Supporting Information

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SI Materials and Methods

Antibodies Used in This Study. We used the following antibodies (with supplier and clone information):

From BD Biosciences: NKp30 (p30-15), NKp44 (p44-8.1), NKp46 (9E2/NKp46), NKG2D (1D11), 2B4 (2B4), DNAM-1 (DX11), CD16 (3G8), CD107a (H4A3), CD107b (H4B4), HLA-DR (TU36), CD86 (GL1), CD40 (5C3), CD69 (FN50), CD62L (DREG-56), TNFSF9 (C65-485), CD54 (HA58), and TNF (MAbD11)

From Miltenyi Biotec: CD56 (REA196) and CD3 (BW264/56)

From Beckman Coulter: CD160 (BY55), KIR2DL1 (EB6), KIR2DL2/3 (GL183), and NKG2A (Z199)

From Biolegend: KIR3DL1 (DX9)

From R&D Systems: TNFSF14 (115520) and KIR2DL3 (180701). For neutralization studies, we used goat polyclonal antibodies against TNFSF14 and TNF from this manufacturer.

From AbD Serotec: CD11c (BU15)

Cell Isolation and Culture. Peripheral blood mononuclear cells (PBMCs) were isolated from healthy donor blood samples using Lymphoprep (Stemcell Technologies). Monocytes were isolated from PBMCs using anti-CD14 microbeads (Miltenyi Biotech) and iDCs prepared by culturing monocytes for 5 d with 800 U/mL GM-CSF and 400 U/mL IL-4 (R&D Systems) in RPMI media with 10% (vol/vol) FCS. NK cells were prepared from PBMCs using a negative isolation kit (Miltenyi Biotec). For experiments using NK and iDC coculture, monocytes and iDCs were prepared and a second blood sample was then used to prepare the NK cells on day 5 of the iDC culture. NK cells were cultured in DMEM media with 10% (vol/vol) FCS and 5% (vol/vol) human antibody serum. The tumor target cell lines (human erythroleukemic K562 cells and the mouse mast cell line P815) were cultured in RPMI with 10% (vol/vol) FCS. Cytokine stimulations used 50 U/mL IFN-I, 20 ng/mL IL-12 and 20 ng/mL IL-18, 300 U/mL IL-2, 30 ng/mL IL-15, or 50 ng/mL PMA plus 500 ng/mL ionomycin (PMA/I; Miltenyi Biotec). Human umbilical vein endothelial cells (HUVECs) from single donors were purchased from Promocell and cultured in endothelial cell basal medium (ECBM) with the manufacturer-supplied supplements (also from Promocell).

Gene Expression Profiling and Validation. Target K562 cells were coincubated with freshly isolated NK cells at a 1:1 ratio in round-bottomed FACS tubes in batches of 3 million cells per tube. Cells were centrifuged at 20 × *g* for 2 min and incubated at 37 °C for 4 h in the presence of 1:1,000 GolgiStop inhibitor (BD Biosciences) and CD107 antibodies. Cells were subsequently stained for NK-cell markers and sorted on a MoFlo cell sorter (Beckman Coulter). $CD56^{dim}$ NK cells were sorted on the basis of cell surface CD107 expression into $CD107^{+}$ (R-NK) and $CD107^{neg}$ (NR-NK) fractions and collected in cold RPMI media with cell purity exceeding 97%. Cells were centrifuged and resuspended in TRIzol reagent (Life Technologies) and snap-frozen. Samples were thawed and further processed as a pooled sample (combining three individual donors from six experiments) and a single-donor sample (from three experiments), with each sample containing approximately 1 million cells. Sample amplification was performed using the Illumina TotalPrep RNA amplification kit (from Life Technologies), according to the manufacturer's instructions. For hybridization, 750 ng of biotin-labeled cRNA was randomly loaded onto an Illumina Sentrix BeadChip Array (HumanRef-8_V3 Beadchips) for expression analysis. After 16 h of hybridization, the Beadchips were washed, Cy3-labeled, and scanned on an Illumina BeadArray reader, and the data were uploaded onto GenomeStudio (Illumina) for background subtraction and conversion into a Partek file for data analysis on Partek Genomics Suite. The data were subjected to $\log_2$ transformation, quantile normalization, and batch effect removal. Principal component analysis was performed to check the clustering of the samples. An ANOVA model was used for determining the differentially expressed mRNAs (R-NK vs. NR-NK) within the single-donor and pooled samples. A 1.5-fold change cutoff (representing size of the change) and a *P* value with a false discovery rate (Benjamini and Hochberg) cutoff of <0.05 (representing the significance of the change) were used to obtain the differentially expressed genes. The array data have been deposited in the Gene Expression Omnibus (ncbi.nlm.nih.gov/geo), under the accession number GSE55977.

