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Line of attack: NK cell specificity and integration of signals

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Summary

Natural killer (NK) cells possess potent cytolytic activity and secrete immune modulating cytokines. The large repertoire of NK cell receptors provides versatility for the identification of infected and transformed cells, and for their elimination by NK cells. NK cell responses also stimulate and regulate the adaptive arm of the immune system. We review current knowledge about the molecular specificity of NK cell receptors and about regulation of NK cell effector functions upon encounter with target cells. Mechanisms of recognition, interplay among receptors, signal integration, and dynamic fine-tuning of NK cell responses are discussed. New insights into molecular checkpoints for NK cell effector function are highlighted and underlying reasons for the complexity in NK cell recognition and signaling are proposed.

Keywords

NK cell; lymphocyte effector functions; secretory lysosomes; NKG2D; inhibitory receptors

INTRODUCTION

Natural killer (NK) cells are a subset of lymphocytes that do not undergo gene rearrangement, which is used by B cells and T cells to generate a vast repertoire of receptors with unique antigen specificity. Accordingly, NK cells belong to the innate arm of the immune system. They participate in early defense against intracellular pathogens, viruses, and tumors. The importance of NK cells in immunity to viruses is underscored by the many strategies developed by viruses to interfere with NK cell recognition systems [1]. Moreover, NK cells interface with adaptive immunity through interactions with dendritic cells and T cells [2]. Thus, NK cells play a role in instructing adaptive immunity and in regulating immune homeostasis. NK cells kill sensitive target cells by polarized release of perforin-containing secretory lysosomes, also called cytotoxic granules. In addition to their strong cytolytic function, NK cells produce cytokines and chemokines in response to soluble mediators, such as IL-12 and IL-18. Cytokines released by NK cells, such as TNF-α and IFN-γ, can promote cellular resistance to infection and influence adaptive immunity.

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Phenotypic characteristics of NK cells were recently covered in this journal [3]. This review will focus on the molecular specificity and regulation of NK cell effector functions, highlighting strategies of recognition, and dynamic fine-tuning of NK cell responses.

MOLECULAR SPECIFICITY OF NK CELL RECEPTORS

NK cells express many receptors that participate in the regulation of effector function. Proper balance in NK cell activation is provided by opposing signals from activating and inhibitory receptors. A large set of activating NK cell receptors is expressed by most peripheral blood NK cells, recognizes a diverse array of molecular structures, and utilizes a variety of signaling pathways (Table 1). In contrast, expression of any given MHC class I-specific inhibitory receptor is restricted to subsets of NK cells. Inhibition occurs through recruitment of tyrosine phosphatases to immunoreceptor tyrosine-based inhibition motifs (ITIM) in the cytoplasmic tail of inhibitory receptors (Table 2). Together, the specificity of activating and inhibitory receptors provides NK cells with multiple strategies to distinguish healthy cells from those in distress. Recently, ligands to orphan receptors have been identified, and progress has been made in understanding how interplay between different receptors contributes to specificity.

Activating receptors

The low-affinity receptor for IgG, CD16, mediates antibody-dependent cellular cytotoxicity (ADCC) and signals through adaptors containing cytoplasmic immunoreceptor tyrosine-based activation motifs (ITAM). Investigations into the mechanism of action for therapeutic antibodies, such as rituximab (anti-CD20) and herceptin (anti-erbB2), which have been used successfully in the clinic, have lead to an increasing appreciation of NK cell-mediated ADCC [4,5]. Several receptors, which activate antibody-independent, natural cytotoxicity are also associated with ITAM-containing signaling adaptors (Table 1). These receptors include NKp30, NKp44, and NKp46, which are referred to as natural cytotoxicity receptors (NCR) [6]. The nature of the ligands for NCRs is still unclear. Although NKp46 has been reported to bind viral hemaglutinin on infected cells [7], cellular ligands have not been identified. NKp46 contributes to enhanced killing of mitotic cells by NK cells, suggesting a role of NK cells in controlling expansion of rapidly dividing cells [8*]. NKp30 mediates killing of immature dendritic cells by NK cells [9]. Surprisingly, an intracellular protein implicated in induction of apoptosis after DNA damage or endoplasmic reticulum stress, called BAT3, was recently described as a ligand of NKp30 [10**]. How BAT3 becomes exposed at the cell surface is not known. Furthermore, immunostaining of several tumor cells with soluble forms of NKp30 and NKp44 resulted in intracellular staining, suggesting that translocation from the inside to the surface of cells may be a common theme among ligands of NCRs [11*]. In support of this notion, the human cytomegalovirus tegument protein pp65, which is not expressed at the surface of infected cells, has also been identified as a ligand for NKp30 [12]. However, binding of pp65 results in inhibition of NK cell cytotoxicity induced by NKp30, which may represent one of the many evasion tactics developed by human cytomegalovirus to counter detection by NK cells.

