

Natural killer cells: role in local tumor growth and metastasis

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Abstract: Historically, the name of natural killer (NK) cells came from their natural ability to kill tumor cells in vitro. From the 1970s to date, accumulating data highlighted the importance of NK cells in host immune response against cancer and in therapy-induced antitumor response. The recognition and the lysis of tumor cells by NK cells are regulated by a complex balance of inhibitory and activating signals. This review summarizes NK cell mechanisms to kill cancer cells, their role in host immune responses against tumor growth or metastasis, and their implications in antitumor immunotherapies via cytokines, antibodies, or in combination with other therapies. The regulatory role of NK cells in autoimmunity is also discussed.

Keywords: natural killer, tumor, cytotoxicity, natural cytotoxicity receptor

Introduction to natural killer cells in antitumor immune response

Natural killer (NK) cells were discovered in humans and mice in 1975 due to specific functional criteria corresponding to their ability to lyse certain tumor cells in the absence of prior stimulation.¹ They possess a morphology of large granular lymphocytes (Figure 1A) and their receptor genes involved in the recognition of pathogens remain in germinal configuration unlike T and B cells.² Thus, they differ from the T and B lymphocytes by the permanent presence of a significant fraction of educated and primed cells.³ The formulation of the hypothesis of “missing self” by Klas Kärre, based on the fact that NK cells are able to detect and lyse cells with a deficient expression of major histocompatibility complex class I (MHC-I) molecules, allowed a better understanding of the function and the role of NK cells in the immune response.⁴ In the 1990s, several studies highlighted the presence of inhibiting and activating receptors expressed by NK cells⁵ that led to the identification of a new recognition model called “induced-self.”⁶ This new model complements the hypothesis of “missing-self” by explaining why NK cells kill tumor cells expressing MHC-I molecules or save autologous cells with absent MHC-I expression (Figure 2). Indeed, NK cell triggering is the result of a complex balance between inhibitory and activating signals and require not only a deficient MHC-I expression on target cells but also the expression of inducible ligands of activating NK cell receptors.⁷ Consequently, these cells have the ability to recognize and destroy a wide range of abnormal cells (including tumor cells, virus-infected cells, cells bound by an antibody, allogeneic cells), as well as stressed cells, without damaging the healthy and normal “self” cells.⁸ Therefore, NK cells have several important effector functions such as the initiation and amplification of the

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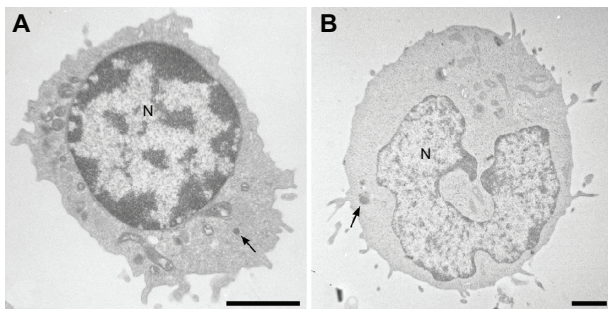


Figure 1 Electron micrographics of natural killer (A) and NK-92 (B) cells showing large lymphocyte-containing granules (arrows).

Note: Scale bar, 2 μm.

Abbreviation: N, nucleus.

inflammatory response, the production of chemokines and cytokines, and the lysis of sensitive target cells.^{9,10}

NK cells represent 5% to 20% of peripheral blood mononuclear cells, usually defined as CD16+ CD56+ CD3- cells and are also found in many tissues such as

