SUPPLEMENTARY MATERIALS AND METHODS

Glucose, Glutamine and FA uptake

Freshly sorted or cytokine-activated NK cells (500k cells) were starved for 30 minutes in glucose/glutamine/pyruvate-free DMEM (Thermo Fisher). ^{3}H-L-Glutamine or ^{3}H-2-Deoxy-D-Glucose (2-DG) (Promega) were added and cells were incubated for 10 minutes at 37°C, 5% CO_2. Cells were washed with cold PBS and SDS 0,1% and transferred to tubes with scintillant to be analyzed in a scintillation counter (Perkin Elmer). The fluorescent dye Bodipy FL-C_{16} (Thermo Fisher) was added to cells in culture for 30 minutes at 37°C, 5% CO_2. Cells were washed and acquired analyzed by FACS.

Single-cell BioMark™

NK cells were sorted as single cells directly in 96-well qPCR plates with the RT mix 1 (5xVILO Reaction Mix, 200U/ul SUPERase-In, 10% NP40, nuclease free water). RT was performed according to manufacturer's protocols (Fluidigm). The dynamic Array IFC chip was prepared according to manufacturer's protocols and analyzed in the Biomark System (Fluidigm). Cycle threshold (Ct) values were collected from the machine, and the relative expression was calculated accounting the primer efficiencies (Pfaffl formula). Results were run in Prism8 and Qlucore (https://qlucore.com/).

SUPPLEMENTARY TABLE

Table 1. Expression levels of genes involved in metabolic pathways; related to Figure 1.

Gene lists were downloaded from the KEGG pathway database and applied to the RNAseq data. Relative expression values for NKDim (red, n=4 donors) and NKBr (blue, n=2 donors). Pathways: Glycolysis, OXPHOS, Pyruvate metabolism and TCA cycle, Mitochondria dynamics, Nucleotide metabolism, Fatty acid metabolism, Proteasome metabolism.

SUPPLEMENTARY FIGURES

Figure S1. Activated NKBr, NKDim upregulate nutrients receptors.

(A-B) Representative plots of the gating strategy for fluorescent-activated cell sorting (FACS) analysis of freshly isolated NK cells from the blood of healthy adult donors. Total ILCs were gated on viable $CD45^+$ Lin^- ($CD3^-CD4^-CD5^-TCR\alpha\beta^-TCR\gamma\delta^-CD14^-CD19^-$) $CD7^+$ cells (orange). NKDim cells are identified as $CD56^{low}CD16^+CD127^-$ cells (red), NKBr as $CD56^{high}CD16^-CD127^+$ cells (blue). Percentage of total NKBr and NKDim cells from total $CD45^+$ healthy adult donors. Results from ten independent donors (median). (B) Expression level of Slc2a1 (GLUT-1) and Slc2a5 (ASCT2). Data extracted from RNAseq analysis. (C) Representative plots of Glut1 and ASCT2 on NKBr and NKDim. FACS analysis of CD71 (transferrin receptors), CD98 (large neutral amino acid transporter LAT1) and CD36 (fatty acid translocase FAT) on freshly sorted blood NK cells or cultured for 18h with IL-15 or IL-15-12-18. Data from three healthy donors. (D) ^{3}H-L-Glutamine and ^{3}H-2-Deoxy-D-Glucose (2-DG) uptake analysis on freshly sorted blood NK cells or cultured for 18h with IL-15 or IL-15-12-18. Data from two independent experiments with one healthy donor each (F-G) Functional analysis of primed and activated NKBr and NKDim cultured or not with indicated inhibitors. FACS analysis of (E) TNF-α, (F) live $CD45^+$ cells, (G) CD107a, Granzyme B and Perforin. Data from six healthy donors. Data are mean ±SEM; not significant (ns) or not indicated; *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$ using two-way ANOVA with Tukey's correction or (A) Student's t-test.

Figure S2. Metabolic profile of freshly sorted NKBr and NKDim.

(A) ATP-linked respiration analyzed by extracellular flux analysis (EFA) in FACS sorted NKBr and NKDim cells isolated from the blood of three healthy donors. (B-D) RNA-Seq heatmaps depicting differentially expressed (log2 FC) genes from pathways related to energy metabolism, comparing FACS sorted NKDim (red, n=4 donors) and NKBr (blue, n=2 donors) cells: (B) Carbohydrate metabolism, (C) OXPHOS and (D) Lipid Metabolism. (E) ATP-linked respiration analyzed by EFA in cultured or not for 18h with IL-15 or IL-15-12-18. Data are mean ±SEM; not significant (ns) or not indicated; *p<0.05; **p<0.01; using two-way ANOVA with Tukey's correction.

Figure S3. TMRM$^+$ NKDim express genes of the OXPHOS pathway. Mitochondrial activity in circulating versus tissue resident NK cells at steady-state.

