling. *Science* 2004;305:1153–7.
- [25] Lanzavecchia A. Mechanisms of antigen uptake for presentation. *Curr Opin Immunol* 1996;8:348–54.
- [26] Esposito-Farese ME, Sautes C, de la Salle H, Latour S, Bieber T, de la Salle C, et al. Membrane and soluble Fc gamma RII/RIII modulate the antigen-presenting capacity of murine dendritic epidermal Langerhans cells for IgG-complexed antigens. *J Immunol* 1995;155:1725–36.
- [27] Fanger NA, Wardwell K, Shen L, Tedder TF, Guyre PM. Type I (CD64) and type II (CD32) Fc gamma receptor-mediated phagocytosis by human blood dendritic cells. *J Immunol* 1996;157:541–8.
- [28] Sedlik C, Orbach D, Veron P, Schweighoffer E, Colucci F, Gamberale R, et al. A critical role for Syk protein tyrosine kinase in Fc receptor-mediated antigen presentation and induction of dendritic cell maturation. *J Immunol* 2003;170:846–52.
- [29] Maurer D, Fiebiger E, Reininger B, Ebner C, Petzelbauer GP, Shi G, et al. Fc epsilon receptor I on dendritic cells delivers IgE-bound multivalent antigens into a cathepsin S-dependent pathway of MHC class II presentation. *J Immunol* 1998;161:2731–9.
- [30] Jurgens M, Wollenberg A, Hanau D, de la Salle H, Bieber T. Activation of human epidermal Langerhans cells by engagement of the high affinity receptor for IgE, Fc epsilon R1. *J Immunol* 2001;155:5184–9.
- [31] Krauss S, Mayer E, Rank G, Rieber EP. Induction of the low affinity receptor for IgE (Fc epsilon RII/CD23) on human blood dendritic cells by interleukin-4. *Adv Exp Med Biol* 1993;329:231–6.
- [32] Pasquier B, Lepelletier Y, Baude C, Hermine O, Monteiro RC. Differential expression and function of IgA receptors (CD89 and CD71) during maturation of dendritic cells. *J Leukoc Biol* 2004;76:1134–41.
- [33] Regnault A, Lankar D, Lacabanne V, Rodríguez A, Théry C, Rescigno M, et al. Fc gamma receptor-mediated induction of dendritic cell maturation and major histocompatibility complex class-I restricted antigen presentation after immune complex internalization. *J Exp Med* 1999;189:371–80.
- [34] Amigorena S. Fc gamma receptors and cross-presentation in dendritic cells. *J Exp Med* 2002;195:F1–3.
- [35] Morelli AE, Larregina AT, Shufesky WJ, Zahorchak AF, Logar AJ, Papworth G, et al. Internalization of circulating apoptotic cells by

- splenic marginal zone dendritic cells: dependence on complement receptors and effect on cytokine production. *Blood* 2003;101:611–20.
- [36] Bajtay Z, Csomor E, Sandor N, Erdei A. Expression and role of Fc- and complement-receptors on human dendritic cells. *Immunol Lett* 2006;104:46–52.
- [37] Albert ML, Pearce SF, Francisco LM, Sauter B, Roy P, Silverstein RL, et al. Immature dendritic cells phagocytose apoptotic cells via  $\alpha_v\beta_5$  and CD36, and cross-present antigens to cytotoxic T lymphocytes. *J Exp Med* 1998;188:1359–68.
- [38] Albert ML, Kim JI, Birge RB. Alphavbeta5 integrin recruits the CrkII-Dock180-rac1 complex for phagocytosis of apoptotic cells. *Nat Cell Biol* 2000;2:899–905.
- [39] Delneste Y, Magistrelli G, Gauchat J, Haeuw J, Aubry J, Nakamura K, et al. Involvement of LOX-1 in dendritic cell-mediated antigen cross-presentation. *Immunity* 2002;17:353–62.
- [40] Mahnke K, Guo M, Lee S, Sepúlveda H, Swain SL, Nussenzweig M, et al. The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. *J Cell Biol* 2000;151:673–84.
- [41] Geijtenbeek TBH, Torensma R, van Vliet SJ, van Duijnhoven GCF, Adema GJ, van Kooyk Y, et al. Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. *Cell* 2000;100:575–85.
