

Dendritic Cells: More Than Just Adaptive Immunity Inducers?

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Abstract: Dendritic cells (DC) are well known for their capacity to induce immune responses and there is also accumulating evidence of their ability to interact with various cell types of the innate system, such as NK, NKT or TCR $\gamma\delta$ cells. These interactions are bi-directional, mediated by soluble or cell surface molecules and have been mainly described in the context of immune responses to infectious agents and tumors.

NK, NKT or TCR $\gamma\delta$ cells induce the maturation of DC, as shown by the increased expression of CD86, IL12 production and priming of T cell responses. On the other hand, mature DC have the ability to activate NK, NKT or TCR $\gamma\delta$ cells for sustained innate immune responses and activated NK cells may kill immature DC. In addition, DC and NK or TCR $\gamma\delta$ cells share similar functions such as cytotoxic and antitumor activity, interferon production and antigen presentation capacity.

Keywords: Antigen-presenting cells (APC), dendritic cells (DC), natural killer cells (NK), TCR $\gamma\delta$ cells, NKT cells.

INTRODUCTION

Historically, the main function of dendritic cells (DC) was defined as the ability to stimulate naïve T cells. However, pivotal experiments by Fernandez *et al.* [1] demonstrated that DC also activate NK cells. More recently, this DC activation was extended to other cell types that play a role in natural innate immunity such as NKT or TCR $\gamma\delta$ cells [2, 3]. Moreover, DC share with natural innate cells the ability to kill tumor cells (Fig. 1).

Conventional DC subsets described in humans include myeloid DC CD11c⁺ (mDC) and plasmacytoid DC CD11c⁻ (pDC). When compared to mDC, pDC lack expression of some myeloid antigens (CD13, CD33) and lymphoid markers (CD2, CD5, CD7) [4]. In addition, pDC produce large amounts of IFN α in response to viral DNA or RNA [5], suggesting that they play an important role in sensing viral infections. Human mDC also differ from pDC in their expression pattern of highly conserved microbial pattern recognition receptors, known as toll-like receptors (TLR). Upon ligand recognition by TLR, DC maturation occurs, followed by secretion of numerous cytokines and chemokines [6]. In steady-state conditions, DC are in an immature stage but in an inflammatory microenvironment, they up-regulate surface antigens such as CD80, CD86 and CCR7 and produce high levels of IL12 and TNF α during a process called maturation (for review see [7]).

Natural Killer (NK) cells are a particular population of lymphocytes (for review [8]) that play an important role in innate immunity (for review see [9]). The "NK" name was originally given after the demonstration of NK cells' ability to kill target cells without prior exposure to them or help from another cell population, in contrast to cytolytic T cells.

NKT lymphocytes are T lymphocytes expressing several NK markers. Upon activation, they are able to produce type

1 as well as type 2 cytokines and display cytotoxic activity [10]. NKT cells bearing an invariant TCR (V α 14J α 28 gene segments in mice and V α 24J α Q in humans) are designated as iNKT cells and are restricted by nonpolymorphic CD1d molecules [11]. One example of a natural CD1d ligand is the lipophosphoglycan from the surface glycocalyx of parasites, which stimulates IFN γ secretion by a subset of NKT cells [12]. Like NK cells, NKT cells can detect altered self-ligands such as ganglioside GD3, overexpressed on human melanoma cells [13]. Therefore, both self and microbial glycolipids presented on CD1d molecules can induce NKT activation. NKT cells are involved in a large number of immune responses including autoimmunity [14] and immunity against viral [15], bacterial [16], fungal [17], parasitic pathogens [18] and tumors [19].

TCR $\gamma\delta$ T cells represent a distinct subset of T cells characterized by a T cell receptor (TCR) with unique structural and antigen-binding features which are different from the classical TCR composed of α and β chains [20]. In contrast to the antigen-recognition by TCR $\alpha\beta$ T cells, TCR $\gamma\delta$ cells do not need any antigen-presenting cell (APC) for the recognition of foreign epitopes [23]. Various populations of TCR $\gamma\delta$ cells reside in the peripheral tissues of mice, including the skin, gut and uterus. Each tissue has its own specific subset of TCR $\gamma\delta$ cells, according to the variable (V) gene used to generate the TCR. Resident TCR $\gamma\delta$ cells represent a first line of defense against infection and exert tissue-specific immune functions. However, in humans, tissue-specific TCR $\gamma\delta$ cells are not as prominent. Indeed, the adult human TCR $\gamma\delta$ cell repertoire is dominated by a polyclonal population bearing the V γ 2V δ 2 TCR and representing ~2 to 8% of peripheral blood T cells. V γ 2V δ 2 T cells recognize phosphorylated isoprenoid precursors and alkylamines which are conserved in the metabolic pathways of many species including plants, pathogens and primates [21]. These cells expand in the presence of many different infectious agents including mycobacteria. In the periphery, TCR $\gamma\delta$ cells express mostly the V δ 1 TCR [22]. TCR $\gamma\delta$ cells display a range of NK cell functions including the rapid secretion of chemokines and cytokines and target cell lysis (for review see [20]). TCR $\gamma\delta$

