



Review

The Receptors Regulating Natural Cytotoxic Effector Functions

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Abstract. Natural cytotoxic effector functions are regulated by a multitude of opposing signals provided by immunoglobulin and lectin-like functional molecules. While inhibitory receptors possess immunoreceptor tyrosine-based inhibition motif (ITIM) cytoplasmic sequences recruiting tyrosine phosphatases, activatory receptors require association with accessory immunoreceptor tyrosine-based activation motif (ITAM)-bearing molecules. One considerable group of natural cytotoxic cell receptors are specific for classical and non-classical class I antigens and detect both qualitative and quantitative changes in the autologous MHC-I phenotype. Non-MHC-I-specific receptors provide signaling in the absence of MHC-I antigens or in response to not well-known stress-induced antigens. NK cell receptors may equally participate in the regulation of target cell functions through contact or soluble mediator-dependent mechanisms. The identification of NK cell regulating molecules has led to the elucidation of more general principles underlying immune homeostasis.

Key words: natural cytotoxicity; NK cells; killer immunoglobulin-like receptor; MHC-I: BY-55.

Introduction

The ability of the immune system to eliminate syngeneic and allogeneic tumor cells without prior sensitization has been defined as natural cytotoxicity³¹. It is mediated by large granular lymphocytes termed natural killer (NK) cells. NK cells are distinct from T and B lymphocytes as they do not express antigen-specific receptors and do not require gene rearrangements for functional maturation²⁹. Cytotoxicity and cytokine release in response to viral,

parasitic and some microbial invasions are the basic functions of NK cells. While cytotoxic T lymphocyte⁵ (CTL) detect processed antigens in the context of self-MHC-I molecules, NK directly recognize antigenic structures with wide expression on the surfaces of target cells. They are efficient in the early phase of immune response, before the clonal expansion of specific T lymphocytes^{49, 66}. Along with their role in innate immunity, NK cells contribute to the development of acquired immunity through cytokine secretion¹⁹.

Abbreviations used: CTL – cytotoxic T lymphocyte, HCMV – human cytomegalovirus, ILT – immunoglobulin-like transcript, ITIM – immunoreceptor tyrosine-based inhibition motif, ITAM – immunoreceptor tyrosine-based activation motif, KIR – killer immunoglobulin-like receptor, LIR – leukocyte immunoglobulin-like receptor, NK – natural killer, SH2 – Src-homology domain 2, SHP – SH2-containing tyrosine phosphatase, TM – transmembrane, AIRM1 – adhesion inhibitory receptor molecule 1, NAIL – NK cell activation-inducing ligand, Mo – monocytes, MICA – MHC class I-related chain A, MICB – MHC class I-related chain B, GPI – glycosylphosphatidyl-inositol, DC – dendritic cells.

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Until very recently no specific receptors regulating NK cell effector functions were known. The best studied NK cell activating receptor, CD16, is equally expressed by monocytes and T cells, mediates cytokine secretion and antibody-dependent cellular cytotoxicity, but is not responsible for other modes of natural cytotoxicity²⁴. Some epitopes of the T cell activating receptor CD2 may also activate NK cell cytotoxicity⁶⁷. However, its ligand, CD58, alone does not confer sensitivity to NK cell lysis, suggesting rather a co-stimulatory role for CD2³⁶. The CD28/B7 T cell activation pair is also implicated in natural cytotoxicity at certain differentiation stages³. It was demonstrated, however, that B7-positive targets could be killed by CD28-negative NK cells, predicting the existence of other NK cell activating receptors¹⁸.