- [42] Dzionek A, Osma Y, Nagafune J, Cella M, Colonna M, Facchetti F, et al. BDCA-2, a novel plasmacytoid dendritic cellspecific type II C-type lectin, mediates antigen capture and is a potent inhibitor of interferon alpha/beta induction. *J Exp Med* 2001;194:1823–34.
- [43] Willment JA, Gordon S, Brown GD. Characterization of the human beta-glucan receptor and its alternatively spliced isoforms. *J Biol Chem* 2001;276:43818–23.
- [44] Bates EE, Fournier N, Garcia E, Valladeau J, Durand I, Pin JJ, et al. APCs express DCIR, a novel C-type lectin surface receptor containing an immunoreceptor tyrosine-based inhibitory motif. *J Immunol* 1999;163:1973–83.
- [45] Ryan EJ, Marshall AJ, Magaletti D, Floyd H, Draves KE, Olson NE, et al. Dendritic cell-associated lectin-1: a novel dendritic cell-associated, C-type lectinlike molecule enhances T cell secretion of IL-4. *J Immunol* 2002;169:5638–48.
- [46] Colonna M, Samaridis J, Angman L. Molecular characterization of two novel C-type lectin-like receptors, one of which is selectively expressed in human dendritic cells. *Eur J Immunol* 2000;30:697–704.
- [47] Valladeau J, Ravel O, Dezutter-Dambuyant C, Moore K, Kleijmeer M, Liu Y, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. *Immunity* 2000;12:71–81.
- [48] Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, Middel J, et al. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell* 2000;100:587–97.
- [49] Halary F, Amara A, Lortat-Jacob H, Messerle M, Delaunay T, Houles C, et al. Human cytomegalovirus binding to DC-SIGN is required for dendritic cell infection and target cell trans-infection. *Immunity* 2002;17:653–64.
- [50] Colmenares M, Puig-Kroger A, Pello OM, Corbi AL, Rivas L. Dendritic cell (DC)-specific intercellular adhesion molecule 3 (ICAM-3)-grabbing nonintegrin (DC-SIGN, CD209), a C-type surface lectin in human DCs, is a receptor for *Leishmania* amastigotes. *J Biol Chem* 2002;277:36766–9.
- [51] Tassaneetrithep B, Burgess TH, Granelli-Piperno A, Trumpfheller C, Finke J, Sun W, et al. DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. *J Exp Med* 2003;197:823–9.
- [52] Cambi A, Gijzen K, de Vries JM, Torensma R, Joosten B, Adema GJ, et al. The C-type lectin DC-SIGN (CD209) is an antigen-uptake receptor for *Candida albicans* on dendritic cells. *Eur J Immunol* 2003;33:532–8.
- [53] Tailleur L, Schwartz O, Herrmann JL, Pivert E, Jackson M, Amara A, et al. DC-SIGN is the major *Mycobacterium tuberculosis* receptor on human dendritic cells. *J Exp Med* 2003;197:121–7.
- [54] Van Kooyk Y, Geijtenbeek TB. DC-SIGN: escape mechanism for pathogens. *Nat Rev Immunol* 2003;3:697–709.
- [55] Van Kooyk Y, Engering A, Lekkerkerker AN, Ludwig IS, Geijtenbeek TB. Pathogens use carbohydrates to escape immunity induced by dendritic cells. *Curr Opin Immunol* 2004;16:488–93.
- [56] Harshyne LA, Zimmer MI, Watkins SC, Barratt-Boyes SM. A role for class A scavenger receptor in dendritic cell nibbling from live cells. *J Immunol* 2003;170:2302–9.
- [57] Newman SL, Holly A. *Candida albicans* is phagocytosed, killed, and processed for antigen presentation by human dendritic cells. *Infect Immun* 2001;69:6813–22.
- [58] Syme RM, Spurrell JC, Amankwah EK, Green FH, Mody CH. Primary dendritic cells phagocyte *Cryptococcus neoformans* via mannose receptors and Fc gamma receptor II for presentation to T lymphocytes. *Infect Immun* 2002;70:5972–81.
- [59] Urban BC, Willcox N, Roberts DJ. A role for CD36 in the regulation of dendritic cell function. *Proc Natl Acad Sci USA* 2001;98:8750–5.