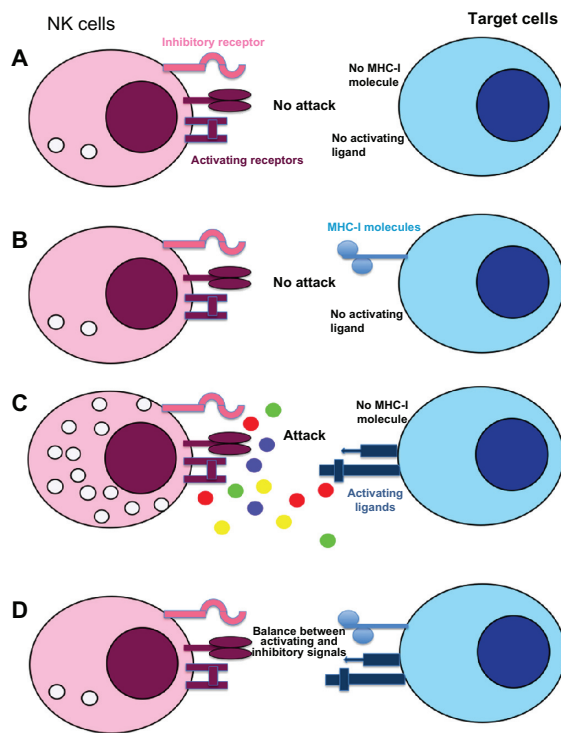


Figure 2 Recognition mechanisms of target cells by NK cells: “missing and induced self” theory. NK cell response is not initiated if neither ligands for NK-activating receptors nor MHC-I are expressed on target cells (A). If inhibitory receptors interact with MHC-I molecules without ligands for activating receptors no cytotoxicity is observed (B), whereas engagement of these receptors in absence of MHC-I molecule induced a strong NK cell response (C). In most cases, NK cell response depends on a balance between inhibitory and activating receptor signaling (D). Normal cells are protected against NK cell cytotoxicity because they usually express MHC-I molecules and no or low level of activating receptor ligands.

Notes: In contrast, cell transformation could induce a down-modulation of MHC-I molecules and/or an overexpression of ligands for activating receptors resulting in NK cell recognition and tumor cell lysis.

Abbreviations: MHC-I: major histocompatibility complex class I; NK, natural killer.

liver, peritoneal cavity, placenta, or the uterine mucosa.^{11–14} Human NK cells can be divided into two subpopulations according to the density of CD16 and CD56 expression on their surface (Figure 3). The majority of NK cells in blood (90%–95%) or at inflammation sites have a moderate expression of CD56 (CD56^{dim}) and a strong expression of CD16 (Figure 3). These cells possess a high cytotoxic potential.¹⁵ The CD56^{bright} subpopulation predominates in lymph nodes, expresses no or low levels of CD16, displays little cytotoxicity, and mainly produces cytokines upon activation (Figure 3).¹⁶ CD56 is not expressed on mouse NK cells, but recently Hayakawa and Smyth¹⁷ categorized these cells depending on their CD27 expression. Mouse CD27^{bright} NK cells share several characteristics with human CD56^{bright} NK cells. Accordingly, they predominate in lymph nodes and produce large amounts of cytokines. Recently, the discovery of a new NK marker, NKp46, allowed to define human and mice NK cells because, in contrast to others markers (CD16 and CD56 for humans or DX5 or NK1.1 for mice), NKp46 is exclusively expressed by all NK cells in both species.¹⁸

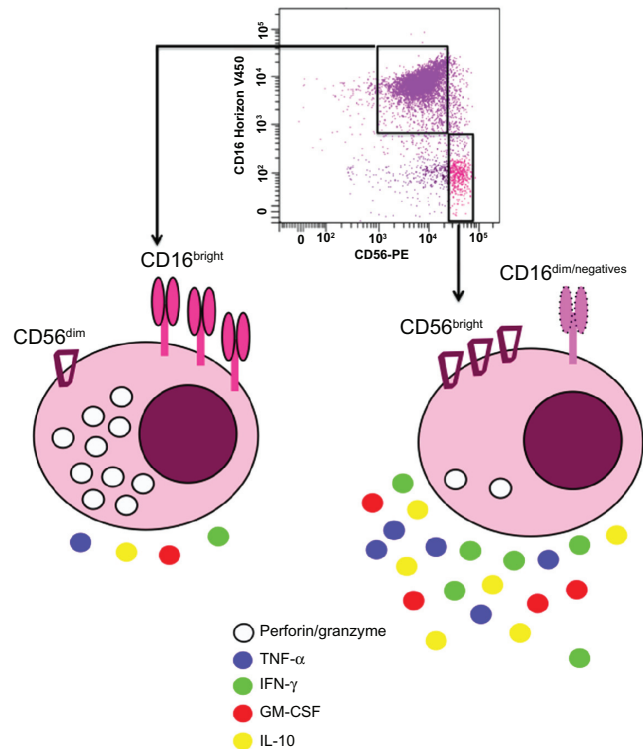


Figure 3 Human natural killer cell subsets based on CD56 and CD16 expressions: Around 90% of natural killer cells isolated from the blood display dim level of CD56 and high density of CD16 (CD56^{dim}CD16^{bright}).