Although initially defined as MHC-unrestricted, NK cells preferentially kill targets lacking some or all of their MHC-I molecules, while MHC-I genetic reconstitution confers protection to target cells⁵⁹. On this basis, the hypothesis of "missing self surveillance" was formulated and the existence of MHC-I-specific inhibitory receptors on NK cells was predicted⁴³. It is now well accepted that lysis of MHC-deficient cells results from the failure of NK cells to receive the corresponding inhibitory signal. The number of MHC-I-specific human NK receptors identified is constantly increasing⁶. They belong either to the immunoglobulin or C-type lectin receptor superfamilies. Most of them contain one or more cytoplasmic immunoreceptor tyrosine-based inhibition motifs (ITIMs). Upon receptor coligation, ITIMs are phosphorylated and recruit protein tyrosine phosphatases which mediate effector NK cell inhibition^{8, 36}. Some of these molecules lack signaling capacity but can associate with accessory subunits containing the activation immunoreceptor tyrosine-based activation motif (ITAM) and, consequently, function as activatory receptors^{37, 45, 73}. NK cell-specific receptors which do not necessarily recognize MHC-I molecules have been also identified lately^{55, 68, 71}. Thus, natural cytotoxicity seems to be the result of a complex interplay of positive and negative signals, depending on the particular conditions of immune response. This review summarizes the present knowledge of NK cell functional molecules with a focus on receptors for classical and non-classical MHC-I antigens.

NK Cell Receptors of the Ig Superfamily

Killer immunoglobulin-like receptors (KIRs)

KIRs are type I transmembrane glycoproteins (gp) whose molecular weight (mw) differs depending on the

number of Ig-like domains in the extracellular portion and on the length of the cytoplasmic tail (Table 1). They are encoded by a multigene family on human chromosome 19q, containing about 12 genes with limited allelic variation⁷². KIR genes are expressed on overlapping subsets of NK cells and a subpopulation of T cells^{16, 46, 48}. The HLA-I specificity of KIRs has been inferred from functional and binding studies^{28, 42, 51, 54, 63} and confirmed by direct genetic transfer⁵⁷. KIRs recognize a subregion of comparatively low polymorphism in the $\alpha 1$ domain of the MHC-I heavy chain, between 77 and 83 aminoacid residues. Consequently, the different types of KIRs are specific for sets of classical HLA-I allotypes. The first KIRs were identified with the help of monoclonal antibodies (mAbs) raised against alloreactive NK clones^{16, 27, 51}. Monoclonal antibodies EB6 and GL183 identified p58 surface structures on partially overlapping NK subsets, which inhibited NK cytotoxicity upon engagement with HLA-C alleles. It was established that EB6 and GL183 mAbs reacted with two groups of NK clones, expressing, respectively, p58.1 (KIR2DL1)* and p58.2 (KIR2DL2) receptors. The first group of clones could be inhibited by Cw2, Cw4, Cw5, Cw6 HLA-C2 alleles (C2), while the protective alleles specific for p58.2 were Cw1, Cw3, Cw7 and Cw8 (C1). It was shown that the specific mAb-mediated removal of p58 receptors results in lysis of the HLA-C-protected target cells. Thus, it was proved that NK cells possess MHC-I-specific inhibitory receptors preventing them from autoimmune reactions against normal cells. The removal of the corresponding protective MHC-I alleles (as may occur in viral infection or tumor transformation) leads to effective lysis of the target cells.

The discovery of another clonally distributed NK receptor, NKB1, followed soon^{25, 42}. It shows a high degree of homology with p58, though characterized by 3 Ig-like domains and a molecular weight of 70 kDa. NKB1 (p70) is specific for Bw4⁺ HLA-B alleles and, upon their recognition, inhibits NK cell cytotoxicity. Further on, using the mAbs Q66 and Q241, a disulfide-linked dimer of 140 kDa (p140) was identified which mediated negative signaling to NK lysis upon engagement of HLA-A3 or HLA-A11 alleles. Its cDNA was slightly different from that of p70 (50 aa in the extracellular region) encoding for 3 Ig-like domains and 2 ITIMs in the cytoplasmic tail⁵⁴.

The isolation and cloning of the corresponding cDNAs showed that, in spite of the differences in the

* A nomenclature denoting the number of Ig domains (D); length of cytoplasmic tail (L, S) and serial number of receptors.