- [60] Shimaoka T, Nakayama T, Kume N, Takahashi S, Yamaguchi J, Minami M, et al. Cutting edge: SR-PSOX/CXC chemokine ligand 16 mediates bacterial phagocytosis by APCs through its chemokine domain. *J Immunol* 2003;171:1647–51.
- [61] Villadangos JA, Heath WR. Life cycle, migration and antigen presenting functions of spleen and lymph node dendritic cells: limitations of the Langerhans cell paradigm. *Sem Immunol* 2005;17:262–72.
- [62] Sozzani S. Dendritic cell trafficking: more than just chemokines. *Cytokine Growth Factor Rev* 2005;16:581–92.
- [63] McWilliam AS, Nelson D, Thomas JA, Holt PG. Rapid dendritic cell recruitment is a hallmark of the acute inflammatory response at mucosal surfaces. *J Exp Med* 1994;179:1331–6.
- [64] McWilliam AS, Napoli S, Marsh AM, Pemper FL, Nelson DJ, Pimm CL, et al. Dendritic cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli. *J Exp Med* 1996;184:2429–32.
- [65] Stumbles PA, Strickland DH, Pimm CL, Proksch SF, Marsh AM, McWilliam AS, et al. Regulation of dendritic cell recruitment into resting and inflamed airway epithelium: use of alternative chemokine receptors as a function of inducing stimulus. *J Immunol* 2001;167:228–34.
- [66] Gombert M, Dieu-Nosjean MC, Winterberg F, Bunemann E, Kubitz RC, Da Cunha L, et al. CCL1-CCR8 interactions: an axis mediating the recruitment of T cells and Langerhans-type dendritic cells to sites of atopic skin inflammation. *J Immunol* 2005;174:5082–91.
- [67] Neutra MR, Pringault E, Kraehenbuhl JP. Antigen sampling across epithelial barriers and induction of mucosal immune responses. *Annu Rev Immunol* 1996;14:275–300.
- [68] Kraehenbuhl JP, Hopkins SA, Kerneis S, Pringault E. Antigen sampling by epithelial tissues: implications for vaccine design. *Behring Inst Mitt* 1997;98:24–32.
- [69] Neutra MR, Mantis NJ, Kraehenbuhl JP. Collaboration of epithelial cells with organized mucosal lymphoid tissues. *Nat Immunol* 2001;2:1004–9.
- [70] Pope M, Haase AT. Transmisión, acute HIV-1 infection and the quest for strategies to prevent infection. *Nat Med* 2002;9:847–52.
- [71] Niedergang F, Didierlaurent A, Kraehenbuhl JP, Sirard JC. Dendritic cells: the host Achilles's heel for mucosal pathogens? *Trends Microbiol* 2004;12:79–88.
- [72] Rescigno M, Rotta G, Valzasina B, Ricciardi-Castagnoli P. Dendritic cells shuttle microbes across gut epithelial monolayers. *Immunobiology* 2001;204:572–81.
- [73] Gewirtz AT, Madara JL. Periscope, up! Monitoring microbes in the intestine. *Nat Immunol* 2001;2:361–7.

- [74] Rescigno M, Borrow P. The host-pathogen interaction: new themes from dendritic cell biology. *Cell* 2001;106:267–70.
- [75] Niess JH, Brand S, Gu X, Landsman L, Jung S, McCormick BA, et al. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 2005;307:254–8.
- [76] Colonna M, Pulendran B, Iwasaki A. Dendritic cells at the host-pathogen interface. *Nat Immunol* 2006;7:117–20.
- [77] Gordon S. Pattern recognition receptors: doubling up for the innate immune response. *Cell* 2002;111:927–30.
- [78] Akira S. Mammalian Toll-like receptors. *Curr Opin Immunol* 2003;15:5–11.
- [79] Reis e Sousa C. Toll-like receptors and dendritic cells: for whom the bug tolls. *Semin Immunol* 2004;16:27–34.
- [80] Mazzoni A, Segal DM. Controlling the Toll road to dendritic cell polarization. *J Leukoc Biol* 2004;75:721–30.
- [81] Kaisho T, Akira S. Regulation of dendritic cell function through toll-like receptors. *Curr Mol Med* 2003;3:759–71.
