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Review

Paired NK cell receptors controlling NK cytotoxicity

Noa Stanietsky, Ofer Mandelboim *

The Lautenberg Center for General and Tumor Immunology, The BioMedical Research Institute Israel Canada, The Hebrew University Hadassah Medical School, Jerusalem 91120, Israel

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ABSTRACT

Human natural killer (NK) cells possess an arsenal of receptors programmed to regulate the NK cell functions, once encountering a target cell. In general, the activating receptors mediate cytotoxicity when engaged by their tumor specific, stress induced, virally encoded, or rarely, self ligands. Whereas, the inhibitory receptors bind self molecules, mostly MHC class I, presented on all normal and healthy nucleated cells. However, NK cells also possess numerous, highly homologous, pairs of receptors that sometimes even share the same ligands but display divergent functions. In this review we describe the NK cell repertoire of paired receptors and discuss questions regarding their function and mode of action. We focus primarily on the three PVR-binding receptors; the co-stimulatory DNAM1 and CD96 and the inhibitory TIGIT.

1. Paired inhibitory and activating NK cell receptors

NK cells, which belong to the innate immune system, are able to quickly kill virally infected and malignant cells. The complicated repertoire of activating and inhibitory receptors that regulate NK activity helps to ensure that NK cells would be able to efficiently kill invading pathogens but not normal self cells [1]. The differences in the function of the inhibitory and activating NK cell receptors are reflected by the different ligands recognized by the various receptors. While the activating NK cell receptors recognize pathogen-derived, stress-induced, tumor specific and surprisingly sometimes even self ligands, the inhibitory receptors, in general, recognize self proteins, mainly MHC class I [2]. The differences in the inhibitory and activating ligands repertoire probably exist to guarantee the discrimination between self and non-self. Therefore, it was surprising to discover the existence of pairs of highly homologous proteins that in some cases even share the same ligands, but display divergent functions (Table 1). In this review we discuss the properties of the various members of the human paired NK receptors and mainly focus on reviewing the activity of the PVR-binding receptors in an attempt to better understand the biological function of the paired receptors.

2. Paired receptors: MHC class I binding proteins

Most of the paired receptors belong to the killer cell immunoglobulin-like receptors (KIR) family. This family includes inhibitory receptors with a long intra cytoplasmic domain containing a variable number of immunoreceptor tyrosine-based inhibitory motifs (ITIM), and activating or co-activating receptors, with a nearly identical extracellular region containing shorter intra cytoplasmic domain which lacks ITIMs (Table 1). These short killer activating receptors (KAR) also display a unique transmembrane sequence, which contains a charged amino acid that interacts with an activating adaptor molecule [3].

The ligands of most of the KARs are unknown (Table 1) and most of the known KAR ligands are MHC class I proteins which are also recognized by their KIR inhibitory counterparts. For example, both the inhibitory KIR2DL1 and its activating counterpart KIR2DS1 bind HLA-C molecules containing a lysine residue at position 80 ((HLA-C^{Lys80}, Table 1) and [4,5]). Inhibitory KIR2DL2/3 and activating KIR2DS2 bind HLA-C proteins containing an asparagine residue at position 80 ((HLA-C^{Asn80}, Table 1) and [4,6]). In both cases and in all other examples in which the same ligand is recognized by the KIR and the KAR, the binding of the inhibitory receptors is always stronger (Table 1).

As mentioned above, the ligands of many KARs are still unknown. One notable example of a distinctive KAR that has no known ligands is KIR3DS1, which correlates with better prognosis of HIV-infected individuals [7,8]. Although this receptor possesses an almost identical extracellular domain to that of its inhibitory KIR3DL1 counterpart [9], there is no direct evidence that KIR3DS1 can indeed interact with MHC class I proteins [9].

An example of paired receptors was also noted in the C-type lectin family of receptors. The CD94/NKG2A constitutes an inhibitory receptor, while its counterpart CD94/NKG2C that lacks ITIMs,

* Corresponding author.
E-mail address: oferm@ekmd.huji.ac.il (O. Mandelboim).