The NK cell activation receptor NKG2D associates with the adaptor protein DAP10, which carries a tyrosine motif distinct from the ITAM. NKG2D binds several ligands, including MICA/B and ULBP1/2/3/4. Expression of these ligands is upregulated on infected, stressed, and transformed cells [13]. The DNA damage response induces expression of NKG2D ligands [14]. Detection of tumor cells by NKG2D can be counteracted by soluble NKG2D ligands, which are shed from the cell surface after cleavage by protease ERp5 [15*]. Soluble ligands provoke internalization of NKG2D from the cell surface. While NKG2D provides an important defense mechanism against tumors [16], it can also contribute to autoimmunity [17,18].

Many of the other NK cell activation receptors signal through motifs in their own cytoplasmic tail, and through pathways that have not been characterized for every receptor. DNAM-1 binds nectins CD112 and CD155, which are components of cellular junctions. On NK cells, DNAM-1 may facilitate surveillance of damaged endothelium and transformed cells [19,20]. 2B4, CRACC, and CD2 bind ligands that are predominantly expressed on hematopoetic cells. The structures of CRACC homophilic interactions and 2B4 in complex with CD48 were recently solved [21,22]. At 11 nm and 11.5 nm, the membrane spacing required for homophilic CRACC and 2B4-CD58 interactions, respectively, is similar to the space required for KIR-MHC class I interaections [21,22]. Thus, activating receptors such as 2B4 and CRACC could potentially intermix with inhibitory KIR at the NK cell immune synapse, facilitating dynamic assessment of activation thresholds. NKp80 is another NK cell activation receptor with unknown signaling properties. The cellular ligand of NKp80 was recently identified as AICL [23*]. The NKp80 and AICL genes are closely linked in the NK cell gene complex on chromosome 12. Expression of AICL is confined to granulocytes and macrophages, and is upregulated by inflammatory stimuli [23*]. Thus, NKp80-AICL interactions may be important for NK cell-myeloid cell crosstalk during immune reactions.

Inhibitory receptors

NK cell reactivity is controlled by inhibitory receptors with specificty for different MHC class I alleles. Receptors such as KIR in humans and Ly49 in mice allow NK cells to sense cells with reduced expression of MHC class I, thereby complementing T cell mediated immunity. Further, the clonal distribution of MHC class I-specific inhibitory receptors on individual NK cells, and the repertoire of receptors specific for different MHC class I allotypes, can give rise to NK cell alloreactivity. Such NK cell alloreactivity may be exploited in clinical immunotherapy in order to reduce graft-versus-host-disease while providing beneficial graft-versus-leukemia effects [24]. Besides receptors for classical MHC class I molecules, NK cells may indirectly gauge MHC class I expression on target cells by interaction between the CD94/NKG2A receptor complex and HLA-E, a non-classical MHC class I molecule that presents MHC class I leader peptides. The crystal structure of CD94/NKG2A, in combination with mutagenesis studies, has led to a model for the CD94/NKG2A–HLA-E complex. According to the model, the CD94 chain has a more dominant role in interaction with HLA-E, as compared to NKG2A [25].

