Supplementary Table S1: Expression of cannabinoids targets in NK cells

Target	Cell model	Method	SL	Observation	Reference
GPCRs					
CB1	Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	Rank order of CB1 RNA level: B cells > NK cells >> monocytes > polymorphonuclear cells > CD8 cells > CD4+ cells In NK: low level when compared to CB2	21
	Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	CB1 << CB2	23
	Human uterine NK cells isolated after elected pregnancy termination or abortion	RT-PCR	ND	High level, CB1 ≈ CB2	26
	NK cells infiltrating tumor in tissue sections of non-small cells lung cancer (sections from human patients and murine model)	In situ hybridization/ immunofluorescence, microscopy of tumor sections	ND	CB1 mRNA low level	25
CB2	Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	CB2 >> CB1 Rank order of RNA level: B cells > NK cells >> monocytes > polymorphonuclear cells > CD8 cells > CD4+ cells	21
	Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	CB2 >> CB1	23
	Human uterine NK cells isolated after elected pregnancy termination or abortion	RT-PCR	ND	High level, CB1 ≈ CB2	26
	Primary human NK cells isolated from peripheral blood of healthy donors	Flow cytometry Fluorescent microscopy	PM	Highest expression in NK cells in comparison to other leukocytes. High variation from donor to donor.	22
	NK KHYG1 cell line	Northern blot	ND	High CB2 mRNA level	27
	NK cells infiltrating tumor in tissue sections of non-small cells lung cancer (sections from human patients and murine model)	In situ hybridization/ immunofluorescence, microscopy	ND	High CB2 mRNA level Rank order in human: NK >> CD3/CD8 cells and M2 macrophages Rank order in mice: NK ≈ M2 macrophages, CD3 cells > CD8 and myeloid cells	25
	Human cytokine-induced killer cells: CD3-CD56+ (NK) and CD3+CD56+ (NKT)	Flow cytometry	ND	No CB2 expression was determined in freshly isolated NK and NKT cells. After 14 days of incubation with cytokines (IL2, IFNγ), 98% of NKT were CB2-positive.	28
	Human cytokine-induced killer cells: CD3-CD56+ (NK) and CD3+CD56+ (NKT)	Immunocytochemistry and flow cytometry	PM and cytosol	Differential expression depending on cytokines' concentration during in vitro incubation (14 days)	29
GPR18	human NK cells differentiated in vitro from umbilical cord – derived CD34+ cells	Microarray analysis	ND	Upregulation of the receptor in differentiated NK cells	30
GPR55	Primary human NK cells	Flow cytometry, Western blot, confocal microscopy	PM	Stimulation increases NK cytotoxicity against K562 target cells. Stimulation increases granzyme B and IFNγ production	31
D2	Enriched Primary murine NK cells population from splenocytes	Western blot from nucleate lysates and RT-PCR	ND	Low D2 mRNA levels in comparison to other dopamine receptors. Stimulation decreases NK cytotoxicity against YAC-1 target cells	32
5HT1A	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays with the 5-HT1A receptor antagonist	ND	Stimulation increases NK cytotoxicity against target cells Stimulation promote NK proliferation Stimulation favors antigen dependent cell contact	33
	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays with the 5-HT1A receptor antagonist	ND	Antagonism decreases NK cytotoxicity against target cells	34
δ / μ / k opioid receptors	Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	Rank order of opioid receptors expression is μ > k > δ	36
	Murine RNK16 cell line	Fluorescent microscopy in non-permeabilized cells	PM	Stimulation increases perforin, granzyme B and IFNγ production	37
Ion channels					
VGSCs	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays in the presence of the channel agonist	ND	agonists induces depolarization and cytotoxicity inhibition against K562 target cells	73
VGCCs	-Primary murine NK cells - Primary human NK cells isolated from peripheral blood of healthy donors	RNA-Seq	ND	Human NK cells express higher levels of the mRNA of the subunits of VGCCs in comparison to murine NK cells	76
VDAC 1	Primary human NK cells isolated from peripheral blood of healthy donors	Microarray analysis	ND	Expression corelates with NK infiltration to tumors	79, 137
TRPM8	Primary human NK cells isolated from peripheral blood of healthy donors	PCR and SNP analysis	ND	SNPs reduces NK cytotoxic activity against K562 cells	59