(A) NKBr and NKDim were cultured with IL-15 or IL-15-12-18 +/- 10µM rotenone and 10µM antimycin A for 18h. TMRM intensity was measured by FACS. Summary plot of three independent experiments with one healthy donor each. (B-D) Metabolic pathway gene profiles of TMRM$^+$ and TMRM$^-$ NKDim cells freshly sorted from the blood of healthy donors. Analysis done by high throughput PCR (Fluidigm BioMark HD). (B) representative plot of TMRM$^+$ NKBr and NKDim, (C) Single cells data and (D) OXPHOS gene expression profiles in bulks of 500 cells each summarized from two healthy donors. (E) FACS analysis of NK cells from pediatric tonsils. Tonsil NK (Ton-NK) cells were gated on lymphoid size and granularity, singlet and viable CD45$^+$Lin$^-$ CD7$^+$CD127$^-$CD56$^+$CD16$^-$ population. (F) Percentage of Ton-NK from total CD45$^+$. Results from 18 donors (G) Mitotracker green and TMRM measurements in freshly sorted blood NKDim, NKBr and Ton-NK cells (H) Mitotracker green and TMRM ratio. Data from five healthy donors. Data are mean ±SEM; not significant (ns) or not indicated; *p<0.05; ***p<0.001; using two-way ANOVA with Tukey's correction or Student's t-test.

Figure S4. Combinatorial effect of IL-12/18 on NKDim metabolic profile

(A) TMRM and Mitotracker measurements of NKBr and NKDim cultured in the indicated conditions for 18h. Data were plotted together with results from NKBr and NKDim from Figure 4. (B-D) Cultured NKBr and NKDim were incubated for 18h with the indicated inhibitors. (B) CD45$^+$ live cells, (C) TNFα, (D) CD107a, Granzyme B and

Perforin were measured by FACS. Data from three independent experiments with at least two donors each. Data are mean ±SEM; not significant (not indicated), p>0.05; *p<0.05; **p<0.01; ****p<0.0001 using two-way ANOVA with Tukey's correction.

Figure S5. Activated NKDim and NKBr have fragmented mitochondria.

(A) TMRM intensity in fragmented versus total NKBr and NKDim cells. Dots represent technical replicates. (B-C) Freshly sorted (B) NKDim and (C) NKBr stained with Mitotracker green or TMRM to analyze mitochondria fragmentation and membrane polarization by confocal microscopy. Cytokines were added after time point 0h (shown in Figure 5) and images were taken every 6h. Data from three healthy donors. Data are mean ±SEM; ***p<0.001; ****p<0.0001 using two-way ANOVA with Tukey's correction.

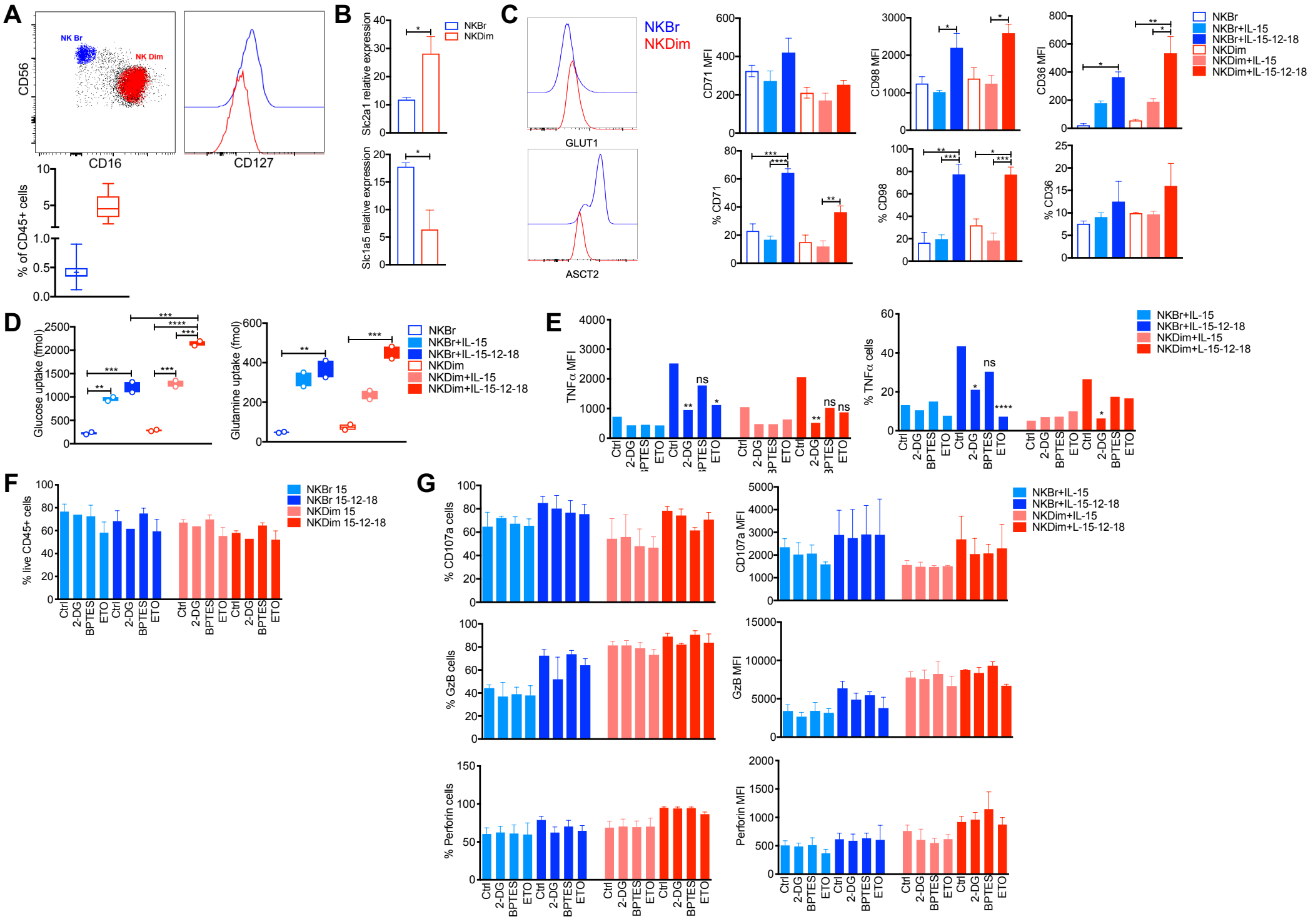
Figure S6. Mdivi-1 improves cytokine production in NKDim.