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Table 1
Paired receptors on human NK cells.

Receptor	ITIM	Ligand	Relative affinity	Signal	Ref.
KIR2DL1	2	HLA-CLys80	High	–	[4,5]
KIR2DS1	0	HLA-C^{Lys80}	Low	+	
KIR2DL2	2	HLA-C^{Asn80} HLA-C^{Lys80}? HLA-B?	High	–	[6,65]
KIR2DS2	0	HLA-C^{Asn80}	Low	+	
KIR2DL3	2	HLA-C^{Asn80} HLA-C^{Lys80}? HLA-B?		–	[65]
KIR2DS3	0	?		+	
KIR2DL4	1	HLA-G		±	[22,23,66]
KIR2DS4	0	HLA-Cw4 A non-HLA ligand		+	[15,67]
KIR2DL5	2	?		–	[68]
KIR2DS5	0	?		+	[69]
KIR3DL1	2	HLA-Bw4 HLA-Bw6?		–	[70–72]
KIR3DS1	0	HLA-Bw4?		+	[7,8]
KIR3DL2	2	HLA-A3,A11		–	[73]
KIR3DL3	1	?		?–	
CD94/NKG2A	2	HLA-E	High	–	[10]
CD94/NKG2C	0	HLA-E	Low	+	
CD300a	4	?		–	[19]
CD300c	0	?		+	
DNAM1/CD226	0	PVR/CD155 Nectin2/CD112	114–119 nM Low	+	[49]
Tactile/CD96	1	PVR/CD155	37.6 nM	+	
TIGIT/WUCAM	1	PVR/CD155 Nectin2/CD112 Nectin3/CD113	1–3 nM Low 38.9 nM	–	

The table shows the paired receptors expressed on NK cells. The number of immunoreceptor tyrosine-based inhibitory motifs (ITIM) is indicated. When ligands were identified, they are indicated, otherwise they are marked with "?". – represents negative inhibitory signal, whereas + indicates positive activating signal. When the binding affinity is known, it is indicated (*Kd*). Otherwise, the strength of the signal mentioned is relative to its inhibitory counterpart.

forms a triggering receptor, and both of them bind to HLA-E (Table 1 and [10]).

Because the KAR interactions with their ligands seem to be weak compared to their inhibitory counterparts, it is quite difficult to make a general conclusion that indeed the MHC class I proteins are the ligands of the various KARs. Alternatively, it is quite possible that the binding of the various KARs to the MHC class I proteins is weak because the MHC class I proteins are not the "real" KAR ligands. Indeed, one of the puzzling questions in the field with this regard is why should NK cell develop killer receptors against self MHC class I proteins? One possible explanation is that the KARs are more sensitive to the peptide repertoire presented by a given MHC class I protein. Thus, when the cells are infected with a certain pathogen, the peptide repertoire is slightly changed and this change might be better recognized by the KARs. Indeed, it was shown that peptides could affect the recognition by inhibitory receptors [6,11] and could even antagonize the inhibitory receptor function [12]. Nevertheless, it is a bit difficult to assume that the small changes in the peptide repertoire of infected cells (that often are limited to less than 1%) would have a dramatic effect on the KAR versus KIR recognition. With that regard, although Fadda et al. [12] elegantly demonstrated an antagonistic effect of certain peptides on KIR mediated inhibition, the lowest ratio they have used in their work was 10% antagonistic to 90% inhibitory peptides. We think, that a ratio of 1% antagonistic to 99% inhibitory peptides would probably imitate better physiological situations. It will be interesting to test whether in the context of "real infection" peptide antagonism could be observed. Finally, the observations indicating that a single KIR could recognize many different MHC proteins, which contain different peptide repertoire, suggest a minor role for peptides in the KIR recognition ([4] and Table 1).