Table 1. Receptors regulating NK cell functions

Group	Receptor	Molecular weight (kDa)	Specificity	Structure	Expression
KIRs	KIR2DL1(p58.1)	58	C2	2D, 2 ITIM	NK-clonal, T subset
	KIR2DL2(p58.2)	58	C1	2 Ig, no ITIM	
	KIR2DS1(p50.1)	50	C2		
	KIR2DS2(p50.2)	50	C1		
	KIR2DS3(p50.3)	50	?	3D, 2 ITIM	
	KIR3DL1(p70)	70	Bw4		
	KIR3DL2	70/140	A3/A11	2D, 1 ITIM	all NK, T subset
	KIR2DL4 (p49)	49	HLA-G		
ILTs	ILT-1 (LIR 7)	70	MHC-related antigens	4D, no ITIM	Mo, NK
	ILT-2 (LIR 1)	110	MHC-I broad	4D, 3 ITIM	Mo, B, NK, T
	ILT-3 (LIR 5)	55–60	Immunoglobulins (?)	2D, 3 ITIM	Mo, DC, B
	ILT-4 (LIR 2)	95	MHC-I broad	4D, 3 ITIM	Mo, B, DC, NK
	ILT-5 (LIR 3)			4D, 4 ITIM	Mo, B, DC
	LIR 4		?	soluble	NK, B
	LIR 6			2/4D, no ITIM	Mo, B
Other Ig-like receptors	NKp44	44	?	no ITIM	NK-restricted
	NKp46	46		2D, no ITIM	
	NKp30	30		1 Ig, no ITIM	
	p75/AIRMI	75		3D, 1 ITIM	
	BY55	80	MHC-I broad	1D, GPI-anchored	NK subset, T subset
Lectin-like receptors	CD94/NKG2A	30/43	HLA-E	2 ITIM	all NK, T subset
	CD94/NKG2B	30/39		no ITIM	
	CD94/NKG2C		MICA, MICB		
	CD94/NKG2E	?			
	NKG2D				
NKRP1	80			NK, T, Mo	

extracellular regions, p58, p70 and p140 all contained two ITIMs in their cytoplasmic regions. Upon receptor engagement, ITIMs are tyr-phosphorylated and bind to the Src-homology domain 2 (SH2) domain of protein tyrosine phosphatase (SHP-1), responsible for the negative signalling (Fig. 1). Thus, human NK cells are provided with an array of MHC-I allotype-specific inhibitory receptors, preventing NK reactivity against normal cells. It was shown that KIRs inhibit both NK cell cytotoxicity and cytokine production, though these two functions are not always coordinately triggered and regulated³⁴. The repertoire of known KIRs seems to be biased towards recognition of HLA-C and HLA-B4 phenotypes. However, the KIR locus appears to be polygenic and polymorphic within the human population and are far from being completely defined⁷⁰. In line with this notion, a novel structurally divergent KIR (KIR2DL4) has lately been characterized¹⁴. The cl.

15.212 encoded for a 49 kDa protein sharing 50% homology with p50, p70 and p140, with 2 Ig-like domains and a single ITIM in the cytoplasmic portion. Unlike the other KIRs, this receptor is not clonally distributed but is detected on all human NK cells and a subset of KIR⁺ T cells. Another peculiarity of p49 is the putative existence of a soluble form, since a cDNA lacking the transmembrane sequence has been isolated. It was shown that soluble recombinant KIR2DL4 Ig binds to cells expressing only the non-classical HLA-G molecule and that KIR2DL4 inhibits the lysis of HLA-G⁺ targets. Having in mind that HLA-G expression is restricted to fetal trophoblasts, this new KIR may be important at the maternal/fetal interface⁶⁴.

