

DCs activates NK cells

with

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What is known about different ways of NK cell activation?

Francesca Granucci: Natural Killer (NK) cells are specialized cells of the innate immune system that exert their functions against pathogen-infected or tumor cells. NK cell activity is primed during the early phases of an immune response, a few hours after infection. NK cells comprise about 15% of circulating lymphocytes and are also found in peripheral tissues. NK cells exert their activity by producing high amount of IFN γ , that activates a strong inflammatory response, and

by having direct cytotoxic function. The functions of NK cells are regulated by a balance of activating and inhibiting signals. These signals are transmitted by inhibitory receptors, which bind class I major histocompatibility complex (MHC) molecules, and activating receptors, which bind ligands on tumors and pathogen-infected cells. Other than surface receptors, cytokines, such as IL-2, IL-12, IL-18 and type I interferons (IFNs) have been shown to promote NK cell priming.

How can DCs activates NK cells? Are cytokines involved?

Francesca Granucci: Recently, a predominant role for DC in activation of NK cells has been described both in mouse and in man. The first place of contact between NK cell and DC could be the site of infection where both resident and recruited DC would be able to activate NK cells. Activated DC can migrate to the draining lymph nodes where they can probably stimulate resident and newly recruited NK cells.

Two pathways for DC-mediated NK cell activation are known in mouse. One dependent on IL-4 and the other one dependent on microbial stimuli (1,2). An appropriate cytokine milieu containing IL-4 renders DC competent for NK cell activation independently from the presence of microbial stimuli, although the presence

of microbial stimuli increase the efficiency of NK cell activation; alternatively, following microbial encounter DC become capable to efficiently activate NK cells. DC differentiated in presence of IL-4 are strong producers of IL-12 following activation with inflammatory stimuli. This cytokine has been shown to be required to obtain optimal IFN γ production by NK cells. In the context of viral infections, another DC-derived cytokine able to promote efficient IFN γ production by NK cells is IL-18 (3). In absence of DC exposure to IL-4 and in response to bacterial challenges or to bacterial cell products, DC-derived IL-2 plays a major role in eliciting IFN γ production by NK cells (2).

The biological relevance of NK cell activation

mediated by DC during bacterial infections resides mainly in the secretion of IFN γ , which represents the principal phagocyte-activating factor. The role of DC-derived IL-2 in inducing IFN γ production by NK cells has been studied in the mouse system. Nevertheless, also human monocyte derived DC cultured *in vitro* in presence of IL-15 and not in presence of IL-4 can produce IL-2, thus, it would be interesting to investigate whether, also in humans, IL-2 could play a role in stimulating NK cells in a context in which IL-15 is present.

Bacterially activated DC can also induce NK cell cytotoxic function. This phenomenon is type I IFN-dependent and IL-2-independent. The production of type I IFNs by myeloid DC has been recently shown in the context of viral infections (4). In agreement with this observation, we have found that myeloid DC can produce type I IFNs also following bacterial activation (2). The precise contribution of myeloid and plasmacytoid DC in the production of type I IFNs *in vivo* in response to different type of infections remains to be determined.

Is the type of stimuli important for TH1 or TH2 responses?

Francesca Granucci: The vertebrate immune system has evolved to detect and control invasions of microorganisms. Such perturbations are perceived by cells of the innate immune system that express Pattern Recognition Receptors (PRRs). These receptors bind a number of microbial products collectively named Microbial Associated Molecular Patterns (MAMPs). Among PRRs, Toll Like Receptors (TLRs) are the best characterized. Particularly significant for the understanding of host-parasite interactions is the binding of MAMPs with TLRs expressed on DC. This interaction leads to a complex genetic reprogramming of DC that show a sequential acquisition of different regulatory functions in innate and adaptive immunity (5). Among the microbial stimuli, some ones bind TLRs and other ones act in a TLR-independent manner. Ten TLRs have been identified so far. Microbial products that activate DC in a TLRs-independent manner are represented by toxins, such as pertussis toxin (PT) and cholera toxin (CT). We have been able to demonstrate that TLR-dependent and not TLR-

independent microbial stimuli confer to DC the ability to elicit IFN γ production by NK cells. Moreover, migrating DC activated with specific full maturation stimuli are able to recruit or to induce NK cell proliferation at the draining lymph nodes (6). Consistent with the observation of Martin-Fontecha and colleagues (7), the stimuli that we found able to confer to DC NK cell stimulatory capacity (in terms of IFN γ production and lymph node accumulation) were typically associated *in vivo* with TH1 responses. In particular, LPS and CpG were able to induce DC-mediated NK cell activation (IFN γ production) and recruitment *in vitro* and *in vivo*, while the TH2 stimulus Pam3Cys, though could stimulate DC to elicit IFN γ production from NK cells *in vitro* in BALB/c background, was not able to promote *in vivo* DC-mediated NK cell recruitment/proliferation at the draining lymph nodes.

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