Although it is usually considered sufficient for inhibition, binding of an inhibitory receptor to MHC class I is not the only system in place to prevent autoreactivity of NK cells. Several other inhibitory receptors, which bind to non-MHC class I ligands, have been identified (Table 2). The lectin-like receptor KLRG1 binds cadherins, in both humans and mice [26*,27*]. This could serve as a system to detect potentially metastatic epithelial tumors that downregulate cadherin expression. NKR-P1, another lectin-like receptor, binds to lectin-like Clrb/Ocil molecules in mice, and the related LLT1 in humans [28–31]. More information on the regulation of expression of NKR-P1 ligands is required to determine the functional implications of this receptor-ligand interaction. LAIR-1 is an inhibitory receptor that binds to collagen and is widely expressed on immune cells [32*]. Several members of the Siglec family of receptors, which bind sialyl groups with various specificities, carry ITIMs in their cytoplasmic tail. Additional inhibitory receptors have been described, such as IRp60, for which a ligand has not been identified yet. The biological reasons for this array of inhibitory receptor–ligand systems are still elusive. It is possible that differential expression of ligands for inhibitory receptors facilitates detection by NK cells of various types of cells, each of which may rely on a few specific ligands to inhibit NK cells.

INTRACELLULAR SIGNALING

Receptor cooperation

The multiplicity of NK cell activation pathways may have been selected to counteract attempts by pathogens to circumvent NK cell-mediated immune surveillance. One of the major questions in NK cell biology is why engagement of multiple activating receptors is required and how the interplay among so many receptors results in controlled activation. A reductionist approach, using insect cells transfected with ligands for human NK cell receptors, revealed that combinations of distinct and synergistic signals from different receptors were required to induce efficient NK cell cytotoxicity [33]. Engagement of CD16 was sufficient to induce degranulation. Engagement of the integrin LFA-1 with its ligand ICAM-1 was sufficient to induce not only adhesion, but also granule polarization [33]. Lysis of target cells requires the combination of granule polarization induced by LFA-1 and degranulation induced by CD16. No natural cytotoxicity receptor was sufficient to induce cytotoxicity [34*]. For natural cytotoxicity, only the co-engagement of pairs of activating receptors synergistically induced degranulation and cytokine production [34*]. The term co-activation receptor has been proposed to describe natural cytotoxicity receptors that can only function as synergistic pairs [34*]. The molecular signals that form the basis for synergistic activation have not been defined yet. A system that balances the need to provide effective immune surveillance and to avoid immune pathology may have evolved from combinations of receptor synergy–dependent activation with negative regulation through several types of inhibitory receptor–ligand interactions.

Given the number of distinct activating receptors and the variety in NK cell activation pathways, initiation of NK cell effector function is more complex than activation of other lymphocyte subsets, as illustrated by a recent article characterizing expression of proximal signaling proteins in different lymphocyte subsets [35].

Proximal activation signals

Upon activation of NK cells by target cells, early signals are transmitted by Src-family kinases, which initiate activation pathways. In the case of ITAM-coupled receptors, Syk family kinases propagate activation signals. However, ITAM-containing adaptors and Syk family kinases are not essential for natural cytotoxicity, presumably due to the multiplicity of activation receptors [36,37*]. Substantial redundancy in proximal activation signals endows NK cells with the ability to mount a full response through different and independent signaling pathways. As a result of this multiplicity, only a few molecules have been shown to be required for natural cytotoxicity in mouse knockout models. Phospholipase C (PLC)-γ2 is an important mediator of degranulation, cytotoxicity, and cytokine production [38–40]. Pharmacological inhibition of PLC-γ abrogates degranulation, cytotoxicity and cytokine production by human NK cells, in addition to early signals for intracellular calcium mobilization [41]. Likewise, pharmacological inhibitors of phosphoinositide 3-kinase (PI3K) abrogate NK cell degranulation, cytotoxicity, and cytokine production, but do not necessarily impair mobilization of intracellular calcium [41]. The study of phosphoinositide 3-kinase function in NK cells is complicated by the fact that knocking out two out of the four p110 subunits results in embryonic lethality. Analysis of viable p110γ and p110δ knockout mice has revealed a requirement for p110δ in NK cell cytokine production, while NK cells from p110γ and p110δ double knockout mice demonstrate impaired cytotoxicity as well [42*,43*].