For validation, NK cells were sorted on a Beckman Coulter MoFlo cell sorter on the basis of CD107 expression after K562 stimulation, as detailed above. RNA extraction was performed with an on-column DNase I digestion step (Sigma–Aldrich). First-strand DNA synthesis was carried out using SuperScript II (Life Technologies), and expression was analyzed using predesigned Taqman Expression Assays (Life Technologies). Samples were normalized to 18S RNA gene expression and compared using the ΔΔCT method.

Analytical Degranulation Assays Against K562 and P815 Cells. NK cells were incubated with target cells at a 1:1 ratio for 6 h in the presence of anti-CD107a antibody and GolgiStop. NK cells were then stained for CD56, CD3, and TNFSF14 and analyzed on an LSRII flow cytometer (BD Biosciences). P815 cells were used as target cells in reverse antibody-dependent cellular cytotoxicity experiments by loading with combinations of receptor-activating antibodies (or IgG control) at 7 μg/mL for 20 min at room temperature and then washed once before combining with NK cells.

KIR Ligand Typing. DNA was isolated from PBMCs and purified using column-based isolation (Sigma–Aldrich). KIR ligand typing was performed using an Olerup SSP KIR HLA typing PCR kit following the manufacturer's instructions. For some donors, the KIR haplotype was established using an Olerup SSP KIR typing kit.

ELISA. Supernatants were collected from NK cells cultured at 2.5 million cells per milliliter and stimulated with either 300 U/mL IL-2, 30 ng/mL IL-15, or 50 ng per 500 ng/mL PMA/I (or in media alone) for 24 h. Supernatants were diluted and assayed using either a TNFSF14 ELISA (R&D Systems) or TNF sandwich ELISA (Peprotech).

For the analysis of TNFSF14 and TNF production by IL-2– and IL-15–treated licensed and unlicensed populations, NK cells were isolated from donors typed for the expression of KIR ligands (Fig. S3). The licensed and unlicensed NK cells were cell-sorted (using FACS) as $CD56^{dim}CD3^{neg}$ cells that were either self-KIR^{+}, $NKG2A^{+/-}$ (licensed cells), or self-$KIR^{neg}NKG2A^{neg}$ (unlicensed cells). These sorted populations were cultured at a density of 1 million cells per milliliter in media alone or in media supplemented with 300 U of IL-2 or 30 ng/mL IL-15 for 24 h. These populations were analyzed by flow cytometry and ELISA.

NK and DC Coculture. Sorted NK cells were cocultured with iDCs at a 1:1 ratio for 48 h with either media alone, 12 μg/mL neutralizing anti-TNFSF14 antibody (goat polyclonal; R&D Systems), anti-TNF (goat polyclonal; R&D Systems), or normal goat IgG. Cytokine-activated NK cells (300 U/mL IL-2 or 30 ng/mL IL-15) were cocultured at an NK/DC ratio of 1:3 for 15 h. DC maturation was identified by expression of CD86 gating on $CD11c^+$ DCs.