- [82] Cambi A, Figdor CG. Dual function of C-type lectin-like receptors in the immune system. *Curr Opin Cell Biol* 2003;15:539–46.
- [83] McGreal EP, Miller JL, Gordon S. Ligand recognition by antigen-presenting cell C-type lectin receptors. *Curr Opin Immunol* 2005;17:18–24.
- [84] Yang D, Chen Q, Stoll S, Chen X, Howard OM, Oppenheim JJ. Differential regulation of responsiveness to fMLP and C5a upon dendritic cell maturation: correlation with receptor expression. *J Immunol* 2000;165:2694–702.
- [85] Morelli AE, Thomson AW. Dendritic cells under the spell of prostaglandins. *Trends Immunol* 2003;24:108–11.
- [86] Del Prete A, Shao WH, Mitola S, Santoro G, Sozzani S, Haribabu B. Regulation of dendritic cell migration and adaptive immune response by leukotriene B4 receptors: a role for LTB4 in up-regulation of CCR7 expression and function. *Blood* 2007;109:626–31.
- [87] Appel S, Mirakaj V, Bringmann A, Weck MM, Grunebach F, Brossart P. PPAR-gamma agonists inhibit toll-like receptor-mediated activation of dendritic cells via the MAP kinase and NF-kappaB pathways. *Blood* 2005;106:3888–94.
- [88] Idzko M, Panther E, Corinti S, Morelli A, Ferrari D, Herouy Y, et al. Sphingosine 1-phosphate induces chemotaxis of immature and modulates cytokine-release in mature human dendritic cells for emergence of Th2 immune responses. *FASEB J* 2002;16:625–7.
- [89] Coutant F, Perrin-Cocon L, Agaoglu S, Delair T, Andre P, Lotteau V. Mature dendritic cell generation promoted by lysophosphatidylcholine. *J Immunol* 2002;169:1688–95.
- [90] Panther E, Idzko M, Corinti S, Ferrari D, Herouy Y, Mockenhaupt M, et al. The influence of lysophosphatidic acid on the functions of human dendritic cells. *J Immunol* 2002;169:4129–35.
- [91] Sozzani S, Longoni D, Bonocchi R, Luini W, Bersani L, D'Amico G, et al. Human monocyte-derived and CD34+ cell-derived dendritic cells express functional receptors for platelet activating factor. *FEBS Lett* 1997;418:98–100.
- [92] Yang D, Chen Q, Gertz B, He R, Phulsuksombati M, Ye RD, et al. Human dendritic cells express functional formyl peptide receptor-like-2 (FPR2) throughout maturation. *J Leukoc Biol* 2002;72:598–607.
- [93] Mazzoni A, Young HA, Spitzer JH, Visintin A, Segal DM. Histamine regulates cytokine production in maturing dendritic cells, resulting in altered T cell polarization. *J Clin Invest* 2001;108:1865–73.
- [94] Fulcher JA, Hashimi ST, Levroney EL, Pang M, Gurney KB, Baum LG, et al. Galectin-1-matured human monocyte-derived dendritic cells have enhanced migration through extracellular matrix. *J Immunol* 2006;177:216–26.
- [95] Dai SY, Nakagawa R, Itoh A, Murakami H, Kashio Y, Abe H, et al. Galectin-9 induces maturation of human monocyte-derived dendritic cells. *J Immunol* 2005;175:2974–81.
- [96] Vray B, Camby I, Vercauteren V, Mijatovic T, Bovin NV, Ricciardi-Castagnoli P, et al. Up-regulation of galectin-3 and its ligands by *Trypanosoma cruzi* infection with modulation of adhesion and migration of murine dendritic cells. *Glycobiology* 2004;14:647–57.
- [97] Guruli G, Pflug BR, Pecher S, Makarenkova V, Shurin MR, Nelson JB. Function and survival of dendritic cells depend on endothelin-1 and endothelin receptor autocrine loops. *Blood* 2004;104:2107–15.
- [98] Nahmod KA, Vermeulen ME, Raiden S, Salamone G, Gamberale R, Fernandez-Calotti P, et al. Control of dendritic cell differentiation by angiotensin II. *FASEB J* 2003;17:491–3.
- [99] Marteau F, Gonzalez NS, Communi D, Goldman M, Boeynaems JM, Communi D. Thrombospondin-1 and indoleamine 2,3-dioxygenase are major targets of extracellular ATP in human dendritic cells. *Blood* 2005;106:3860–6.
