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The dialogue between human natural killer cells and dendritic cells

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The interaction of NK cells with dendritic cells (DCs) appears to play an important role in both innate and adaptive immune responses to pathogens. In peripheral inflamed tissues the simultaneous engagement of receptors for danger (e.g. Toll-like receptors), which are expressed by both NK cells and DCs, results in cell activation and the acquisition of functional properties necessary for controlling, and possibly rapidly eliminating, pathogens by innate effector mechanisms. Moreover, NK cells are needed to select the most appropriate DCs that display the functional properties suitable for subsequent T-cell priming. This NK-cell-mediated programming of DC maturation is modulated by cytokines released during the early stages of inflammatory responses (i.e. IL-12, IFN-γ, IL-4). NK cells and DCs continue their interactions in secondary lymphoid organs where both cell types play a role in the control of T-cell priming.

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Current Opinion in Immunology 2005, **17**:306–311

This review comes from a themed issue on
Lymphocyte effector functions
Edited by Lorenzo Moretta

Available online 11th April 2005

0952-7915/$ – see front matter

DOI 10.1016/j.coi.2005.03.004

Introduction

The effector function of NK cells is regulated by a balance between opposite signals delivered by a set of MHC class-I-specific inhibitory receptors and by several activating receptors and co-receptors responsible for NK cell triggering. By the combined use of these receptors, NK cells can discriminate between normal MHC class I positive (MHC-class I^+) cells and cells that have lost the expression of MHC class I molecules as a consequence of tumour transformation or viral infection [1].

It has become evident in recent years, however, that the actual role of NK cells is not confined to the destruction of virus-infected cells or tumours [2,3]. Indeed, NK cells can interact with other innate immune cells that are present during the early phases of inflammatory responses. These interactions can result in shaping both the innate immune response within inflamed peripheral tissues and the adaptive immune response in secondary lymphoid organs. An interesting example of the interactions between NK cells and other innate immune cells is the so-called 'NK–DC cross-talk' which follows the recruitment of both NK cells and DCs to sites of inflammation in response to infection [4–6]. Following priming by pathogen-derived products, the reciprocal NK–DC interactions result in potent activating bi-directional signalling, which regulates both the quality and the intensity of innate immune responses. Thus, pathogen-primed NK cells in the presence of cytokines released by DCs become activated.

In turn, activated NK cells release other cytokines that favour DC maturation and select the most suitable DCs for subsequent migration to lymph nodes and efficient T-cell priming. In addition, a specialized subset of NK cells can be recruited directly to the lymph nodes to participate in the process of T-cell priming via the release of IFN-γ.

Here, I will briefly summarize the most relevant recent findings supporting the notion that interactions between NK cells and DCs are likely to play a crucial role not only in shaping innate immune responses but also in the editing process that precedes the priming phase of adaptive responses.

The human NK-cell receptors that are involved in target cell killing

It is a common notion that the inhibitory effect mediated by MHC class-I-specific receptors on NK-cell function protects normal cells from the attack of autologous NK cells, while rendering cells with compromised MHC class I expression (e.g. following tumour transformation or viral infection) susceptible to NK-cell-mediated killing [7–10]. In humans, two main families of HLA-class I-specific inhibitory surface receptors have been identified; those belonging to the immunoglobulin superfamily termed killer immunoglobulin-like receptors (KIRs), which are specific for allelic determinants expressed by groups of HLA-A, -B or -C allotypes, and the CD94–NKG2A heterodimer (related to the C-type lectins), which is specific for the non-classical HLA class I molecule HLA-E.

A series of triggering receptors are implicated in NK-cell activation, resulting in natural cytotoxicity. Among these, expression of the so called 'natural cytotoxicity receptors' (NCRs), which include NKp46, NKp30 and NKp44, is

restricted to NK cells and are thus the most reliable markers for human NK-cell identification [11]. Another surface receptor that plays a relevant role in NK-cell-mediated cytolysis of tumours is NKG2D, which is also expressed by most cytolytic T cells and is specific for the stress-inducible MICA/B or UL16 binding proteins (ULBPs) [12,13].