Notes: These cells are more cytotoxic via perforin and granzyme secretion¹⁵ than natural killer cells showing bright expression of CD56 and no or low expression of CD16 (CD56^{bright}CD16^{low}). These latter cells produce more cytokines.¹⁶

Abbreviations: GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon γ; IL-10, interleukin 10; TNF-α, tumor necrosis factor α.

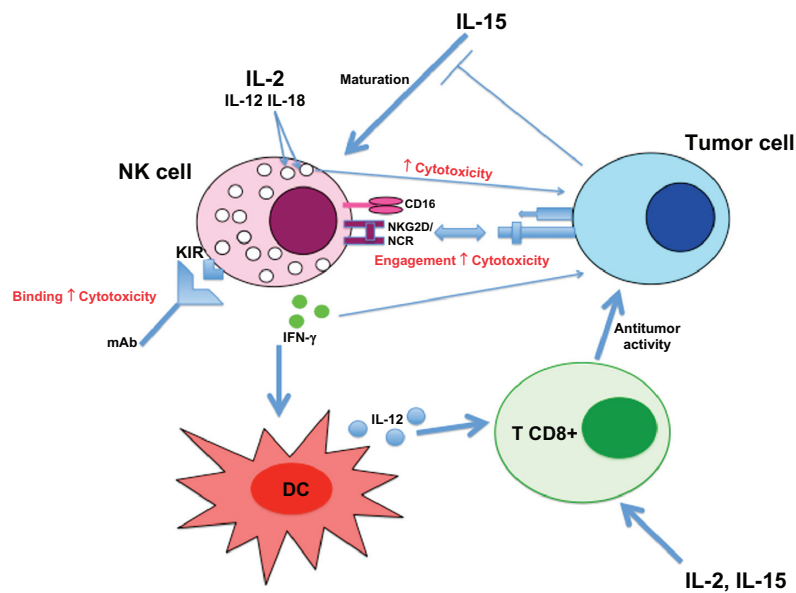


Figure 4 Overview of NK cell responses against tumor cell.

Abbreviations: NK, natural killer; DC, dendritic cell; IFN- γ , interferon γ ; IL, interleukin; KIR, killer-cell immunoglobulin-like receptor; mAb, monoclonal antibody; NCR, natural cytotoxicity receptor; TNF- α , tumor necrosis factor α .

Several NK cell lines have been established from lymphoma or peripheral blood mononuclear cells such as NK-92¹⁹ (Figure 1B) or NKG,²⁰ respectively.

From their discovery, NK cells were described as white blood cells able to lyse tumor cells such as K562, a tumor cell line generated from a patient with chronic leukemia.²¹ Shortly thereafter, NK cells were shown to eliminate circulating tumor cells in mice,²² but also to kill spontaneously cells deficient for MHC-I.⁴ The generation of mice genetically deficient for NK cells or depleted of these cells by antibodies, highlighted that NK cells have a role in immunosurveillance of cancer and the ability to prevent the tumor growth.^{23–25} Indeed, the transplantation of lymphoma cells in mice conduct to a more aggressive tumor growth in NK cell deficient mice compared to wild type mice.²⁶

Review of the activation and mechanism of action of NK cells

Unlike T and B lymphocytes, NK cells will not rearrange their genes encoding for receptor antigen recognition, but they have the ability to recognize target cells directly through inhibitory or activating receptors expressed on the cell surface. The balance between stimulatory and inhibitory signals will determine the activation status of NK cells since lysis of the target cell will only happen when the activating signals outweigh the inhibitory signals. The first checkpoint is the expression of MHC-I molecules.^{4,27} In fact, downregulation of MHC-I is observed during tumor transformation²⁸

or viral infection²⁹ and prevents the binding of inhibitory receptors of NK cells to the target cell. Simultaneously, ligands for activating receptor of NK cells must be expressed on the target cell to trigger NK cell cytotoxicity. These ligands are absent or expressed in low amounts on normal cells, although they are highly expressed on potentially harmful cells as a consequence of cellular stress, viral infection, or tumor transformation.