- [100] Page G, Miossec P. RANK and RANKL expression as markers of dendritic cell-T cell interactions in paired samples of rheumatoid synovium and lymph nodes. *Arthritis Rheum* 2005;52:2307–12.
- [101] Basu S, Srivastava P. Immunological role of neuronal receptor vanilloid receptor 1 expressed on dendritic cells. *Proc Natl Acad Sci USA* 2005;102:5120–5.
- [102] Morita R, Ukyo N, Furuya M, Uchiyama T, Hori T. Atrial natriuretic peptide polarizes human dendritic cells toward a Th2-promoting phenotype through its receptor guanylyl cyclase-coupled receptor A. *J Immunol* 2003;170:5869–75.
- [103] Panther E, Corinti S, Idzko M, Herouy Y, Napp M, la Sala A, et al. Adenosine affects expression of membrane molecules, cytokine and chemokine release, and the T-cell stimulatory capacity of human dendritic cells. *Blood* 2003;101:3985–90.
- [104] Aliberti J, Viola JP, Vieira-de-Abreu A, Bozza PT, Sher A, Scharfstein J. Cutting edge: bradykinin induces IL-12 production by dendritic cells: a danger signal that drives Th1 polarization. *J Immunol* 2003;170:5349–53.
- [105] Weijzen S, Velders MP, Elmishad AG, Bacon PE, Panella JR, Nickoloff BJ, et al. The Notch ligand Jagged-1 is able to induce maturation of monocyte-derived human dendritic cells. *J Immunol* 2002;169:4273–8.
- [106] Kim KD, Lim HY, Lee HG, Yoon DY, Choe YK, Choi I, et al. Apolipoprotein A-I induces IL-10 and PGE2 production in human monocytes and inhibits dendritic cell differentiation and maturation. *Biochem Biophys Res Commun* 2005;338:1126–36.
- [107] Ohl L, Mohaupt M, Czeloth N, Hintzen G, Kiafard Z, Zwirner J, et al. CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. *Immunity* 2004;21:279–88.
- [108] Randolph GJ, Angeli V, Swartz MA. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. *Nat Rev Immunol* 2005;5:617–28.
- [109] Sánchez-Sánchez N, Riol-Blanco L, Rodríguez-Fernández JL. The multiple personalities of the chemokine receptor CCR7 in dendritic cells. *J Immunol* 2006;176:5153–9.
- [110] Reis e Sousa C. Activation of dendritic cells: translating innate into adaptive immunity. *Curr Opin Immunol* 2004;16:21–5.
- [111] Amsen D, Blander JM, Lee GR, Tanigaki K, Honjo T, Flavell RA. Instruction of distinct CD4 T helper fates by different notch ligands on antigen-presenting cells. *Cell* 2004;117:515–26.
- [112] Tu L, Fang TC, Artis D, Shestova O, Pross SE, Maillard I, et al. Notch signaling is an important regulator of type 2 immunity. *J Exp Med* 2005;202:1037–42.
- [113] Pulendran B. Variagation of the immune response with dendritic cells and pathogen recognition receptors. *J Immunol* 2005;173:2457–65.
- [114] Pulendran B, Smith JL, Caspary G, Brasel K, Pettit D, Maraskovsky E, et al. Distinct dendritic cell subsets differentially regulate the class of immune response in vivo. *Proc Natl Acad Sci USA* 1999;96:1036–41.
- [115] Maldonado-Lopez R, De Smedt T, Michel P, Godfroid J, Pajak B, Heirman C, et al. CD8 $\alpha$ <sup>+</sup> and CD8 $\alpha$ <sup>-</sup> subclasses of dendritic cells

- direct the development of distinct T helper cells in vivo. *J Exp Med* 1999;189:587–92.
- [116] Sporri R, Reis e Sousa C. Inflammatory mediators are insufficient for full dendritic cell activation and promote expansion of CD4+ T cell populations lacking helper function. *Nat Immunol* 2005;6:163–70.
- [117] Tang Q, Krummel MF. Imaging the function of regulatory T cells in vivo. *Curr Opin Immunol* 2006;18:496–502.
