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HLA Reduces Killer Cell Ig-like Receptor Expression Level and Frequency in a Humanized Mouse Model

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NK cells use NK cell receptors to be able to recognize and eliminate infected, transformed, and allogeneic cells. Human NK cells are prevented from killing autologous healthy cells by virtue of inhibitory NKR, primarily killer cell Ig-like receptors (KIR) that bind “self” HLA class I molecules. Individual NK cells stably express a selected set of KIR, but it is currently disputed whether the fraction of NK cells expressing a particular inhibitory KIR is influenced by the presence of the corresponded HLA ligand. The extreme polymorphism of the KIR and HLA loci, with wide-ranging affinities for individual KIR and HLA allele combinations, has made this issue particularly hard to tackle. In this study, we used a transgenic mouse model to investigate the effect of HLA on KIR repertoire and function in the absence of genetic variation inside and outside the KIR locus. These H-2Kb−/− and H-2Db−/− mice lacked ligands for inhibitory Ly49 receptors and were transgenic for HLA-Cw3 and a K B haplotype. In this reductionist system, the presence of HLA-Cw3 reduced the frequency of KIR2DL2 cells, as well as the surface expression levels of KIR2DL2. In addition, in the presence of HLA-Cw3, the frequency of NKG2A+ cells and the surface expression levels of NKG2A were reduced. In line with these findings, both transgene-encoded KIR and endogenous NKG2A contributed to the rejection of cells lacking HLA-Cw3. These findings support the idea that HLA influences the human KIR repertoire. The Journal of Immunology, 2013, 190: 000–000.

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Abbreviations used in this article: KIR, killer-cell Ig-like receptor; MFI, mean fluorescence intensity.

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conclusion from these studies is that much larger studies would be necessary to examine the effect of cognate HLA on the inhibitory KIR repertoire (11). Furthermore, such studies should be based on allele-level KIR genotyping because KIR polymorphism affects the level and frequency of KIR expression (9, 10).

To circumvent these issues, we used a KIR and HLA-Cw3 transgenic mouse model on a H-2Kb– and H-2Db–deficient C57BL/6 background. This mouse is transgenic for an almost intact and fully sequenced KIR B haplotype (12, 13), which includes the HLA-Cw3–specific KIR2DL2. Similar to KIR genes in humans, these genes are expressed stochastically in this mouse, so that individual KIR genes are expressed only on a subset of NK cells. The absence of H-2Kb and H-2Db eliminated any impact of the endogenous inhibitory interactions between Ly49 and MHC class I. We show that in these mice, a functional interaction between HLA-Cw3 and KIR2DL2 reduces the expression intensity and frequency of KIR2DL2.

Materials and Methods

Mice

Mice transgenic for a KIR B haplotype and on a mixed (C57BL/6 and CBA) genetic background (13) were back-crossed 8 times onto C57BL/6 (Jackson) mice (14). This KIR B haplotype has been sequenced in full and contains the following intact genes: KIR3DL3*003, KIR2DS2*001, KIR2DL2*003, KIR2DL4*005, KIR3DS1*013, KIR2DL5A*001, KIR2DS5*002, and KIR2DS1*002 (15). The presence and integrity of the KIR locus was checked after every backcross by KIR genotyping. C57BL/6 (B6) mice transgenic for genomic HLA-Cw*0304 construct (15) were a kind gift from Eric Vivier (Centre d’Immuno- logie de Marseille-Luminy, Marseille, France). To obtain KIR or HLA transgenic mice on a H-2Kb– and H-2Db–deficient background, KIR–/–, HLA-Cw3+/+, and control B6 mice were crossed with H-2Kb+/– × H-2Db+/– β2m–/– mice, also on a B6 background (16). Mice with the desired phenotype (KbDb β2mKIR+, KbDb β2m+HLA-Cw3+, or KbDb β2m+HLA-Cw3+) were selected from the F2 and used for further breeding to obtain KIR+/– × D2m–/– × KIR+ × D2m–/– × HLA-Cw33+/–, and KIR+/– × D2m–/– × HLA-Cw33+/– mice. To avoid integration artifacts, mice heterozygous for the KIR and HLA transgenes were used for experiments: KIR+/–, HLA-Cw3+/–, and KIR–/–, HLA-Cw3+/– mice, all on a KIR+/–, HLA-Cw3+/– background. The experiments were approved by the Leiden University Medical Center (Leiden, The Netherlands) animal experimental committee, and performed according to local guidelines.

