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The Role of Activating and Inhibitory NK Cell Receptors in Antitumor Immune Response

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Abstract

Natural killer (NK) cells express many newly identified activating and inhibitory receptors that upon engagement by cognate ligands on target tumor cells regulate NK cell anti-tumor activity. Recently, several paired NK cell receptor families that include receptors with similar binding specificities but opposite function have been defined. The expression of most important activating receptors, natural killer group 2D (NKG2D), natural cytotoxic receptors (NCR), DNAX accessory molecule-1 (DNAM1) and activating killer cell immunoglobulin-like receptors (KAR) is often decreased, while the expression of most prominent inhibitory NK cell receptors, killer cell inhibitory immunoglobulin-like receptors (KIR) and CD94/NKG2A, may occasionally be increased in malignancies. These data indicate that impaired NK cell antitumor response results from NK cell receptor alterations induced by suppressive factors in the tumor microenvironment, including cytokines, growth factors, enzymes and metabolites, as well as by chronic NK cell receptor engagement by the tumor. The established alterations in NK cell receptor expression in cancer patients represent potential disease biomarkers and may aid in choosing therapies that upregulate activating or block inhibitory receptor function. Accumulating knowledge of NK cell biology has been helpful in creating novel therapeutic approaches that by release from tumor-influenced immunosuppression potentiate NK cell activity in cancer patients.

Keywords: NK cells, inhibitory and activating receptors, immunosuppression, cancer, immunotherapy

1. Introduction

Natural killer (NK) cells are equipped with multiple activating and inhibitory cell surface receptors and play a key role in controlling tumor growth and metastasis. NK cells have

originally been described to belong to the innate arm of the immune system and are able to discriminate between normal and transformed cells on the basis of major histocompatibility complex (MHC) class I molecule expression in the organism. As normal cells express major histocompatibility complex (MHC) class I molecules that engage NK cell inhibitory receptors, they are protected from NK cell-mediated lysis. Therefore, according to the “missing-self” hypothesis, activation of NK cells occurs in contact with malignantly transformed cells that have lost MHC class I molecules and that have additionally acquired stress-induced ligands for activating NK cell receptors. Maintenance of NK cell antitumor function relies on the balance between these activating and inhibitory signals mediated by NK cell receptors [1].

Considering that NK cells are defined as CD3⁺CD56⁺CD16^{+/-} cells according to the density of expression of these receptors, these cells are divided into two subsets. The larger cytotoxic subset with high density of CD16, low density of CD56 (CD56^{dim}CD16^{bright}), and abundant perforin and granzyme granules, and the other, smaller regulatory subset with low density or absence of CD16, high density of CD56 (CD56^{bright}CD16^{dim/-}) and the ability to produce abundant cytokines including interferon-gamma (IFN- γ), tumor necrosis factor (TNF), interleukin (IL)-10, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [2]. CD56^{bright}CD16^{dim} subset has a greater migratory potential and is recruited into tumor tissue, although CD56^{dim}CD16^{bright} NK cells have also been detected in certain tumors [3]. Recent data have shown in mucosa-associated lymph tissue (MALT), the presence of a novel family of tissue-resident innate lymphoid cells (ILC), with NK-like characteristics. This novel family is classified into three groups (ILC1, ILC2, and ILC3) and contrary to classical cytotoxic NK cells, considered to belong to ILC1 group, the involvement of other ILC subsets in cancer progression or resistance is still controversial [4].

Several new families of receptors have been recently identified on NK cells and growing knowledge indicates that some families are composed of paired receptors that in spite of binding similar ligands have opposite, activating, or inhibitory function [5]. The most important activating NK cell receptors are NKp46, NKp30, and NKp44 that belong to natural cytotoxic receptors (NCR) family, natural killer group 2D (NKG2D) that belongs to NKG2 calcium-dependent lectin-like (NKG2 C-lectin) family, DNAX accessory molecule 1 (DNAM1) that belongs to the family of nectin-binding adhesion molecules and activating killer cell immunoglobulin-like receptors (KAR). On the contrary, the most important family of inhibitory NK cell receptors belongs to killer cell immunoglobulin-like (KIR) receptor family, while NKG2 C-lectin family also includes inhibitory CD94/NKG2A NK cell receptors (**Table 1**). Upon binding ligands, these activating and inhibitory NK cell receptors cooperate and determine NK cell cytotoxicity against transformed cells [6]. However, tumor-derived immunosuppressive factors play a major role in evading NK cell responses to tumors by interfering with NK cell activation pathways or the complex receptor array that regulate NK cell activation and antitumor activity [3, 7].