NKG2D is a co-activation receptor that recruits PI3K and Grb2–Vav to the phosphorylated tyrosine in DAP10 [44*]. While dependent on Src-family kinase activity, DAP10 signaling does not require Syk. Upon engagement by ligands on target cells, NKG2D clustering depends on DAP10-mediated PI3K activity [45]. Surprisingly, specific knock-down of DAP10 in

mouse lymphocytes resulted in impaired IL-15 responses of NK cells [46**]. When normally expressed, DAP10 is associated with the IL-15 receptor βγ-chains, and is phosphorylated by the IL-15 receptor-associated kinase Jak3. This bidirectional regulation between the IL-15 receptor and NKG2D provides a direct link between cytokine receptor stimulation and activation of NK cell cytotoxic function, and reveals further complexity in the regulation of NK cell responses [46**].

Inhibitory signals

The potent inhibition of NK cells by ITIM-containing receptors is mediated by a block at an early step of the signaling pathway for activation. Engagement of inhibitory receptors prevents actin cytoskeleton dynamics [47*,48], thereby preventing actin-dependent processes, such as coalescence of lipid rafts [49], recruitment and phosphorylation of co-activation receptors 2B4 and NKG2D to lipid rafts [50,51], and dephosphorylation of ezrin-radixin-moesin proteins, which connect actin filaments to membrane structures [48]. A direct substrate of SHP-1 during inhibition is Vav1, which is an essential regulator of actin dynamics [52]. An interesting imaging study in which phosphorylated inhibitory KIR was visualized, has shown that tyrosine phosphorylated KIR molecules are not evenly distributed over NK–target cell contact area but forms microclusters [53*]. The inhibitory receptor LAIR-1, which is expressed on most hematopoietic cells, has a unique ability to inhibit independently of tyrosine phosphatases SHP-1 and SHP-2. Even though its phosphorylated ITIM binds to the SH2 domains of SHP-1 and SHP-2, as is typical for ITIM family receptors, LAIR-1 can also deliver inhibitory signals by binding the SH2 domain of tyrosine kinase Csk, which negatively regulates Src-family kinases by phosphorylation of a C-terminal tyrosine [54*]. Further work is clearly needed to unravel the mechanism of ITIM-mediated inhibition and explain the basis for its potency.

STEPS IN NK CELL ACTIVATION

Target cell–mediated activation of NK cell effector functions involves formation of an immunological synapse, which is dependent on cytoskeletal changes, and occurs in a sequential manner following specific stages and checkpoints. Briefly, discrete steps involve contact and adhesion, which initiate receptor signaling, F-actin rearrangement and actinosome formation, followed by receptor clustering and polarization of secretory lysosomes towards the immune synapse, where they fuse with the plasma membrane and release cytotoxic granule contents [41,55]. Other signals lead to the production and release of cytokines and chemokines. It is not clear yet how activating signals diverge to induce different effector functions such as cytotoxicity and cytokine production. The following sections will examine current knowledge on how NK cells determine appropriate action upon encounter with target cells.

Intracellular proteins implicated in lytic granule polarization and exocytosis

Efficient target cell lysis requires lytic granule polarization towards the target and exocytosis. These two distinct processes can be mediated by separate signals. For example, the β2 integrin LFA-1 signals for granule polarization, whereas CD16 signaling results in degranulation without polarization [33]. Work in T cells has shown that upon actin-dependent formation of an immunological synapse perforin-containing granules move towards the minus-end of microtubules. The centrosome becomes juxtaposed to the target cell by an actin-dependent process [56*]. In NK cells, a link between the actin and microtuble cytoskeleton is formed by the Cdc42 interacting protein 4 (CIP4) [57*]. Knockdown of endogenous CIP4 impairs granule polarization to the immune synapse [57*]. Upon mixing with susceptible target cells, formation of a WIP, WASp, actin-, and myosin IIA complex was observed in the NK cell line YTS [47]. RNAi-based knockdown of WIP demonstrated a pivotal role in granule polarization and NK cell cytotoxicity [47,58]. Pharmacological inhibition or knockdown of myosin IIA, a constituent of myosin motor proteins that generate movement along actin filaments,