Different mechanisms are known to be involved in the destruction of tumor cells by NK cells:

- **Perforin/granzyme-mediated cytotoxicity:** The release of cytotoxic granules composed of perforin and granzymes³⁰ is the fastest and also the most powerful way to lyse tumor cells. By creating a synapse with the target cell, NK cells will drop, at this junction, perforin and granzyme molecules inducing the lysis of the target cell.³¹ Mice deficient for perforin are less efficient (about 10 to 100 times) to suppress syngeneic MHC-I deficient tumor cells, suggesting that this molecule is required for NK cell cytotoxicity.³² Moreover, many studies have shown that perforin is important for the immunosurveillance of several spontaneous malignancies³³ whereas the role of granzymes is less characterized.³⁴
- **Death receptor mediated apoptosis:** The death of the target cell, induced by apoptosis via tumor necrosis factor (TNF) family ligands, Fas ligand (CD178), TNF, and TRAIL (tumor-necrosis factor-related apoptosis-inducing ligand),³⁵ is an alternative to the release of granules.

This second mechanism, which is slower (several hours) and often less efficient than the previous one, requires the presence of the TNF family ligand expression on the surface of NK cells. These ligands will bind to a receptor Fas on the surface of the target cell. The effectiveness of this pathway is controlled by various factors such as expression of the receptor for FasL or TRAIL by the cancer cells or intracellular mechanisms protecting against apoptosis. For example, a murine subset of NK cells in liver expressing TRAIL has been shown to kill cancer cells and clear tumors from the liver.³⁶

- Interferon- γ effector functions: After activation, NK cells secrete various cytokines such as interferon γ (IFN- γ), TNF- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-10, or IL-13 and their antitumor activities can be mediated by IFN- γ .³⁷ Indeed, IFN- γ produced by NK cells contributes to eliminate tumor metastases and sarcoma induced by methylcholanthrene in a murine model.³⁸ This cytokine inhibits proliferation of tumor cells in vitro and indirectly the tumor growth in vivo by inducing the antiangiogenic factors, IP-10.³⁹ IFN- γ has been also described to enhance NK cell cytotoxicity by overexpressing adhesion molecules or by increasing the sensitivity of tumor cells to cytotoxicity mediated by granule release or death receptor engagement.⁴⁰ TRAIL expression on murine liver NK cells is dependent on IFN- γ expression and contributes to the natural antimetastatic role of these NK cells.³⁶ IFN- γ induced TRAIL expression is also implicated in the IL-12 mediated anti-metastatic effect.²⁴

Additionally, IFN- γ plays a role in the stimulation of dendritic cells (DC). In combination with CD40 engagement, IFN- γ induces IL-12 production by DCs.⁴¹ In this way, NK cells contribute indirectly to tumor control by helping the

initiation and maintenance of an efficient T cell-mediated antitumor response via a crosstalk with DC.^{42,43}

Overview on the NK cells receptor types, history, and discovery

NK cell inhibitory receptors

As previously mentioned, it was originally proposed by Kärre et al⁴ that NK cells discriminate target cells from normal cells by the level of MHC-I expression on the cell surface. NK cells preferentially lyse cells expressing few or no MHC-I.⁴⁴ The sensitivity of cells with low MHC-I expression to NK cell lysis may be prevented by the re-expression of these molecules.^{45,46} Three families of inhibitory receptors recognizing MHC-I molecules were described (Table 1): KIR (killer cell immunoglobulin-like receptor, humans),^{47,48} Ly49 (mice),^{49,50} and CD94/NKG2A (human and mice)^{51–53} receptor family.

Immunoreceptor tyrosine-based inhibitory motif (ITIM), present in all cytoplasmic domains of NK cell inhibitory receptors, is able to recruit intracellular tyrosine phosphatases SHP-1 and SHP-2, which inhibit cytotoxicity and cytokine production.⁵⁴

KIR receptors are encoded by about twelve polymorphic genes and are expressed on NK cells and memory T lymphocytes. The binding to one type of KIR receptor is sufficient to prevent activation of NK cells, whereas it usually takes several different activating signals to induce degranulation and death of the target cell. The CD94/NKG2A receptor, conserved in rodents and primates, is expressed on most NK cells and a subset of CD8+ memory T cells.⁵⁵ CD94 has no cytoplasmic signalization domain while the receptor NKG2A contains two ITIM.⁵⁶ KIR, but also murine Ly49 receptors, bind directly to MHC-I molecules, whereas the CD94/NKG2A receptor binds to a peptide derived from