It also might be possible that the KARs "sharpen" the threshold needed for NK cell inhibition and activation. The KIRs binds their cognate MHC class I proteins with a very fast on and off rates [13] and indeed it was demonstrated that different levels of HLA-C proteins determines the efficiency of NK cell inhibition [14]. Thus, it is possible that when the MHC class I protein is also engaged by KAR, which provides a counterbalance activating signal, the inhibitory threshold is better defined.

Alternatively, however, because the KAR binding to MHC class I is of such low affinity it is possible that the "true" ligands of the KARs are not the MHC class I proteins but other tumor-specific or pathogen-derived ligands. Supporting this possibility, we have demonstrated that KIR2DS4 recognizes an unknown melanoma ligand [15]. A further support to this hypothesis comes from the mouse Ly49I and Ly49H pair. It was shown in mice that the inhibitory Ly49I receptor and its highly homologous activating counterpart, Ly49H, share the same ligand; the m157 protein, which is encoded by the mouse cytomegalovirus [16]. The explanation given to the existence of this pair is that the mouse CMV originally used the Ly49I receptor to escape NK cell attack through the interaction with m157, while NK cells responded back through the development of a very similar activating receptor (Ly49H) that recognizes the same ligand [16].

3. Paired receptors: non-MHC class I binding proteins

In addition to MHC class I binding receptors, inhibitory receptors that bind ligands other than MHC class I proteins are also present on NK cells [17]. It is still unclear why these receptors are needed to operate under normal conditions, when every nucleated cell expresses MHC class I proteins. A possible explanation might be to provide an additional inhibitory mechanism against the KAR–MHC class I interactions. However, this explanation is probably unlikely since similarly to the KIRs, the non-MHC class I binding inhibitory receptors also have activating counterparts. For instance, while CD300a contains 4 ITIMs in its cytoplasmic tail, CD300c (which shows 80% identity to CD300a at the extracellular Ig domain) is considered to be an activating receptor. Indeed, the transmembrane region of CD300c contains an unusual charged glutamic acid residue and a short cytoplasmic tail [18]. These two receptors are very similar and all new 13 different mAbs that were generated against either CD300a, or against CD300c were unable to discriminate between the two members [19]. Whether the activating and the inhibitory receptors of this group recognize the same ligand is still unknown. The CEACAM1 receptor, which interacts homophilically with itself, is another example of paired receptors that do not interact with MHC class I proteins [20]. CEACAM1 was shown to have a shorter, activating version, expressed by T cells [21]. Whether NK cells also express the short CEACAM1 protein on their surface is yet unknown.

4. Dr. Jekyll and Mr. Hyde: Inhibitory and activating properties in a single receptor

On top of all of the above examples of paired receptors, proteins which possess both inhibitory and activating properties also exist. For example, receptors such as KIR2DL4 and 2B4 are able to transduce both activating and inhibitory signals, depending on the environment in which they are acting [22–25]. In the absence of SAP,

the human 2B4 receptor, which normally delivers activating signals, is turning into an inhibitory receptor [24] and KIR2DL4, which contains only a single ITIM (Table 1), could potentiate or inhibit various responses depending on whether it is membrane bound or endocytosed into the cell [26]. Interestingly, the NKp44 activating receptor, which activates NK cell cytotoxicity through the usage of the DAP12 adaptor molecule [27], also contains an ITIM motif, which might be able, under certain circumstances (which are still unknown), to deliver an inhibitory signal.

All together, it is surprising to notice that the paired receptors repertoire is actually quite large. However, clearly not all NK cell receptors come as pairs. The receptors NKG2D, which interacts with MICA, MICB and ULBP1-6 [28], NKp46 and NKp44 receptors that recognize various viral hemagglutinins [29,30], NKp30 that interacts with pp65 of human cytomegalovirus [31], BAT3 [32] and B7-H6 [33], NKp80 that interacts AICL [34] and the low affinity Fc receptor CD16 [35] are all powerful killing receptors on NK cells, lacking inhibitory counterparts. We think that what discriminates these activating receptors form those who are paired is the strength of the signal. The activating partner of the paired receptors will always recognize its shared ligand in a lower affinity as compared to its inhibitory counterpart. We suggest that if a new activating receptor would be found to have a low affinity interactions with its ligand, inhibitory counterparts might also exist.

