Identification of an MHC Class I Ligand for the Single Member of a Killer Cell Lectin-like Receptor Family, KLRH1


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Natural killer cells are able to recognize and kill target cells according to differences in MHC class I expression. In rodents, the Ly49 receptors are primarily responsible for this MHC differentiation. We previously described the cloning of a novel C-type lectin-like receptor, KLRH1, encoded in the NK complex adjacent to the Ly49 genes and expressed by subsets of NK and NKT cells. MHC influence on selection of KLRH1+ NK cells in congenic strains suggested that KLRH1 may have an MHC ligand, although we were unable to identify any such ligand. In this study, we have used a sensitive reporter system and Fc fusion protein to demonstrate that KLRH1 binds specifically to the classical MHC class I molecule RT1-A2 of the RTI+ haplotype. Cytolytic activity of KLRH1-transfected RNK-16 cells was also inhibited by target cells expressing RT1-A2+. Thus, KLRH1 represents a novel family of MHC allele-specific inhibitory receptors expressed by NK cells. The Journal of Immunology, 2012, 189: 000–000.

Materials and Methods

Animals

PVG, PVG.R23, PVG.1L, PVG.1Ly1, and PVG.1N were maintained under conventional conditions in Oslo in compliance with guidelines set by the Experimental Animal Board under the Ministry of Agriculture of Norway. PVG.R5 was obtained from Harlan (Bicester, U.K.). Other strains were maintained at the Institute of Laboratory Animal Science (Hannover, Germany). Haplotypes of all the strains are listed in Table I.

Cell lines and reagents

The M2 anti-FLAG mAb was purchased from Sigma (St. Louis, MO). STOK9 (anti-KLRH1) Ab was produced as previously described (14). RNK-16 cells were obtained from Dr. C.W. Reynolds (National Cancer Institute, Frederick, MD) (16). The RNK-16.KLRH1 line has been described previously (14). CHO IdID cells were obtained from Dr. Monty Krieger (Massachusetts Institute of Technology, Cambridge, MA). All other cell lines are from American Type Culture Collection (Manassas, VA). Cell lines were grown in RPMI 1640 supplemented with 10% heat-inactivated FBS, 50 μM 2-mercaptoethanol, and 2 mM l-glutamine (cRPMI). IdID cells were routinely cultured in cRPMI, but prior to experiments were grown for 3 d in DME/F12 supplemented with insulin.

Abbreviations used in this article: KIR, killer-cell Ig-like receptor; LILR, leukocyte Ig-like receptor; β2m, β2-microglobulin.

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transferrin-selenium-X (Invitrogen), 100 U/ml penicillin, and 100 mg/ml streptomycin. Galactose (20 mM) and N-acetyl-galactosamine (200 mM) were added to the medium as indicated.

**Generation of Con A blast-fusion lines**

Con A blasts were generated as previously described (17). After 3 d of culture, Con A blasts were washed with serum-free medium and fused to NS0 myeloma cells using a standard hybridoma fusion protocol. After selection in HAT (1 × 10^{-4} M hypoxanthine, 4 × 10^{-7} M aminopterin, and 1.6 × 10^{-5} M thymidine), cells were screened for MHC class I expression by mAb Ox18 (widely reactive with rat class I MHC) or Aas5 (reactive with specific nonclassical RT1-CE region class I MHC) by flow cytometry.

**Vector construction and transfection**

KLRH1 was expressed as a chimeric molecule by constructing a vector containing the CD3ζ cytoplasmic domain and the transmembrane and extracellular domains of KLRH1. These chimeric cDNAs were shuttled into the BSR vector and used to transfect BWN3G cells. Rat MHC molecules (without leader sequence) were cloned by PCR from cDNA derived from BN or PVG rat strains. The cDNAs were transferred into a vector containing a CD8-leader sequence and an N-terminal FLAG-tag and used to transfect cells.

Cells were transfected by electroporation using a Bio-Rad GenePulser; 3 × 10^6 cells in 400 μl cRPMI were electroporated in 2-mm cuvettes at 120 V and 875 μF. After culturing overnight, cells were plated at 10^5 cells/well and selected in medium containing G418 (1 mg/ml).