HUVEC Stimulation. HUVECs were cultured according to the supplier's instructions (Promocell). HUVECs were used until passage 6, and cultured in endothelial cell basal medium (ECBM) (ECBM with the manufacturer's supplements). For stimulation, cells were washed, trypsinized (endothelial cell detachment kit; Promocell), and plated into six-well plates at a density of 2×10^5 cells per well. Cells were then incubated for 24 h at 37 °C. Before stimulation, cells were transferred to low-serum media [ECBM with 2% (vol/vol) FCS and no further growth factors] for 2 h. NK cell-conditioned medium was then added to the ECBM/2% (vol/vol) FCS at a 1:1 ratio. Cells were cultured for a further 12 h before being analyzed for cell surface ICAM-1 (CD54) expression by flow cytometry.

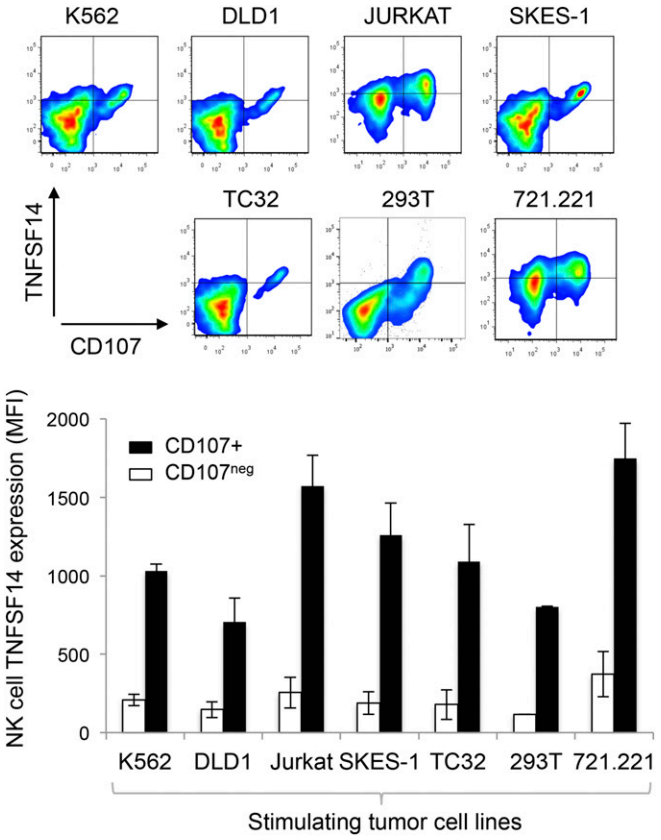

Fig. S1. Multiple human tumor cell lines induce the expression of TNFSF14 on responding ($CD107^+$) NK cells. The target cell lines used are derived from hematopoietic tumors (K562, erythroleukemic cells from chronic myeloid leukemia; Jurkat, T-cell leukemia; 721.221, EBV-transformed B lymphoblastoid cells) and from solid tumors (DLD-1, colorectal; TC32 and SKES-1, Ewing's sarcoma). The 293T cells do not originate from a tumor but are embryonic kidney cells transformed in vitro with adenovirus DNA. In addition, they express SV40 T antigen. (*Top*) Primary human NK cells (isolated from healthy donors) were cocultured for 4 h with the indicated tumor cells (at an effector/target ratio of 1:1). Cell surface CD107 display (a marker of degranulation) and TNFSF14 expression were analyzed by flow cytometry, gating on the $CD56^+CD3^{neg}$ NK-cell population. (*Bottom*) Summary of the TNFSF14 expression [using median fluorescence intensity (MFI)] on the responding (R-NK; $CD107^+$) and nonresponding (NR-NK; $CD107^{neg}$) NK-cell populations. These data were collected using NK cells from three healthy donors, showing SD from the mean.