Molecular cloning of KIRs has led to the identification of highly homologous NK cell receptors with the same MHC-I specificity^{20, 50}. They differ by one charged aa residue in their transmembrane (TM) re-

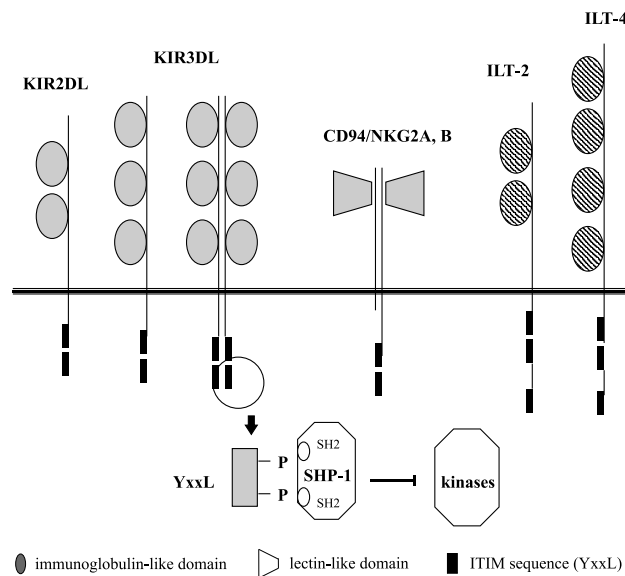


Fig. 1. Human NK cell inhibitory receptors: mechanism of signaling

gions and by a shorter cytoplasmic tail, lacking ITIMs or other signaling motives. Three homologues of p58: p50.1, p50.2 and p50.3 were identified, the first two recognizing the same HLA-C alleles as p58a and p58b, respectively, the third having unknown specificity. In contrast to inhibitory receptors, cross-linking of their homologs leads to Ca^{++} release, cytokine secretion and induction of NK cytotoxic activity. The precise signaling mechanism was only recently suggested: activating KIRs co-operate with low molecular weight proteins containing ITAMs, related to the well-known signaling adapters CD3 ζ and FcR γ III. An ITAM-containing 12 kDa molecule termed DAP-12 was shown to coprecipitate with p50.2. Cross-linking of p58.2/DAP-12 leads to cellular activation and recruitment of ZAP-70 and Syk PTKs, similarly to the signaling pathways in T and B cells³⁷ (Fig. 2).

Immunoglobulin-like transcripts (ILTs)

ILTs (described also as leukocyte Ig-like receptors, LIRs) are encoded by several genes which cluster with those for KIRs at chromosome 19p13.4^{10, 17, 22, 23}. ILTs have either 2 or 4 Ig-like domains. One subset of ILTs displays long ITIM-containing cytoplasmic tails and mediate inhibition of cellular activation (ILT-2, ILT-5); others have a basic aminoacid residue in the TM domain followed by a short cytoplasmic domain – a structure shared by activating KIRs (ILT-1, LIR6). A soluble form lacking TM and cytoplasmic regions has been also identified (LIR4). It was shown that the ITAM-containing protein Fc ϵ R γ chain associates with