Fc-fusion protein vectors were constructed by cloning the extracellular domains of KLRH1–Fc or Dectin-2 into the pMIg2 vector (kindly provided by Erik Dissen, University of Oslo), which contains the mouse IgG2b Fc region with a downstream multiple cloning site to allow in-frame cloning of type II receptors. Fc protein was purified on protein-A affinity columns from conditioned medium after transient transfection of 293T cells.

**Reporter assay**

The BWN3G line was derived by transfecting the BW5147 T cell line with an EGFP reporter construct regulated by three copies of the NFAT promoter element. BWN3G cells transfected with the KLRH1–CD3ζ chimera were seeded at 1 × 10^5 cells/well in cRPMI supplemented with 10 ng/ml PMA. Target cells were added at a ratio of 1:1. In experiments where target and reporter cells could not easily be separated by forward scatter and side scatter, stimulator cells were labeled with SNARF1 (Invitrogen), according to the manufacturer’s protocols, to allow for more efficient differentiation from BWN3G cells. For blocking experiments, mAb was added to cells at 25 μg/ml. Plates were analyzed for EGFP expression by FACS 16 h later using a FACSCalibur flow cytometer (Becton Dickinson, Mountain View, CA). For activation of reporter with Ab, STOK9 was bound to plates by incubating overnight at 5 μg/ml in 50 mM Tris, pH 9.5. Plates were washed three times with PBS before use.

**FIGURE 1.** Generation of a KLRH1 reporter line and MHC-expressing hybridomas targets. (A) Expression of KLRH1–CD3ζ chimera on the surface of BWN3G cells as assessed by FACS with isotype (shaded) or anti-KLRH1 Ab (solid line). Expression levels on KLRH1+ primary NK cells is shown for comparison (dotted line). (B) BWN3G reporter cells either untransfected or transfected with a KLRH1–CD3ζ chimera were stimulated with ionomycin or with plate-bound Ab to KLRH1, and EGFP expression was assessed by FACS. (C) NS0 cells or a representative NS0/PVG hybridoma line (NS0.1C) were assayed for expression of class I MHC with a broadly reactive MHC Ab (Ox18) or an Ab specific for nonclassical class I molecules (Aas5).

**FIGURE 2.** Ligand recognition by KLRH1. BWN3G reporter cells either untransfected or transfected with a KLRH1–CD3ζ chimera were mixed with target cells and assessed 18 h later for expression of EGFP. Broad ligand specificity was determined using a panel of NS0-rat hybridomas (A) and fine specificity determined using YB-2/0 cells transfected with individual FLAG-tagged MHC molecules (B).
Cytotoxicity assays

RNK-16 or RNK-16.KLRH1 effector cells (14) were plated in 96-well plates, and 4 μg of STOK9 or isotype-matched control mAb was added to each well. After 20 min, 51Cr-labeled YB-2/0 cells transfected with RT1-CE16/h−FLAG or RT1-A2n−FLAG were added. The plates were spun at 300 × g for 1 min and incubated for 4 h at 37˚C. Supernatants were harvested with a Titertek harvesting system (Skatron, Norway) and specific lysis calculated.

Results

Screening of Con A blast fusion lines with a novel KLRH1 reporter cell line reveals an MHC ligand in the RT1n haplotype

KLRH1 is encoded adjacent to the Ly49 receptor complex on rat chromosome 4 and shares some sequence similarity with these receptors (14). Because the Ly49 molecules recognize class I MHC, we suspected that KLRH1 may also be MHC specific. Previous attempts to determine ligand specificity using standard strategies had proved unsuccessful (14). We therefore decided to use a sensitive reporter system assay. A reporter line was generated by transfecting the BW5147 lymphoma line with a reporter construct containing EGFP under the control of a 3X NFAT promoter (18). Transfection of this cell line with a CD3/ KLRH1 chimeric construct led to the generation of the reporter line BWN3G.KLRH1ζ (Fig. 1A). This line produced EGFP in response to ionomycin and also in response to cross-linking of the chimeric receptor with an Ab to KLRH1 (Fig. 1B).