Other triggering surface molecules expressed by NK cells appear to function primarily as co-receptors, as their ability to signal seems to depend on the simultaneous co-engagement of NCR or NKG2D. These surface molecules include 2B4, NTB-A, NKp80, CD59 [14] and CD226 [15]. The majority of the cellular ligands recognized by the various activating receptors and co-receptors (including those recognized by NCRs) remain undefined [16•]. The only exceptions are represented by the ligands of NKG2D, as mentioned above, by CD48, which binds 2B4, and by NTB-A, which has been demonstrated to mediate homotypic interactions [17,18]. The ligands recognized by DNAM-1 have recently been identified [19••] as the poliovirus receptor (PVR; also called CD155) and Nectin-2 (CD112), two members of the nectin family, which are also involved in cell–cell adhesion and in leukocyte extravasation [20•]. Remarkably, both PVR and Nectin-2 can be overexpressed on tumour cells of different histotypes [19••]. The recognition of self-ligands that are expressed or overexpressed upon tumour transformation or viral-infection might be a general strategy to focus NK cells on target cells that should be promptly destroyed.

NK cells have receptors for pathogen-associated molecular patterns

An alternative mode of NK-cell activation has recently been identified thanks to the discovery that human NK cells can express Toll-like receptors (TLRs) [21••,22•,23•]. TLRs are pattern recognition receptors (PRRs), which trigger innate immune responses, providing both immediate protection against various pathogens and instructing the adaptive immune system through the induction of DC recruitment and maturation [24]. Ten different TLRs have been described in humans, and most of their specific ligands have been identified. The targets of PRRs are the pathogen-associated molecular patterns (PAMPs). These include lipopolysaccharide (LPS) of gram bacteria, which is recognized by TLR4; bacterial lipoproteins and lipoteichoic acids, which are recognized by TLR2; flagellin (recognised by TLR5); unmethylated CpG typical of bacterial and viral DNA (recognised by TLR9); and double-stranded RNA (dsRNA; recognised by TLR3) as well as single-stranded RNA (recognised by TLR7). As recently shown by Sivori *et al.* [21••], human NK cells, independent of their status of activation, express functional TLR3 and TLR9 (although they do not seem to express other TLRs), thus enabling their response to both viral and bacterial products. In particular, dsRNA or CpG can induce NK-cell priming, which, in the presence of IL-12 secreted by myeloid DCs, results in the release of abundant IFN-γ and TNF-α. Moreover, under these conditions, NK cells upregulate their cytolytic activity against tumour cells and acquire the ability to kill immature myeloid DCs (iDCs) [21••]. Thus, the simultaneous engagement of TLR3 expressed by both NK cells and myeloid DC might be sufficient to initiate the series of events characterizing the early phases of innate immune responses.

Little is known so far regarding the possible cross-talk between human NK cells and plasmacytoid DCs (PDCs). However, as both NK cells and DCs express TLR9, it is conceivable that CpG can prime both cell types. The abundant release of type I IFN [25], a potent inducer of NK cell cytotoxicity, by PDCs suggests that NK–PDC interactions can result in enhanced anti-viral innate protection. After their recruitment to inflamed tissues, NK cells and myeloid iDCs start their dialogue by getting into close physical contact [26–28]. The formation of stimulatory synapses between the two cell types promotes the polarized secretion of IL-12, which is present in preassembled stores in DCs, towards NK cells [29]. This close cell–cell interaction appears to be required for promoting a series of events, including DC-induced NK-cell proliferation, NK-cell-mediated killing of iDCs, NK-cell-mediated cytokine release and NK-cell-dependent DC maturation [4,5].

NK cell–dendritic cell interactions at inflammatory sites: impact on downstream T-cell polarisation

Pathogen-induced inflammatory responses in peripheral tissues are characterized by the release of various cytokines and chemokines by resident DCs and by other cell types including endothelial cells, macrophages, neutrophils, fibroblasts, mast cells and eosinophils. Some of these factors favour the extravasation of NK cells and their subsequent priming. Indeed, the majority of circulating NK cells, characterized by the $CD56^{+}CD16^{+}$ surface phenotype, express chemokine receptors, such as CXCR1 and CX3CR1, which bind CXCL8, CCL3 and CX3CL1 [4].

Moreover, myeloid DCs that are undergoing maturation upon antigen uptake release cytokines including IL-12 and IL-15, which deeply affect the functional behaviour of primed NK cells. Indeed, IL-12 is crucial for the induction of IFN-γ release by NK cells as well as for the enhancement of NK-cell cytotoxicity [3,30], whereas a membrane-bound form of IL-15 appears to play a role in the induction of NK-cell proliferation [31•]. Certain types of myeloid DCs, such as Langerhans cells (LCs), do not secrete bioactive IL-12p70 but they do produce high levels of IL-15 and IL-18. LCs, however, do not induce NK-cell activation, as they lack the IL-15Rα, which is