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MULTI-AUTHOR REVIEW

Mechanisms of NK cell activation: CD4$^+$ T cells enter the scene

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Abstract Natural killer (NK) cells are innate lymphocytes involved in immunosurveillance through their cytotoxic activity and their capacity to secrete inflammatory cytokines. NK cell activation is necessary to initiate effector functions and results from a complex series of molecular and cellular events. We review here the signals that trigger NK cells and discuss recent findings showing that, besides antigen-presenting cells, T cells can play a central role in the initiation of NK cell activation in lymph nodes.

Keywords Natural killer cells · Antigen-presenting cells · CD4$^+$ T cells · NK receptors · IL-12 · IL-2

Introduction

Natural killer (NK) cells are innate lymphocytes that circulate in the blood, lymphatics and tissues where they sample their environment to detect abnormal cells [1]. Upon stimulation, they kill tumor cells and infected cells thus contributing to tumor surveillance and pathogen clearance [2]. Natural cytotoxicity results from a coordinated series of events which include contact with target cells, adhesion, synapse formation, granule polarization and granule exocytosis [3–6]. NK cells also secrete cytokines and chemokines which regulate and orientate immune responses [7, 8]. Thus, NK cells actively interact with their environment and contribute to the fine tuning of immune responses. To exert their functions, NK cells are stimulated by different mechanisms. Schematically, NK cell activation results from a combination of soluble and contact-dependent signals. It involves cytokines, the engagement of a combination of activating and inhibitory receptors and requires cellular interactions. NK cells constitute quite a heterogeneous population of cells. They express a combination of germline-encoded NK receptors (NKRs) acquired in a stochastic and variegated manner and can display different cytokine receptor profiles [9–11]. Interestingly, some subsets were found to be associated with a specific location (i.e. decidual NK cells or mucosa-associated NK cells) [12–20]. The signals required for their activation differ with their stage of maturation, whether they have been educated, primed or previously activated (memory-like NK cells) [21].

In this review, we will examine the various components triggering NK cell activation. We will not review signaling pathways activated which are extensively described elsewhere [6, 22–25]. Rather, we will focus on signals and cellular interactions necessary to trigger NK cells in secondary lymphoid organs, at the sites of infection or within tumors. Emphasis will be put on new players, CD4$^+$ T cells which have recently been shown to be critical for the regulation of the initiation of NK cell activation in lymph nodes [26].

Mechanisms of NK cell activation: basic principles

In contrast to T cells and B cells which predominantly use a single antigen receptor for their activation, NK cells are

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triggered by the combined action of cytokines and the engagement of activating and inhibitory receptors. Cytokines which have been involved in NK cell activation in vitro and in vivo include IL-12, IFN-α/β, IL-15, IL-2 and IL-18, [1, 7, 8, 27]. IL-12 is the most potent inducer of IFN-γ [28, 29] whereas type I IFNs are key regulators of NK cell cytotoxicity in the context of viral infections [30]. In addition, IL-2 and IL-15 are implicated in NK cell development, homeostasis and in activating NK cell cytotoxicity and secretion of cytokines [31]. IL-18 was also found to trigger NK cell functions in combination with IL-12 or type I IFNs [32]. Cytokines act individually or in combinations. They also often contribute to augment signaling through activating NKRs.

