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

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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.

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].

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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 μm) 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-α 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): FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) [26–28], FcεRI [29,30], FcεRII (CD23) [31], and FcαR1 (CD89) [32]. Interestingly, Amigorena and colleagues demonstrated that internalization of immune complexes by FcγR 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, αvβ3, and αvβ5 [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_3CR1

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^2 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_3CR1 (the receptor for fractalkine/CX_3CL1, 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_3CR1-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_3CR1-deficient mice show a delayed pathogen uptake by DCs from the lumen and, as a consequence, an intrinsic unability 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

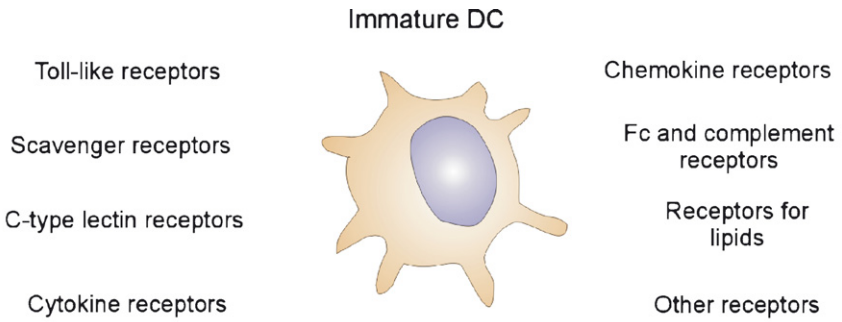
Fig. 1 summarizes information about the families of receptors expressed by immature DCs which enable them to sense their surrounding environment looking for ongoing dangerous processes. As a component of the innate immune system, DCs can recognize a limited but highly conserved set of molecular structures 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 trigger 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 maturate into different functional profiles according to the nature of the stimulus.

3.2. Maturation enables DCs to activate naive 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 recognize 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 PgE2 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



Toll-like receptors	C-type lectin receptors	Scavenger receptors	Cytokine receptors	
TLR1	MR	SR-A	TGF-β	IL-4
TLR2	DEC-205	CD36	Lymphotoxin	IL-5
TLR3	DC-SIGN	LOX-1	GM-CSF	IL-6
TLR4	BDCA-2	MARCO	Type 1 IFNs	IL-10
TLR5	DECTIN-1	[37, 39, 56]	IFN - γ	IL-13
TLR6	DCIR		TNF-α	IL-15
TLR8	DCAL		IL-1	IL-16
TLR9	CLEC		IL-2	IL-21
TLR10	[16, 40-47, 82, 83]		IL-3	
[77-81]			[1-4, 8, 9]	

Chemokine receptors	Fc and complement receptors	Receptors for lipids	Receptors for other signals
CCR1	Fcγ RI, II, III	PgE2 and D2	N-formil peptides (FPR)
CCR2	Fcε RI, II	LB4 (BLT1)	Histamine (HR1 - HR2)
CCR3	Fcα RI	Fatty Acids (PPAR)	Galectins 1, 3 and 9
CCR4	CR3	Sphingosylphosphorylcholine	Endothelin 1 (ETA and ETB)
CCR5	CR4	Psychosine	Angiotensin II (AT1 and AT2)
CCR6	C5a	Lysophosphatidylcholine	ATP (P2 purinoreceptors)
CCR8	[26-36, 84]	Sphingosine 1-phosphate	RANKL (RANK)
CXCR4		Platelet activator factor	Vanilloids (VR1)
[1-4, 62, 65]		[85-91]	Atrial Natriuretic peptide (GC-A)
			Adenosine (AR)
			Bradykinin (B2R)
			Notch ligands
			Apoliprotein A-1
			[92-106]

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_H1, T_H2 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-α (signal 3), mature DCs promote the differentiation of TCD4+ lymphocytes into T_H1 cells, producing IFN-γ, as well as the differentiation of T CD8+ lymphocytes into cytotoxic cells [1,4,3,110]. Alternatively,