Table I Main receptors on NK cells involved in anti-tumor immune response

Function	Receptors	Ligands	Species	Ref
Inhibition	KIR (long cytoplasmic tail)	HLA-A,B,C allotypes	H	42,43
	Ly49A/C	MHC class I	M	44,45
	CD94-NKG2A	MHC-E	H, M	48,50
Activation	CD16	IgG	H, M	
		HPV	H	61
	NKG2D	MICA/B-RAET	H	
		RAET-H60	M	
	NKp30	B7-H6, Heparan sulfate	H	75–78
	NKp44	Heparan sulfate	H	76
	NKp46	Heparan sulfate, unknown tumor ligands	H, M	75,76,121

Abbreviations: HLA, human leucocyte antigen; H, Human; Ig, immunoglobulin; M, mouse; MHC, major histocompatibility complex; MICA/B, major histocompatibility complex class I-related; RAET, retinoic acid early transcript.

the signal sequence of MHC-I.^{50,54} All inhibitory receptors are found by overlapping NK cell subpopulations since each cell expresses only a few types of inhibitory receptors. Consequently, NK cells have many complex combinations of MHC-I repertoire randomly distributed on the cells. The only rule that seems to be established is that all NK cells have at least one inhibitory receptor specific for MHC-I molecule to avoid autoreactivity.

NK cell-activating receptors

In addition to inhibitory receptors, NK cells express a wide range of activating receptors. Their biological role is not yet fully known because all their ligands have not been identified. The main activating receptors involved in tumor lysis are CD16, NKG2D receptor, and the natural cytotoxicity receptors (NCR)⁵⁷⁻⁶⁰ (Table 1).

The activating receptors have no ITIM in their cytoplasmic domains. Instead, they have charged residues in their transmembrane domains, which are necessary for the association with adapter proteins. These proteins have short extracellular domains and, therefore, do not participate in ligand binding. The intracellular domains of these adapter proteins have docking sites for signaling molecules that play a role downstream of the stimulation. Most of the adapter proteins (FcεRγI, CD3ζ, DAP12, and DAP10) contain immunoreceptor tyrosine-based activation motif in their cytoplasmic domains, which enable them to associate with ZAP70 and/or proteins of syk kinases family.^{61,62}

CD16 is a low-affinity receptor for the Fc portion of immunoglobulin (FcγRIII). This receptor with a transmembrane domain (FcγRIIIa) is found on the surface of NK cells but also on some DC, T lymphocytes, monocytes, and macrophages, and a glycosylphosphatidylinositol-linked receptor (FcγRIIIb) is expressed on neutrophils.⁶³ When IgG molecules recognize specific antigens on a tumor cell, NK cells, via CD16, are able to bind tumor cell coated with antibodies and induce tumor cell death. This reaction called antibody-dependent cell-mediated cytotoxicity is a dominant component of antibody based immunotherapy against tumors.⁶⁴ Recently, CD16 has been implicated in the recognition of human papillomavirus by NK cells in uterine preneoplastic lesions.⁶⁵

NKG2D, unlike the other NKG2 receptors, does not have an ITIM sequence and is not associated with CD94.⁶⁶ It is expressed on most NK cells but also on γδ and CD8+ T cells. It is associated with the adapter molecule DAP10 in humans, and DAP10 and DAP12 in mice.^{67,68} Binding of NKG2D ligands, such as MICA or MICB, leads to an increase

in proliferation, cytotoxicity, and production of cytokines and chemokines (IFN-γ, GM-CSF, TNF-α).⁶⁹ Expression of NKG2D ligands is observed on many tumor cell lines and tumor tissues.^{70,71}