NK cell recognition of targets is largely dominated by the interaction of germline-encoded activating and inhibitory receptors with ligands expressed by targets [33]. The permanent expression of inhibitory NKRs specific for major histocompatibility complex (MHC) class I molecules counterbalances activating signals and confers "missing self" specificity to NK cell recognition [34–37]. Additional non-MHC ligands binding to inhibitory receptors also contribute to NK cell tolerance to self. This is the case for the mouse Clrb molecule binding to NKR-P1B/D [38, 39] and for human LLT1 binding to NKR-P1A (CD161) which provide an inhibitory signal to NK cells independent of MHC class I molecules ([40–42], and C. Germain and V.M. Braud, unpublished data). Other examples include mouse 2B4 binding CD48 [43], KLRG1 interacting with cadherins [44–47], LAIR-1 binding to collagen [48], siglecs binding to sialic acids [49] or CEACAM1 homophilic interactions [50]. NK cell tolerance to "self" implies that, in the absence of inhibitory signals, NK cells are turned on. Activation is not "spontaneous", but it depends on the triggering of activating receptors [3]. Some activating NKRs have adapted to recognize "altered or induced" self ligands. This is the case for NKG2D which interacts with stress-induced ligands such as MICA/MICB or ULPBs in humans and Rae1, H60 or MULT-1 in mice [51, 52] or for DNAM-1 which binds to PVR or nectin-2 [53–55]. Activating KIRs may have adapted to more specifically recognize MHC class I molecules loaded with viral peptides [56, 57]. In addition, activating leukocyte immunoglobulin-like receptors (LILRs) which were shown to bind to unfolded HLA molecules may contribute to recognition of infected cells [58]. Other activating receptors interact with pathogen-encoded molecules. NK cells expressing these particular activating NKRs are increased following certain viral infections. Ly49H-expressing NK cells are expanded during MCMV infection as a result of binding to the MCMV-encoded cell surface ligand m157 [59–63]. Influenza hemagglutinin was found to interact with NKp46 receptor and this interaction is critical for the control of the infection [64, 65]. The CD94/NKG2C$^+$ NK cell subset is increased in HCMV-seropositive individuals suggesting that they recognize a viral ligand, although this has not yet been formally demonstrated [66]. An increase of NKp30$^+$ NK cells is also associated with chronic HCV infection [67] while an expansion of the KIR3DS1$^+$ subset is associated with acute HIV infection [68]. In addition to this specific recognition, pathogens may also be directly recognized by NK cells through the Toll-like receptors (TLRs) they express [69–72]. Besides these mechanisms of activation, most NK cells express the FcγRIII CD16 responsible for antibody-dependent cellular cytotoxicity (ADCC).

Signals from activating NKRs are tightly regulated. This is needed to avoid uncontrolled immune response towards self. As discussed previously, the expression of inhibitory receptors to self ligands, in particular MHC class I molecules, is a major regulatory mechanism [35]. In addition, Long et al. demonstrated that cross-linking of a single activating NKR on freshly isolated "resting" NK cells was not sufficient to trigger NK cell functions. Rather, a synergy among activating receptors was needed to reach a threshold of signaling [4, 5, 73]. This threshold can also be reached when cytokine stimulation is combined with cross-linking of activating NKRs [74]. In addition, chronic exposure to activating ligands contributes to NK cell hyporesponsiveness by inducing the downregulation of the corresponding activating NKRs or signaling molecules. This was demonstrated when NK cells developed in the continuous presence of NKG2D [75–77], Ly49D [78] or Ly49H [79, 80] ligands and for mature NK cells [79]. Low level expression of NKp46, NKp44 and NKp30 has also been associated with defects in NK cell functions in human healthy donors and patients suffering from chronic myeloid leukemia [81, 82] or infected with HIV [83].

NK cell responsiveness also depends on whether NK cells are "educated", "licensed" or "armed" [84–87]. Many reviews have covered this topic, which will therefore not be discussed in detail here [88–92]. Briefly, NK cells are hyporesponsive when they cannot recognize self-MHC class I molecules via their inhibitory receptors. The mechanism of "hyporesponsiveness" is hotly debated and may either imply that MHC class I molecules instruct NK cells to become responsive ("licensing model") or be due to the fact that a lack of this interaction "disarms" NK cells [85, 93]. This was originally demonstrated in developing NK cells and was later shown to be quantitative, depending on the strength of the MHC class I signal. More recent studies have also shown that this process can occur in mature NK cells which can be re-programmed [94–96]. These data suggest that a certain plasticity of NK cell responsiveness exists. In vivo, both unlicensed and licensed NK cells seem to be able to be activated, but unlicensed

NK cells provided better protection to MCMV infection [97]. Whether this suggests that expression of inhibitory receptors for MHC class I molecules could be detrimental or whether other receptors such as CD94/NKG2A play a role remains to be assessed.