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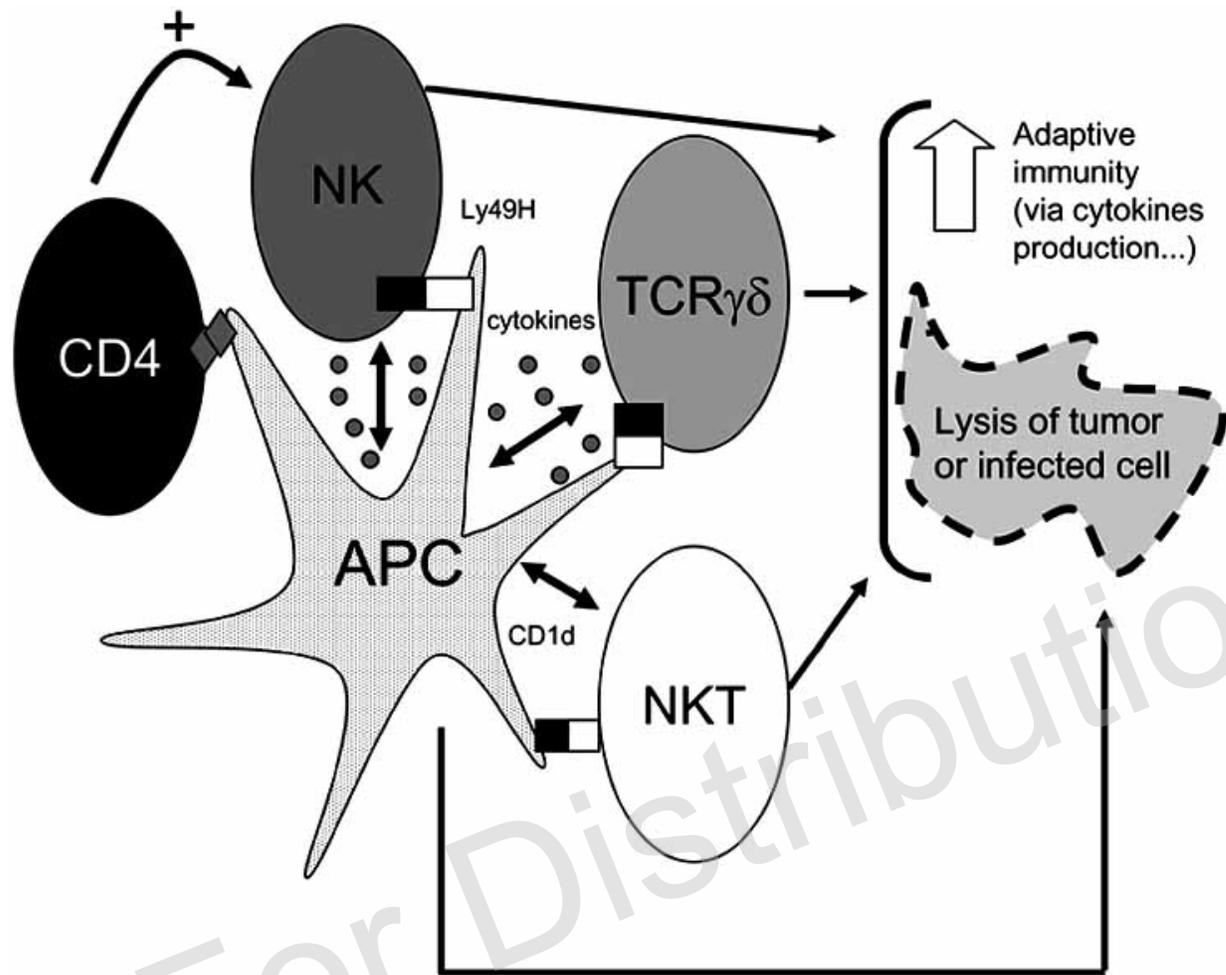


Fig. (1). Schematic representation of the central role of antigen-presenting cells (APC) in the natural immunity.

cells are key players of innate immunity, and arguably the most complex and advanced cellular representative of the innate immune system (for review [24]).