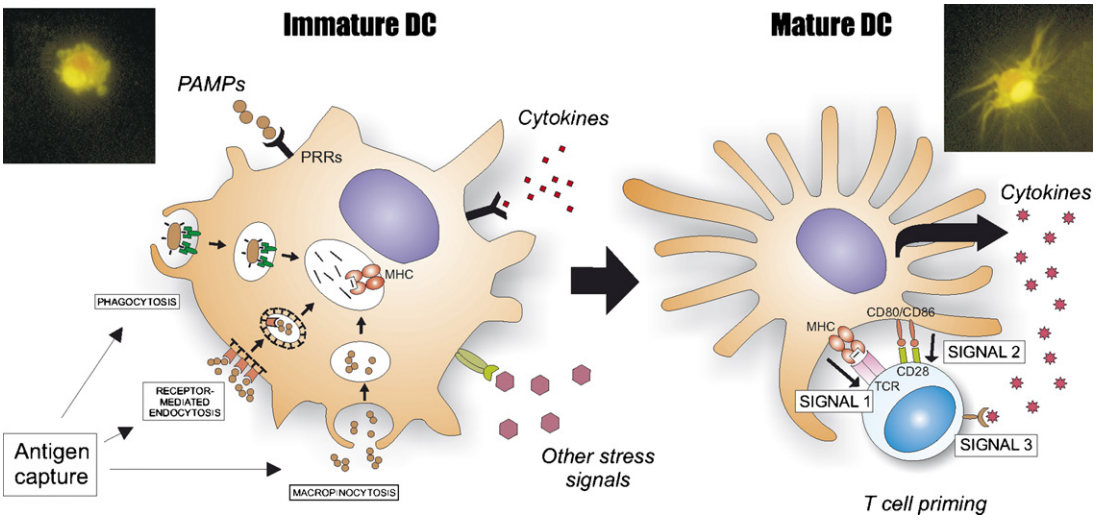


Fig. 2. Functional profile of immature and mature DCs. Immature DCs efficiently sample antigens from the surrounding environment by macropinocytosis, receptor-mediated endocytosis and phagocytosis. On the other hand, they express a high diversity of receptors which enable them to recognize PAMPs, cytokines, 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+ lymphocytes into T_H2 cells, producing IL-4, IL-5 and IL-13, cytokines which are silenced in the T_H1 lineage [4,110–112]. T_H1 cells are crucial for cellular immunity against intracellular pathogens while T_H2 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_H1 versus T_H2 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-α and β, IL-1, IL-6, and TNF-α [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+ T cell clonal expansion, but failed to drive the differentiation of CD4+ T cells into T_H1 effectors, due to the unability of DCs to produce IL-12. By contrast, exposure to pathogen components resulted in fully activated DCs that promoted T_H1 immunity. These observations support the notion that the main function of PPRs 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 $CD4^+$ $CD25^+$ regulatory T cells (T_R 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 $CD4^+$ $CD25^+$ 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_H1 versus T_H2 responses. Exposure to helminth products usually induces the differentiation of DCs that drives the development of T_H2-like responses, while the same DCs when exposed to LPS stimulate T_H1 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_H1 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_H2 stimulus schistosome egg stimulate T_H2 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-γ, TNF-α, 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-α and IFN-γ, 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 α-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 γδ 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-α by γδ 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 $CD4^+$ T cells into T_H1 effectors. Neutrophil-DC interaction is mediated by the binding of DC-SIGN on DCs to the β2 integrin Mac-1 on neutrophils. This interaction induces the maturation of DCs through a mechanism completely dependent on the production of TNF-α 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 phatogenic 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^{12} 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+ cells into T_H2 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+ lymphocytes into T_H2 cells, even after exposure to a T_H1 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_H1-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_H1 responses, favouring the differentiation of CD4+ T lymphocyes into T_H2 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_H2 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+ 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