Specific subsets of NK cells and their location

Until recently, NK cells have been regarded as a functionally rather uniform population of cells which kill and secrete cytokines such as IFN-γ under the influence of defined stimuli. It has now become clear that NK cell diversity is broad and so are NK cell activation signals. Diversity comes partly from different development pathways [98]: NK cells originate not only from the bone marrow but also from the thymus [99]. Different stages of maturation have been identified based on the expression profile of CD11b and CD27 markers [100–102]. Signals required for their full maturation still need to be identified and may depend on the tissue-specific environment. In addition, several groups have recently demonstrated that some subsets of NK cells can become long-lived cells that mount a secondary response to specific antigens [21, 103–105]. It will be interesting to define whether this property is intrinsic to NK cells or results from a specific mode of activation or if specific NK-cell extrinsic signals generate these long-lived cells.

Diversity in NK cell subsets is often associated with distinct effector functions in specific locations. New NK cell subsets have been identified at epithelial surfaces (uterus, tonsils, intestinal mucosa and skin) [16–20, 106, 107]. Interestingly, these subsets display different transcriptional profiles and respond to specific cytokines and signals from the microflora environment [18, 20, 106–108]. Uterine NK cells seem to be specialized in the secretion of cytokines and angiogenic factors rather than cytotoxicity to allow normal placentation and successful pregnancy. Signals regulating their effector functions are still to be fully characterized but are in part regulated through inhibitory and activating NKRs [109, 110]. They likely depend on the specific local cytokine environment and on the interaction with fetal trophoblast cells. Mucosa-associated NK cells were identified in human tonsils and Peyer's patches as NK-like cells secreting IL-22 in response to IL-23 [16]. They may correspond to human stage 3 NK cells that secrete IL-22 and require IL-1β for their maintenance and expansion [101, 111, 112]. Interestingly, they seem to display some plasticity depending on whether IL-1β, IL-7 or IL-2 are used to sustain their survival and proliferation [112]. In mice, a similar population of intestinal NK-like cells has been described with a phenotype resembling but in some aspects also distinct from lymphoid tissue inducer (LTi) cells [17–20, 113, 114]. Further investigations are needed to define the lineage relationship and physiological role of these new NK cell and NK-like cell subsets as well as the signals required to trigger their effector functions.

NK cell activation requires cellular interactions with APCs

An optimal NK cell activation results from cytokine stimulation and engagement of activating receptors, and it requires interaction with immune cells and in particular with antigen-presenting accessory cells (APCs). Initially, dendritic cells (DCs) were described to contribute to NK cell-mediated anti-tumor responses by enhancing NK cell cytotoxicity and IFN-γ production [115]. In vitro studies later confirmed that mature DCs can activate NK cell effector functions and proliferation [116–118]. DCs were also found to be required for in vivo NK cell activation upon MCMV infection [119]. Since these pioneer works, the central role of DCs and also macrophages on NK cell activation has been demonstrated in various experimental systems [120–125]. They activate NK cells via the cytokines they produce and through membrane-bound molecules. APCs seem to be crucial at several levels. First, at the initiation of NK cell activation, a first step of priming seems to be required to allow naïve NK cells to acquire NK cell functions [124, 126]. Lucas et al. [124] demonstrated that this priming occurred in the draining lymph nodes and was provided by DC trans-presenting IL-15. Membrane-bound IL-15Rα-IL-15 complexes were found to activate NK cells through direct cell–cell contact [127]. Interestingly, IL-15, together with IL-2, was found to be the most potent cytokine which induced translation of granzyme B and perforin in resting NK cells [128]. In addition, priming may involve IL-18 signaling, as the IL-18R/MyD88/IRAK4 pathway is required for ex vivo IFN-γ production by NK cells in response to IL-12 and IL-18 contributing to the NK cell response in visceral leishmaniasis [129, 130]. In addition to NK cell priming, evidence has also accumulated to show that DC/NK cross-talk is central to NK cell triggering of effector functions. Indeed, DC-derived type I IFNs mostly produced by plasmacytoid DC (pDC) stimulate NK cell cytotoxic activity but limit IFN-γ production through a control of IL-12 secretion by DCs [30, 131–133]. DC-derived IL-12 is the most potent stimulator of IFN-γ and other cytokines secreted by APCs as IL-18, IL-15 and IL-2 synergize with IL-12 to induce IFN-γ and enhance NK cell cytotoxicity [27–29, 31, 32, 134]. APCs not only produce cytokines that activate NK cells but they also physically interact with them [135–137]. This is required for several reasons. First, this interaction allows a better delivery of cytokines through the formation of