Hence, the obvious question is why the previously mentioned pairs of proteins have developed? It is possible that the paired receptors have been generated because it might have been easier to build up two closely related proteins that recognize either different ligands or function differently under certain conditions. Alternatively, it is possible that the paired receptors indeed bind the same ligand and that these receptors were developed to fine tune the delicate balance of NK inhibition and activation. In the next sections we will elaborate on the function of PVR binding receptors TIGIT, DNAM1 and CD96 in the fine tuning of NK cell cytotoxicity.

5. PVR/CD155 and nectin2/CD112

The human nectin family members are Ig-like adhesion molecules that homophilicaly or hetrophilically trans-interact with each other [36]. Nectin2/CD112 mediates cell to cell adhesion by either homophilic interaction with nectin2 on a neighboring cell or through heterophilic interaction with nectin3. Nectin2 is ubiquitously expressed on the surface of cells of various tissues, especially on epithelial cells, neurons and fibroblasts [36]. CD155 was originally identified as the cellular receptor for poliovirus [37] and therefore it was named polio virus receptor (PVR). Since PVR shares structural similarity with nectins [36] it was also named nectin-like molecule-5 (necl-5). Unlike other nectin family members, PVR can not interact homophilically with itself. However, it can heterophilically trans-interact with nectin3 and with the ECM protein vitronectin for the establishment of adherent junctions [38] and cell-matrix adhesion [39], respectively. PVR is expressed at low levels in many human cell types of epithelial origin, and was also detected on monocytes [40]. In mice, PVR is additionally expressed on many hematopoietic cells [41]. Importantly, PVR was found to be overexpressed in tumor cell lines and primary tumors [42–47]. As discussed below, the presence of PVR on various tumors and on normal cells is also sensed by the immune system through the usage of the triumvirate receptors CD96, DNAM1 and TIGIT.

PVR is able to signal and interestingly, it contains an ITIM motif in its cytoplasmic tail, which may lead to the inhibition of various processes. Indeed, it was shown that the PVR inhibitory signal could facilitate cell detachment from extracellular matrix which leads to cell migration [48]. Additionally, as further discussed below, it was recently demonstrated that PVR could manipulate DC functions through its interaction with TIGIT on T cells [49]. Surprisingly, engagement of PVR could also lead to activation of some cellular responses as it was demonstrated that PVR is able to augment cell proliferation which is triggered by growth factors [50]. Thus, PVR itself could be considered as a member of the "Dr. Jekyll and Mr. Hyde" family of receptors. All together, the enhanced PVR expression by tumor cells enables them to detach, migrate, proliferate, metastasize and also to be recognized by immune cells.

6. PVR and nectin2 are recognized by two co-stimulatory receptors on NK cells

Members of the nectin family were shown to be recognized by immune cells [36]. Specifically, nectin2 has been identified as a ligand for the DNAM1/CD226 receptor, whereas PVR serves as a ligand for both DNAM1 and Tactile/CD96 receptors [51,52]. Both DNAM1 and CD96 are co-stimulating receptors, expressed by cytotoxic lymphocytes, act to promote adhesion to ligand-expressing targets and to enhance the cytolytic capability of NK cells and CTLs [53–55].

CD96 belongs to the Ig superfamily of receptors and it contains three IgV like domains. The cytoplasmic domain of CD96 contains a single putative ITIM motif [52]. However, despite the presence of an ITIM-like sequence, CD96 engagement does not inhibit NK cell cytotoxicity, but rather leads to an enhancement of NK cell-mediated tumor lysis, although less efficiently than other receptors, such as DNAM1 [52]. Because CD96 contains an ITIM motif, it might function as an inhibitory receptor under special, yet unknown, conditions (perhaps analogous to those of NKp44).