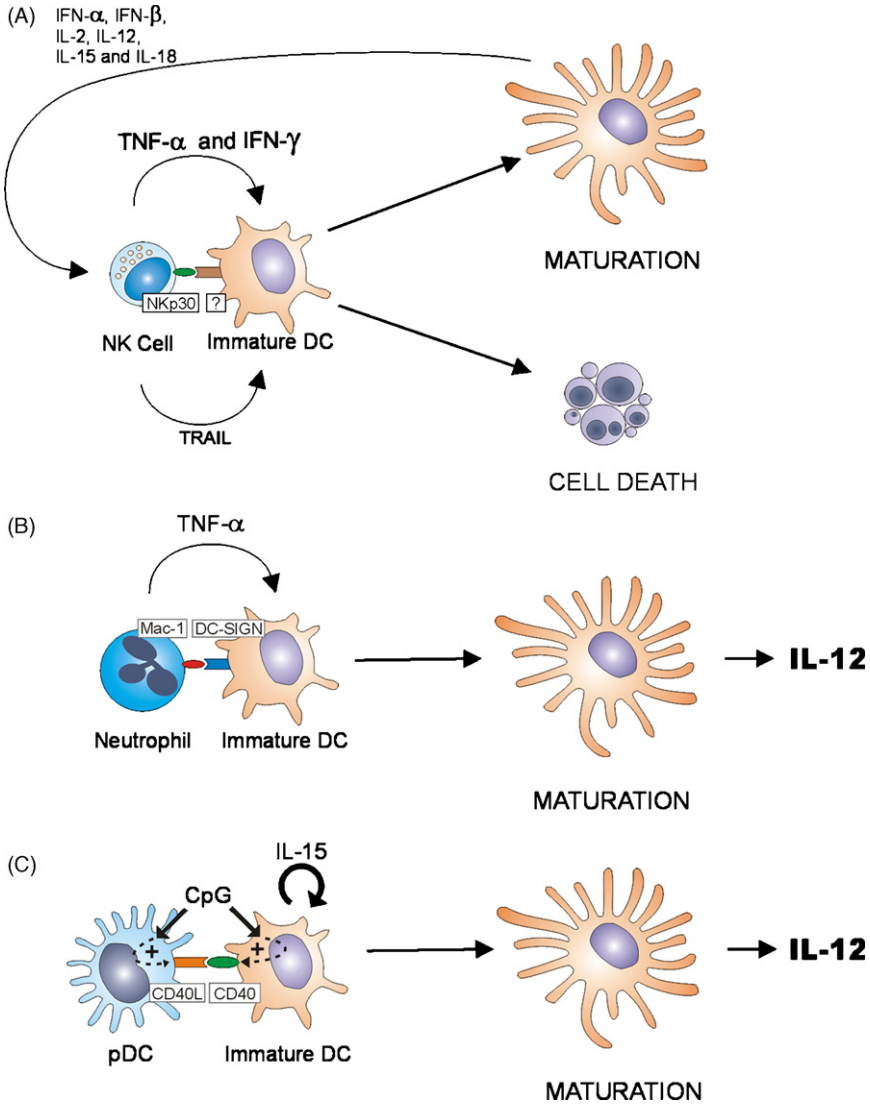


Fig. 3. Modulation of DC function by innate immune cells. (A) NK cells modulate the function of DCs by two alternative mechanisms. They can kill immature DCs through a TRAIL-mediated mechanism or, alternatively, they can stimulate the maturation of DCs by both, cell–cell contact-dependent mechanisms and the production of TNF-α and IFN-γ. Both processes require the participation of the NK activating receptor NKp30. (B) Neutrophils can stimulate the maturation of DCs and the production of IL-12. This process is mediated by the interaction of DC-SIGN on DCs and the β2 integrin Mac-1 on neutrophils. This interaction leads to the maturation of DCs through a mechanism dependent on the production of TNF-α 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 IL-15, and also a modest synthesis of IL-12. In turns, IL-15 stimulates DCs in an autocrine way through the IL-15 receptor, enhancing the expression of CD40 on DCs. CpG DNA also stimulates plasmacytoid DCs via TLR9 inducing the expression of CD40L on a subset of these cells. These CD40L+ plasmacytoid DCs stimulate CD40-expressing DCs augmenting the production of IL-12 and conferring resistance to *Listeria monocytogenes* infection.

tightly regulated both by angiotensin-converting enzyme, a kinin-degrading peptidase, and by endogenous IL-10 [104]. Soruri and colleagues have shown that the complement anaphylatoxin C5a induce "in vivo" the differentiation of human monocytes into mature DCs by TNF-α and prostaglandin 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 hsp90 [159]. Together, these observation 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.

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