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Introductory Chapter: A Brief Overview on Natural Killer Cells

Mourad Aribi

1. Introduction

Natural killer (NK) cells represent about 5–15% of circulating lymphocytes [1] and belong to the innate immune system, in particular due to their invariant antigen receptors. Morphologically, as opposed to "small lymphocytes," most of them are typically large azurophilic granules containing lymphocytes (LGL) [2], characterized by high cytoplasmic:nuclear ratio. They have initially been referred to as k or null lymphocytes (non-B and non-T cells), with the highest cytotoxic capacity [3, 4], because they lack conventional T-cell membrane markers and the surface membrane immunoglobulin (smIg) [5, 6]. NK cells mediate resistance against intracellular pathogens, mainly viral-infected, bacteria-infected and protozoa-infected cells, and have the potential to restrain cancer and metastasis. They are also able to contribute to the activation and the regulation of the immune responses, as well as the orientation of adaptive immune responses [7, 8]. More recently, NK cells were recognized as a subtype of type 1 innate lymphoid cells (ILC1), which express the transcription factor T-box expressed in T cells (T-bet), and defined by the production of the T helper cell type 1 (Th1)-associated cytokine interferon gamma (IFN-γ) and the inability to produce Th2 cell-associated and Th17 cell-associated cytokines [9]. As a result of collective work, this book has therefore the ultimate purpose to address the most fundamental aspects of NK cells, as well as their clinical applications for cancer immunotherapy.

2. Lineage of NK cells

NK cells constitute a third lymphoid line derived from a common T-cell and B-cell bone marrow precursor. Unlike T cells, NK cells do not have a specialized differentiating organ, are matured inside of bone marrow, and can develop even in athymic mice. The acquisition of their functions

does not use recombination-activating gene (RAG) enzymes for rearrangement of their receptor genes or complete V(D)J recombination as is the case for T cells or B cells [10] and is considered as the only lymphocytes without a clonally specific receptor [11]. Additionally, in contrast to the conventional $\alpha\beta$ T cells, the genesis of NK cells appears to be independent of the self-major histocompatibility complex (MHC), although they have different recognition specificities of allogeneic MHC molecules.

Mature NK cells are able to self-renew and possibly persist in the host for months or years. Nevertheless, unlike long-lived CD8^{+} and CD4^{+} T cells that retain a "memory-like" phenotype and function after homeostatic proliferation, expanded NK cells return to a quiescent phenotype and respond with comparable kinetics against viral challenge [10].

3. Localization of NK cells

NK cells are present in the bloodstream and in the lymphatic vessels [12], as well as in placenta, spleen, liver, lungs, tonsils, peripheral ganglia, and bone marrow where they act as sentinels. Nevertheless, it appears that they have no access to other tissues apart from inflammatory responses. Of note, it has been reported that the homeostasis-driven NK cells can reside in both lymphoid and nonlymphoid organs for a long time [13].

4. LGL surface markers

4.1. CD3^{−} LGL markers

In human, the LGL population can be separated into CD3^{+} and CD3^{−} subtypes. The majority of LGL TCR^{−}CD3^{−} expresses CD16 (or FcγRIIIA, low-affinity receptor for the Fc portion of immunoglobulin G, 90%), CD56 (neural cell adhesion molecule [N-CAM], > 95%), and some markers of T cells, such as CD7 (100%), CD11b (80–80%), CD2 (70–80%), CD4 (<5%), and CD8 (15–20%).