NK cell expression of KIR and Ly49

Mononuclear cells were isolated from spleen using a Ficoll-Hypaque gradient and incubated with fluorescently labeled Abs. Samples were acquired on an LSR II (BD Biosciences) and analyzed using BD FACSDiva software. For each NKR, the results from HLA-Cw3 and one lacking HLA-Cw3, were acquired on a Becton Dickinson LSRII and analyzed using BD FACSDiva software. NK1.1+ cells, using an in-house Alexa Fluor 647–conjugated Ab (clone 181703; R&D Systems). A PE-conjugated Ab to KIR2DL2, KIR2DS2, and Ab 1F12 to selectively stain KIR2DL2 (19). Stained GAVDPLLAL tetramers (National Institutes of Health Tetramer Core Facility, Emory University, Atlanta, GA) were used to selectively stain KIR2DL2, and Ab 1F12 to selectively stain KIR2DS2 (19). Stained samples were acquired on a Becton Dickinson LSR II and analyzed using BD FACSDiva software. For each NKR, the results from HLA-Cw3+/+ and HLA-Cw3–/– mice were compared using a two-sided Student t test, without correcting for multiple comparisons.

NK responsiveness to crosslinking of Nkp1c (NK1.1)

Splenic NK cells were stimulated with plate-bound PK136 Ab (specific for NK1.1/Nkp1c/Kib1c) for 5 h, with addition of brefeldin A after 1 h, and analyzed for intracellular accumulation of IFN-γ (using Ab clone XMG1.2; BD), as described (20, 21). To test whether NK cell subsets expressed different levels of IFN-γ after stimulation, the results were analyzed using the Friedman test, and if the resulting p value was < 0.05, post hoc analysis using the Dunn multiple comparison test determined whether IFN-γ production differed significantly between NK cell stains with specific NKR Abs (e.g., KIR2DL2/S2’ NGK2A+ or KIR2DL2/S2’ NGK2A–) and NK cells that did not stain with these Abs (e.g., KIR2DL2/S2’ NGK2A–).

In vivo rejection of target cells

In vivo rejection of CFSE-labeled spleen cells was performed as described (22). Briefly, two different populations of spleen cells, one internal syn- genic control expressing HLA-Cw3 and one lacking HLA-Cw3, were labeled with 0.5 μM and 5 μM CFSE (Invitrogen), respectively, and mixed in a 1:1 ratio. On days 1, 3, and 6 (or days 2, 4, and 6) after i.v. injection (day 0) of this mixture (107 of each type), peripheral blood of recipient mice was collected and analyzed by FACS. The relative rejection of HLA-Cw3+ target cells was calculated as follows: (1 – (acquired number of CFSE+) cells in sample/acquired number of CFSE+ cells in sample) × 100%. In some experiments, NK cells or NGK2A– cells were depleted by i.p. injection of 200 μg protein A–purified Ab PK136 or 16a11, respectively, in 200 μl PBS on day −4 and day −1. As both Abs are mouse IgGs, plain PBS was used instead of an isotype-matched control Ab. To compare the resulting survival curves, the areas under the curve (AUC) were calculated for each individual mouse, and they were compared between groups of mice, using the two-tailed Mann–Whitney U test. However, when testing the effect of Ab-mediated depletion, one-tailed p values were calculated, because depletion of NK cells or NK cell subset should reduce rejection rates.