More specifically expressed on NK cells, the principal NCR are NKp46, NKp44, and NKp30.^{59,72,73} Molecular cloning of NCR confirmed that they were structurally distinct although they belong to the same immunoglobulin superfamily.⁷⁴ NKp46 (human and mice) and NKp30 (human) are expressed on both resting and activated NK cells, while the NKp44 receptor is only present on IL-2-activated human NK cells and a minor subset of γδ T cells.⁷² The density of NCR on the cell surface varies with individuals and there is a direct correlation between NCR expression on human NK cells and their capacity to kill tumor cells.⁷⁵ NKp46, the first identified NCR, is a 46 kDa glycoprotein with a transmembrane domain that interacts with the adapter molecule CD3ζ.^{59,76} The activation of NKp46 leads to mobilization of calcium in the development of cytolytic activity and cytokine production.⁵⁹ Monoclonal antibodies against NKp46 block the lysis of a wide range of tumor cells showing that this receptor plays a major role in NK cell cytotoxicity.⁷⁷ This function of NKp46 is negatively regulated by the interaction between inhibitory receptors and MHC-I. NKp44 is a 44 kDa glycoprotein whose expression is inducible by IL-2, suggesting that it could contribute to the increased efficiency of activated NK cells to lyse tumor cells.⁷² NKp44 acts in association with the immunoreceptor tyrosine-based activation motif on the adapter molecule DAP12. The blocking of NKp44 by monoclonal antibodies induces a partial inhibition of the cytolytic activity against some tumor cells and this inhibition is strongly enhanced by the addition of antibodies blocking NKp46.⁷⁸ NKp30 is a glycoprotein of 30 kDa that associates with the adapter molecules CD3ζ and FcεRγI.⁷³ Its expression at the cell surface is correlated with NKp46. In addition, NKp30 cooperates with NKp46 and NKp44 to induce NK cell cytotoxicity against a variety of target cells.⁷³ NKp46, NKp44, and NKp30 bind to heparan sulfates on the surface of tumor cells.^{79,80} In addition, NKp30 is involved in the lysis of tumor cells by binding to factor BAT3 (HLA-B associated transcript (3) or to B7-H6 present on their surface.^{81,82}

Role of NK cells in immune response against tumor growth and metastasis

In vivo and in vitro studies have shown that NK cells can eliminate tumor cells.⁸³ In mice, tumor rejection is dependent upon the presence or absence of NK cell receptor ligands on

the tumor. Especially the lack of MHC-I expression, overexpression of NKG2D ligands (H60, Rae1 β , Rae1 δ , Rae1 γ , Mult-1), or costimulatory signals makes the tumor more susceptible to lysis by NK cells.⁸⁴ Moreover, engagement of NCR complements NKG2D pathway in the killing of tumor cells by NK cells.⁸⁵ Little is known about the mechanism of NK cell migration in tumor, but selectins seem to play a role in this recruitment.⁸⁶ However, Smyth et al^{25,87} showed that mice deficient in NK cells are more susceptible to methylcholanthrene-induced sarcomas, demonstrating that NK cells play a role in tumor immunosurveillance. NK cells also protect against the growth of B cell lymphomas in mice lacking perforin and β 2 microglobulin.⁸⁸ Moreover, NK cells participate to immune response against metastasis; in an immunotherapy protocol using synthetic oligodeoxynucleotides containing CpG motifs, NK cells prevent pulmonary metastasis and peritoneal dissemination.⁸⁹ In a mouse model, NK cells inhibit pulmonary metastasis formation after IFN- γ treatment.⁹⁰

Also, in humans, there is evidence that NK cells play a role in the tumor immunosurveillance. An 11-year follow-up survey has shown that a low NK cell activity is associated with an increased cancer risk.⁹¹ This was confirmed in several human malignancies. For example, a decrease of NK cell activity is observed in patients with hereditary colorectal adenocarcinoma^{92,93} and melanoma patients with metastatic disease have an impaired perforin-dependent NK cell cytotoxic mechanism.⁹⁴ Tumor growth can disturb the functional maturation of NK cells by interrupting the IL-15 signaling pathway,⁹⁵ but further studies are necessary to better understand the immunologic basis of NK cell defects in tumor.

As already mentioned, NK cells collaborate with antigen-presenting cells to amplify the immune response.⁹⁶ This collaboration can help to induce a T cell-mediated antitumor immunity.⁹⁷ After the implantation of MHC-I low tumor cells in mice, the release of IFN- γ by NK cells stimulate the maturation of DC to a IL-12-producing DC1 phenotype that promote a strong and protective antitumor CD8+ T cell response.^{42,98}

Implications for tumor management

The observation that IL-2 increased *in vitro* the cytotoxic activity of NK cells against tumor cells⁹⁹ has been conducted to perform clinical trials with adoptive transfer of high doses of this cytokine in patients with metastatic melanoma or renal cell carcinoma.^{100,101} Due to systemic toxicity of IL-2 and to the fact that IL-2 preferentially drives expansion of regulatory T cells, which can inhibit antitumor immunity, other cytokines, such as IL-15, were tested in

nonhuman primates. IL-15 shares similar properties with IL-2 and Berger et al¹⁰² showed that intermittent administration of IL-15 should be considered in clinical studies. Also other cytokines, such as IL-12 and IL-18, synergistically enhance NK cytotoxicity against tumor targets and IFN- γ production by NK cells.^{103,104}