(A-B) Freshly sorted NKDim and NKBr were cultured with IL-15 for 18h with or w/o Mdivi-1. TMRM intensity was analyzed by FACS. (B-D) Cultured NKBr and NKDim were incubated for 18h with or w/o Mdivi-1. (B) $CD45^+$ live cells, (C) TNFα, (D) CD107a, Granzyme B and Perforin were measured by FACS. Data from three independent experiments with at least two donors each. Data are mean ±SEM; not significant (ns or not indicated), p>0.05; *p<0.05; **p<0.01; ***p<0.001 using two-way ANOVA with Tukey's correction.

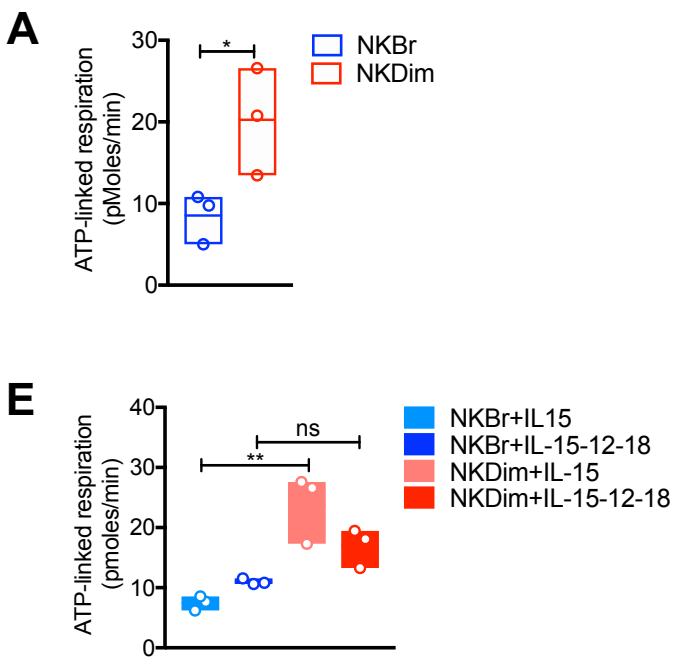
Figure S7. CMV^+ donors have polarized mitochondria.