Results

HLA-Cw3 tetramers stain KIR2DL2

To assess the influence of HLA on KIR expression in a system with minimal genetic variation and minimal influence of endogenous mouse NK systems, we compared KIR expression between MHC class I–deficient (H-2Kb–/– × H-2Db–/–) mice expressing a human KIR locus in the presence or absence of HLA-Cw3. To detect the corresponding inhibitory receptor KIR2DL2, we used HLA-Cw3 tetramers. These should bind KIR2DL2, but not the very similar activating receptor KIR2DS2, because only KIR2DL2 shows measurable binding to HLA-Cw3 (Fig. 1A). Furthermore, the tetramer bound a subset of GL183+, but not GL183– cells, consistent with the idea that GL183 + cells include the latter population (GL183 +tetramer+ cells, but not GL183 –tetramer+ cells). The specific activity of the latter Ab was designated as NK2A. The NK2A–specific 16a11 Ab conjugated in- house to Alexa Fluor 647 was also used (18). KIR2DL4 was also detected using an in-house Alexa Fluor 647–conjugated Ab (clone 181703; R&D Systems). A PE-conjugated Ab to KIR2DL2/KIR2DL3/KIR2DS2 (clone GL183, Coulter Immunotech) was used to detect KIR2DL2/KIR2DS2, because the mouse does not carry the KIR2DL3 gene. APC-labeled HLA-Cw3/ GAVDPLLAL tetramers were used to selectively stain KIR2DL2, and Ab 1F12 to selectively stain KIR2DS2 (19). Stained samples were acquired on a Becton Dickinson LSR II and analyzed using BD FACSDiva software. For each NKR, the results from HLA-Cw3+/+ and HLA-Cw3+/– mice were compared using a two-sided Student t test, without correcting for multiple comparisons.

NK responsiveness to crosslinking of Nkp1c (NK1.1)

The percentage of NK cells expressing KIR2DL2 and/or KIR2DS2 varied greatly between mice (Fig. 1B). We compared KIR2DL2 expression in the presence or absence of its ligand HLA-Cw3. Consistent with reports in humans, the presence of the HLA-Cw3 transgene reduced the KIR2DL2 mean fluorescence intensity (MFI) nearly 2-fold (Fig. 1B), while leaving KIR2DS2 staining unaffected. On average, the frequency of KIR2DL2+ cells within NK cells was also ∼ 2-fold reduced (Fig. 1B), and again no
and Kb reagents were normalized for the average MFI values obtained with the tetramer staining. In each experiment, the MFI values for NK cells staining with these reagents were normalized for the average MFI values obtained with the tetramer staining.

As previously reported for these same KIR transgenic mice on a C57BL/6 background (14), GL183 (KIR2DL2/KIR2DS2) tetramer staining was not significantly different between HLA-Cw3− and HLA-Cw3+ mice (Figs. 1B, 2A). This lack of difference resulted because the majority of GL183+ NK cells expressed KIR2DS2, whereas only a minority expressed KIR2DL2 (Fig. 1B). Thus, HLA-Cw3 reduced the frequency as well as the intensity of NK cell KIR2DL2 expression, but not of other, non–HLA-Cw3–binding KIR present in the transgene.

The introduction of HLA-Cw3 did not alter the expression frequencies of mouse Ly49 receptors (Fig. 2A), but was associated with a slight, but significant, reduction in the expression frequency and intensity of NKG2A (Fig. 2A), an inhibitory mouse receptor for the MHC class Ib molecule Qa-1. With another NKG2A–specific Ab (18) in an additional set of mice, this effect of HLA-Cw3 on NKG2A expression frequency and intensity was confirmed (Supplemental Fig. 2). Even though these mice do not express a ligand for it, Ly49G2 surface expression intensity, but not frequency, was elevated in the presence of HLA-Cw3. In general, individual KIR and Ly49 genes are expressed largely independently of other KIR and Ly49 genes. Yet, in our mice KIR2DL4 was preferentially coexpressed on the same cell with KIR2DL2/KIR2DS2, and the opposite was true for NKG2A and KIR2DL2/KIR2DS2 (Fig. 2B). These coexpression biases were unaffected by the presence of HLA-Cw3. In summary, HLA-Cw3 significantly reduced the expression frequency and intensity of the endogenous CD94/NKG2A receptor.

**HLA-Cw3 increases responsiveness of NKG2A+ NK cells**

NK cells expressing inhibitory receptors that bind endogenous MHC class I are more responsive to activating stimuli than are NK cells that do not express such “useful” inhibitory receptors (7, 20, 21). Hence, the presence of HLA-Cw3 might also influence the potency of NK cells expressing an HLA-Cw3–specific inhibitory receptor. In mice lacking both mouse and human MHC class Ia molecules (Kb, Db, and HLA-Cw3), NK cells were poorly responsive to NK1.1 crosslinking, irrespective of the receptors they expressed (Fig. 3). In the presence of HLA-Cw3, KIR2DL2/KIR2DS2+ NK cells produced slightly more IFN-γ than did KIR2DL2/KIR2DS2− NK cells, but this increase was not statistically significant. In contrast, the responsiveness of NKG2A+ NK cells was greatly increased in the presence of HLA-Cw3, suggesting that NKG2A+ NK cells are also educated by HLA-Cw3 in this model system.