DNAM1 is a transmembrane glycoprotein consisting of an extracellular region with two IgV-like domains, a transmembrane region and a cytoplasmic region containing tyrosine- and serine-phosphorilated sites [56,57]. It is expressed on the majority of monocytes, T cells and NK cells as well as on small subsets of B cells [56]. In monocytes, and possibly also in other immune cells, DNAM1 plays a role in transendothelial migration, where it facilitates the adherence to endothelial cells and migration between cell junctions [58]. DNAM1-deficient mice demonstrated enhanced tumor spread, suggesting that DNAM1 might contribute to tumor surveillance in vivo [53,59]. However, PVR is also recognized by a powerful inhibitory receptor, TIGIT, and thus the absence of DNAM1 might lead to a stronger TIGIT-mediated inhibition of immune cell activities and this could be the primary cause of the enhanced tumor spread.

7. TIGIT: a new inhibitory, PVR-binding receptor

TIGIT was first identified by Yu et al. as a surface protein containing an extracellular IgV-like domain, a transmembrane domain and an intracellular domain which includes one ITIM motif [49]. It was demonstrated to be expressed on NK cells and on all T cell subsets (including Treg and memory T cells), except for naïve $CD4^+$ T cells [49]. The receptor was named TIGIT for 'T cell immunoglobulin and ITIM domain', however it was later demonstrated to have an important function in controlling NK activity as well [54]. Therefore, its name seems to be a bit misleading.

Three ligands were identified for TIGIT: nectin2, nectin3 (which is still in question [54]) and PVR, which binds TIGIT with the highest affinity (Table 1 and [49]). It was suggested that TIGIT on T cells could not deliver a direct inhibitory signal and that T cells are inhibited by TIGIT in an indirect manner; through the triggering of PVR activity in DCs [49]. The engagement of PVR by TIGIT lead to PVR-mediated signaling that induced IL-10 production by DCs,

followed by reduced production of pro-linflammatory cytokines [49]. These observations are quite surprising and are still not completely understood because it is not clear why the engagement of PVR by DNAM1 or CD96 would not result in a similar, indirect inhibitory effect on T cells. On the contrary, DNAM1 was demonstrated to have activating properties in T cells [60]. Several possible explanations might be suggested to explain this discrepancy, which may include either the high binding affinity of TIGIT to PVR or alternatively, various T cell subsets with different functions.

Shortly after Yu et al. findings were published, Boles et al. reported about the identification of the same receptor, demonstrated that it binds PVR and named it WUCAM (Washington University Cell Adhesion Molecule) [61]. Although WUCAM mRNA is expressed in T and in NK cells, and WUCAM cDNA was even cloned from NK cells, Boles et al. found that the TIGIT/WUCAM protein expression is limited to follicular B helper T cells and to a variable proportion of T and NK cells upon activation. We think that the discrepancy observed in the various works regarding the expression of TIGIT [49,54,61] is probably due to different mAbs used by the various groups. Boles et al. showed that PVR is abundantly expressed by follicular DCs within the germinal center. Hence, it was suggested that WUCAM/TIGIT-PVR interactions may be important in regulating T cell function within the germinal center, contributing to T cell-dependent B cell responses [61]. This hypothesis was supported by another study demonstrating a defect in IgG and IgA production following orally ingested antigens in PVR-deficient mice [41]. Thus, TIGIT might have different functions, depending on the cell type being investigated.

Our group also independently identified TIGIT (we initially used the name VSIG9, as appeared in the databases) and also noticed that it binds PVR and nectin2 [54]. In collaboration with Prof. Jonjic's group we have generated seven monoclonal antibodies directed against TIGIT and in agreement with the results of Yu et al., we observed that TIGIT is expressed by many T cell subsets as well as by NK cells [54]. We demonstrated that TIGIT engagement on NK cells leads to an ITIM-mediated inhibition, via the use of a yet unknown phosphatase and further showed that TIGIT binds PVR and nectin2 but not nectin3 [54]. Importantly, we have shown that TIGIT, together with MHC class I-specific inhibitory receptors, protects primary fibroblasts from NK mediated killing. Thus, we suggested that TIGIT-PVR interaction may provide an "alternative self" mechanism for MHC class I inhibition that might be important under special conditions, perhaps when NK cells extravasate to infected tissues.

