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NK cells in innate immunity

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NK cells have an important role in innate immune responses, particularly in anti-viral immunity. Recent studies have revealed a molecular basis for NK cell recognition of virus-infected cells, implicating the activating KIR and Ly49 receptors and NKG2D in this process. Additionally, mutual cooperation between NK cells and dendritic cells suggests that these innate cells can shape the nature of an adaptive immune response. These findings, as well as advances in understanding NK cell development and homeostasis, indicate that NK cell biology is more sophisticated than previously appreciated.

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Abbreviations

CMV	cytomegalovirus
DC	dendritic cell
HCMV	human CMV
HCV	hepatitis C virus
IFN	interferon
IL	interleukin
IL-15R	IL-15 receptor
MCMV	mouse CMV
MEF	myeloid elf-like factor
NK	natural killer

Introduction

NK cells have emerged as pivotal players in immune responses against pathogens and tumors. Research during the past decade has focused on the identification of the cell surface receptors and effector molecules that NK cells use in target-cell recognition and destruction. Attention now turns to determining both the role of NK cells *in vivo* in innate immunity and their contribution to adaptive immunity. Although many of the NK-cell activating and inhibitory receptors, their ligands and signaling pathways have been discovered [1], the biological relevance of these molecules in host defense, how they are regulated during development, and elucidation of the interactions between NK cells and other hematopoietic cells are critical issues to address. Here, we review recent advances in our understanding of these processes.

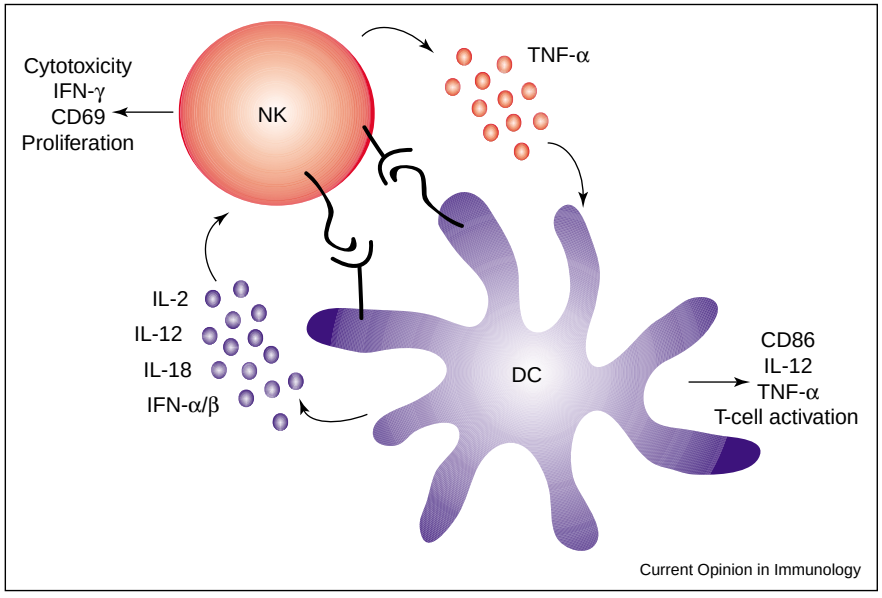
NK cell–dendritic cell crosstalk

It has long been appreciated that NK cells can kill immature dendritic cells (DCs), in the same way as they kill other target cells *in vitro*, but more recently it has been shown that NK cells and DCs reciprocally activate one another during an immune response (Figure 1). The original description of NK–DC crosstalk was published in a report by Fernandez *et al.* in 1999 [2], in which the anti-tumor response of mouse NK cells was shown to be enhanced by DCs *in vivo*. These authors also described co-culture conditions in which DCs enhance the cytotoxicity of NK cells against 'third party' targets and also induce NK cell secretion of IFN-γ. This type of co-culture system has since been exploited to define the requirements for NK–DC crosstalk.