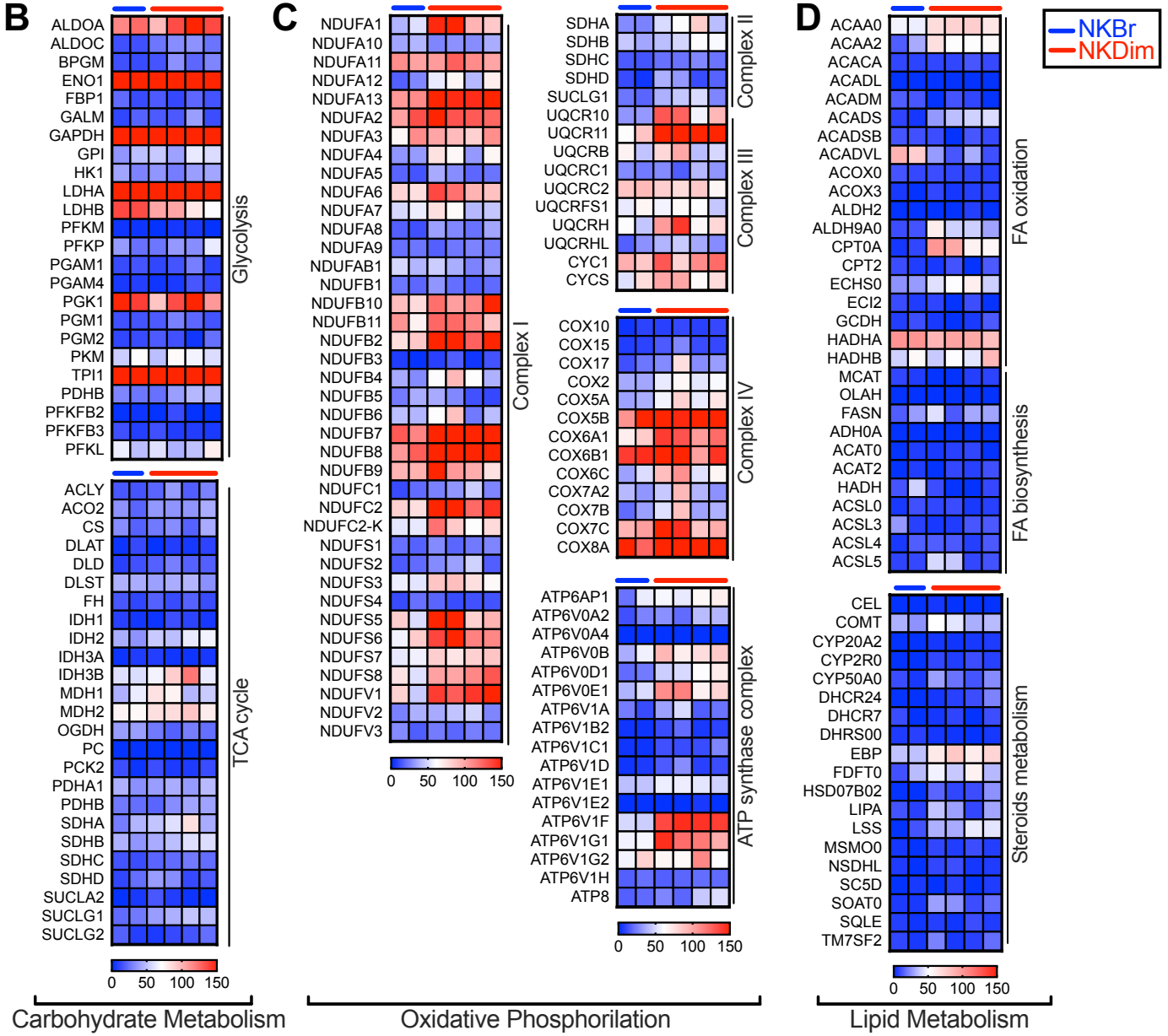
(A-B) Analysis of NKDim subsets in donors with different levels of mitochondria polarization (CMV^+ vs CMV^-, respectively high versus low level of TMRM); (A) representative FACS analysis of NKG2C, NKG2A in $NKDimCD57^+$ and $NKDimCD57^-$ subsets and histogram depicting TMRM levels in the indicated subsets; (B) TMRM intensity in the identified subsets. (C) Granzyme B and Perforin were measured by FACS in the indicated culture conditions. Data are mean ±SEM; not significant (not indicated), **p<0.01; ***p<0.001; using one-way ANOVA.