The objective of this chapter is to present current data based on the knowledge of many newly identified activating and inhibitory NK cell receptors whose balance regulates NK cell antitumor activity. Numerous alterations in NK cell receptor expression and signaling pathways induced by tumor-derived immunosuppressive factors that are responsible for poor

Receptor families		Ligands	Signaling molecules	
NCR	Activating	NKp46	HSPG, heparin, vimentin	FcR γ and CD3 ζ , ZAP70/Syk
		NKp44	NKp44L	DAP12, ZAP70/Syk
		NKp30a, b	B7-H6, BAG-6	CD3 ζ , ZAP70/Syk
	Inhibitory	NKp44	PCNA	ITIM, SHP1, 2
		NKp30c	?	?
Paired receptors				
NKG2	Activating	NKG2D	MICA/B, ULBP1-6	DAP10, Grb2, Vav, SOS
		CD94/NKG2C	HLA-E	DAP12, ZAP70/Syk
	Inhibitory	CD94/NKG2A		
		CD94/NKG2E	HLA-E	ITIM, SHP1, 2
		CD94/NKG2F		
KIR	Inhibitory	2DL1/L2/L3	HLA-C	ITIM, SHP1, 2
		3DL1/L2/L3	HLA- A, -B	
	Activating	2DS1/S2/S4	HLA-C/?	DAP12, ZAP70/Syk
		3DS1	?	
Adhesion molecules	Activating	DNAM-1	PVR, nectin-2	ITSM, Vav, PLC γ
	Inhibitory	TIGIT	PVR, nectin-2	ITIM, SHP1, 2
		TACTILE		
Fc γ RIII	Activating	CD16	Fc IgG	FcR γ and CD3 ζ , ZAP70/Syk
NKPR1	Activating	CD161	?	?
	Inhibitory		LLT1	ITIM, SHP1, 2

Table 1. NK cell activating and inhibitory receptors.

NK cell cytotoxic function in cancer patients will be defined. Understanding of the alterations in NK cell receptors and function can contribute in the assessment of biomarkers of the state of malignant disease and may aid in the selection of immunotherapy that supports an effective NK cell antitumor response.

2. NK cell receptors

2.1. Natural cytotoxic receptors

The NCR represent a group of human NK cell activating receptors that belong to the immunoglobulin superfamily and include NKp46, NKp30, and NKp44. NKp46 and NKp30 are

constitutively expressed on all activated and resting NK cells, whereas NKp44 expression on NK cells requires activation by IL-2. This makes NKp46 and NKp30 the only NK-specific markers known today, although recent evidence suggests that a very small subset of T cells expresses NKp46 [8].

Tumor-associated ligands for most NCR have only been recently described. B7-H6 was the first identified cellular ligand for an NCR expressed on the surface of cancer cells that binds to the activating receptors NKp30 [9]. Recently, a novel isoform of the mixed lineage leukemia-5 (MLL5) nuclear protein was proposed as a cancer cell-expressed ligand for NKp44 [10]. Ligands for NKp46 have been described to have viral structural motives that belong to hemagglutinin-like molecules or to be heparan sulfate proteoglycans (HSPG) [11]. The cytoplasmic domains of NCR do not possess any signaling motives except for NKp44 that contains an immunoreceptor tyrosine-based inhibition motif (ITIM) that has been reported functional only upon binding to certain ligands. Therefore, NCR associate with CD3 ζ -chain, Fc ϵ RI γ and DAP12 adaptor proteins that undergo phosphorylation of their immunoreceptor tyrosine-based activation motives (ITAM), recruit sarcoma homology 2 (SH2) domains of spleen tyrosine kinase (Src)/zeta-chain-associated protein kinase 70 (ZAP70) and ultimately lead to extracellular signal-regulated kinase (ERK) activation and cytotoxic granule mobilization [8].

Conversely, it has recently been shown that the constitutively inactive cytoplasmic ITIM domain of NKp44 receptor becomes functionally active only upon binding proliferating cell nuclear antigen (PCNA) leading to the inhibition of NK cell function [12] that might be involved in tumor immune evasion. Similarly, as NKp30 is comprised of three different isoforms, NKp30a, b, and c it has been shown that binding of NKp30c induces an immunosuppressive signal by producing IL-10 that is associated with reduced NK cell effector functions. Therefore, the final outcome of NKp44 and NKp30 activation depends on the presence of ligands on target cells, as well as receptor isoforms expressed on the surface of NK cells, respectively [13].