**KIR- and NKG2A-dependent rejection of “missing self” HLA-Cw3 in vivo**

To test whether KIR and HLA mediated “missing self”–recognition in these mice, we analyzed the rejection of Kb−/−/Db−/− spleen cells by KIR and HLA transgenic Kb−/−/Db−/− mice (Fig. 4). “Missing self”–rejection was tested by an in vivo assay based on differential labeling of donor cells using CFSE dye (22). Mixed CFSE<sup>high</sup> Kb−/−/Db−/− and control CFSE<sup>low</sup> Kb−/−/Db−/−/HLA-Cw3+− spleen cells were injected i.v. into Kb−/−/Db−/−KIR+−/−/HLA-Cw3−− or control Kb−/−/Db−/−KIR+−/−/HLA-Cw3+− mice. Both types of recipient mice swiftly rejected ∼80% of HLA-Cw3−−negative Kb−/−/Db−/−/KIR+−/−/HLA-Cw3+−− target cells (Fig. 4A). The presence of the KIR transgene did not significantly increase the rejection rate, showing that KIR were not necessary for rejection.

Because the presence of HLA-Cw3 affected NK cell NKG2A expression levels, as well as the frequency and functionality of NKG2A+ NK cells, we next tested whether these cells contributed to rejection (Fig. 4B). In Kb−/−/Db−/−/HLA-Cw3+−− mice, depletion of NKG2A+ cells before and during the experiment greatly reduced the rejection of Kb−/−/Db−/− cells. To isolate the effect of KIR on rejection, the fate of injected Kb−/−/Db−/− cells...
**Figure 2.** The presence of HLA-Cw3 reduces mouse NKG2A expression frequency and intensity on NK cells from Kb+/− mice. Spleen cells from Kb+/−D−/−/KIR+−/− mice transgenic (HLA-Cw3+/−) or not (HLA-Cw3−/−) for HLA-Cw3 were stained with Abs to CD3, NK1.1, KIR2DL2/2DS2, and KIR2DL4 in combination with Abs directed against mouse Ly49 receptors or NKG2A. (A) Frequency of surface expression of individual mouse (Ly49s, NKG2A) or human (KIR2DL4, KIR2DL2/2DS2, and KIR2DL4 in combination with Abs directed against mouse MHC class I. Ly49C and Ly49H) both bind H-2Kb (absent from the mice), and NKG2A binds Qa-1. Data are from two experiments using a total of four K b/db mice. Horizontal bars represent median and 25th to 75th percentiles, and whiskers (top and bottom panel) with endogenous mouse NKRs was quantified in transgenic mice, the presence of HLA-Cw3 reduced the proportion KIR+−/− and Kb+/−/KIR−−/− HLA-Cw3+−/− mice. The MFI values for NK cells positive for individual receptors were normalized for the MFI values obtained using Kb+/−/D−/−/KIR+− HLA-Cw3−/− mice, as in Fig. 1B. (B) Coexpression of transgenic KIR2DL2/KIR2DS2 (top panel) or KIR2DL4 (bottom panel) with endogenous mouse NKRs was quantified in terms of deviation from the “product rule” (4). O represents the observed frequency of cells coexpressing KIR2DL2/KIR2DS2 or KIR2DL4 and a particular mouse NKR among NK cells, and E represents the product of the individual expression frequencies of these human and mouse receptors on NK cells, that is, the expected frequency of cells expressing these receptors. Coexpression values for KIR2DL2/KIR2DS2 and KIR2DL4 were also calculated. Data are from eight Kb+/−/D−/−/KIR+−/−/HLA-Cw3+/−/− mice and eight Kb+/−/D−/−/KIR+−/−/HLA-Cw3+/−/− mice. Horizontal bars represent median values, boxes extend from the 25th to the 75th percentile, and whiskers represent the total range of measurements. *p < 0.05, **p < 0.005.

was compared between NKG2A-depleted Kb+/−/D−/−/HLA-Cw3+/−/− mice having or lacking the KIR transgene (Fig. 4C). When NKG2A+ cells were depleted, rejection of Kb+/−/D−/− cells was dependent on the presence of the KIR transgene (Fig. 4C). Additional depletion of NK cells in these KIR transgenic mice reduced rejection to the level of control KIR-less mice, supporting the idea that all KIR-dependent rejection in NKG2A-depleted mice was mediated by NK cells. In conclusion, the mouse CD94/NKG2A receptor dominated the “missing HLA” response in KIR and HLA transgenic mice, and only upon depletion of NKG2A+ NK cells did KIR-mediated rejection become apparent.