remarkably does not interfere with granule polarization, but impairs granule exocytosis [59*]. Rab27a and Munc13-4 are also required for granule exocytosis. Loss-of-function mutations in these proteins cause fatal autosomal recessive immunodeficiencies in humans and mice [60,61]. Fusion of of $Rab27a^+$ late endosomes and $Munc13\text{-}4^+$ recycling endosomes occurs prior to lytic granule exocytosis [62*]. Surprisingly, in Rab27a-deficient patients, CD16-mediated ADCC is intact but NKp30-mediated NK cell cytotoxicty is impaired [63]. In contrast, Munc13-4 is indispensable for NK cell mediated degranulation and cytotoxicity induced by several stimuli [64,65]. Finally, a fatal autosomal recessive immunodeficiency is associated with loss-of-function mutations in syntaxin 11, a soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) motif containing protein. Granule exocytosis is defective in NK cells from syntaxin 11-deficient patients [66*]. Moreover, knockdown of syntaxin 11 results also in impaired NK cell cytotoxicity [67*]. However, the exact vesicular fusion step that syntaxin 11 mediates and the partners involved in forming a SNARE complex required for membrane fusion remain to be elucidated.

Regulation of cytokine release by intracellular proteins

An important role of the Carma1/Bcl10/Malt1 complex in activation of NF-κB and induction of multiple cytokines by ITAM-coupled receptors has been demonstrated in mouse knockout models [68*,69*]. Absence of Bcl10 or Malt1 impaired also activation of p38 and JNK [69]. In contrast cytokine production induced by IL-12 and IL-18 was normal in Bcl10-deficient mice [69]. CD45-deficient mice exhibit decreased cytokine production but normal cytotoxicity [70–72]. Receptor tyrosine phosphatase CD45 deficiency augments tyrosine phosphorylation upon stimulation of ITAM-associated receptors, but impairs phosphorylation and activation of Erk, and JNK, abrogating cytokine transcription [71]. IFN-γ production is exacerbated in adaptor protein MIST-deficient CD4+ T cells, suggesting that MIST negatively regulates IFN-γ production [73]. Expression of the Src-family kinase Fgr paralleled the suppressive effect of MIST in NK cells, and an Fgr–MIST interaction is required for the suppression of NK cell receptor-induced IFN-γ expression [73]. Several soluble factors, such as IL-12 and IL-18, induce cytokine production by NK cells. IFN-γ release. by. NK. cells in response to interleukins is augmented by the protein SET [74]. SET mediates this effect by suppressing PP2A phosphatase activity, a negative regulator of NK cell cytokine production [74].

An unusual receptor of the KIR family, KIR2DL4, induces secretion of pro-inflammatory cytokines by resting NK cells in response to soluble HLA-G [75*]. Signaling occurs in early endosomes into which KIR2DL4 internalizes soluble HLA-G. Besides a role in promoting inflammatory responses at sites of HLA-G expression, this unusual signaling pathway may also promote vascularization at the maternal–fetal interface in early pregnancy in response to soluble HLA-G produced by trophoblast cells of the fetus [75*].

DYNAMIC TUNING OF NK CELL EFFECTOR RESPONSES

NK cells undergo a maturation process for acquisition of effector function. The intrinsic capacity of each NK cell to respond to activation signals is adjusted (“tuned” or “calibrated”) according to expression of MHC class I-specific inhibitory receptors and of available MHC class I ligands. NK cells that lack inhibitory receptors for self MHC class I molecules are hyporesponsive [76,77*]. Different models have been proposed to account for this property of inhibitory NK cell receptors. According to the “licensing” model an ITIM-dependent instructive signal is given to the NK cell by inhibitory receptor–MHC class I interaction [78]. The “arming/disarming” model proposes that continuous stimulation of NK cells that do not receive inhibitory signals results in unresponsiveness [79]. The nature of the signal for NK cell tuning and the point at which it regulates NK cell activity are still unknown.