immunological synapses. These synapses have been shown to promote the polarization of IL-12 or IL-18 and their delivery at the synaptic cleft [138, 139]. In addition, NK/DC interactions permit trans-presentation of IL-15 [124, 126, 127]. Interestingly, a rapid accumulation of IL-15Rα was observed at the synapse formed following NK/DC conjugate formation [140]. Lastly, direct contact of NK cells with APCs provides stimulatory and co-stimulatory signals. Expression of ligands for activating receptors such as NKG2D or NKp46 were detected on DCs, macrophages or monocytes following TLR stimulations or infections with bacteria, viruses or parasites [64, 65, 122, 141–145]. Similarly, ligands of co-stimulatory molecules have been detected on activated APCs and contribute to NK cell activation. This is the case for activation-induced C-type lectin (AICL) found expressed on activated monocytes which interacts with NKp80 on NK cells [146]; for CD48 expressed on LPS-stimulated macrophages and interacting with 2B4 [145]; for CD80 induced upon *Toxoplasma gondii* infection which binds CD28 on NK cells [147]; for CD40 expressed on activated macrophages interacting with CD40L [148]; and for glucocorticoid-induced TNF-receptor-related protein ligand (GITRL) expressed on virus- or CpG-activated pDCs which interacts with GITR on NK cells [149].

NK cell interactions with APCs occur primarily in secondary lymphoid organs where the initiation of NK cell activation takes place. They also occur at the infection or tumor sites where NK cell effector functions participate in the control of immune responses. In draining lymph nodes, murine NK cells are detected in the paracortex in direct contact with DCs [135]. In humans, NK and DCs colocalize in T cell areas of lymph nodes [150–152]. NK cells were initially found to be slowly motile [135], but it was later established that the positive selection of NK cells using CD49b mAb decreased their motility in lymph nodes once transferred into naïve animals [135, 137]. Transfer of labeled NK cells purified by negative selection or the use of $NCR1^{GFP/+}$ mice demonstrated that NK cells are in fact highly motile in lymph nodes and that they engage short and dynamic interactions with DCs or B cells [136, 137]. Such behavior may allow them to rapidly sample the local cytokine environment of DCs that contribute to their activation [136]. This finding is consistent with the observation that NK cells establish dynamic contacts with their targets [153]. Besides draining lymph nodes, NK/DC cross-talk has been reported in the spleen of animals infected with MCMV, in particular contributing to expansion of $Ly49H^+$ NK cells [119]. NK cells were also detected in close proximity to APCs at the site of inflammation or infection. They were, for example, detected in the skin of patients infected with the yeast *Malassezia* [154]. Cell contact with autologous activated monocytes or macrophages was also found to be required to activate NK cells to secrete IFN-γ upon challenge with *Staphylococcus aureus* and *Lactobacillus johnsonii* [155], Influenza A or Sendai virus [142], *Plasmodium falciparum* [156] or *Salmonella enterica* [157].

A previously unappreciated role for $CD4^+$ T cells in NK cell activation in vivo