NCR, aside from direct antitumor cytotoxicity can also mediate the production of proinflammatory cytokines by NK cells that have an immunoregulatory role and engage in orchestrating antitumor immune response. In this sense, it has been shown that cross-linking of NKp46 and NKp44 resulted in NK cell production of IFN γ and TNF that are responsible for dendritic cell (DC) maturation and regulation of adaptive response to tumors. However, binding of inhibitory NKp30c induces production of IL-10 that reduces NK cell function [14].

Downregulation of NCR expression can be induced by soluble factors such as transforming growth factor beta (TGF- β), IL-10, L-kynurenine, a product of tryptophan degradation by tumor-derived indolamin-2,3-dioxygenase (IDO). Decreased expression of some NCR has been reported in several malignancies, namely low NKp46 in melanoma, pancreatic, gastric, cervical cancer, and acute myeloid leukemia (AML) [15–17], NKp44 in numerous solid and hematological malignancies, and NKp30 in breast, hepatocellular cancer (HCC), chronic lymphocytic leukemia (CLL), and AML [15, 16, 18–20]. Moreover, ILC3 cells expressing NKp44 activating receptor in human nonsmall-cell lung cancer (NSCLC) tissue were shown to have tumor protective role [4]. However, overexpression of PCNA in certain tumors results in NKp44 receptor-mediated inhibition of NK cell activity [8].

2.2. Families of paired receptors in NK cells

2.2.1. NK group 2 calcium-dependent lectin-like receptor family

This family of calcium-dependent lectin-like receptors includes CD94-NKG2-A/C/E/F/H heterodimer and NKG2D homodimer receptors present on NK cells. This family is composed of paired NK cells receptors with similar binding specificities to nonclassical MHC class I molecules on the surface of potential target cells but either activating or inhibitory functions [21].

2.2.1.1. Natural killer group 2D

It is an activating receptor expressed on virtually all NK cells. NKG2D recognizes a number of MHC-class-I-related molecules, major histocompatibility complex class I chain-related molecule (MIC) A/B and UL16-binding protein (ULBP) expressed on cells in stressful conditions, such as transformation [22]. Owing to their ability to trigger activation of the immune system, it has now been shown that their expression is very tightly controlled at transcriptional level [23]. NKG2D is a pivotal activating receptor that upon binding stress-induced ligands and phosphorylation of intracellular adaptor protein DNAX-activation protein 10 (DAP10) recruits various signaling pathways and induces tumor cytotoxicity [24].

Decreased expression of NKG2D in cancer patients is mediated by TGF β and IL-10 produced by tumor cells and immunosuppressive immune cells, tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg) in the tumor microenvironment [25]. Also, persistent stimulation of NKG2D receptor by its tumor cell-associated ligands, as well as, soluble ligands induced by matrix metalloproteinases (MMP) proteolytic cleavage from tumor cells may lead to functional exhaustion of NK cells [26].

Downregulation of NKG2D expression together with degradation of its intracellular signal transducing adapter, DAP10 [27], by its ligand has also been shown in experimental settings of conjugate formation between NK cells, not only of healthy individuals but also of metastatic melanoma patients, with K562, an erythromyeloid cell line, or FemX, a melanoma-derived tumor cell line [28–30]. This effect is more pronounced for K562 tumor cells as they highly express MICA/B ligands specific for NKG2D receptors [31], while for FemX tumor cell line so far no data exist regarding the expression of MICA/B ligands, although it can be assumed that, as most tumor cells, this cell line expresses some level of these stress-induced ligands. The importance of NKG2D receptor in NK cell cytotoxic function underlies a significant positive correlation of its expression with NK cytotoxicity in healthy individuals, as well as in melanoma patients, in spite of different levels of expression [32–34].

These data indicate that activating NKG2D receptor has a role in NK cell tumor immunosurveillance and in immune-mediated rejection of tumor cells and that NKG2D downregulation as a consequence of tumor immunoediting favors tumor progression [13].