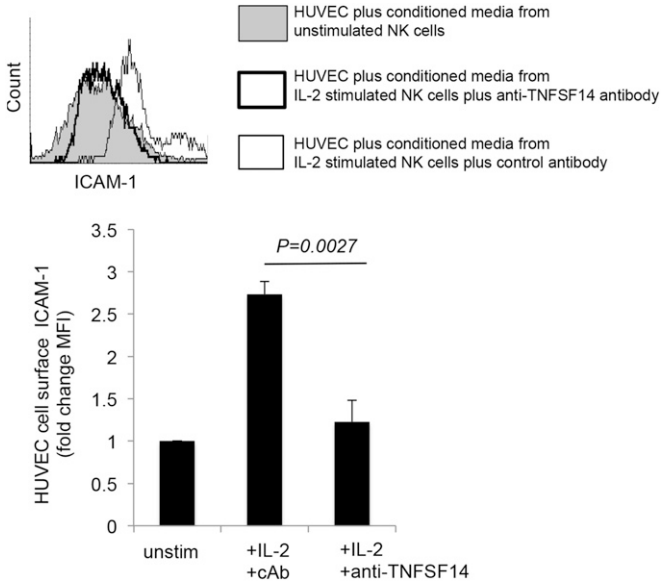

Fig. S2. NK cell-derived TNFSF14 induces ICAM-1 expression on endothelial cells. HUVECs were cultured for 12 h in conditioned media, either from unstimulated NK cells or from NK cells stimulated for 24 h with 100 U/mL IL-2 in the presence of an anti-TNFSF14 antibody or cAb present at 10 μg/mL. (*Top*) HUVEC cell surface ICAM-1 expression was analyzed by flow cytometry. (*Bottom*) Analysis of three independent experiments (from three healthy donors) showing standard error, based on the fold change in ICAM-1 expression (with conditioned media from unstimulated (unstim) NK cells assigned a value of 1). The *P* value was calculated using a paired Student's *t* test.