Supplementary 1

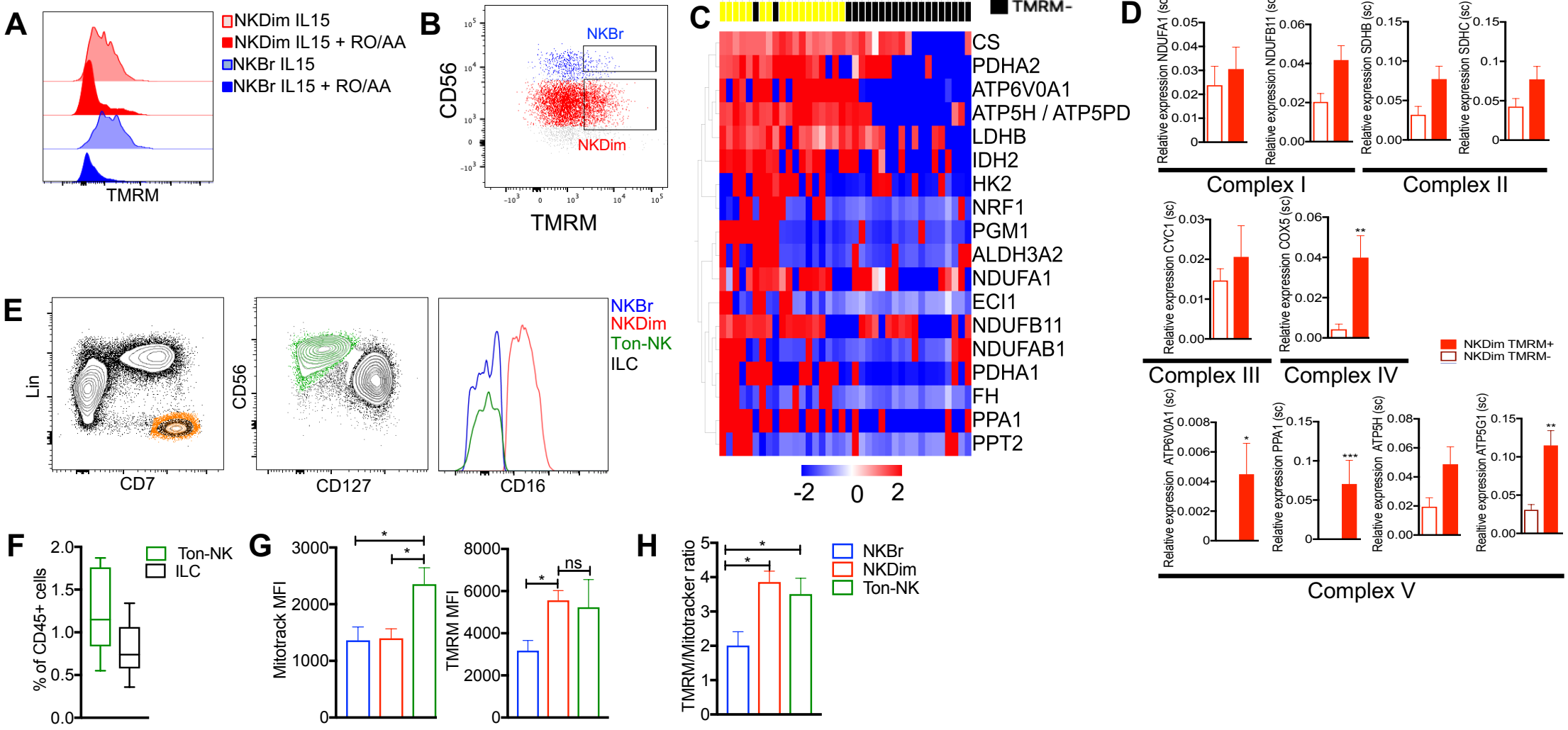


Supplementary 2