4.2. CD19^{−}CD3^{−} NK cell subsets

NK cells are CD3^{−}CD19^{−} LGLs [14]. They thus lack two main markers of T cells (CD3^{+}) and B cells (CD19^{+}). In human peripheral blood, five NK cell subpopulations can be separated depending on the relative presence and expression levels of CD16 and CD56 markers [15]:

1. CD56^{bright} CD16^{−} (50–70% of CD56^{bright})

2. CD56^{bright} CD16^{dim} (30–50% of CD56^{bright})

3. CD56^{dim} CD16^{−} (small proportion)

4. CD56^{dim} CD16^{bright} (at least 90% of all peripheral blood NK cells)

5. CD56^{−} CD16^{bright} (small proportion)

	NK cell subgroup	
	CD16^{bright}CD56$^{dim/+}$ NK cells	CD16$^{dim/-}$CD56^{bright} NK cells
Proportion	≥90% of PBNKCs	≤10% of PBNKCs
Cytotoxic/lytic granules	+++	+
ADCC function	+++	+
LAK cell activity	+++	+++
Natural cytotoxicity	+++	+
Cytokine production	+	+++
Immunoregulation	+	+++
NK cell migration	Migration to the sites of acute inflammation (arrive very early to the sites of inflammation)	Migration to the SLOs

ADCC, antibody-dependent cell-mediated cytotoxicity; LAK, lymphokine-activated killer; NK, natural killer; PBNKCs, peripheral blood natural killer cells; SLO, secondary lymphoid organs.

Table 1. Key features of CD16^{bright}CD56$^{dim/+}$ and CD16$^{dim/-}$CD56^{bright} NK cells.

The NK cells can also be separated into two subgroups according to the expression levels of the CD16 and CD56 markers in healthy individuals (**Table 1**).

5. Immune roles of NK cells

After maturation, NK cells migrate to the blood to provide innate defense against tumor cells and metastases, as well as infected cells by intracellular pathogens (such as viruses, bacteria, and protozoan parasites). Additionally, NK cells are also involved in the acute rejection of bone marrow transplants [16]. Finally, in addition to their ability to secrete various cytokines and regulate the immune response, activated NK cells are also involved in tissue remodeling through their ability to secrete matrix metalloproteinases (MMPs), in both physiological and pathological abnormalities, within the tumor microenvironment, through the cleavage of CD16 from the cell surface [17].

6. MHC I as molecular basis of target recognition by NK cells

The activation of NK cells does not require prior sensitization with an antigen. However, their activities are inversely correlated with the density of MHC class I molecules (MHC I), which are expressed on the surface of certain nucleated cell lines, with the exception of red blood cells and certain tissues such as salivary glands, brain, cornea, anterior chamber of the eye, liver, testis, fetotrophoblast, hair matrix, and proximal nail matrix [18].

7. "Missing self" hypothesis

NK cells lack antigen-specific receptors, but their activation can be blocked by an inhibitory signal generated by their recognition of MHC I alleles on host cells. However, the absence of MHC molecules I triggers an activating signal [19]. Nevertheless, the recognition of MHC I molecules would be one of the major causes of the tumor escape from NK cell immune surveillance and activation. Therefore, among the current therapeutic strategies is the use of monoclonal antibodies that target the NK cell inhibitory receptors.

8. NK cell-activating and inhibitory receptors

NK cells express two major types of receptors, inhibitory and activating receptors, that may belong to one of the following receptor categories:

 (i)   Immunoglobulin superfamily (IgSF) - activating or inhibitory - receptors.

 (ii) C-type lectin family - activating or inhibitory - receptors.

(iii) Natural cytotoxicity - activating - receptors (NCRs).

NK cell receptors can be either MHC class I-dependent or MHC class I-independent receptors (**Table 2**).

8.1. MHC class I-dependent receptors

8.1.1. Killer cell immunoglobulin-like receptors

Killer cell immunoglobulin-like receptors (KIRs) are a family of type I transmembrane glyco-proteins belonging to the immunoglobulin superfamily (IgSF) receptors and grouped together with other receptors of the same IgSF. KIR genes are found in a cluster on human chromosome 19q13.4 within the 1 Mb leukocyte receptor complex (LRC) [28].

KIR molecules are also expressed by some T-cell subtypes. The ligands for several KIRs are subsets of MHC I molecules.