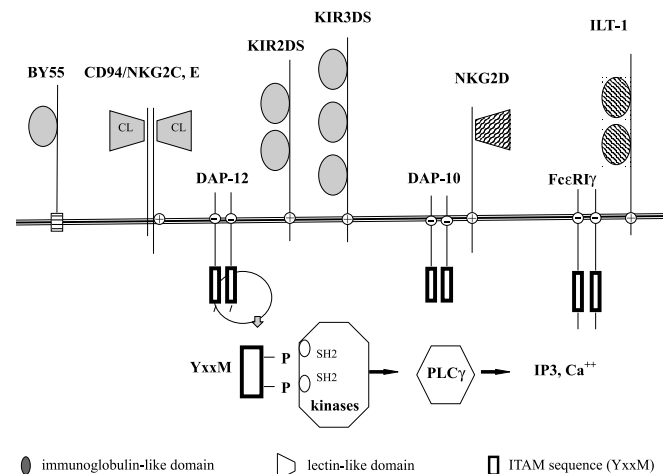


Fig. 2. Human NK cell activatory receptors: mechanism of signaling

ILT-1 and its homologues (ILT-1-like protein, ILT-7)⁵³. Unlike KIRs, ILTs have a variable and broad cellular expression, including the myelomonocytic lineage, B cells, dendritic and other antigen-presenting cells, T and NK subsets (Table 1). ILTs show a different type of specificity for MHC-I molecules, if any: ILT-2 and ILT-4 have a broad specificity for classical and non-classical MHC-I molecules. While ILT-2 does not interact efficiently with HLA-C or HLA-E phenotypes, it detects a HCMV UL18 protein, distantly homologous to HLA-I molecules and possibly functioning as their surrogate during HCMV infection⁴¹. A specificity for MHC-I-related molecules such as CD1, MR1 and MIC, has been proposed for ILT-1⁵³. The physiological role of ILTs is far from defined, but it is clear that MHC-I-specific inhibition is not a privilege for NK cells. Owing to their broad expression, ILTs might establish thresholds for leukocyte activation and antigen presentation and down-modulate inflammatory responses, thus preventing autoreactivity.

Other Ig-like NK receptors

The group of Ig-like human NK activating receptors is constantly increasing, though the ligands of the newly identified molecules are not always known. Several activating receptors with strictly NK-restricted expression, whose genes also localize at chromosome 19, have been lately described. While NKp44 is detected exclusively on activated NK cells⁷¹, NKp46 is expressed on both resting and activated human NK cells, induces the lysis of human and murine tumor cells and is the first NK-restricted molecule involved in the triggering of natural cytotoxicity^{58, 68}. NKp44 and NKp46 may synergise in the process of MHC-nonrestricted lysis. While NKp44 confers activating signals through

DAP-12, NKp46 was shown to assemble with CD3 ζ signaling protein. Since both receptors induce the killing of MHC-I-negative tumor cells, MHC-I molecules were ruled out as putative ligands. NKp30 is another NK-specific receptor which, upon cross-linking, induces a strong activation signal, while its mAb-mediated masking leads to inhibition of NK cytotoxicity. It is also associated with CD3 ζ and as a rule co-operates with NKp46 and/or NKp44 in the induction of NK cytotoxicity; however it is a major triggering receptor in the killing of certain tumors⁵⁵.

Another Ig super family NK cell-specific receptor which regulates MHC-nonrestricted cytotoxicity through unknown ligands is the sialoadhesin p75, termed also adhesion inhibitory receptor molecule 1 (AIRM1)²⁶. It is characterized by 3 Ig-like domains and one ITIM in the cytoplasmic tail. Its cross-linking inhibits the spontaneous NK-cell-mediated cytotoxicity as well as the triggering mediated by the activating receptors CD16, NKp46 or NKp44. A human homologue of the mouse NK cell activating receptor 2B4 was described as NK cell activation-inducing ligand (NAIL)⁹. Through its counterstructure, CD48, NAIL induces the proliferation of B cells and cytokine secretion of dendritic cells, while recombinant CD48 induces the cytotoxicity and IFN- γ secretion by the corresponding NK cells³³.

In summary, the emerging group of non-MHC-specific NK cell receptors complies with the idea that NK cell triggering may be regulated by different receptor-ligand interactions, depending on the target cells and the particular conditions of immune response. p75/AIRM1 might rather recognize undefined sialylated proteins, possibly expressed on normal cells with physiologically low amounts of HLA-I in order to protect them. On the other hand, p75 might function at earlier stages of NK cell differentiation when HLA-I-specific receptors are not yet expressed, thus complementing their protective role.

We have identified a novel Ig-like MHC-I-specific receptor, different from all hitherto described functional molecules. This KIR-related molecule, termed BY55, is weakly homologous to the first Ig-C2 domain of KIR2DL4 (22% identity, 44% similarity)². It is expressed by 40–70% of PB NK cells (CD56^{dim+} CD16⁺), most TCR γ/δ lymphocytes, a subset of CD8^{high+} peripheral blood T cells, and all intestinal intraepithelial T lymphocytes⁴⁴. The expression of BY55 defines cells with high cytotoxic activity in both peripheral blood and umbilical cord blood⁷. BY55 is expressed as a multimeric 80 kDa structure; unlike all described KIRs, it is lost from the cell surface and is released in