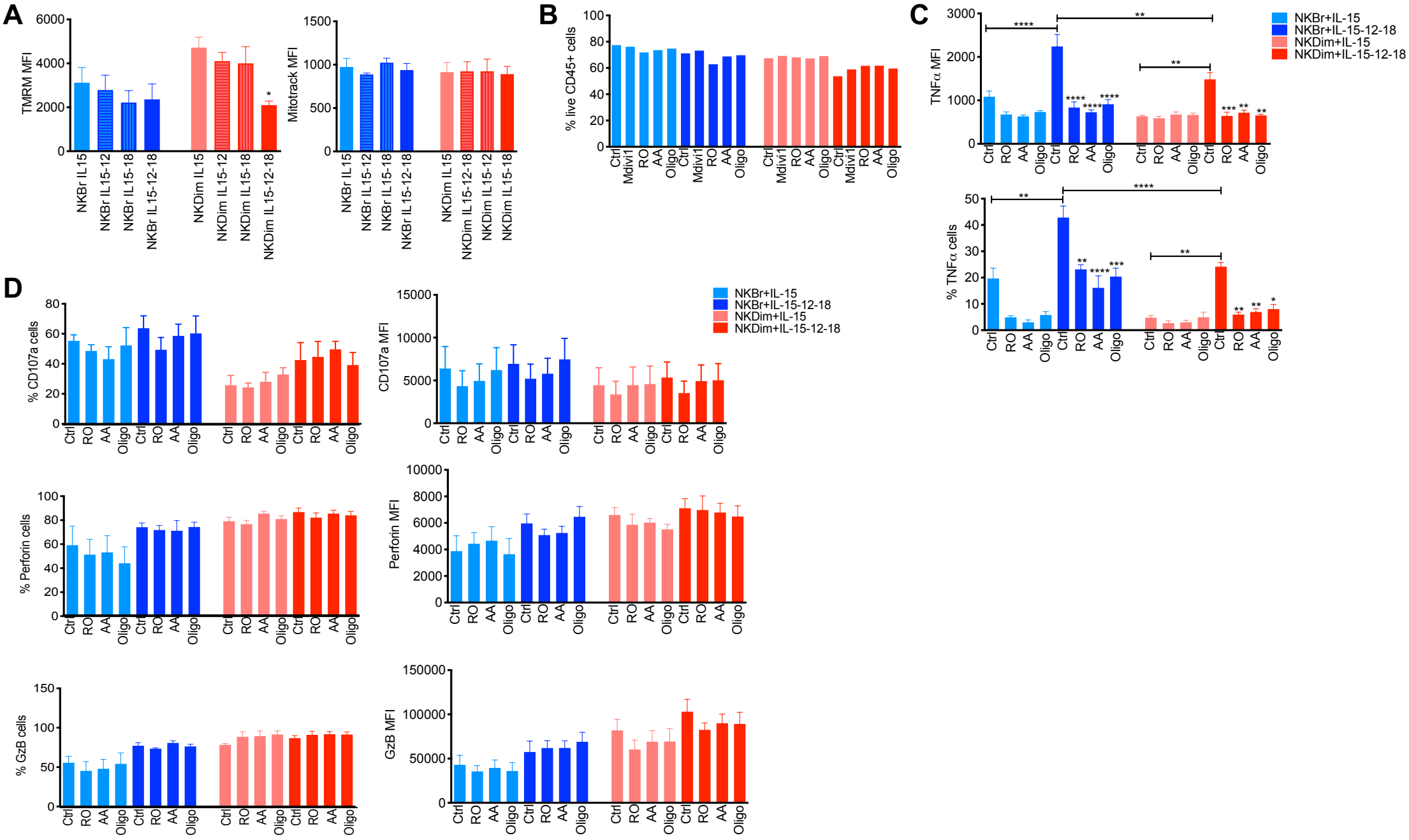




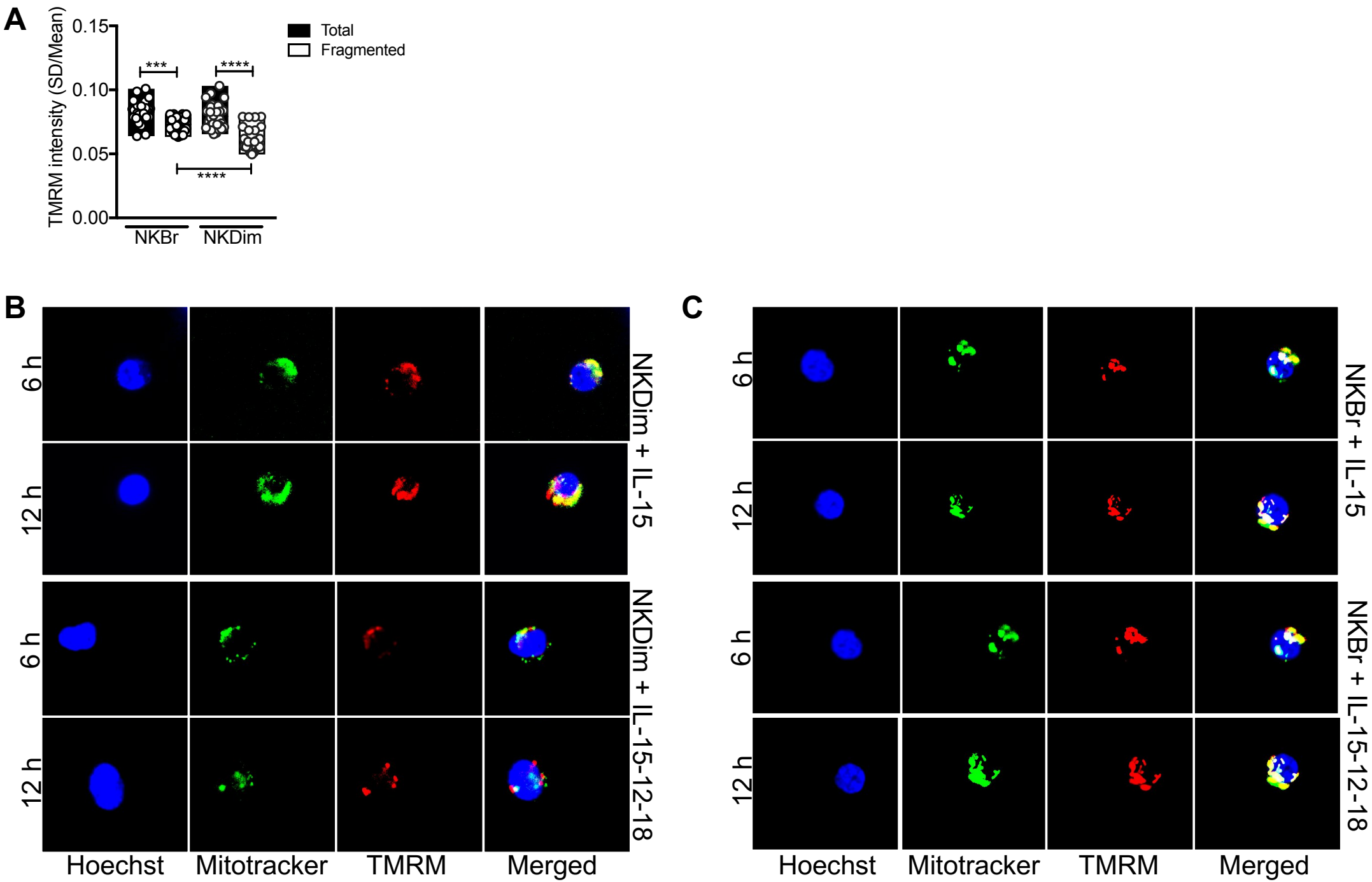