INTERACTIONS BETWEEN DENDRITIC CELLS AND NATURAL KILLER CELLS

The first evidence for the role of DC in natural immunity was provided by the work of Fernandez *et al.* [1] which showed a direct activation of NK cells by DC *in vivo*. Subsequently, the DC/NK interactions were found to be multidirectional [25]. Although NK cell activation *in vitro* has been documented by using a variety of mouse or human DC [9], most studies focused on the interactions between NK cells and mDC, even though NK cells also have the ability to interact with pDC [25]. For example, upon stimulation through TLR9, pDC can activate NK cells to kill various tumor cells [26].

It is still unclear whether the DC maturation status influences their ability to activate NK cells. In some studies, immature DC require a maturation stimulus to activate NK cells [27], whereas other reports show that immature and

mature DC are equivalent in their ability to activate NK cells [28, 29].

The *in vivo* relevance of NK cell activation by DC is demonstrated in murine tumors [1] and viral models [30] and is related to a particular DC subset expressing CD8 α +. After infection of C57Bl/6 mice with cytomegalovirus, the expansion of NK cells induced by DC was shown to specifically involve the Ly49H receptor on NK cells [9]. On the other hand, NK cells can respond to polyinosinic-polycytidylic acid (poly(I:C)), a synthetic mimic of viral RNA, directly *via* TLR3 and independently from DC [31]. In bacterial infections, interactions between NK cells and DC also result in the rapid induction of NK cell activation and in the lysis of uninfected DC.

The DC-induced activation of resting NK cells *in vitro* requires direct cell contacts resulting in a polarized secretion of preassembled stores of IL12 by DC towards NK cells within the synapse between both cell types [32]. Cytokines such as IL18, IL15, IL2 and type I interferon also play a crucial role in this cross-talk, for example, murine DC require the presence of IL-15R to prime NK cells [33], and IL2-deficient DC are severely impaired in their ability to

activate NK-cell response both *in vitro* and *in vivo*, as revealed by antibacterial and antitumor responses [27]. It seems that the different subsets of DC activate NK cells at several steps of the immune response, with the pDC promoting early activity of NK cells followed by mDC stimulation and finally activation of a subpopulation of NK cells (Ly49H+) by mDC. Early release of IL12 by pathogen-activated DC could be the link between NK/mDC and NK/pDC interactions [26].

Conversely, NK cells can activate DC. Optimal DC *in vitro* activation by NK cells requires both cell-cell contacts and TNF α production [29]. Cell-cell contacts can be mediated *via* the receptor NKp30, and inhibitory receptors including some Killer Immunoglobulin-like Receptors (KIR) or NKG2A receptors can negatively regulate this activation [35]. In lymph nodes, NK cells may have an important role in the initiation of T-cell responses by contributing to DC maturation. Indeed, under *in vitro* conditions where DC are suboptimally activated with type-I IFN, NK cells license DC to prime T-cell responses [36]. In some cases, T-cell-mediated tumor rejection is dependent on DC activation by NK cells [37]. Type-I IFN secreted during NK-cell-mediated tumor rejection is critical for CTL generation, particularly when tumors express CD70, CD80 or CD86 [38]. Furthermore, Adam *et al.* [39] reported that NK-cell-DC crosstalk may bypass the T helper arm in CTL induction against tumors expressing NKG2D ligands.

In contrast, activated NK cells can also kill immature uninfected DC [40] or graft-derived DC in transplant models [41]. Killing of DC by activated NK cells may negatively regulate inflammatory responses [42]. Among NK receptors, NKp30 seems to play an important role in the maturation and control of apoptosis in DC. However, the up-regulation of HLA-E expression on DC protects them from NK lysis through the CD94/NKG2A inhibitory receptor [43]. The interactions between NK cells and DC *via* NKp30 differ according to the ratio between NK cells and DC. A low NK/DC (1/5) ratio results in DC activation whereas at high (5/1) ratio, NK cells kill immature DC [28, 29]. In contrast, pDC seem to display an intrinsic resistance to lysis by NK cells but exposure of pDC to IL3 increases their susceptibility to NK cell cytotoxicity [25]. Until now, DC killing by NK cells *in vivo* has been demonstrated only in murine transgenic [42] or transplantation models with no evidence so far that DC killing occurs *in vivo* under normal physiologic conditions.