2.2.1.2. Heterodimeric NK group 2 calcium-dependent lectin-like A/B/C/E/H receptors

These heterodimer receptors consist of CD94 subunit that is associated with the member of the NKG2 family (A/B/C/E/H). Prototypic member of this family CD94-NKG2A has an ITIM that

consequently leads to the inhibition of NK cell activity by inducing dephosphorylation of surrounding tyrosine kinases and adaptor proteins. By contrast, receptors CD94-NKG2-C, CD94-NKG2-E, and CD94-NKG2-H, associate with DAP12 and function as activating receptors that participate in NK cell antitumor response. These receptors bind to nonclassical MHC class I, human leukocyte antigen (HLA)-E molecules on the surface of malignantly transformed target cells [21].

Interestingly, the ligand for this receptor family, HLA-E molecule assembles at the endoplasmic reticulum with peptides derived from the leader peptides of HLA-A, B, C, and G molecules and as in malignant transformation, the expression of classical MHC class I molecules is downregulated, the expression of HLA-E is consequently upregulated [35]. The importance of the inhibitory activity of NKG2A receptor expression is demonstrated in breast cancer and colorectal cancer (CRC) as its increased expression is associated with poor disease prognosis [18, 36]. Conversely, decreased expression of NKG2C activating receptor resulting in NK cell dysfunction has so far been reported for AML [37].

2.2.2. Killer cell immunoglobulin-like receptor family

This is a well-known paired NK cell receptor family with either inhibitory or activating functions that interact specifically with MHC class I molecules and their tissue protective role is based on the higher binding affinity and signal transduction by inhibitory KIR receptors, compared to activating KAR receptors, for MHC class I ligands. According to KIR expression on NK cells, they are divided into KIR haplotype A and B, with A being more frequent and including inhibitory receptors compared to B that includes both types of receptors with predominance of activating receptors [38].

The most prominent inhibitory killer cell immunoglobulin-like receptors (KIR) are KIR2DL1 (CD158a), KIR2DL2/3 (CD158b), and KIR3DL1-2 and inhibit NK cell activity through an ITIM by recruiting SH2 domain protein tyrosine phosphatases (SHP)-1 and -2 and adaptor proteins, including DAP-10. Moreover, blocking actin cytoskeleton-dependent raft recruitment of different receptors may be a general mechanism by which inhibitory receptors control NK cell activation [39]. Thus, activating KAR, such as KIR2DS1, KIR2DS4, and KIR2DL4, associate with DAP12 adaptor protein that deliver activation signals through an ITAM that after phosphorylation by sarcoma (Src) family kinases recruit Syk/ZAP-70 tyrosine kinases to mediate downstream activation signaling [40]. Clinical studies have correlated KIR gene content with cancer [41]. It has recently been reported that higher expression of inhibitory CD158a and CD158b receptors, especially in patients that express their specific HLA-C ligands, is associated not only with susceptibility to tumors but also with disease progression, shown by increase in NK cells with these receptors in advanced stages of melanoma [42, 43].

Inhibitory KIR receptor upregulation on NK cells in malignant tumors has been reported to be associated with immunosuppressive, as well as immunostimulatory cytokines [44–48]. Higher expression of certain inhibitory KIR receptors has been shown in pancreatic, gastric, and CRC without association with disease progression [15]. Other studies in patients with metastatic melanoma, as well as in NSCLC and breast cancer, show an increase in the expression of CD158a and CD158b inhibitory KIR receptors on NK cells [33, 49–51] that in

melanoma negatively correlates with NK cell cytotoxicity [33]. In this sense, as inhibitory KIR play prominent roles in regulating NK cell activation therapeutic strategies designed to diminish KIR function that may be able to potentiate NK cell activity in treating patients with malignancies.

2.2.3. Family of nectin-binding adhesion molecules

It is an important family of adhesion molecules that includes CD226 (DNAM1), CD96 (T cell-activated increased late expression (TACTILE)), and T-cell immunoglobulin and ITIM domain (TIGIT). These receptors bind nectin proteins, CD112 (nectin-2), and CD155 (poliovirus receptor (PVR)) and have been recently identified as crucial regulators of NK cell function. This is another family of paired NK cell receptors with similar binding specificities on the surface of target cells but with either activating (CD226) or inhibitory (CD96 and TIGIT) functions [5].