8. PVR-binding receptors: triumvirate control

As opposed to all other paired receptors mentioned above (possibly with the exception of KIR2DL2, KIR2DS2 and KIR2DL3 that bind HLA-C with Asn80, Table 1), PVR is actually recognized by three different receptors; two co-stimulating receptors (CD96 and DNAM1) and one inhibitory receptor (TIGIT). All three receptors seemed to be expressed by all NK cells (including the $CD16^-$ and $CD16^+$ NK cells in the blood) and the expression of all of them was not significantly altered following IL-2 activation [54]. It will be interesting to test whether the expression of all of the triumvi-

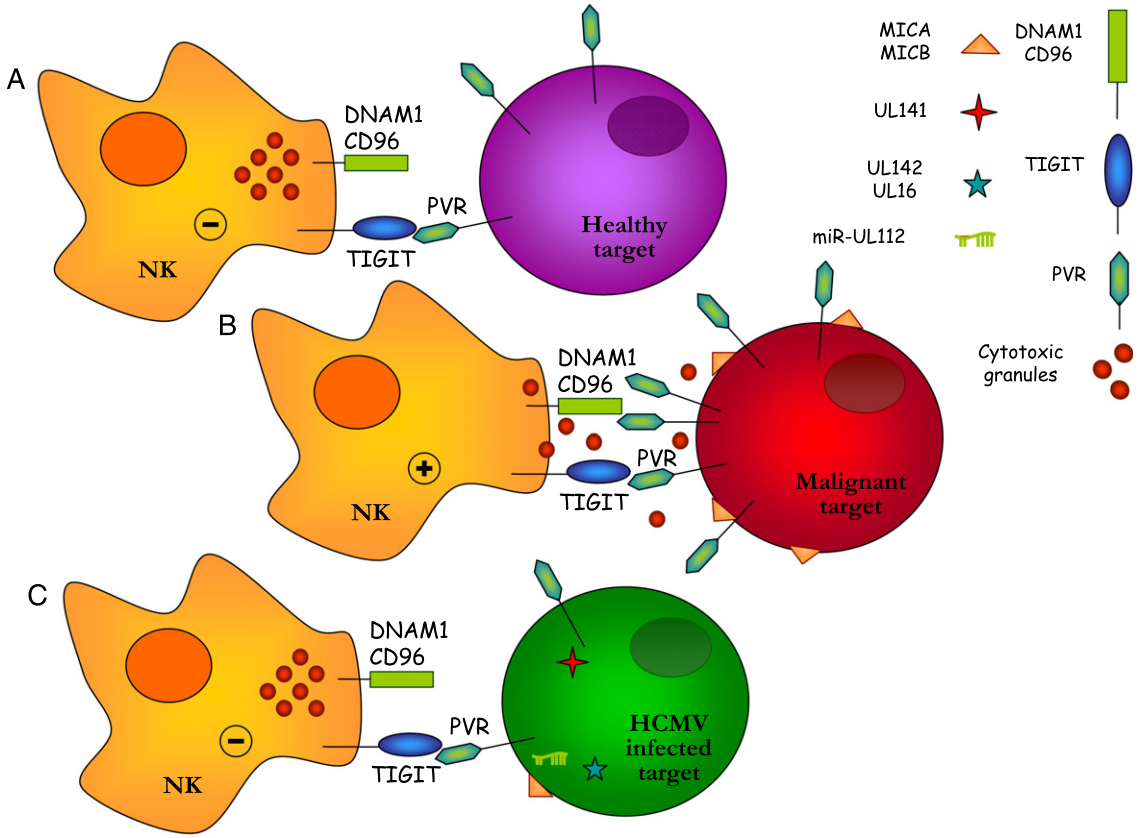

Fig. 1. The fine tuning model of PVR. (A) Normal healthy cell expresses low levels of PVR. When it encounters an NK cell, inhibition is dominant, because TIGIT has the highest affinity to PVR among the three PVR-binding receptors and because on normal cells there is little or no upregulation of ligands for other activating receptors, hence DNAM1 and CD96 probably could not be co-stimulated. (B) In tumors, PVR and for example, the stress induced ligands MICA and MICB, are upregulated. Thus, under these conditions, when encountering an NK cell, MICA and MICB would trigger the activity of NKG2D. PVR, at the same time, would be recognized by DNAM1 and CD96. The balance of signals would turn towards activation and the malignant target cell would be killed. (C) In viral infections such as HCMV, MICA and MICB are downregulaed by viral protein and by miRNA based mechanisms (UL142, UL16 and miR-112). However, PVR expression is only partially down regulated (by the viral protein UL141). Thus, during HCMV infection, there will be less activation and consequently less co-stimulation. At the same time, TIGIT-mediated inhibition will prevail due to its high affinity to PVR.

rate PVR binding receptors is different among various NK subsets such as decidual, endometrial, lymph nodes, tonsils and IL-22 producing NK cells, and whether various stimuli, other than IL-2, will differentially affect the expression of the various PVR-binding receptors.

Since all of the PVR-binding receptors bind the same ligand, albeit with different affinities, our suggestion is that one of the primary functions of these receptors is to fine tune immune cells' activities. However, it would be exciting to test whether these three receptors will additionally affect the other PVR activities mentioned above, which are not immune related (detachment, migration and proliferation).