8.1.1.1. Dominant receptors on NK cells

NK cell functions are regulated by a balance between activating and inhibitory signals [29]. Their receptors recognizing the same MHC I or other ligands are polymorphic and highly homologous and can induce two opposite signals, but one of them dominates signal transduction. Usually, the presence of MHC I molecules on a cell generates a dominant negative signal, but some ligands induced by abnormal or virus-encoded cell damage can stimulate activating receptors and generate a dominant positive signal. Additionally, the absence of MHC I molecules is not sufficient to induce a dominant activating signal, especially in normal cells. From the molecular point of view, it is the length of the cytoplasmic domain that determines the function of NK cells. Thus,

long-tailed receptors (L) are associated with an inhibitory function upon ligand binding *via* an immune tyrosine-based inhibitory motif (ITIM), while short ones (S) lack the ITIM and instead associate with the TYRO protein tyrosine kinase-binding protein to transduce activating signals. In the rare situation where an NK cell co-expresses an inhibitory and an activating KIR (KAR) with the same specificity, the inhibitory receptors block activation signals at an early step [30].

NK cell receptors					Ligands
Inhibitory NK cell receptors	MHC class I-dependent receptors	IgSF receptors	KIR2DL	(1) KIR2DL1/NKAT1 (CD158a)	HLA-Cw2, HLA-Cw4, HLA-Cw5, HLA-Cw6
				(2) KIR2DL2/NKAT6 (CD158b1)	HLA-Cw1, HLA-Cw3, HLA-Cw7, HLA-Cw8
				(3) KIR2DL3/NKAT2 (CD158b2)	HLA-Cw1, HLA-Cw3, HLA-Cw7, HLA-Cw8
				(4) KIR2DL5 (CD158f)	Unknown
			KIR3DL	(1) KIR3DL1/NKAT3 (CD158e1)	HLA-Bw4
				(2) KIR3DL2 (CD158k)	HLA-A3/ HLA-A11
				(3) KIR3DL3 (CD158z)	Unknown
			ILT	(1) IL-T2 (CD85j)	HLA-A, HLA-B, HLA-C, CMV UL-18
				(2) IL-T5 (CD85a)	Unknown
				(3) IL-T8 (CD85c)	Ligand still needs to be identified
		CTLRs	CD94-NKG2A/B	CD159a	HLA-E loaded with HLA-A, HLA-B, HLA-C, or HLA-G leader peptide
	MHC class I-independent receptors	CTLRs	KLRG1		E-cadherin
			NKR-P1A	CD161	LLT1

NK cell receptors					Ligands
Activating NK cell receptors/KARs	MHC class I-dependent receptors	IgSF receptors	KIR2DL	KIR2DL4/KIR103 (CD158d)[*]	HLA-G, HLA-Bw4
			KIR2DS	(1) KIR2DS1 (CD158h)	HLA-Cw2, HLA-Cw4, HLA-Cw5, HLA-Cw6
				(2) KIR2DS2 (CD158j)	HLA-Cw1, HLA-Cw3, HLA-Cw7, HLA-Cw8
				(3) KIR2DS3/NKAT7	With no detectable avidity for C1, C2, or any other HLA class I epitope
				(4) KIR2DS4 (CD158i)	HLA-C (weak)
				(5) KIR2DS5 (CD158g)	With no detectable avidity for C1, C2, or any other HLA class I epitope
			KIR3DS	KIR3DS1/NKB1 (CD158e2)	Ligand still needs to be identified (HLA-Bw4-I80, HLA-Bw4-T80, allotype HLA-B*2705?)
		CTLRs	CD94-NKG2C	CD159c	HLA-E loaded with HLA-A, HLA-B, HLA-C, or HLA-G leader peptide
			CD94-NKG2E/H	CD159a	HLA-E loaded with HLA-A, HLA-B, HLA-C, or HLA-G leader peptide
			NKG2D	CD314	MICA, MICB, ULBP1, ULBP2, ULBP3, ULBP4
	MHC class I-independent receptors	IgSF receptors	NCR1	NKp46 (CD335)	Viral HA and NDHN
			NCR2	NKp44 (CD336)	Viral HA
			NCR3	NKp30 (CD337)	BAT3, B7-H6 on human tumor cells