2.2.3.1. Stimulatory nectin-binding adhesion molecule

Costimulatory adhesion receptor DNAM1, a member of immunoglobulin-superfamily has recently been shown to have a role in the recognition of tumor cells and NK cell-mediated responses to tumors. It binds to PVR and nectin-2, and recruits the tyrosine kinase fibroblast endothelial kinase (Fyn) and serine threonine protein kinase C (PKC). Moreover, interaction of DNAM1 with target cell ligands induces actin polymerization and activation of other surface receptors, which permit stable interaction of NK cells and target cells. Furthermore, the involvement of this receptor in the NK cell-mediated responses to tumors is beginning to be elucidated and results to date suggest that DNAM1 has a role in the recognition of tumor cells, as well as migration of NK cells [35, 52].

The importance of DNAM1 has been reported in breast cancer, CRC, AML, and melanoma [17, 18, 37, 53] and in melanoma, it has been shown that tumor-associated fibroblasts (TAF) by modulating the surface expression of DNAM-1 based on cell-to-cell interactions could inhibit NK cell function [54]. Also, DNAM1 ligand CD155 upregulation on multiple myeloma (MM) cells has been reported and resulted in increased sensitivity to NK cell-mediated lysis [55].

2.2.3.2. Inhibitory nectin-binding adhesion molecules

TIGIT and TACTILE (CD96) receptors that unlike activating DNAM1 receptor contain an ITIM motive subsequently inhibit NK cell antitumor activity and counteract DNAM-mediated activation. These receptors are important in settings in which the tumor is mainly non-immunogenic, as it does not express stress ligands or costimulatory molecules, which is a common situation for many epithelial cell malignancies. For this reason, these inhibitory molecules may be promising therapeutic targets for the treatment of malignancies [5].

2.3. CD16 (Fc γ receptor IIIA)

This is one of the most important NK cell cytotoxic receptors that contains two extracellular Ig-like domains and is involved in both direct [56] and, as an Fc gamma receptor type IIIA, is

involved in antibody-dependent cell-mediated cytotoxicity (ADCC) [57], as well as cytokine production, proliferation, and postactivation NK cell apoptotic death [56].

CD16, as well as NKp46, associates with two cytoplasmic domains composed of Fc ϵ RI γ or T-cell receptor (TCR) ζ chains that comprise ITAM, which upon ligand-binding become phosphorylated and induce signal transduction by activation of nonreceptor tyrosine kinases Syk and ZAP-70 [57].

The expression of CD16 as a prominent NK cell cytotoxic receptor has been found to be decreased on NK cells in breast cancer and MM patients [18, 58] not only due to postactivation receptor internalization but also following target cell induced activation of MMP, namely ADAM 17, as shown during *in vitro* NK cell cultivation with tumor cells [59, 60]. Moreover, as CD16 defines the two functionally different NK cell subsets, its decreased expression influences the ratio of these subsets, leading to the loss of the CD16^{bright} cytotoxic subset, a finding that has been detected in numerous malignancies such as breast cancer, MM, and melanoma [6, 33].

2.4. Natural killer cell surface protein P1A

This is a member of the C-type lectin family that is primarily designated as an activating receptor that plays a role in NK cell-mediated cytotoxicity and it has been previously shown that natural killer cell surface protein P1A (NKR-P1A)/CD161 participates in triggering NK cell cytotoxicity against numerous human tumor cell lines [61], while more recently, it has been suggested that its activating mechanism may require interaction with costimulatory receptors [62]. On identification of its lectin-like transcript 1 (LLT1) ligand, its inhibitory potential has recently been described, but its function still remains controversial. In support of the inhibitory function of NKR-P1A, it has been shown that its cytoplasmic tail contains tyrosine residue in an atypical motive (AxYxxL) that may function as a weak ITIM [63, 64]. There are some reports of decreased expression and cytokine-mediated upregulation of NKR-P1A/CD161 in metastatic melanoma and MM [29, 33, 58].

3. Tumor-induced immunosuppression

It has now been well documented that tumor-induced immunosuppression affects NK cell receptor repertoire and leads to progressive local and systemic inhibition of NK cell function. In tumors, a complex composition of immunosuppressive molecules TGF- β , IL-10, IDO, prostaglandin E2 (PGE2), vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), and reactive oxygen species (ROS) are produced by regulatory immune cells such as Treg, MDSC, TAM, and by tumor cells themselves (**Figure. 1**). These factors generate a chronic inflammatory immunosuppressive milieu that leads to the suppression of the antitumor effector NK cell function that supports tumor progression [3, 7, 13, 65]. In this sense, considering that the expression of activating NK cell receptors is decreased in most malignancies, and as some studies report that the expression of inhibitory KIR and CD94/NKG2A receptors on NK cells in different tumors remains unchanged, this suggests that activating receptors are main targets of tumor-mediated suppression [13].