We generated cell lines from Con A blasts by fusing them with NS0 myeloma cells using standard hybridoma fusion techniques. These fusion lines express high levels of classical class I MHC molecules (as assessed by staining with Ox18), as well as non-classical class I MHC molecules (as assessed by staining with Aas5, which binds to the RT1-U molecule, which is present in the majority of rat haplotypes including RT1n which has been designated RT1-CE16 (19, 20) (Fig. 1C and data not shown). To determine whether our in-house MHC congenic rat strains on the PVG background expressed a ligand for KLRH1, we screened NS0/Con A blast fusions from six different haplotypes with the BWN3G.KLRH1ζ reporter line. The reporter cells produced EGFP in response to the NS0.1N but none of the other fusion lines tested, suggesting that the ligand for KLRH1 is a molecule encoded in the MHC of n haplotype (Fig. 2A). Screening the fusion lines with reporters expressing Ly49 receptors gave different patterns of activation, ruling out the possibility that the n haplotype is simply activating transfected lines nonspecifically (M. Daws and K.-Z. Dai, unpublished observations).

KLRH1 specifically recognizes the classical class I MHC molecule RT1-A2n

The n haplotype is that of the BN rat, and the complete genomic sequence of the MHC is available for this strain (19). We used this genomic sequence to design primers to clone every MHC molecule from the classical RT1-A region and the first cluster of class I genes of the nonclassical RT1-CE/N/M region (the CE part). These molecules were cloned into FLAG-tag expression vectors and transfected into the YB-2/0 rat lymphoma line. Screening of these transfected lines with the BWN3G.KLRH1ζ reporter line revealed that KLRH1 specifically recognizes the classical class I molecule RT1-A2n (Fig. 2B and data not shown).

To characterize further the recognition of A2n by KLRH1, we used Abs to block the interaction between the two molecules. Addition of mAb Ox18 (which binds to a public epitope shared by many rat class I MHC molecules) had no effect on activation of the BWN3G.KLRH1ζ reporter line by YB.A2n. In contrast, FLAG Ab (which binds to the N-terminal FLAG-tag on the transfected MHC molecules) was able to block reporter activation almost completely (Fig. 3A).

FIGURE 3. Characterization of KLRH1 ligand-recognition. BWN3G reporter cells were mixed with target cells and assessed 18 h later for expression of EGFP. (A) BWN3G.KLRH1ζ cells were mixed with target cells expressing FLAG-tagged RT1-A2n–FLAG alone, or together with an Ab against the FLAG tag, or a broadly reactive MHC class I Ab (Ox18). (B) BWN3G reporter cells either untransfected or transfected with a KLRH1–CD3ζ chimera were mixed with 293T cells or 293T cells expressing RT1-A2n–FLAG. (C) BWN3G.KLRH1ζ cells were mixed with Id1D cells expressing RT1-A2n–FLAG; galactose or N-acetyl-galactosamine was added to reconstitute N-glycosylation or O-glycosylation, respectively. The bottom panels show the corresponding expression of RT1-A2n–FLAG on the surface of the Id1D cells. (D) YB-2/0 cells expressing RT1-A2n–FLAG or RT1-A2n–FLAG were stained with KLRH1–Fc or Dectin-2–Fc together with a PE-labeled secondary Ab.
It has previously been reported that Ly49 recognition of mouse MHC molecules is dependent upon β2-microglobulin (β2m) and that human β2m is unable to substitute for mouse β2m (21, 22). To test whether this was also the case for KLRH1 recognition, we transfected RT1-A2n into the human cell line 293T. In this cell line, RT1-A2n must use human β2m to form the mature surface-expressed MHC molecule. As shown in Fig. 3B, the BWN3G.KLRH1z reporter line was still activated by 293T.A2n, suggesting that KLRH recognition of A2n is not dependent upon rat β2m.