**Discussion**

We used humanized inbred mice to investigate the effect of HLA on KIR repertoire and function in a controlled reductionist system. In these MHC class Ia-deficient (Kb/db) and KIR transgenic mice, the presence of HLA-Cw3 reduced the proportion of KIR2DL2+ cells as well as the surface expression levels of KIR2DL2. In addition, HLA-Cw3 reduced the expression frequency and intensity of NKG2A. In line with these observations, both KIR and NKG2A contributed to the rejection of “missing self” target cells lacking HLA-Cw3.

Studies on human NK cell repertoires in most cases showed no HLA effect on KIR expression frequencies (5, 6, 9, 11), except in very specific circumstances. For example, in individuals homozygous for specific inhibitory KIR binding their ligand with high affinity (KIR2DL1 or KIR3DL1*001/KIR3DL1*015/KIR3DL1*020), the presence of ligand was associated with increased frequencies of NK cells expressing these receptors, but only in the absence of too many additional inhibitory KIR–ligand interactions (8, 9). A similar, albeit less pronounced, effect was observed for KIR2DL3 and C1 (8). These effects were detected in individuals homozygous for KIR A haplotypes, characterized by the absence of KIR2DL2, KIR2DL5, and most activating receptors (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DS1). In whites, such A-homozygous individuals make up less than half of the population.

KIR repertoires in individuals carrying KIR B haplotypes have been more difficult to study, mainly because Abs specific for inhibitory KIR cross react with activating KIR present in B, but not A, haplotypes. Group 1 HLA-C (HLA-Cα1-α3) effects on KIR2DL2

**Figure 3.** The presence of HLA-Cw3 increases the responsiveness of NKG2A+ NK cells. Spleen cells from Kb+/−/D−/−/KIR+−/−/HLA-Cw3+/−/− (HLA-Cw3−/−) and Kb+/−/D−/−/KIR+−/−/HLA-Cw3+−− mice were stimulated with plate-bound anti-NK1.1 for 5 h, and accumulation of intracellular IFN-γ in NK cells (CD3 DX5) was subsequently analyzed by flow cytometry. NK cells were subdivided according to their expression of KIR2DL2/KIR2DS2, of which the inhibitory KIR2DL2 binds HLA-Cw3, and their expression of inhibitory mouse receptors binding mouse MHC class I. Ly49C and Ly49H both bind H-2Kb (absent from the mice), and NKG2A binds Qa-1. Data are from two experiments using a total of four K b/db mice. Of the inhibitory KIR2DL2/KIR2DS2 and five Kb+/−/D−/−/KIR+−/−/HLA-Cw3+−− mice. Lines connect data from individual mice. For each receptor combination, the results were compared between cells expressing a particular receptor (e.g., KIR2DL2/2DS2/NKG2A) and those lacking that receptor (e.g., KIR2DL2/2DS2/NKG2A−). **p < 0.01.
There are relatives of CFS high (Cw3 and in (16a11(NKG2A)-depleted (CLys-80; ref 25). These problems were circumvented in our hu-
manized mice, because we were able to use HLA-Cw3 (group 1
HLA-C) tetramers to detect specifically KIR2DL2, and because we compared mice lacking or having an HLA-C group 1 allele. In these mice, the presence of HLA-Cw3 decreased the frequency of KIR2DL2+ NK cells. Thus, in this model system with a genetically homogeneous background, the presence of an HLA ligand clearly did influence the expression frequency of the corres-
ponding inhibitory KIR.