- [118] Zou W. Regulatory T cells, tumour immunity and immunotherapy. *Nat Rev Immunol* 2006;6(4):295–307.
- [119] Randolph DA, Fathman CG. Cd4+Cd25+ regulatory T cells and their therapeutic potential. *Annu Rev Med* 2006;57:381–402.
- [120] Pasare C, Medzhitov R. Toll pathway-dependent blockade of CD4-CD25-T cell-mediated suppression by dendritic cells. *Science* 2003;299:1033–6.
- [121] Pasare C, Medzhitov R. Toll-dependent control mechanisms of CD4 T cell activation. *Immunity* 2004;21:733–41.
- [122] Whelan M, Harnett MM, Houston KM, Patel V, Harnett W, Rigley KP. A filarial nematode-secreted product signals dendritic cells to acquire a phenotype that drives development of Th2 cells. *J Immunol* 2000;164:6453–60.
- [123] Vieira PL, de Jong EC, Wierenga EA, Kapsenberg ML, Kalinski P. Development of Th1-inducing capacity in myeloid dendritic cells requires environmental instruction. *J Immunol* 2000;164:4507–12.
- [124] Huang Q, Liu D, Majewski P, Schulte LC, Korn JM, Young RA, et al. The plasticity of dendritic cell responses to pathogens and their components. *Science* 2001;294:870–5.
- [125] de Jong EC, Vieira PL, Kalinski P, Schuitemaker JH, Tanaka Y, Wierenga EA, et al. Microbial compounds selectively induce Th1 cell-promoting or Th2 cell-promoting dendritic cells in vitro with diverse Th cell-polarizing signals. *J Immunol* 2002;168:1704–9.
- [126] Agrawal S, Agrawal A, Doughty B, Gerwitz A, Blenis J, Van Dyke T, et al. Cutting edge: different Toll-like receptor agonists instruct dendritic cells to induce distinct Th responses via differential modulation of extracellular signal-regulated kinase-mitogen-activated protein kinase and c-Fos. *J Immunol* 2003;171:4984–9.
- [127] Dillon S, Agrawal A, Van Dyke T, Landreth G, McCauley L, Koh A, et al. A Toll-like receptor 2 ligand stimulates Th2 responses in vivo, via induction of extracellular signal-regulated kinase mitogen-activated protein kinase and c-Fos in dendritic cells. *J Immunol* 2004;172:4733–43.
- [128] Colucci F, Caliguri MA, Di Santo JP. What does it take to make a natural killer? *Nat Rev Immunol* 2003;3:413–25.
- [129] Lodoen MB, Lanier LL. Natural killer cells as an initial defense against pathogens. *Curr Opin Immunol* 2006;18:391–8.
- [130] Deng L, Mariuzza RA. Structural basis for recognition of MHC and MHC-like ligands by natural killer cell receptors. *Semin Immunol* 2006;18:159–66.
- [131] Munz C, Steinman RM, Fujii SI. Dendritic cell maturation by innate lymphocytes: coordinated stimulation of innate and adaptive immunity. *J Exp Med* 2005;202:203–7.
- [132] Degli-Eposti MA, Smyth MJ. Close encounters of different kinases: dendritic cells and NK cells take centre stage. *Nat Rev Immunol* 2005;5:112–22.
- [133] Wilson JL, Heffler LC, Charo J, Scheynius A, Bejarano MT, Ljunggren HG. Targeting of human dendritic cells by autologous NK cells. *J Immunol* 1999;163:6365–70.
- [134] Carbone E, Terrazzano G, Ruggiero G, Zanzi D, Ottaiano A, Manzo C, et al. Recognition of autologous dendritic cells by human NK cells. *Eur J Immunol* 1999;29:4022–9.
- [135] Della Chiesa M, Vitale M, Carlomagno S, Ferlazzo G, Moretta L, Moretta A. The natural killer cell-mediated killing of autologous dendritic cells is confined to a cell subset expressing CD94/NKG2A, but lacking inhibitory killer Ig-like receptors. *Eur J Immunol* 2003;33:1657–66.
- [136] Gerosa F, Baldani-Guerra B, Nisii C, Marchesini V, Carra G, Trinchieri G. Reciprocal activating interaction between natural killer cells and dendritic cells. *J Exp Med* 2002;195:327–33.