As well as the NK-cell-DC-T-cell sequence, a DC-T-cell-NK-cell pathway has also been identified *in vivo*. Van Den Broeke *et al.* [44] reported that an injection of unpulsed mature bone marrow-derived DC protects BALB/C mice against syngeneic CT26 colon carcinoma or LL/2 lung carcinoma inoculation and that the tumor protection is mediated by NK cells. Activation of NK cells is CD4 T-cell-dependent and relies strongly on the expression of costimulatory molecules on DC, suggesting that mature DC stimulate CD4 T cells that can, subsequently, directly activate NK cells through IL-2 secretion [44].

Since the interactions between NK cells and DC require cell contacts, there must be a common meeting ground for these cells, recently proposed as lymph nodes or inflammation sites (for review see [45]). For example, NK cells and

DC are in direct contact in dermal sites of yeast infection [46], and CD56^{bright} NK cells are present in normal resting lymph nodes in close proximity to activated DC [47]. In mice, injection of mature DC promotes rapid recruitment of NK cells to lymph nodes in a CCR7-independent, CXCR3-dependent manner [48], whereas they are excluded from these tissues under normal conditions. Interestingly, pDC express homing molecules similar to those expressed by CD56^{bright} NK cells, including L-selectin, CXCR3 and, after activation, CCR7. Therefore, pDC are likely to migrate from the blood through high endothelial venules just as NK cells do, before co-localising in the lymph node and activating each other. In inflammation sites, such as the skin from patients infected with some types of yeast, increased numbers of NK cells have also been demonstrated in close proximity to DC, providing evidence for NK-DC contacts in peripheral tissues *in vivo* [46].

INTERACTIONS BETWEEN DENDRITIC CELLS AND NATURAL KILLER T LYMPHOCYTES

Natural Killer T (NKT) cells bearing an invariant TCR (iNKT) need DC to become activated, as shown by the stimulation of human V α 24⁺CD8⁺ NKT cells in the presence of monocyte-derived DC pulsed with α -Galactosylceramid (α -GalCer). On the other hand, Kitamura *et al.* [49] suggested that iNKT are able to activate DC and to modulate the adaptive immune response induced by them. The interaction of NKT cells with antigen-capturing DC allows the induction of antigen-specific, IFN γ -producing CD4⁺ and CD8⁺ T cells. Murine DC maturation has been documented *in vitro* and *in vivo* after iNKT cell stimulation by the synthetic α -GalCer presented by CD1d molecules on DC [50] and iNKT cells have been proposed to have a CD40 signaling mediated adjuvant effect for T cell-mediated immunotherapy [50, 51]. These data suggest that DC activated by a population of innate lymphocytes, such as NKT cells, can activate another group of innate lymphocytes, such as NK cells, to induce antitumor effects. In addition, other data suggest that iNKT cells mediate a cross-talk between DC subsets (mDC and pDC) known to express mutually exclusive TLR and cytokine profiles [52].

Like NK cells, NKT cells could also, under certain conditions, kill both immature and mature DC. These cells expressing inhibitory NK receptors are restricted by HLA-E molecules and are able to kill most NK-susceptible tumor cell lines [53]. Interestingly, in *Leishmania infantum* infections, immature DC up-regulate CD1d and are efficiently killed by NKT cells, whereas they are resistant to NK cell-mediated lysis due to an up-regulation of HLA-E expression which protects them through the inhibitory receptor CD94/NKG2A on NK cells [54].

INTERACTIONS BETWEEN DENDRITIC CELLS AND TCR $\gamma\delta$ CELLS

In 1996, Yokota *et al.* [55], suggested that an interaction occurs between TCR $\gamma\delta$ and APC, since murine Langerhans cells (LC), a sub-family of DC localized in squamous epithelium, are in close contact with TCR $\gamma\delta$ cells. Contacts between TCR $\gamma\delta$ and DC are also detected in the murine lung [24] and compared to TCR $\alpha\beta$ T cells, TCR $\gamma\delta$ cells are more frequently found in connection with macrophages and DC

[56]. Finally, evidence was provided that TCR $\gamma\delta$ T cells control the recruitment and differentiation of peritoneal macrophages in the presence of a bacterial infection [57].