Activation of NK cells by dendritic cells

The induction of IFN-γ production [2–6], cytotoxicity [2–6], CD69 expression [5,7] and proliferation [4] in resting NK cells *in vitro* has been documented by using mouse DC cell lines, mouse bone-marrow-derived DCs, human monocyte-derived DCs and human cord-blood-derived DCs. The mechanism by which DCs activate resting NK cells *in vitro* requires direct cell contact, but probably also involves soluble factors [2–6]. These *in vitro* studies suggested that a range of cytokines produced by DCs, including IL-12, IL-18 and type I IFN, are required for the induction of the various NK effector functions [2,3,5,6], but the data are conflicting and no general consensus has emerged. Interestingly, IL-2 is produced by DCs and is necessary for DC-induced IFN-γ production by NK cells *in vitro* and *in vivo* [6]. In addition, the maturation state of the DCs might influence their ability to activate NK cells. Several studies have shown that immature DCs require a maturation stimulus to activate NK cells [5,6], whereas others have shown that immature and mature DCs are equivalent in their ability to activate NK cells [4,7]. The *in vivo* relevance of NK activation by DCs has been demonstrated in murine tumors [2] and viral models [8••], both implicating the $CD8\alpha^+$ DC subset. During infection of C57Bl/6 mice with mouse cytomegalovirus (MCMV), the expansion of NK cells induced by DCs was shown to specifically involve the Ly49H receptor on NK cells and the cytokines IL-12 and IL-18 [8••].

Figure 1



Crosstalk between NK cells and dendritic cells. NK cells and dendritic cells (DCs) have the ability to reciprocally activate one-another, both *in vitro* and *in vivo*. This crosstalk includes cell contact involving unknown receptor-ligand pairs and soluble mediators produced by the two cells. The cytokines, TNF-α, IL-2, IL-12, IL-18 and IFNs, have all been implicated in this process. The end result of these interactions is NK cells activated for cytotoxicity, IFNγ production, and proliferation and DC that have matured and are capable of cytokine production and T cell activation.

Activation of dendritic cells by NK cells

The other side of the reciprocal NK–DC interaction is how the DCs are activated or matured by interactions with NK cells, as measured by DC cytokine production, induction of co-stimulatory molecules or ability to stimulate T-cell responses. Although fewer studies have investigated the mechanism of this process, it is known that optimal DC activation by NK cells *in vitro* requires both cell contact and TNF-α production [5,7]. It is unclear whether resting NK cells can activate DCs, but NK cells pre-activated with IL-2 are potent DC activators, both alone or in synergy with inflammatory stimuli, such as lipopolysaccharide. Interestingly, Piccioli *et al.* [7] showed that the outcome of the NK–DC interaction is tightly regulated by the ratio of the two cell types; at low NK:DC ratios, DC maturation prevails, whereas at high NK:DC ratios, NK killing of DC prevails. Two *in vivo* studies demonstrate DC activation by NK cells. The MCMV study discussed above [8••] shows that NK cells are necessary for the maintenance of $CD8\alpha^+$ DCs during viral infection, again through the Ly49H NK receptor. Mocikat *et al.* [9••] reported that, in an *in vivo* study of tumor rejection, NK cells were required for IL-12 production by DCs, and this interaction was then responsible for the generation of a protective $CD8^+$ T-cell response. In these *in vivo* models, NK cell activation presumably occurs through virally induced cytokines [8••] or by the direct interaction of the tumor cells with NK cells [9••].

Sites at which NK cells and dendritic cells meet

Although it appears that reciprocal NK–DC interactions can occur both *in vitro* and *in vivo*, the location of the *in vivo* interactions remains to be determined. One possibility is that this happens at sites of inflammation, where resident immature DCs are found and NK cells migrate in response to inflammation. Supporting this notion, it has been shown that NK cells and DCs are in direct contact with each other in the dermal sites of a yeast infection [10]. Another possibility is that NK cells meet mature DCs within the lymph nodes. Two recent papers have shown that human NK cells are found within both inflamed and non-inflamed lymph nodes [11•,12•], where they might meet maturing DCs that have arrived from sites of inflammation or infection.

NK cells and viral infection

Although NK cells become activated early after challenge with both viral and bacterial pathogens, they are mainly thought to be critical for the clearance of viral infections. This is highlighted by the fact that many viruses have developed specific mechanisms to interfere with NK cell effector functions [13]. In particular, NK cells are required for the control of herpesviruses, both in humans and in mice. We will go on to discuss the case of CMV, a member of the herpesvirus family, for which much of the evidence for NK involvement in anti-viral immune responses has been documented. Increasingly, immune