- [137] Ferlazzo G, Tsang ML, Moretta L, Melioli G, Steinman RM, Munz C. Human dendritic cells activate resting natural killer (NK) cells and are recognized via the Nkp30 receptor by activated NK cells. *J Exp Med* 2002;195:343–51.
- [138] Walzer T, Dalod M, Robbins SH, Zitvogel L, Vivier E. Natural-killer cells and dendritic cells: “l’union fait la force”. *Blood* 2005;106:2252–8.
- [139] Fujii S, Shimizu K, Kronenberg M, Steinman RM. Prolonged IFN-gamma producing NKT response induced with alpha-galactosylceramide-loaded DCs. *Nat Immunol* 2002;3:867–74.
- [140] Hermans IF, Silk JD, Gileadi U, Salio M, Mathew B, Ritter G, et al. NKT cells enhance CD4+ and CD8+ T cell responses to soluble antigen in vivo through direct interaction with dendritic cells. *J Immunol* 2003;171:5140–7.
- [141] Leslie DS, Vincent MS, Spada FM, Das H, Sugita M, Morita CT, et al. CD1-mediated gamma/delta T cell maturation of dendritic cells. *J Exp Med* 2002;196:1575–84.
- [142] Conti L, Casetti R, Cardone M, Varano B, Martino A, Belardelli F, et al. Reciprocal activating interaction between dendritic cells and pamidronate-stimulated gamma/delta T cells: role of CD86 and inflammatory cytokines. *J Immunol* 2005;174:252–60.
- [143] van Gisbergen KP, Sanchez-Hernandez M, Geijtenbeek TB, van Kooyk Y. Neutrophils mediate immune modulation of dendritic cells through glycosylation-dependent interactions between Mac-1 and DC-SIGN. *J Exp Med* 2005;201:1281–92.
- [144] Ludwig IS, Geijtenbeek TB, van Kooyk Y. Two way communication between neutrophils and dendritic cells. *Curr Opin Pharmacol* 2006;6:408–13.
- [145] Kuwajima S, Sato T, Ishida K, Tada H, Tezuka H, Ohteki T. Interleukin 15-dependent crosstalk between conventional and plasmacytoid dendritic cells is essential for CpG-induced immune activation. *Nat Immunol* 2006;7:740–6.
- [146] Pulendran B. Division of labor and cooperation between dendritic cells. *Nat Immunol* 2006;7:699–700.
- [147] Niess JH, Reinecker HC. Dendritic cells in the recognition of intestinal microbiota. *Cell Microbiol* 2006;8:558–64.
- [148] Bilsborough J, Viney JL. Gastrointestinal dendritic cells play a role in immunity, tolerance, and disease. *Gastroenterology* 2004;127:300–9.
- [149] Sato A, Hashiguchi M, Toda E, Iwasaki A, Hachimura S, Kamino-gawa S. CD11b+ Peyer’s patch dendritic cells secrete IL-6 and induce IgA secretion from naive B cells. *J Immunol* 2003;171:3684–90.
- [150] Rimoldi M, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM, et al. Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. *Nat Immunol* 2005;6:507–14.
- [151] Ziegler SF, Liu YJ. Thymic stromal lymphopoietin in normal and pathogenic T cell development and function. *Nat Immunol* 2006;7:709–14.
- [152] Kapsenberg M. Tweaking of memory T helper 2 cells by TSLP. *Immunity* 2006;24:673–5.
- [153] Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med* 2006;203:269–73.
- [154] Vermeulen M, Giordano M, Trevani AS, Sedlik C, Gamberale R, Fernandez-Calotti P, et al. Acidosis improves uptake of antigens and MHC class I-restricted presentation by dendritic cells. *J Immunol* 2004;172:3196–204.
- [155] Vermeulen ME, Gamberale R, Trevani AS, Martinez D, Ceballos A, Sabatte J, et al. The impact of extracellular acidosis on dendritic cell function. *Crit Rev Immunol* 2004;24:363–84.

- [156] Soruri A, Riggert J, Schlott T, Kiafard Z, Dettmer C, Zwirner J. Anaphylatoxin C5a induces monocyte recruitment and differentiation into dendritic cells by TNF-alpha and prostaglandin E2-dependent mechanisms. *J Immunol* 2003;171:2631–6.