N-linked glycosylation of A2n contributes to optimal recognition by KLRH1

There have been several reports suggesting that Ly49 receptor recognition of MHC is influenced by glycosylation of the MHC molecule (23, 24). This recognition is unlikely to be due to direct sugar recognition by Ly49 because the lectin-like domain of Ly49 is not a functional calcium-binding lectin. However, it is possible that the carbohydrates influence the stability of the binding surface. To assess the effect of MHC glycosylation upon KLRH1 recognition of A2n, we expressed A2n in the ldlD cell line. This line lacks the enzyme UDP-galactose/UDP-galactosamine 4-epimerase, and in the absence of exogenously added galactose and N-acetyl-galactosamine it fails to add N-linked and O-linked carbohydrate groups (25). Addition of galactose restores N-linked glycosylation, whereas addition of N-acetyl-galactosamine restores O-linked glycosylation. In the presence of galactose and N-acetyl-galactosamine, ldlD.A2n activates the BWN3G.KLRH1z reporter line (Fig. 3C). In the absence of both sugars, activation is reduced, but not absent. Addition of N-acetyl-galactosamine (restoring O-linked glycosylation) does not affect activation, whereas addition of galactose (restoring N-linked glycosylation) restores activation to its maximum level (Fig. 3C, top panels). Differences in reporter activation cannot be explained by differences in the expression of RT1-A2n on the cell surface (Fig. 3C, bottom panels). Thus, recognition of RT1-A2n by KLRH1 is affected by N-linked glycosylation.

Soluble KLRH1 binds to A2n transfectants

To rule out formally the unlikely possibility that expression of KLRH1–CD3ζ chimera induced the expression of another receptor that mediated recognition of RT1-A2n, we generated a soluble fusion protein combining the extracellular domain of KLRH1 with the Fc domain of mouse IgG2b. This KLRH1–Fc protein was used to stain YB-2/0 cells transfected with different MHC class I molecules. KLRH1–Fc bound specifically to A2n-transfectants, whereas a control protein containing the extracellular domain of rat Dectin-2 did not bind to any of the transfectants (Fig. 3D).

Expression of A2n prevents killing by KLRH1+ NK cells

To determine if recognition of A2n by KLRH1 has functional consequences, we performed a killing assay using the rat NK cell line, RNK-16, transfected with full-length KLRH1 cDNA. Killing of YB.CE16n transfectants by untransfected and KLRH1-transfected RNK-16 was similar and was not affected by the addition of Ab (Fig. 4). In contrast, there was no killing of YB.A2n targets by RNK.KLRH1. Addition of Ab to KLRH1 restored killing to the levels seen in response to untransfected RNK-16 cells, whereas addition of isotype control had no effect (Fig. 4).

KLRH1 has exquisite specificity for A2n

To examine further the ligand specificity of KLRH1, we generated NS0/Con A blast fusions from a large number of rat congenic lines.
strains (Table I). Of the 18 new haplotypes tested, only one, NS0.11, was able to stimulate BN.1G KLRH1\textsuperscript{c} (Fig. 5). The 1I haplotype is a composite haplotype (n-a-a) that is of n-haplotype in the RT1-A region (i.e., contains the A\textsuperscript{2n} MHC allele). The R37 congenic strain (b-b-n), which is of n-haplotype in the nonclassical CE/N/M region, does not activate KLRH1-reporters, implying that there are no additional ligands of n-haplotype in this region of the MHC. Thus, of the 24 haplotypes tested, and all the different class I molecules that make up these haplotypes, KLRH1 recognition appears to be limited to only one molecule, the classical class I molecule RT1-A\textsuperscript{2n}. Although different rat haplotypes express different numbers of MHC class I genes and may lack one or more RT1-A genes, several of the haplotypes tested are known to express an RT1-A2 or A2-like class I molecule (26). It can hence be concluded that the KLRH1 receptor is specific for the A2 allelic variant expressed in the n haplotype.

**Discussion**

Recognition of MHC molecules is central to the function of NK cells (27). The importance of this function is demonstrated by the wide variety of solutions that nature has developed for recognition of MHC. Beginning with archetypical KIR3DL, KIR3DX (28), Ly49, and NKG2/CD94 receptors, different species have expanded different receptor families to achieve the same goal—mosaic expression of receptors recognizing subsets of MHC alleles (29). In addition to these central MHC-recognizing receptor families, NK cells express a number of other receptors that recognize classical and nonclassical class I MHC and MHC class I-like molecules (8, 11–13).