KIR expression frequencies varied greatly between mice, and the degree of variation was similar to that of the endogenous Ly49 and CD94/NKG2A receptors. It is unlikely that this was due to genetic variation between mice, as they had been backcrossed extensively to a C57BL/6 background. Furthermore, interindivid-ual variation in Ly49 and CD94/NKG2A expression frequen-
cies was also observed in the nontransgenic inbred C57BL/6 strain (26). The probability of Ly49 expression is regulated by overlapping and bidirectional promoter elements and differs between Ly49 genes, depending on the relative efficiencies of the forward and reverse promoters (27). Bidirectional promoters have also been found for KIR genes, suggesting that such probabilistic transcriptional switches also control stochastic expression of the KIR genes (28). Taken together, these findings indicate that, as with mice carrying a genomic Ly49A transgene (29), regulatory elements necessary for stochastic KIR expression were contained within the transgene, which contained an almost intact KIR locus, in-
cluding intronic and intergenic sequences. In all cases, it is unclear what causes the variation in receptor expression frequencies among genetically identical mice.

In addition to the effect of HLA-Cw3 on the proportion (i.e., the percentage) of NK cells expressing KIR2DL2 and CD94/NKG2A, the presence of HLA-Cw3 also reduced the expression levels (i.e., the MFI) of these receptors. This effect of ligand on receptor MFI was previously reported both in humans (9) and in mice (30). It most likely results from ligand-induced receptor downmodulation, and may help to correct for differences in receptor-ligand affinity (30). For example, strong rejection induced by high-affinity interactions would be dampened by lowering the expression level of the NKK involved.

In the Kb-/-Db-/- mice transgenic for KIR and HLA-Cw3, NKG2A+ cells contributed to the rejection of “missing HLA-
Cw3.” In line with this finding, the introduction of HLA-Cw3 in KIR transgenic Kb-/-Db-/- mice affected the expression of NKG2A, as well as the responsiveness of NKG2A+ NK cells. Importantly, Kb-/-Db-/- mice transgenic for HLA-Cw3 only already rejected Kb-/-Db-/- target cells, and this rejection was inhibited by Ab-mediated depletion of NKG2A+ cells. NKG2A is an inhibitory receptor binding Qa-1, whose surface expression in C57BL/6 mice largely depends on its loading with the H-2Db leader peptide AMAPRTLLL. The very similar HLA-Cw3 leader peptide VMAPRTLIL also binds Qa-1 and thereby induces a functional ligand for CD94/NKG2A in Kb-/-Db-/- mice (31, 32). Thus, the recognition by CD94/NKG2A of HLA-Cw3 leader peptides bound to Qa-1 likely contributes to the education, selec-
tion, and function of the NK cell repertoire in HLA-Cw3 transgenic Kb-/-Db-/- mice, irrespective of the presence of KIR. Therefore, NKG2A may also have contributed to the rejection of “missing HLA-Cw3” targets in the KIR2DL3 and HLA-
Cw3 transgenic Kb-/-Db-/- mice described by Sola and col-
leagues (33).

Upon the deletion of NKG2A+ cells, KIR-dependent rejection of “missing” HLA-Cw3 by KIR and HLA-Cw3 transgenic Kb-/-Db-/- mice was considerably greater than what we observed previously in KIR and HLA-Cw3 transgenic mice on a wild-type C57BL/6 background (14). This finding is reminiscent of the experiments of Johansson et al. (30), who found that the education
of NK cells by weak Ly49 ligands was attenuated by the presence of strong Ly49 ligands. Hence, in transgenic mice on a wild-type C57BL/6 background, the presence of the strong interaction between Ly49C and H-2Kd may have obscured the detection of “missing” HLA-Cw3. In agreement with the differences in KIR-mediated rejection, the presence of KIR2DL2/KIR2DS2 on NK cells did not detectably increase their responsiveness in mice on a wild-type C57BL/6 background (14), but on a K^B^/K^D^/K^D^/K^D^ background a small but nonsignificant increase in responsiveness was detected. Because only a third of KIR2DL2/KIR2DS2^+ NK cells expressed KIR2DL2, this weak response may have been due to dilution rather than poor responsiveness of KIR2DL2^+ NK cells. As in our hands HLA-Cw3 tetramer stains did not work in cells expressing KIR2DL2, this weak response may have been due to dilution rather than poor responsiveness of KIR2DL2^+ NK cells. As in our hands HLA-Cw3 tetramer stains did not work in combination with intracellular IFN-γ staining, we were unable to discriminate between these possibilities.

Our data show that in a setting with little or no variation in genetic background, a functional interaction between the products of a single inhibitory KIR allele and a single HLA allele reduced both the surface expression levels of that KIR and the fraction of NK cells expressing it. This finding supports the idea that HLA influences the human KIR repertoire.

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Disclosures

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