a soluble form after activation. Identification of its cDNA showed that BY55 is a cysteine-rich, 134 aa gp, containing one Ig-like domains and no cytoplasmic tail, since it is a glycosylphosphatidylinositol membrane-anchored receptor. In conformity with this structure, we have not succeeded in demonstrating any inhibitory or activating effects of BY55 on the effector cells. However, participation of BY55 in some signaling complexes cannot be excluded, as has been recently shown for other GPI-anchored molecules³². We have demonstrated a broad specificity of BY55 for both MHC-I classical and non-classical molecules, similar to ILT-2, ILT-4 and p49. Unlike these, optimal binding of BY55 requires a prior aggregation of its ligand. Further on, upon binding of MHC-I complexes on previously activated T cells, BY55 delivered a potent second signal for their proliferation. Thus we have demonstrated for the first time a triggering effect of an MHC-I-specific NK receptor on a MHC-I-bearing cell¹.

NK Receptors of the C-Lectin Superfamily

The first family of MHC-I-specific NK receptors defined was the Ly49 family of lectin-like homodimers recognizing polymorphic H-2 class I molecules in mice⁷⁴. Although human homologues have not been described, other C-type lectines, all mapping at human chromosome 12, regulate natural cytotoxicity in man.

The CD94/NKG2 receptors are heterodimers composed of the invariant CD94 chain and a member of the polymorphic NKG2 family of proteins encoded by 5 closely linked genes (A, B-splice variant of A, C, E, D/F). CD94 is a 30 kDa gp, forming disulphide-linked heterodimers with p39 or p43 forms of NKG2 receptors^{12, 13, 39, 60}. CD94 functions primarily as a chaperone to transport NKG2 receptors to the cell surface. The NKG2A, NKG2C and NKG2E proteins are structurally diverse: NKG2A/B have 2 ITIMs, while the other forms lack signaling motives in their cytoplasmic tail. This fact explains the controversial results initially obtained in functional studies: ligation of CD94-induced activation of intracellular PTKs in some clones, and inhibition of CD16-induced phosphorylation in others⁵⁶. The cellular expression of CD94/NKG2 receptors shows no clonality: they are detected on practically all NK cells plus a T cell subset including TCR $\alpha\beta$ ⁺CD8⁺ and TCR $\gamma\delta$ ⁺ lymphocytes, thus co-expressing with different KIRs⁴⁷. The nature of the inhibitory signals conferred by NKG2A/B is similar to that of KIRs, as an association of NKG2A with the cytoplasmic PTP SHP-1 has been shown¹⁵. NKG2C

and NKG2E possess charged aa residues in their TM domains and were shown to interact with DAP-12 to transmit activation signals³⁷. Initial results from blocking and functional tests implicated CD94/NKG2 in the recognition of several HLA-A, -B, -C and -G ligands. However, no obvious structural features could distinguish protective from non-protective alleles. Recently it was demonstrated that CD94/NKG2 receptors interact with the non-classical HLA-E molecule in complex with peptides derived from the leader sequences of other HLA-I molecules⁴⁰. It was confirmed that this interaction is peptide-dependent and -specific and that HLA-E is the primary, if not sole, ligand of CD94/NKG2¹¹. HLA-E has been demonstrated to interact specifically with both CD94/NKG2C and NKG2A/B receptors, thus regulating both positively and negatively natural cytotoxicity. Since the level of surface expression of HLA-E depends on the synthesis of all other HLA-I molecules, CD94/NKG2 appears to function as a regulation system complementary to KIRs. While the clonally distributed KIRs “survey” particular HLA-I epitopes, CD94/NKG2 might detect quantitatively the overall level of HLA-I expression, which is lowered in a number of viral infections. Further on it might be operative when particular NK cells lack the appropriate KIR. Finally, since both HLA-E and CD94/NKG2 expression are induced by IFN- γ , IL-12 and IL-15, the system should be responsive to the effects of cytokines produced during inflammation^{15, 62}.