Furthermore, NK cell dysfunction due to decreased activating NK cell receptor expression may be mediated by chronic tumor cell ligand-NK cell receptor engagement that leads to an exhausted NK cell phenotype characterized by upregulated programmed death 1 (PD-1) checkpoint immunoreceptor expression [66]. Conversely, the appearance of soluble NK cell ligands due to proteolytic cleavage from tumor cells also leads to NK cell dysfunction due to chronic NK cell receptor stimulation in the absence of target tumor cells [26].

In this sense, it has now been established that during the development of solid tumors, NK cells are frequently rendered functionally impaired as a consequence of cancer immunoediting that induces immune tolerance to tumors owing to impairment of NK cell receptor repertoire and signaling, as well as immunoselection of nonimmunogenic tumor cells.

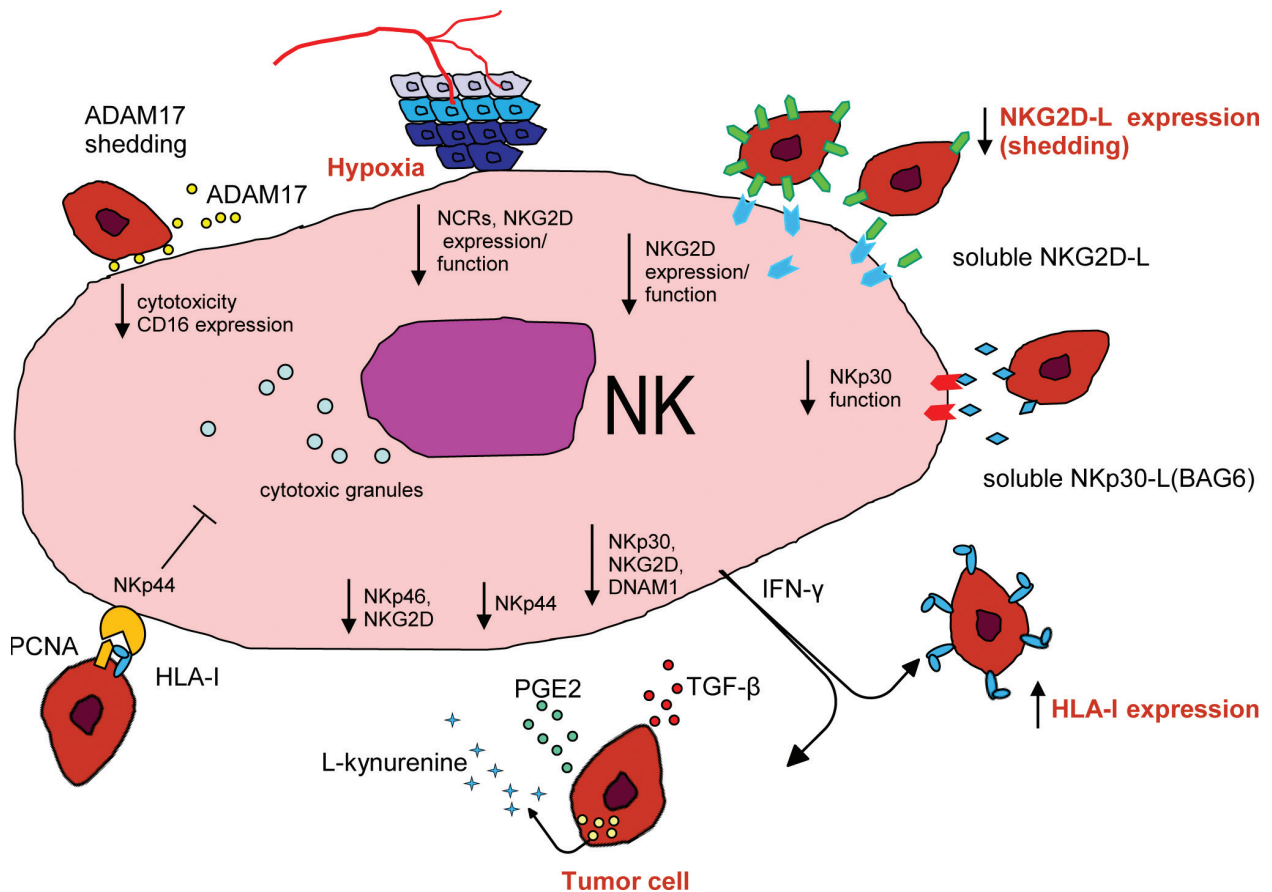


Figure 1. Mechanisms of NK cell receptor dysregulation in tumors. The tumor induces alterations in NK cell activating receptors by producing suppressive tumor-derived mediators including immunosuppressive cytokines (transforming growth factor beta - TGF- β), enzymes (indolamin-2,3-dioxygenase - IDO), factors (L-kynurenine, prostaglandin E2 - PGE2) that together with the presence of hypoxia can suppress NK cell antitumor activity. Chronic engagement of NK cell activating receptors with either tumor cell surface-expressed or shed NK cell ligands (NKG2D ligand - NKG2D-L) leads to progressive inhibition of NK cell antitumor response. Also, tumor-expressed proliferating cell nuclear antigen (PCNA) associated with HLA-I molecule by binding NKp44 activating receptor induces unconventional inhibitory signals in NK cells. Moreover, interferon gamma (IFN- γ) released by NK cells induces increased expression of HLA-I molecules on tumor cells, as well as tumor-produced IDO, that lead to inhibition of NK cell function.

4. NK cell receptors as therapeutic targets in cancer immunotherapy

As NK cell antitumor activity is regulated by numerous activating and inhibitory NK cell receptors, alterations in NK cell receptor expression and signaling underlie diminished cytotoxic NK cell function. Based on this and on predictive *in vitro* findings [6, 46–48, 67–70], cytokines, including IFN α , IL-2, IL-12, IL-15, and IL-18 have been used systemically or for *ex vivo*–activation and expansion of NK cells and have led to improved NK cells antitumor activity by increasing the expression of NK cell activating receptors and by inducing cytotoxic effector molecules [71–75]. Moreover, this cytokine-based therapy enhances NK cell proliferation and regulatory function, and it has been shown that it induces NK cells exhibiting cytokine induced memory-like properties [76] that represent a newly-defined NK cell subset with improved NK cell activity and longevity.