Tumor-targeted monoclonal antibodies can induce NK cell antibody-dependent cell-mediated cytotoxicity and the rapid degranulation of NK cells results in tumor cell destruction.¹⁰⁵ The clinical efficacy of monoclonal antibodies directed against CD20 (rituximab), Her2/neu (trastuzumab), epidermal growth factor receptor (cetuximab), or disialoganglioside (GD2) is, at least partially, due to NK antibody-dependent cell-mediated cytotoxicity.¹⁰⁶⁻¹⁰⁹ Moreover, in a Phase I trial, coadministration of IL-12 with trastuzumab enhances the antitumor response induced by the antibody.¹¹⁰

Besides the development of protocols to stimulate NK cell activity, inhibitory receptors on NK cells could be the target for antitumor therapy. Blocking Ly49 inhibitory receptors enhanced antitumor activity *in vitro* and *in vivo*¹¹¹ and in human, antibodies blocking KIR are currently tested in a Phase II clinical trial.¹¹² NK allogeneic recognition via their KIR repertoire has a major role in reducing the risk of relapse by inducing a graft versus leukemia effect after allogeneic hematopoietic stem cell transplantation.¹¹³

NK cells seem important in tumor vaccination with DC, since clinical responses are correlated with superior levels of activated NK cells in responders.¹¹⁴ In a Phase I clinical trial with melanoma patients, DC derived-exosomes enhanced NKG2D-dependent function of NK cells in half of the patients.¹¹⁵ Indirectly, immunotherapy protocols targeting an oncogenic viral protein¹¹⁶ or the recruitment of antigen-presenting cells¹¹⁷ boost NK cell response. Even some chemotherapeutic agents could inhibit secretion of inhibitory soluble NKG2D ligands.¹¹⁸ A NK cell treatment combined with radiation therapy has been proposed, since radiation increases NK-activating ligand (eg, NKG2DL) expression via DNA damage response.¹¹⁹ Figure 4 summarizes the different mechanisms implicated into NK cell response against tumor cells.

Role of NK cells in autoimmunity

NK cells are viewed as effector cells whose rapid killing of transformed or infected cells provides a first-line of defense prior to the initiation of an adaptive immune response against tumor or infection. However, studies on NK cells suggest a broad role in immunity including the potential to function as regulatory cells. While NK cells can assist in DC maturation and T cell polarization, increasing evidence indicates that NK cells

can also prevent and limit adaptive autoimmune responses.¹²⁰ Autoimmune diseases are a multistep process caused by inappropriate activation of cells of the adaptive immune system (T and B cells) which results in cell-specific, organ-specific, or systemic tissue damage.¹²¹ Autoimmunity has been linked to cancer, for example, patients with scleroderma have an increased risk to develop a tumor.¹²² Moreover autoimmunity is associated with immunotherapy of cancer.¹²³

Several studies suggested that NK cells play a role at the different stages of the autoimmune response.¹²⁴ NK cells can either augment or ameliorate autoimmune diseases.^{125,126} A reduction of circulating NK cells has been shown in diverse autoimmune diseases, which contributed to an impaired NK activity.^{127,128} The modulation in the number of circulating NK cells seems to be a primary event instead of an active inflammation/drug administration consequence during autoimmune processes. However, some biotherapies are linked with changes of circulating NK cells compartment. Daclizumab (anti-IL-2R α) treatment in multiple sclerosis¹²⁹ or in uveitis¹³⁰ pathogenesis is associated with an increase in the number of CD56^{bright} NK cells. This augmentation of CD56^{bright} NK cells is correlated with the suppression of the disease activity.¹²⁹ NK cells can also promote autoimmune diseases, ie, autoimmune diabetes is prevented in nonobese-diabetic mice by blocking the activating NK cell receptor NKG2D.¹³¹ In humans, the predisposition to rheumatoid arthritis,¹³² psoriatic arthritis,¹³³ scleroderma,¹³⁴ and psoriasis vulgaris¹³⁵ is linked to the expression of certain KIR and HLA alleles, but the precise role of NK cells in these diseases is still under investigation.

Conclusion

NK cells could be very efficient killers of tumor cells and could help to induce an optimal adaptive immune response against cancer. A better knowledge in the basic biology of NK cells is a key to develop strategies to manipulate NK cells for therapeutic purposes.

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