Secondary lymphoid organs are key sites where adaptive immune responses are initiated. As discussed above, they are also sites where NK cell cross-talk with DCs has been visualized [135, 136]. NK cell activation has long been considered to precede T cell activation and therefore the contribution of T cells to NK cell activation has been poorly analyzed. However, clusters of DCs, T cells and IFN-γ-secreting NK cells could be visualized very early on in the lymph nodes draining the inoculation site in *Leishmania major*-infected mice [135]. This suggested that a cross-talk between T cells and NK cells could occur there. How can T cells contribute to NK cell activation? Early in vitro work by Fehniger et al. [152] demonstrated that IL-2 secretion by a T cell clone could stimulate $CD56^{bright}$ NK cells in the presence of APCs and recombinant IL-12. In addition, He et al. [158] found that IFN-γ secretion by NK cells in PBMCs incubated with Influenza A virus was dependent on the presence of $CD4^+$ T cells and could be abolished by neutralization of IL-2. More recently, a similar observation was made when PBMCs were challenged in vitro with *P. falciparum*-infected red blood cells [159]. Depletion of either $CD4^+$ T cells, $CD8^+$ T cells, $\alpha\beta TCR^+$ T cells or $\gamma\delta TCR^+$ T cells significantly reduced IFN-γ secretion by NK cells. In this situation, there was no requirement for NK cell contact with T cells, but T cell help was provided by the secretion of IL-2. It is clear from these in vitro studies that T cell-derived IL-2 is one mechanism that activates NK cells. This is consistent with the widely established role of IL-2 in the stimulation of NK cell proliferation and effector functions in vitro [160]. The key question remaining to answer was whether NK/T cross-talk occurs in vivo and whether T cell-derived-IL-2 also plays a central role in vivo. In humans, two populations of NK cells are distinguished based on the level of expression of CD56 [9, 161]. The $CD56^{bright}$ $CD16^-$ KIR^- NK cell subset, which expresses the high affinity IL-2 receptor composed of IL-2R α-chain (CD25), β-chain (CD122) and γ-chain (CD132), is enriched in secondary lymphoid organs [150, 152]. The NK cell subset which is the most responsive to IL-2 therefore co-localizes with T cells, suggesting that T cell-derived IL-2 could regulate NK cell activation in vivo. Formal demonstration was provided when NK cell activation was shown to be specifically

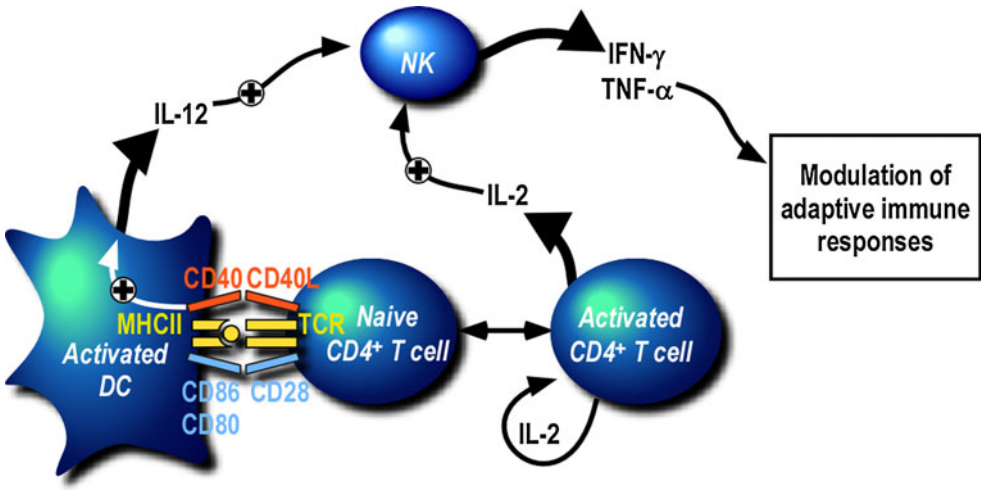

Fig. 1 $CD4^+$ T cell-dependent activation of NK cells in lymph nodes. Upon immunization or infection, DCs present antigen to naïve $CD4^+$ T cells in lymph nodes draining the immunization or inoculation sites. This event results in the activation of T cells which secrete IL-2 and upregulate the high affinity IL-2 receptor and CD40L. Activated $CD4^+$ T cells contribute to further maturation of DC and their secretion of IL-12. Both cytokines, IL-2 and IL-12, synergize to initiate NK cell activation which results in the secretion of IFN-γ and TNF-α, critical for the development of subsequent adaptive immune responses