Regulation of NK cell responsiveness and effector functions occur also in mature, circulating NK cells in response to cytokines. Type I interferons and cytokines that bind to the common γ-chain-containing receptors, such as IL-2 and IL-15, enhance NK cell responses. In mice, circulating NK cells do not express abundant perforin and granzyme B, until cytokine stimulation induces translation of pre-existing mRNA [80]. Recent experiments have suggested that such priming is delivered by contact with dendritic cells and trans-presentation of IL-15 [81*]. Priming of NK cells, which occurs in lymph nodes, is required for both cytotoxicity and IFN-γ production. In contrast to mice, human circulating NK cells, including NK cells from cord blood [66], contain abundant perforin and granzyme. In addition to stimulation of cytotoxic granule component synthesis, IL-2 enhances NK cell degranulation, at least in part through a syntaxin 11-independent pathway [66].

CONCLUDING REMARKS

Advances in characterization of NK cell receptor specificities have provided insight into diverse strategies used by NK cells for discrimination among target cells. Appreciation of the complexity in NK cell recognition and signaling will hopefully illuminate the role of NK cells in disease and facilitate their use in clinical applications. For further mechanistic understanding and prediction of NK cell responses, more detailed knowledge of the individual signaling pathways of disparate activating receptors and, upon co-engagement, the integration of such diverse signals, are required. Increased understanding of molecular checkpoints for NK cell effector function may provide targets for therapeutic intervention. Additional studies on the dynamic tuning of NK cell responsiveness during immune responses might uncover disfunctions, which underly pathology, and the means to harness the potent effector functions of NK cells in clinical settings.

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Table 1

Specificity and signalling of human NK cell activating receptors

Receptor	Signaling	Cellular ligand	Function
FcγRIIIa (CD16)	TCR$\tilde{\zeta}$/FcRγ – ITAM	IgG	Elimination of antibody coated cells (ADCC)
NKp30 (CD337)	TCR$\tilde{\zeta}$/FcRγ – ITAM	BAT3	Surveillance of genotoxic stress/transformation
NKp44 (CD336)	DAP12 – ITAM	?	?
NKp46 (CD335)	TCRζ/FcRγ – ITAM	?	Surveillance of mitotic cells
KIR (CD158xxx)	DAP12 – ITAM	HLA class I	?
CD94/NKG2C (CD159c)	DAP12 – ITAM	HLA-E	?
NKG2D (CD314)	DAP10 – YxNM	ULBP, MICA, MICB	Surveillance of tumor cells and genotoxic stress
NKp80	?	AICL	NK cell – myeloid cell cross-talk
DNAM-1 (CD226)	?	CD112, CD155	Surveillance of tissue integrity
2B4 (CD244)	ITSM	CD48	Interaction with hematopoetic cells
CRACC (CD319)	ITSM	CRACC (CD319)	Interaction with hematopoetic cells
CD2	?	CD58	Interaction with hematopoetic and endothelial cells
KIR2DL4 (CD158d)	?	HLA-G (soluble)	Trophoblast-induced vascular remodelling?
LFA-1 (CD11a/CD18)	?	ICAM	Recruitment and activation during inflammation, granule polarization

Table 2

Specificity and signalling of human NK cell inhibitory receptors

Receptor	Signaling	Cellular ligand	Function
KIR (CD158)	ITIM	HLA class I alleles	Assess loss of MHC class I alleles
LIR1, LILR1 (CD85j)	ITIM	HLA class I	Assess loss of MHC class I expression
CD94/NKG2A (CD159a)	ITIM	HLA-E	Gauge MHC class I expression
KLRG1	ITIM	E-, N-, P-cadherin	Assess loss of tissue integrity
NKR-P1 (CD161)	ITIM	LLT1	?
LAIR-1 (CD305)	ITIM	Collagen	Control activation in extracellular matrix
Siglec-7 (CD328)	ITIM	Sialic acid	?
Siglec-9 (CD329)	ITIM	Sialic acid	?
IRp60 (CD300a)	ITIM	?	?