Here again, the TCR $\gamma\delta$ cells-DC interactions are bidirectional [3, 58]. TCR $\gamma\delta$ are activated by DC infected *in vitro* by the Bacille Calmette-Guerin (BCG) as indicated by elevated CD69 expression on their cell surface, IFN γ secretion and cytotoxic activity. Consequently DC-stimulated TCR $\gamma\delta$ cells help the DC to prime a significantly stronger antimycobacterial CD8 T cell response [3]. Activation of TCR $\gamma\delta$ cells with isopentenyl pyrophosphate (IPP) or aminobiphosphonates (pamidronate; PAM) led to a significant up-regulation of CD86 and MHC class I molecules and to the acquisition of functional features typical of activated DC [58]. Cell-cell contacts are required for stimulation with PAM but not IPP [58]. In return, DC induce CD25 and CD69 up-regulation on TCR $\gamma\delta$ cells as well as IFN γ and TNF α secretion by TCR $\gamma\delta$ cells [58]. TCR $\gamma\delta$ cells activated by the synthetic phosphoantigen bromohydrin pyrophosphate (BrHPP) induce the production of IL12 by DC, an effect involving IFN γ production. The relevance of this finding to DC function was demonstrated by the increased production of IFN γ by alloreactive T cells when stimulated in a mixed leukocyte reaction with DC preincubated in the presence of activated TCR $\gamma\delta$ cells. These data suggest that TCR $\gamma\delta$ cell activation results in DC maturation and therefore enhanced TCR $\alpha\beta$ T cell responses.

DC AND "NATURAL CELLS" SHARE SIMILAR FUNCTIONS

Besides their APC function, DC may acquire cytotoxic properties [59, 60], for example in response to stimulation with type I IFN [61]. In fact, human DC can induce *in vitro* growth arrest and apoptosis of tumor cells [60, 62, 63]. DC able to kill tumor cells have been also described in rat models [64]. Cytotoxic DC activity seems to be independent of Fas-associated death domain but dependent on caspase-8 [60], whereas the DC negative effect on tumor proliferation is likely to be caspase-8 independent and does not require cell contacts [63].

Recently, Taieb *et al.* [65] described a new subset of murine DC involved in tumor surveillance. These cells are CD11c⁺B220⁺Ly6C⁻ and express NK markers such as NK1.1 and NKG2D. They produce large amounts of type I IFN, IFN γ and IL12 and may kill cells lacking self-major histocompatibility complex molecules in a TRAIL-dependent manner. For these reasons, they have been coined "IFN-producing killer dendritic cells (IKDC)" [66]. These cells are found not only in tumors, but also in primary and secondary organs of naïve mice [65]. Although IKDC possess NK markers and functions [66], they constitute a distinct cell population and differ in their developmental origin since Rag2^{-/-}IL2rg^{-/-} mice lack canonical NK cells but possess functional IKDC in the spleen [65]. To date, no exact human equivalent of mouse IKDC has been reported. Other types of DC bearing NK cell receptors have been identified, such as bitypic cells expressing both CD11c and the NK cell marker DX5 in the context of lymphocytic choriomeningitis virus (LCMV) infection [67]. In a mouse autoimmune diabetes model, treatment with CD40L induces the presence of this bitypic- NK/DC regulatory cell population [68]. These cells

can kill NK sensitive target cells and present OVA antigen [68].

On the other hand, activated NK cells could become potent APC [69]. After activation, NK cells can up-regulate MHC class II, CD80, and CD86 molecules and acquire independent unique mechanisms of antigen capture and presentation, involving activating receptors such as NKp46, NKp30 and NKG2D [69]. NK cells may also acquire functional APC-like properties after target cell killing [69]. Studies on the T cell-activating potential of human NK cells in different clinical conditions revealed that a pro-inflammatory, but not immunosuppressive, microenvironment can up-regulate T-cell-activating molecules on NK cells [69]. Even a subtype of TCR $\gamma\delta$ cells (V δ 2⁺ T cells) upon microbial activation can display antigen and provide enough co-stimulatory signals to induce a strong naïve $\alpha\beta$ T cell proliferation and differentiation [70]. TCR $\gamma\delta$ cells also express DC activation markers, such as MHC class II, CD80 and CD86 [71]. Expression of MHC class II and ligands for T cell costimulatory molecules is not a guarantee for APC capability since eosinophils, for example, express significant levels of MHC class II and CD86 on their surface after activation but cannot process antigen [72]. The APC function of TCR $\gamma\delta$ cells seems to be associated with the expression of CCR7, allowing their migration to lymph nodes. This expression is early but transient [73] suggesting that the APC function of TCR $\gamma\delta$ cells would be more effective in the early stage of antimicrobial immune processes. The mechanisms controlling antigen uptake and processing in these cells are, however, still unknown and since *in vivo* studies are understandably difficult to perform in humans, there is no evidence that these cells function as APC.

In conclusion, there is accumulating evidence that DC maturation by innate lymphocytes coordinates innate and adaptive immunity. The interactions between DC and "natural cells" may be particularly critical in situations where immune surveillance requires efficient early innate responses.

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