abrogated in draining lymph nodes of *L. major*-infected-$CD4^+$ T cell-deficient mice [26]. Importantly, newly primed antigen-specific $CD4^+$ T cells secreting IL-2 were required to initiate NK cell activation. But in contrast to the above in vitro studies, this work also highlighted that the role of $CD4^+$ T cells was not simply to provide IL-2 but also to regulate DC maturation and DC secretion of IL-12. Indeed, the in vivo neutralization of both IL-2 and IL-12 was needed to significantly decrease IFN-γ secretion by NK cells in draining lymph nodes. In addition, $CD4^+$ T cell help was found to be dependent on CD40/CD40L interaction [162, 163]. These findings indicate that the activation of antigen-specific $CD4^+$ T cells primed by DCs presenting MHC class II/peptide complexes is a prerequisite for NK cell secretion of IFN-γ upon *L. major* infection. These data could be related to observations made in cancer models in which $CD4^+$ T cell control of tumor growth was found to be dependent on a cooperation with NK cells [164] or innate immune cells expressing markers of NK cells [165]. In these situations, IFN-γ which is essential for the control of tumor growth was secreted by NK cells with the help of $CD4^+$ T cells and a contribution of IL-2. A similar requirement for $CD4^+$ T cells is also found following immunization with OVA where NK cell secretion of IFN-γ early on in draining lymph nodes only occurs in the presence of activated OVA-specific $CD4^+$ T cells [26]. Based on these data, one can propose a sequential model of activation involving DC, $CD4^+$ T cells and NK cells in lymph nodes (Fig. 1). The first event which occurs is the presentation of antigenic peptides by DC to $CD4^+$ T cells. This step of priming triggers the activation of T cells and the secretion of IL-2. Activated $CD4^+$ T cells upregulate CD25 to respond more efficiently to IL-2 and they also upregulate CD40L. IL-2 secreted by T cells contributes directly to NK cell activation and this is amplified as NK cells acquire the high affinity IL-2R upon activation. In addition, activated T cells contribute to the maturation of DC in a CD40/CD40L- and IL-2-dependent way resulting in the secretion of IL-12 by DCs. This cytokine synergizes with IL-2 to activate NK cells. Based on this model, one would expect that NK cells are efficiently activated by IL-2 produced by endogenous memory $CD4^+$ T cells after a secondary challenge. Consistent with this, augmented $CD4^+$ T cell-dependent NK cell responses were observed in PBMCs restimulated with inactivated rabies virus in vaccinated individuals [166]. But the requirement for T cell help is likely to be less critical in situations where efficient maturation of DCs can be achieved by other means and in particular through TLR stimulation. This may be the case in *Listeria monocytogenes* or *Mycobacterium tuberculosis* infections where NK cell activation has been observed in $Rag^{-/-}$ animals and therefore does not require $CD4^+$ T cells [167, 168].

Interestingly, iNKT cells may play a similar role. Injection of alpha-galactosyl ceramide (αGalCer) intravenously led to the activation of NK cells which was dependent on prior activation of iNKT cells and their secretion of IFN-γ [169]. Whether IL-12 also plays a role has not been examined, but activated iNKT cells have been found to contribute to DC maturation in a CD40/CD40L-dependent way [170].

Lastly, the cross-talk of NK cells with T cells may not always lead to NK cell activation but also to suppression of

NK cell effector functions. Indeed, regulatory T cells have also been involved in dampening NK cell functions [171, 172].

Concluding remarks

An increasing interest to better understand the molecular and cellular requirements for NK cell activation in vivo correlates with accumulating evidence of the importance of NK cells in controlling diseases. Their role in tumor immunosurveillance in mice and humans is now well documented [2, 173]. NK cell activation is also thought to limit pathogen invasion until the adaptive immune response establishes long-lasting immune control [174]. This was elegantly illustrated recently in a model of infection with mousepox in which mice genetically resistant to mousepox lose resistance at mid-age because NK cells are no longer efficiently recruited in lymph nodes draining the primary site of infection [175]. Pursuing our efforts to decipher signals regulating NK cell activation will be useful for the development of novel NK cell-based immunotherapies as NK cell clinical relevance is emerging [173, 176–178].

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