Adapted from Ref. [20] and completed from Refs. [21–26]. Costimulatory NK cell receptors are not presented here.[*]An unusual activating KIR with L cytoplasmic and hybrid D0-D2 structure domains, displaying very weak inhibitory potential [27]. BAT3, B-associated transcript 3; B7-H6, B7 homolog 6; HLA, human leukocyte antigen; HLA-Bw4-I80, HLA-Bw4 molecules containing an isoleucine in position 80; ILTs, immunoglobulin-like transcripts; ILRs, immunoglobulin-like receptors; HA, hemagglutinin; IgSF, immunoglobulin superfamily; KAR, killer cell-activating receptors; KIR, killer cell immunoglobulin-like receptor; LLT1, lectin like transcript-1; CTLR, C-type lectin-like receptor; MICA/MICB, major histocompatibility complex class I-related chain A/B; KLRG1, co-inhibitory receptor killer cell lectin like receptor G1; NCR, natural cytotoxicity receptor; NK cell, natural killer cell; NDHN, Newcastle disease hemagglutinin-neuraminidase; NKAT, natural killer-associated transcript; ULBP, UL-16-binding proteins.

Table 2. Inhibitory and activating human NK cell receptors.

### 8.1.1.2. Classification of KIR molecules

KIR molecules are classified into two types according to the number of extracellular Ig-like domains (D), 2D and 3D, and by whether they have a long (L) or short (S) cytoplasmic domain (**Figure 1**) [31].

8.1.2. CD94-NKG2 C-type lectin receptor complex

C-type lectin receptors are characterized by calcium-dependent carbohydrate recognition domain (CRD) and the presence of one or more C-type lectin-like (CTLD) domains. They play a crucial role in enabling NK cells to discriminate between self and nonself [32, 33]. The CD94-NKG2 C-type lectin receptors have been found to be expressed predominantly on the surface of a majority of NK cells and on subsets of CD8+ T cells [34] and to be involved in NK cell-mediated recognition of MHC I molecules [35]. They are encoded by the NK gene complex (NKC) on human chromosome 12 (12p13.3–12p13.4). NKG2 receptors recognize the nonclassical MHC class I HLA-E molecule and can provide either an activating signal through their noncovalently association with the immunoreceptor tyrosine-based activation motif (ITAM)-containing DNAX adaptor protein of 12 kDa (DAP12) or an inhibitory signal when they contain an immunoreceptor tyrosine-based inhibitory motif (ITIM).

The cell surface molecule CD94 is a common invariant chain in five different disulfide-linked heterodimeric transmembrane glycoprotein complexes, including CD94-NKG2A, CD94-NKG2B, CD94-NKG2C, CD94-NKG2E, and CD94-NKG2H [36].