TRPV1	-Primary human NK cells isolated from peripheral blood of healthy donors -NKL cell line -Primary murine NK cells	Western blot of total lysate	ND	Stimulation limits NK degranulation against K562 or 221 target cells; Decreases NKL cytotoxicity against target cells; Increases intracellular calcium;	51
	Primary murine NK cells	Functional assays in the presence of channel antagonist	ND	Antagonism promotes NK enrichment	138
TRPV2	Primary murine NK cells Primary human NK cells	RNA-seq	ND	Depending on the source NK cells expression ranges from 10-30-fold times higher to any other tissue	139
GABAA	Primary murine NK cells Primary human NK cells isolated from peripheral blood of healthy donors	RT-PCR	ND	Stimulation decreases NK degranulation against YAC-1 target cells	68
Glycine receptor alpha 2	Primary human NK cells isolated from peripheral blood of healthy donors	Flow cytometry	ND	NK cells express higher levels of GlyR subunits in comparison to monocytes	71
AChRs	Primary human NK cells	PCR and SNP analysis	ND	SNPs reduces NK cytotoxic activity against K562 cells	59
Enzymes					
CYP1B1	Primary human NK cells	RNA-seq	ND	Naïve NK cells express lower levels of the protein in comparison to expanded NK cells in vitro. Increased expression corelates with metabolism perturbations and NK-dysfunction against target cells	80
CYP3A4	Primary human NK from lymphoma	RT-PCR	ND	Expression corelates with chemoresistance	81
CYP3A5	Primary human NK from lymphoma	RT-PCR	ND	Expression corelates with chemoresistance	81
CYP3A7	Primary human NK from lymphoma	RT-PCR	ND	Expression corelates with chemoresistance	81
PLA 2	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays in the presence of PLA inhibitor	ND	Inhibition decreases NK cytotoxicity against K562/RL1 target cells	84, 85
	Primary human adherent NK cells	Functional assays in NK cells with enriched PLA expression	ND	Inhibition decreases NK cytotoxicity against K562 target cells. Overexpression enhances NK cytotoxicity against K562, MOLT-4 & U937 target cells	140
COX 2	Nasal type extra nodal NK cell lymphoma	Immunohistochemistry	C	Expression levels corelates with poor survival	87
FAAH	Primary murine NK cells	Functional assays in the presence of the protein inhibitor	ND	Inhibition decreases NK migration/infiltration	93
ETC Complex I	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays in the presence of the protein inhibitor	ND	Protein regulates NK metabolism and functional responses	96, 141
ETC Complex II	Primary human NK cells isolated from peripheral blood of healthy donors	Functional assays in the presence of the protein inhibitor	ND	Protein regulates NK metabolism and functional responses	142
ETC Complex IV	Primary murine NK cells	Functional assays in the presence of the protein inhibitor	ND	NK impaired metabolism; impaired expansion upon infection	143
Transporters					
P-gp	Primary human NK cells isolated from peripheral blood of healthy donors	Flow cytometry	ND	NK cells expresses higher levels of P-gp protein in comparison to other leukocytes. Inhibition decreases NK cytotoxicity against K562 target cells	99
	YTN cell line	Functional assays in the presence of the protein inhibitor	ND	Inhibition decreases YTN cytotoxicity against target cells	100
	Primary NK cells enriched from human umbilical cord and peripheral NK cells from healthy donors	Indirect immunocytofluorescence	PM	Higher expression of P-gp was observed in umbilical cord cells in comparison to peripheral NK cells	101
	Primary NK leukemia (Aggressive Natural Killer Leukemia; ANKL)	Flow cytometry	ND	High P-gp levels was observed in oncological phenotype of NK cells	102
ABCG2	Nasal type extra nodal NK cell lymphoma	RT-PCR Western blot	ND	Expression confers chemoresistance	105
FABP5	Primary murine lung NK cells	Functional assays with FABP5 -/- NK cells	ND	Deficiency leads to decreased granzyme B and IFNγ production Deficiency impairs NK maturation Deficiency in NK cells favors lung tumor metastasis	106
ENT1	Primary human NK cells YTS human cell line: NK cells derived from a patient with acute lymphoblastic leukemia	RT-qPCR	ND	NK from oncological donors express higher levels of the protein	144
	Nasal type extra nodal NK cell lymphoma/ YT cell line	RT-PCR	ND	Expression favors gemcitabine uptake and cytotoxicity	145

SL: Subcellular location; C: cytosol; M: mitochondria; PM: plasmatic membrane; N: nucleus.

CYP: cytochrome P450; HMG-CoAr: 3-hydroxy-3-methylglutaryl-CoA reductase; PLA: phospholipase A; COX: cyclooxygenase; FAAH: Fatty acid amide hydrolase; ETC: electron transport chain; VGSCs: voltage gated sodium channels; VGCCs: voltage gated calcium channels; VDAC: voltage dependent anion channel; TRP: transient receptor potential; GABA: gamma-aminobutyric acid; GlyR: Glycerin receptor; AChR: acetylcholine receptor; D2: dopamine receptor 2; 5HT: 5-hydroxytriptamine receptor; P-gp: P glycoprotein; FABP: Fatty acid-binding protein; ENT: equilibrative nucleoside transporter.