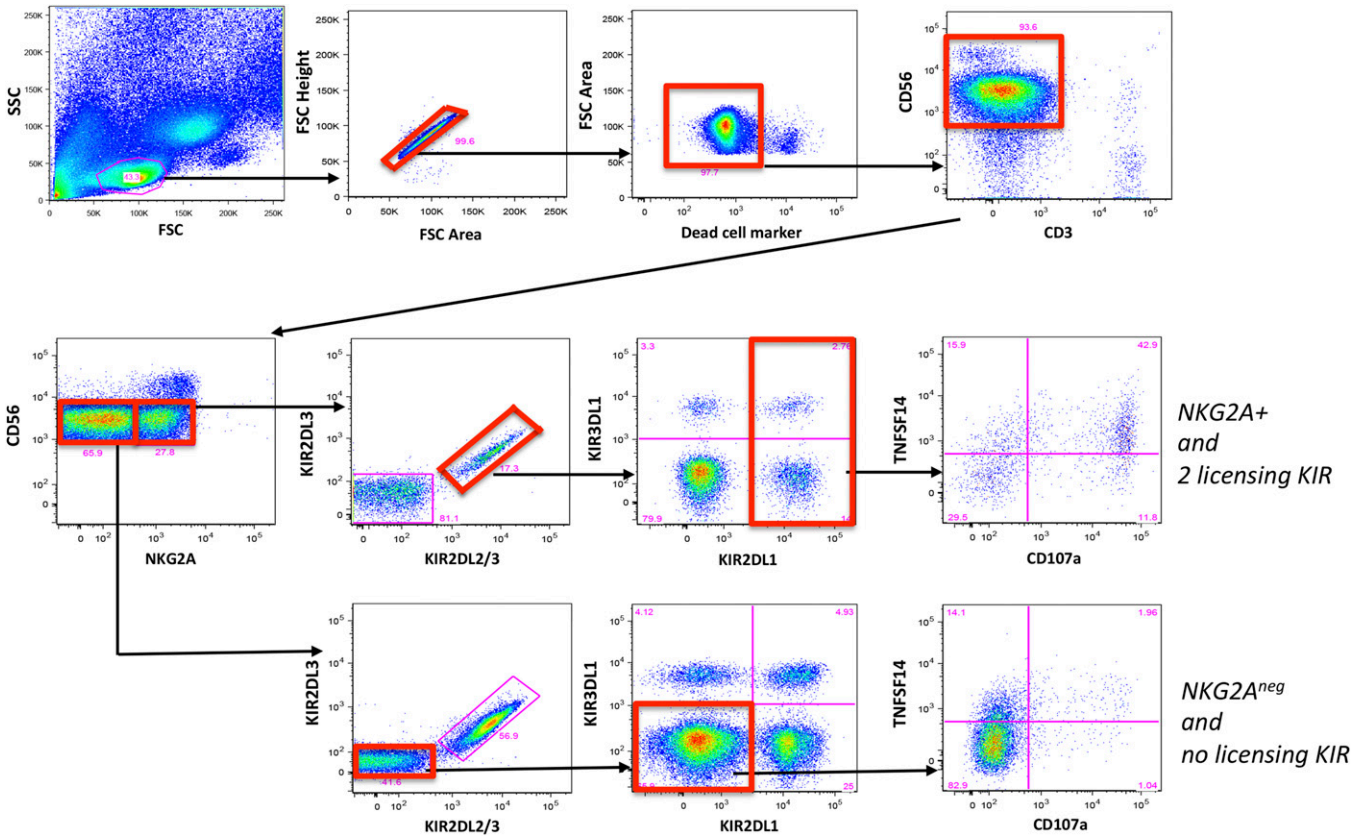

Fig. S3. TNFSF14 expression on NK-cell subsets expressing licensing KIRs and NKG2A. Purified NK cells were cocultured with K562 for 6 h in the presence of anti-CD107a antibody. Cells were subsequently stained for KIRs, NKG2A, and TNFSF14. NK cells were gated as singlet live cells, and then as gated CD56^{dim} NK cells divided by NKG2A expression, and were further categorized by educating KIR expression, based on HLA ligand typing. The MFI of TNFSF14 induction was calculated for zero, one, or two educating KIRs in NKG2A^{neg} vs. NKG2A^{+} populations. For simplicity, TNFSF14 and CD107 expression is shown for NKG2A^{neg} with no educating KIR and for NKG2A^{+} with two educating KIRs, although all combinations were calculated. An average was taken of multiple populations expressing only a single educating KIR. The donor shown has ligands for KIR2DL1 (HLA-C2), KIR2DL2 (HLA-C1/C2), and KIR2DL3 (HLA-C1), but not for KIR3DL1 (HLA-Bw4^{neg}). FSC, forward scatter; SSC, side scatter.