Supplementary 3



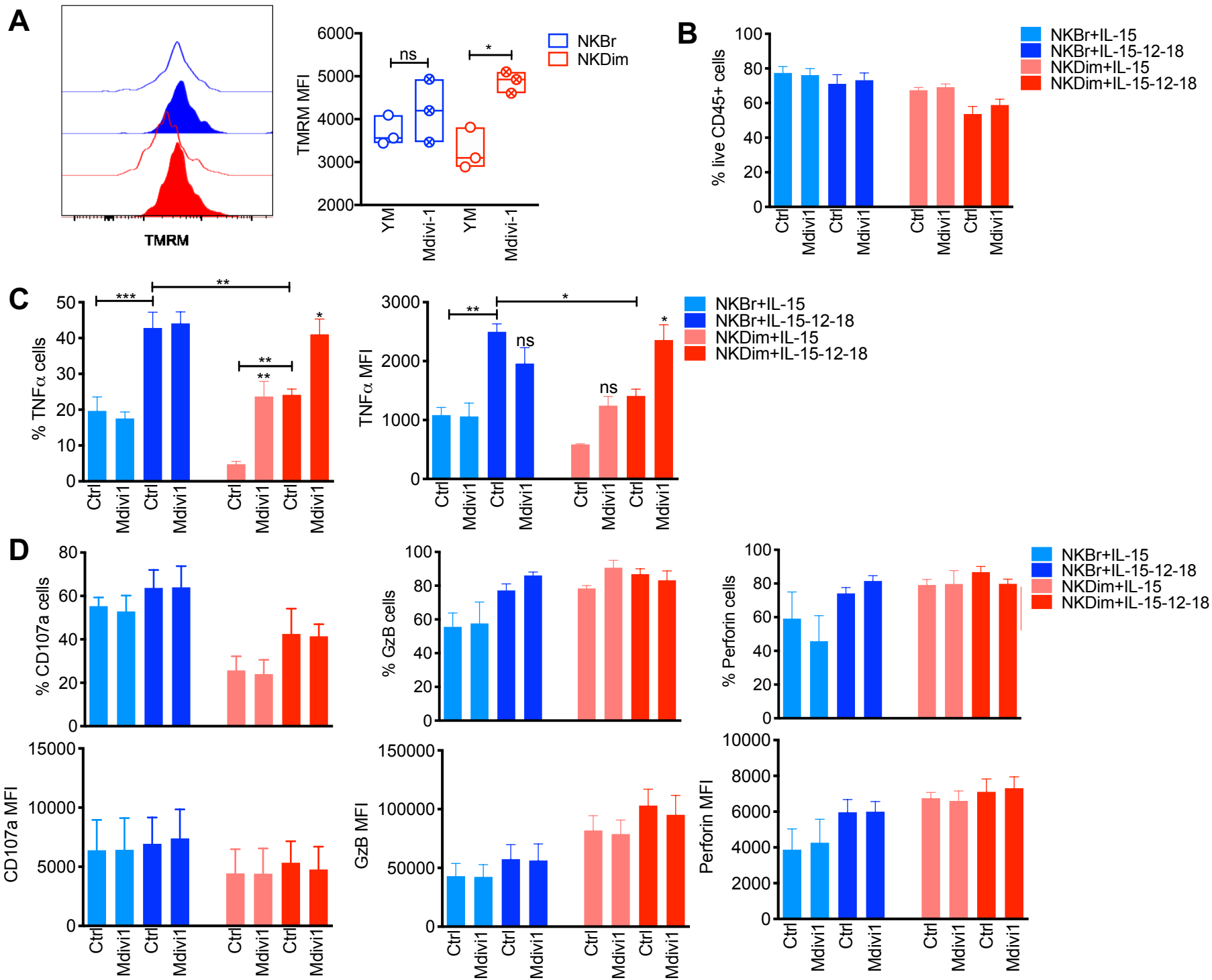
Supplementary 4