In this study, we demonstrate recognition of classical class I by an additional receptor, KLRH1. Unlike the central receptor families, which consist of a number of receptors with varying allelic specificities, KLRH1 is a single receptor with an apparently limited specificity for the classical MHC molecule RT1-A\textsuperscript{2n}.

Structural studies of Ly49 in complex with MHC have revealed the possibility of two distinct binding epitopes on MHC: site 1 on the top face of MHC, and site 2 on the underside of MHC and in contact with residues of the β2m subunit (30). Functional studies suggest that site 2 is the most important of these sites, and the sensitivity of Ly49 recognition to changes in the β2m subunit support this conclusion (21, 22). We prefer a model where KLRH1 binding occurs in a “site 1” mode of interaction. A major reason for this conclusion is that it is thought that site 2 binding requires the ligand binding site to be “hooked” under the MHC molecule by the long stalk of Ly49. It is likely that the short stalk of KLRH1 would sterically hinder this mode of binding. In addition, the ability of KLRH1 to recognize RT1-A\textsuperscript{2n} in the presence of xenogeneic β2m suggests that β2m does not form an essential part of the binding epitope. Blockade of reporter activation by FLAG Ab (the N-terminal FLAG lies close to site 1) but not by Ox18 (binds to the α3-domain close to site 2) may also support a site 1 binding mode (Fig. 2A). Notably, KLRH1–Fc binding can be partially blocked by Ox18 (data not shown), suggesting that the soluble protein may also be able to access and bind to “site 2” on the MHC.

It seems strange that a receptor with such exquisite sensitivity for a single classical MHC allele should be evolutionarily conserved.

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**Table I. Derivation of rat hybridoma lines and haplotypes**

<table>
<thead>
<tr>
<th>Rat Strain</th>
<th>NS0 Fusion Cell Line</th>
<th>RT1 Haplotype (A-B/D-CE/N/M)</th>
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<tr>
<td>LEW.1A</td>
<td>NS0.1A</td>
<td>a (a-a-a)</td>
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<tr>
<td>LEW.1AV1</td>
<td>NS0.1AV1</td>
<td>v1 (a-a-v1)</td>
</tr>
<tr>
<td>PVG</td>
<td>NS0.1C</td>
<td>c (c-c-c)</td>
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<tr>
<td>BN.1E</td>
<td>NS0.1E</td>
<td>e (a-c-?)\textsuperscript{a}</td>
</tr>
<tr>
<td>LEW.1F</td>
<td>NS0.1F</td>
<td>f (f-f-f)\textsuperscript{a}</td>
</tr>
<tr>
<td>DA.1G</td>
<td>NS0.1G</td>
<td>g (g-l-g)\textsuperscript{b}</td>
</tr>
<tr>
<td>DA.1H</td>
<td>NS0.1H</td>
<td>h (h-h-h)\textsuperscript{b}</td>
</tr>
<tr>
<td>DA.1I</td>
<td>NS0.1I</td>
<td>i (n-a-a)\textsuperscript{b}</td>
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<tr>
<td>LEW.1K</td>
<td>NS0.1K</td>
<td>k (k-k-k)\textsuperscript{b}</td>
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<td>l (l-l-l)</td>
</tr>
<tr>
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<td>NS0.1LM1</td>
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</tr>
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<td>NS0.1LV?</td>
<td>lv? (l-l-lv)\textsuperscript{b}</td>
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<tr>
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<td>NS0.1M</td>
<td>m (m-m-?)\textsuperscript{b}</td>
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<tr>
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<td>NS0.1O</td>
<td>o (d-a-a-?)\textsuperscript{b}</td>
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<tr>
<td>BN.1B</td>
<td>NS0.3R37</td>
<td>r37 (b-b-n)</td>
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</table>

\textsuperscript{a}Haplotypes are given in standard notation, with the letters corresponding to the RT1-A (classical class I), RT1-B/D (class II), and RT1-CE/N/M (nonclassical class I) regions of the MHC, respectively.