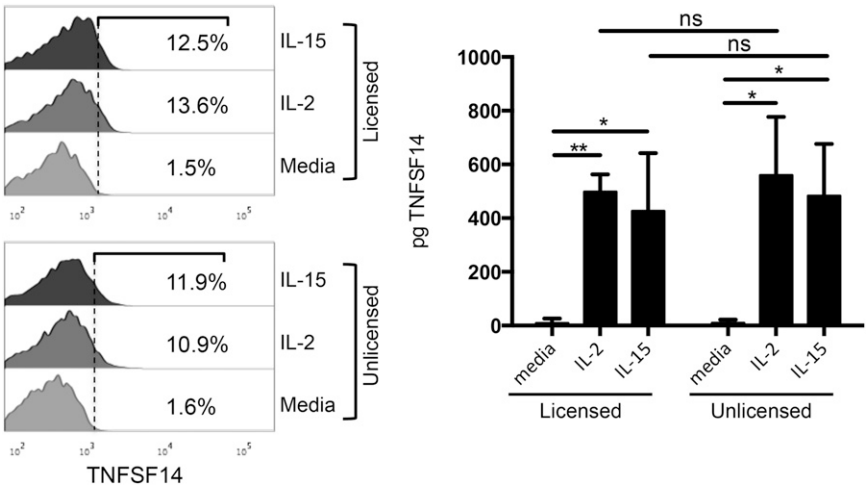

Fig. S4. TNFSF14 production by licensed and unlicensed NK cells stimulated with IL-2 or IL-15. NK cells were isolated from donors typed for the expression of KIR ligands. The licensed and unlicensed NK cells were cell-sorted (using FACS) as $CD56^{dim}CD3^{neg}$ cells that were either self-KIR^{+}, $NKG2A^{+/-}$ (licensed cells), or self-$KIR^{neg}NKG2A^{neg}$ (unlicensed cells). These sorted populations were cultured at a density of 1 million cells per milliliter in media alone or in media supplemented with 300 U IL-2 or 30 ng/mL IL-15 for 24 h. (*Left*) Cell surface expression of TNFSF14 in the different cell populations (determined using flow cytometry in the presence of a dead cell discriminator). The percentage of cells expressing TNFSF14 is indicated. (*Right*) Quantitation of soluble TNFSF14 measured by ELISA. The data show the means values (and SD) from four donors and analysis using a paired *t* test. ns, nonsignificant.

Table S1. Genes up-regulated (>1.5 fold; $P < 0.05$) in R-NK cells compared with NR-NK cells and listed in Fig. 1