Considering the effect of tumor-derived immunosuppressive molecules on the decrease in the expression of activating NK cell receptors, early stage clinical trials have been introduced that use monoclonal antibodies, alone or in combination, to neutralize TGF- β , IDO, or PD-1 checkpoint inhibitor in different malignancies that led to improved antitumor NK cell function [77].

Since inhibitory KIR play prominent roles in regulating NK cell activation, therapeutic strategies in cancer to diminish KIR function have been developed. In autologous settings, anti-inhibitory KIR monoclonal antibody therapy has been introduced to support autologous NK cell administration by rendering them with higher antitumor activity, as reported in AML and MM. On the other hand, allogeneic hematopoietic stem cell transplants (HSCT) based on partially KIR/HLA mismatched alloreactive NK cell transfer that relieve donor NK cells from inhibition by recipient's MHC class I molecules, show beneficial graft-versus-tumor (GvT) effect in both pediatric and adult high-risk leukemia [78].

Moreover, it has been recognized that classical and novel pharmacological agents, such as proteasome inhibitors or histone deacetylase inhibitors and certain chemotherapeutics [72, 74, 75], upregulate cognate ligands for activating receptors on tumor cells and provide better NK cell antitumor response.

Also, a new effective approach, in clinical trials, designed to enhance NK cell–tumor cell interaction includes genetically modified NK cells expressing cytokine transgenes, chimeric antigen receptors (CARs), or overexpressing activating receptors that recognize NK cell ligands on tumor cells are showing promising results.

As it has been shown that therapeutic antibodies that are already in use for cancer treatment also trigger NK cell-mediated ADCC activity [79, 80] have been modified to increase binding of their Fc fragment to CD16 on NK cells. These therapeutic antibodies by binding CD16 receptor induce a potent activating signal, which overcomes inhibitory signals and results in both cytotoxicity and cytokine responses [81] that enhance NK cell activation against tumor cells.

5. Conclusion

The knowledge of NK cells has grown to include many newly identified activating and inhibitory NK cell receptors and defined alterations in receptor expression and signaling pathways that are responsible for poor NK cell cytotoxic function in cancer patients, may be considered as biomarkers of the state of disease. These findings regarding NK cell receptors may aid in the selection of classical and newly developed therapies that favorably modulate NK cell receptor expression and function, and release them from tumor-derived immunosuppression in order to achieve an effective NK cell antitumor response.

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