\textsuperscript{b}Unknown or unconfirmed nonclassical class I regions are indicated by a question mark ("?").

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**Figure 5.** Exquisite specificity of KLRH1 ligand recognition. BN3.3G KLRH1\textsuperscript{c} cells were mixed with NS0-rat hybridoma cells from a large panel of rat strains expressing different MHC haplotypes and assessed 18 h later for expression of EGFP.
It is unlikely that the ability to be inhibited by this single MHC allele, expressed by a limited number of individuals, would be important to preserve unless the MHC allele was, for example, one that predisposes to autoimmune disease (such as HLA-B27 in humans). It can then be postulated that rats expressing KLRH1 may be protected from autoimmune disease in populations where RTI-A2 is present. The BN rat strain, which expresses RTI-A2 (but lacks KLRH1), is indeed predisposed to Th2-mediated autoimmune disease, and this disposition has been genetically linked to the MHC (31). However, no linkage to the NK complex on chromosome 4 has been demonstrated.

An alternative possibility is that KLRH1 is able to bind to a wider range of ligands under some circumstances. For instance, cellular stress or infection may lead to alterations in MHC itself or MHC-associated molecules that induce conformational changes in other MHC alleles such that they are now recognized by KLRH1. Although an inhibitory signal may be counterintuitive in the case of infection, the fact that the proportion of KLRH1-expressing NK cells increases after activation (14) may suggest that it has a role in limiting NK-mediated immune responses.

Such exquisite specificity is not unique to KLRH1, however. Several Ly49s have only a single described MHC allele as their ligand, although they have not generally been screened against the large number of MHC haplotypes that we have used in this study. Rat Ly49d has been shown to recognize RTI-A1, and screening of the same panel of hybridomas used here with a Ly49d reporter does not reveal reactivity beyond the expected response against the NS0.1C line, suggesting that Ly49d has a similarly narrow MHC ligand specificity. However Ly49s are a multigene receptor family, whose expression on NK cells is coordinated to give a broader recognition of MHC haplotypes. It may simply be that KLRH1 supplements this Ly49-mediated haplotype recognition. However, the fact that the KLRH1 gene is conserved in the mouse, a species that is separated from the rat by ~20 million years (32), argues strongly for an important and distinct functional role for this receptor in NK cells. Additionally, a pseudogene is present in the dog genome (33), and KLRH1 gene fragments are highly conserved in the human genome in the expected region of the NK complex. Thus, KLRH1 is an evolutionarily ancient gene that was present prior to the separation of rodent, ape, and canine lineages ~100 million years ago.

It should also be noted that although we have screened a relatively large number of MHC haplotypes in this study, this is likely to represent only a minor fraction of the naturally occurring MHC alleles in rats. In man, >1000 alleles have been identified at each classical class I MHC locus. It would be unlikely that no KLRH1 ligands exist among the large pool of MHC alleles present in the entire rat population.

Ly49, KIR, NKG2/CD94, and KLRH1 are present in some form in a wide range of mammals, from rodent to ape. In humans, the KIR family has been expanded to mediate recognition of MHC by NK cells, whereas in rodents the Ly49 family has been expanded instead. In lemurs, it has recently been shown that rather than these two families, the NKG2/CD94 family is expanded (34). It remains possible that the KLRH1 family may be expanded in as yet unidentified mammalian species.

Our identification of KLRH1 as a class I MHC-binding receptor expands the number of receptor families that are known to recognize these rapidly evolving molecules. Unlike the central receptor families, which consist of a number of receptors with varying allelic specificities, KLRH1 is a single receptor with an apparently limited specificity for the classical MHC allele RTI-A2. The sheer number of immune receptors that recognize class I MHC underlines the essential nature of these molecules in the immune system. In addition, the variety of these receptors that are expressed on NK cells emphasizes the central role class I MHC plays in particular in the control of this cell type. The reason for so many different receptors is not currently clear, but it points to a complexity and subtlety in class I-mediated NK cell control that we are only beginning to appreciate.

Disclosures
The authors have no financial conflicts of interest.

References

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