The NKG2D molecule, although encoded by the same gene family, is quite distant from the other members; it shows only limited homology with NKG2A, C and E and does not form heterodimers with CD94^{5, 73}. NKG2D lacks signaling domains in its cytoplasmic portion and was demonstrated to associate with the signal-transducing unit DAP-10. The latter possesses a SH2 domain-binding site recruiting the p85 subunit of the PI3 kinase, thus providing for NKG2D-dependent signal transduction. NKG2D has been defined as a receptor for the stress-inducible MICA and, probably, MICB proteins, frequently expressed by epithelial tumors. It was demonstrated that coexpression of MICA on β 2m-protected Daudi cells rendered them sensitive to lysis by NK cells, which could be inhibited by anti-MICA and anti-NKG2D mAbs⁵. Thus NKG2D, the most common NK receptor known, may serve to signal cellular distress and promote immune responses in spite of the presence of MHC-I molecules.

Another member of the C-lectin SF is hNKR-P1A (CD161), an 80 kDa type II gp homodimer homologous to the murine NKR-P1 molecule. It is expressed on most NK cells, a T cell subset including both CD8⁺ and

CD4⁺ cells, and on all PB-derived monocytes. The functional effects of treating human NK cells with anti-NKR-P1 mAbs have been complex, resulting in no effect, activation or inhibition. This suggests that functionally distinct isoforms of the molecule may exist in humans³⁵.

Conclusion – the Questions to Answer

The increasing knowledge about NK cell functional receptors has revealed some basic principles of innate immunity while others remain to be clarified. In contrast to T and B cell antigen-specific receptors, each NK cell expresses multiple MHC-I specific molecules. Thus NK cells are always ready to react unless restrained by an array of inhibitory receptors. The primary concern of this particular regulation system is to avoid autoreactivity while detecting any pathological deviation in the self-MHC-I phenotype. Two families of MHC-specific receptors complement each other: the C-type lectin heterodimers detect the overall level of MHC-I molecule expression, and the allele-specific KIRs are advantageous for detection of more subtle changes at single MHC loci. Still, very little is known about the molecular mechanisms that regulate the receptor repertoire of individual NK cells. While the expression of at least one self-MHC-I-specific inhibitory receptor is obligatory to avoid autoaggression, the simultaneous expression of several KIRs, some of which not self-MHC-I-specific is not readily explained. Even if alloreactive KIRs simply reflect the stochastic nature of KIRs expression, they have important implications, notably in the field of bone marrow transplantation and maternal/fetal interactions^{65, 69}.

Although a number of NK cell activating receptors have been identified, NK cell triggering is much less understood. The coexistence of homologous inhibitory and activating KIRs has an uncertain physiological role: triggering of NK cell cytotoxicity, amplification of the signal induced in the absence of inhibitory MHC-I antigen, or induction of the inhibitory receptors²⁰. Obviously, NK cell triggering ligands are not restricted to classical MHC-I antigens. Of special interest are molecules widely shared by micro-organisms, tumors and virally infected cells, such as MHC-I non-classical antigens, sialylated carbohydrates and heat-shock proteins. The role of MICA, MICB⁵ and Hsp70⁵² has already been demonstrated, identification of sialylated ligands is very probable in relation to adhesion molecule-related receptors as p75²⁶.

Another vast field for exploration is the cross-talk

between MHC-I-specific and other cell functional receptors. Modulation effects of both KIRs and CD94/NKG2 receptors on cellular immunity during viral infections and tumor growth have been demonstrated with respect to $\gamma\delta$ T cells and antigen-specific CTL^{4, 30, 61}. These effects should be considered not only as a safety mechanism, but as a potential for impairment of immune responses⁴⁶. An emerging theme is the signaling provided by soluble NK cell receptors. Further on, NK receptors may provide variable signals to the corresponding ligand-expressing cells, as was shown for BY55 and for NAIL/CD48, thus playing a more general regulatory role in a variety of immune responses. And finally, neither MHC-I-specific nor ITIM-containing receptors are a privilege of NK cells: they all reflect basic homeostatic mechanisms of the immune system.

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