We suggest the following model for the fine tuning of NK cytotoxicity by the triumvirate PVR binding receptors (Fig. 1), which might apply to other immune cells' activities as well. Under normal conditions (Fig. 1A), PVR is expressed at low levels on many normal healthy cells, helping them to establish adherent junctions. Despite its low level of expression, PVR could probably be recognized by the inhibitory TIGIT (due to the high binding affinity of TIGIT and PVR) and thus the killing of self cells is prevented (although all NK cells express also the PVR-binding, co-stimulatory receptors DNAM1 and CD96). When tumors emerge (Fig. 1B), PVR expression might be up-regulated to enable detachment, migration and proliferation of the developing tumors. The up-regulation of PVR together with the appearance of tumor-specific activating ligands, such as the stress-induced ligands for NKG2D [62], or the B7-H6 ligand for NKp30 [33], would now co-stimulate DNAM1 and CD96 and together tip the balance of NK activation towards cytotoxicity (Fig. 1B).

This model imply that changes in the expression levels of the PVR binding receptors, or in the expression of PVR itself, would also affect NK cytotoxicity. Indeed, changes in PVR expression levels were observed following human cytomegalovirus (HCMV) infection. It was demonstrated that HCMV downregulates PVR and nectin2 to escape DNAM1 and CD96-mediated killing [63,64]. However, the downregulation of PVR, as well as of nectin2, was shown to be partial and not complete [63,64]. Our suggestion is that such moderate expression of PVR and nectin2 on the infected cell surface is the optimal solution for the virus, not only because it avoids DNAM1 and CD96 recognition but also because it might still permit the binding of the inhibitory, high affinity, PVR-binding receptor, TIGIT (Fig. 1C).

In summery, the surprisingly large repertoire of paired receptors expressed by NK cells makes this family of receptors a prominent one in controlling NK activities. It is therefore surprising to see how little we know about the function of many members of this family. One of the reasons might be that many of the ligands of the paired receptors are still unknown. For better understanding of the paired receptors' function a comprehensive in vivo study is needed (in cases where the receptors are shared between human and mice). Additionally, we need to better characterize the expression patterns of the paired receptors, their ligands, their binding affinities, their function on various immune cells and their cooperation with other receptors. All of this will lead to a better understanding of the biological functions of the paired receptors.

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