NKG2F is expressed in the cytosol and therefore does not form heterodimers with CD94. NKG2D (apparently not belonging to the NKG2 family) is expressed on the cell surface of NK cells, γδ T cells, and subsets of CD4+ and CD8+ T cells as a homodimer. It lacks an ITIM sequence and is
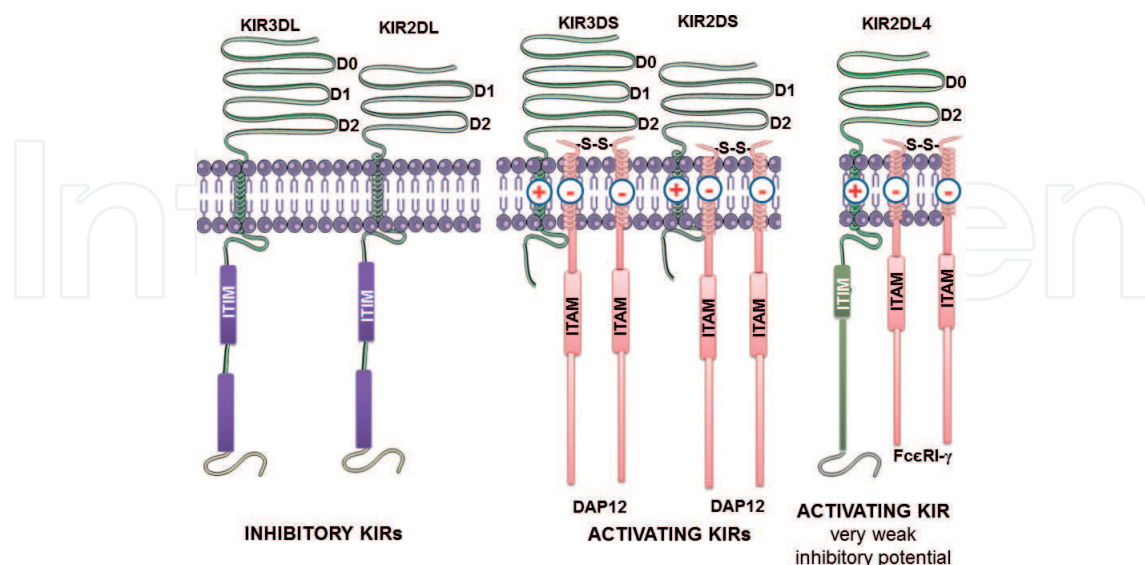
Figure 1. Structure of inhibitory and activating KIRs. DAP12, DNAX adaptor protein of 12 kDa; FcεRI-γ, high-affinity immunoglobulin epsilon receptor subunit gamma; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; KIR, killer cell immunoglobulin-like receptor. This Figure was illustrated using image fragments from Servier Medical Art.

not associated with CD94. Its signaling is achieved by association with two dimers of DAP10, a transmembrane adaptor molecule containing a tyrosine-based signaling motif (YINM), carrying phosphatidylinositol-3 kinase-binding sites in their cytoplasmic tails and recruiting growth factor receptor-bound protein 2 (Grb2) [37].

Both NKG2A and NKG2B are alternative spliced products from a single gene. They can dimerize with CD94 to form inhibitory receptors through their cytoplasmic domains, which contain two ITIMs. Conversely, CD94-NKG2C, CD94-NKG2E, and CD94-NKG2H dimers and homodimer-forming NKG2D and the orphan receptor NKG2F activate NK cells [37–39].

8.2. MHC class I-independent receptors

There are at least three activating and two inhibitory MHC class I-independent receptors.

8.2.1. Natural cytotoxicity receptors

Natural cytotoxicity receptors (NCRs) are composed by a heterogeneous group of molecules belonging to IgSF and include NKp46 (NCR1), NKp44 (NCR2), and NKp30 (NCR3) activating receptors targeting most tumor cell lines. They are characterized by a type I transmembrane domain containing a positively charged amino acid residue and a short cytoplasmic tail. All these transmembrane type I receptors are expressed almost exclusively by NK cells. Binding of one or more of these receptors with a specific ligand leads to the increased NK cell activation and cytotoxicity [40]. It has been reported that these receptors can initiate tumor targeting by recognition of heparan sulfate on cancer cells [41].

8.2.2. C-type lectin receptors

C-type lectin receptors include mostly killer cell lectin-like receptor subfamily G member 1 (KLRG1) and KLRB1 (also known as NK1.1, NKR-P1A, or CD161), which inhibit the cytotoxicity of NK cells and therefore prevent tissue damage. NKR-P1A is encoded by the KLRB1 gene and recognizes lectin like transcript-1 (LLT1) as a functional ligand. Its signaling in NK cells has previously been known to involve the activation of acid sphingomyelinase, which represent the catabolic pathway for N-acyl-sphingosine generation as a second messenger for the induction of apoptosis, proliferation, and differentiation [42]. KLRG1 is expressed by antigen-experienced (memory) CD4^{+} and CD8^{+} T cells and by a large proportion of NK cells and naive phenotype CD4^{+} and CD8^{+} T cells in umbilical cord blood, as well as in a substantial subset of $\gamma\delta$ T cells [43]. KLRG1 can bind three of the classical cadherins (E, N, and R), which are ubiquitously expressed in vertebrates and mediate cell-cell adhesion by homotypic and heterotypic interactions [44]. It has also been postulated to be a marker of senescence [45].