- [157] Rutault K, Alderman C, Chain BM, Katz DR. Reactive oxygen species activate human peripheral blood dendritic cells. *Free Radic Biol Med* 1999;26:232–8.
- [158] Verhasselt V, Goldman M, Willems F. Oxidative stress up-regulates IL-8 and TNF-alpha synthesis by human dendritic cells. *Eur J Immunol* 1998;28:3886–90.
- [159] Basu S, Srivastava PK. Fever-like temperature induces maturation of dendritic cells through induction of hsp90. *Int Immunol* 2003;15:1053–61.



**Juan Sabatté** obtained his MD degree from Buenos Aires University, School of Medicine. He is a PhD student with a fellowship from the National Council for Research and Technology (CONICET). The main focus of his research is to define the mechanisms through which the human immunodeficiency virus (HIV) modulates the function of dendritic cells.



**Julian Maggini** obtained his MD degree from Buenos Aires University, School of Medicine and completed medical residency at the Austral University Hospital (Argentina). He is currently a PhD student with a fellowship from Repsol-YPF. His research project is focused on the ability of innate immune cells to modulate the function of dendritic cells.



**Karen Nahmod** obtained her MD degree from Buenos Aires University, School of Medicine. She is a PhD student with a fellowship from the National Council for Research and Technology (CONICET). The main focus of her research is to determine the influence of the renin-angiotensin-system (RAS) on the differentiation and function of dendritic cells.



**María Marta Amaral** has a degree in Biology from the Buenos Aires University, School of Exact Sciences and Natural Sciences, Argentina. She is a PhD student with a fellowship from the National Agency for the Promotion of Science and Technology (ANPCyT). Her research project is focused on the modulatory actions exerted by histamine on immune cells.



**Diego Martínez** has a degree in Biochemistry from the Buenos Aires University, School of Biochemistry. He is a PhD student with a fellowship from the Buenos Aires University. His research is focused on the mechanisms through which extracellular protons induce the activation of neutrophils and dendritic cells.



**Gabriela Salamone** obtained her PhD in Immunology from the Buenos Aires University, School of Exact Sciences and Natural Sciences, Argentina. She is a member of the scientist research career at the National Council for Research and Technology (CONICET). Her research Project is directed to characterize neuroendocrine mechanisms able to modulate the function of innate immune cells.



**Ana Ceballos** obtained her PhD in Virology from the Buenos Aires University, School of Exact Sciences and Natural Sciences, Argentina. She is a member of the scientist research career at the National Council for Research and Technology (CONICET). The main focus of her research is to characterize the mechanisms through which the human immunodeficiency virus (HIV) modulates the function of dendritic cells and other innate immune cells.



**Mirta Giordano** obtained her PhD in Immunology from the Buenos Aires University, School of Exact Sciences and Natural Sciences, Argentina. She is a member of the scientist research career at the National Council for Research and Technology (CONICET). Over the past 5 years, her research group has contributed broadly to the field of modulation of apoptosis of leukemic cells in chronic lymphocytic leukemia (CLL), the most common adult leukemia in Occident. At present, her research project is directed to understand the association between CLL and autoimmune hemolytic anemia (AHA).



**Mónica Vermeulen** obtained her PhD in Immunology from the Buenos Aires University, School of Exact Sciences and Natural Sciences, Argentina. She is a member of the scientist research career at the National Council for Research and Technology (CONICET). The main focus of her research is to understand the influence of extracellular acidosis on the function of innate immune cells.



**Dr. Jorge Geffner** is an Associate Professor of Immunology at the School of Medicine, Universidad de Buenos Aires, Argentina. He is a biochemist who obtained his PhD in Immunology from the Universidad de Buenos Aires, and is a member of the scientist research career at the National Council for Research and Technology (CONICET), Argentina. He has published over 60 original articles in leading Immunology journals. His research focuses on dendritic cells. Emerging concepts about innate immunity indicate that these cells play a crucial role in sensing environment signals and integrating this information to determine the profile of the adaptive immunity. Considering that the development of acidic microenvironments is a hallmark of inflammatory processes, Geffner and colleagues currently seek to characterize the influence of extracellular acidosis on the function of dendritic cells as well as the mechanisms through which innate immune cells recognize protons as a danger signal.