Gene	Also known as	Gene identification no.	Function
KIR2DL1		3802	Inhibitory receptor for HLA-C2 group (1)
KIR2DL3		3804	Inhibitory receptor for HLA-C1 group (1)
KIR2DL4		3805	Activating receptor for HLA-G (2)
KIR2DL5A		57292	Inhibitory receptor, unidentified ligand (1)
KIR3DL1		3811	Inhibitory receptor for HLA-Bw4 group (1)
KIR3DL2		3812	Inhibitory receptor for HLA-A3/A11 (1)
KIR3DL3		115653	Inhibitory receptor, unidentified ligand (1)
KIR2DS1		3806	Activating receptor for HLA-C2 group (1)
KIR2DS5		3810	Activating receptor, unidentified ligand (1)
KLRC1	NKG2A	3821	Component of inhibitory receptor for HLA-E (3)
KLRC2	NKG2C	3822	Component of activating receptor for HLA-E (3)
CD226	DNAM-1	10666	Activating receptor for PVR and Nectin-2 (4)
CRTAM	CRTAM	56253	Activating receptor for NECL2 (5)
VSTM3	TIGIT	201633	Inhibitory receptor for PVR and Nectin-2 (6)
SLAMF7	CRACC	57823	EAT2-coupled activating receptor (7)
HAVCR2	TIM3	84868	Regulatory receptor (8, 9)
CD69		969	Activation marker; inhibits B-cell and T-cell egress from LN (10)
CD160		11126	HVEM axis (11)
ICOS		29851	CD28 family costimulatory (12)
PTPRC	CD45	5788	Tyrosine phosphatase. required for NK activity (13)
SELL	L-selectin	6402	Adhesion/homing (e.g., to lymph node) receptor (14)
IL-12RB2		3595	Component of the IL-12 receptor (15)
IL-21R		50615	Component of the IL-21 receptor (16)
IL-4R		3566	Component of the IL-4 receptor (17)
TNFRSF1B	TNFR1	16992	Component of TNF-α receptor (18)
TNFRSF4	OX40	7293	Immune regulator (19)
TNFRSF9	4-1BB/CD137	3604	Modulates NK-cell activity (20–22)
TNFRSF7	CD27	939	NK-cell developmental marker (23)
SPRY1		10252	Counteracts RTK signaling, inhibits T cells (24)
SPRY2		10253	Counteracts RTK signaling, inhibits T cells (25)
MAP3K8	COT/TPL2	1326	Regulates TNF-α expression (26)
MAP2K3	MKK3	5606	Mitogen activated kinase, upstream of p38MAPK (27)
PTPN22		26191	Tyrosine phosphatase, regulates activation (28)
CBLB		868	E3 ligase, regulates activation thresholds (29)
PIK3C2B		5287	Class II PI3K, T-cell activation (30)
PIK3CA	p110α	5290	Class IA PI3K, multiple signaling events (31)
PIK3R1	p85α	5295	Class IA PI3K, immune development (32)
TRAF5		7188	TNFRSF signal transduction (33)
LAX1		54900	Negative regulator of T-cell activation (34)
CDC42		998	GTPase, cytoskeletal reorganization and NK cytotoxity (35)
SH2D1B	EAT2	117157	SLAM family signal transduction in NK cells (36)
SH2B1		25970	Inhibitor of growth factor receptor signal transduction (37)
NFIL3	E4BP4	18030	TF, essential for NK development (38)
NFATC1		18018	TF, calcineurin-dependent inducible gene expression (39)
NFAT5		10725	TF, calcineurin-independent gene expression (40)
REL	c-REL	5966	TF, NF-κB component, inducible gene expression (41)
MYC	c-Myc	4609	TF, amplifier of gene expression (42)
EGR1		1958	TF, early growth response 1, immune modulation (43)
EGR2		1959	TF, early growth response 2, immune modulation (43)
EGR3		1960	TF, early growth response 3, immune modulation (43)
PRDM1	BLIMP1	639	TF, NK-cell maturation (44)
XBP1		7494	TF, ER stress response, T-cell differentiation (45)
CSF2	GM-CSF	1437	Cytokine, regulates myeloid cells (46, 47)
IL-3		3562	Cytokine, regulates hematopoiesis (47)
IFNG	IFN-γ	3458	Cytokine, Th1 polarization (48)
IL-8	CXCL8	3576	Chemokine, inflammation/cellular recruitment (49)
CCL3	MIP-1α	6348	Chemokine, inflammation/cellular recruitment (49, 50)
XCL1	Lymphotactin	6375	Chemokine, inflammation/cellular recruitment (50)
TNFSF2	TNF-α	7124	Proinflammatory cytokine (18, 49)
TNFSF6	FasL	356	DcR3 counterstructure in HVEM axis (11)
TNFSF14	LIGHT	8740	Proinflammatory HVEM ligand, HVEM axis (11)
TNFSF9	4-1BBL/CD137L	8744	CD137 ligand (22)
TNFSF15	TL1A	9966	HVEM ligand, HVEM axis (11)

Table S1. Cont.

Gene	Also known as	Gene identification no.	Function
ADAM17	TACE	6868	TNF-α cleaving enzyme (51)
RAB27A		5873	Granule exocytosis, Griscelli syndrome type II (52)
STX11	FHL4	8676	Granule exocytosis, FHL (53)
GZMB		3002	Proapoptotic granule protein (54)

Gene names and synonyms are shown, along with the gene accession number from the National Center for Biotechnology Information (NCBI; ncbi.nlm.nih.gov/gene). The functions indicated are those relevant to NK cells or the immune system where possible. The list of all significantly altered genes is presented in Dataset S1. All array data have been deposited in the Gene Expression Omnibus (ncbi.nlm.nih.gov/geo), under accession number GSE55977. DcR3, decoy receptor 3; ER, endoplasmic reticulum; FHL, familial hemophagocytic lymphohistiocytosis; LN, lymph node; PVR, poliovirus receptor; RTK, receptor tyrosine kinase; SLAM, signaling lymphocyte activation molecule; TF, transcription factor.

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Other Supporting Information Files

Dataset S1 (XLSX)