9. NK cells in alarming situations

Situations related to cellular stress resulting from the presence of intracellular infectious agents and changes in self-elements (the presence of damaged-self [damage-associated molecular

patterns (DAMPs)] or altered-self [tumor-associated molecular patterns (TAMPs)]) induce an increase in the expression of ligands that can "exclusively" stimulate activating receptors (major histocompatibility complex class I-related chain A [MICA], MICB, UL-16-binding proteins [ULBP]1, ULBP2, ULBP3, ULBP4, viral hemagglutinin, Newcastle disease hemagglutinin-neuraminidase, B7-H6, etc.) and consequently activate NK cell cytotoxicity.

10. NK cell-based immunotherapy in cancer

The main current therapeutic strategies, especially in allogeneic hematopoietic cell transplantation (HCT), are based on the use of NK cells through their education to render them alloreactive against tumor targets missing self-MHC ligand. In practice, autologous or haploidentical transplantation of NK cells requires obtaining of a very large number of pure and cytotoxic cells. Additionally, a favorable mismatch of the human leukocyte antigen class I (HLA I) molecules between donor and recipient tissues, or the absence of inhibitory KIR ligands in the recipient's HLA repertoire (KIR mismatch in the receptor-ligand model) allows NK cells in the graft to reduce its rejection by the host and the attack of residual leukemia cells, as well as the best prediction of the risk of relapse (**Figure 2**) [46, 47]. Finally, other promising approaches aim to induce an increase in their cytotoxic activities in the treatment of both hematopoietic and solid cancers by blocking inhibitory receptor signal transduction.
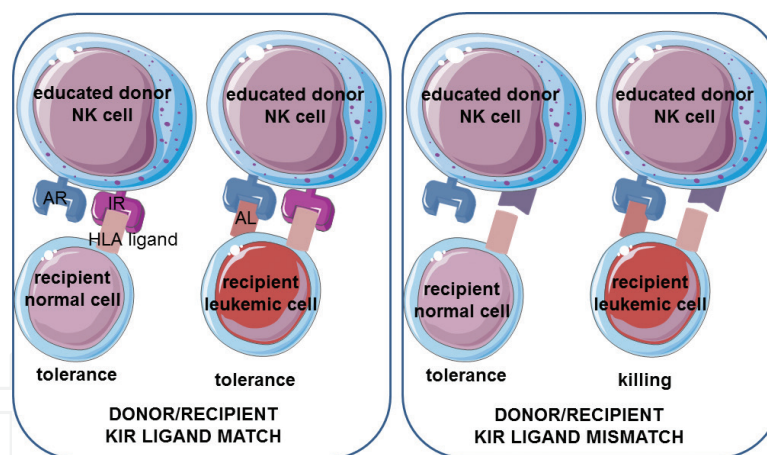
Figure 2. Role of KIR ligand mismatch in killing leukemic targets. AR, activating receptor; AL, activating ligand; IR, inhibitory receptor; KIR, killer cell immunoglobulin-like receptor. (Adapted from Ref. [26]. Images of cells are provided from Servier Medical Art.).

11. Conclusions

The specific structural and functional features of NK cells describe them as major players in innate antitumor immunosurveillance and in the fight against infection. Their availability at the proximity of cellular stress signals allows them to effectively control both the process of carcinogenesis and the development of infectious diseases. Nevertheless, their activities seem

to be strongly immunomodulated by cell microenvironment factors. Therefore, one of the best therapeutic strategies should create an ideal microenvironment for NK cell infiltration within target tissues while decreasing functions of their inhibitory receptors and enhancing their cytotoxic activities. Such a strategy should contribute not only to substantially increase the efficacy of targeted immunotherapies but also to prevent relapse after transplantation.

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