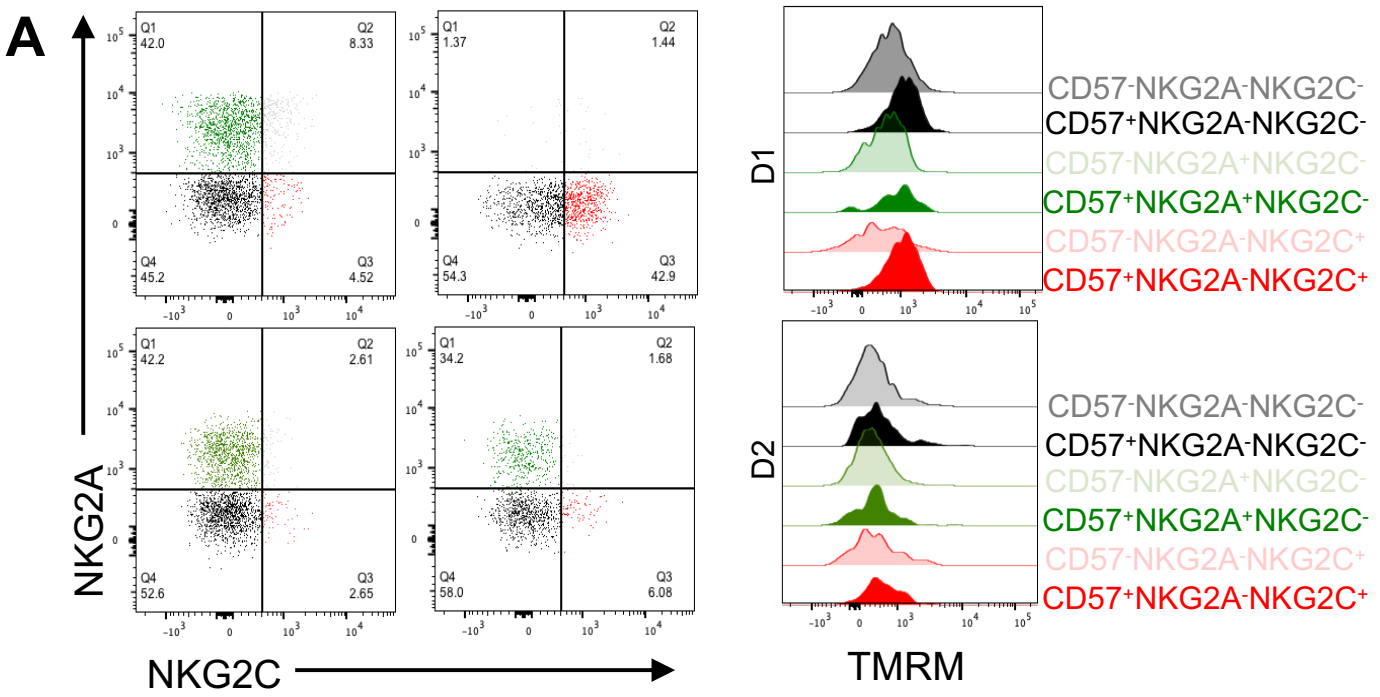
Supplementary 5

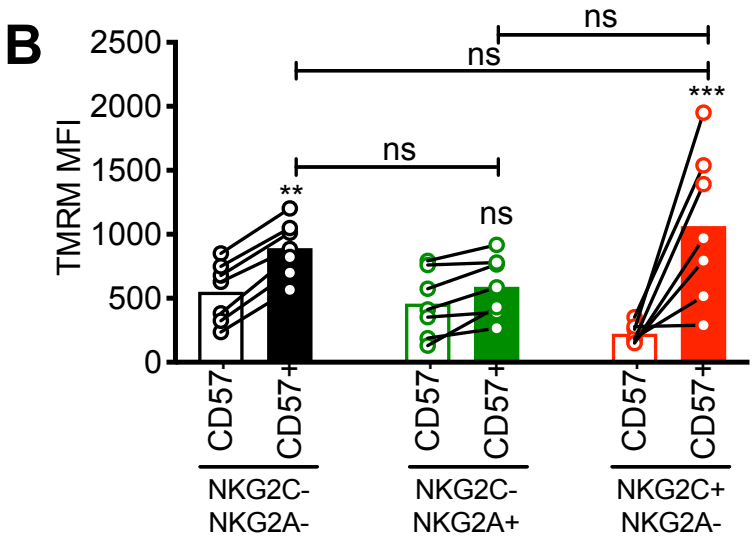


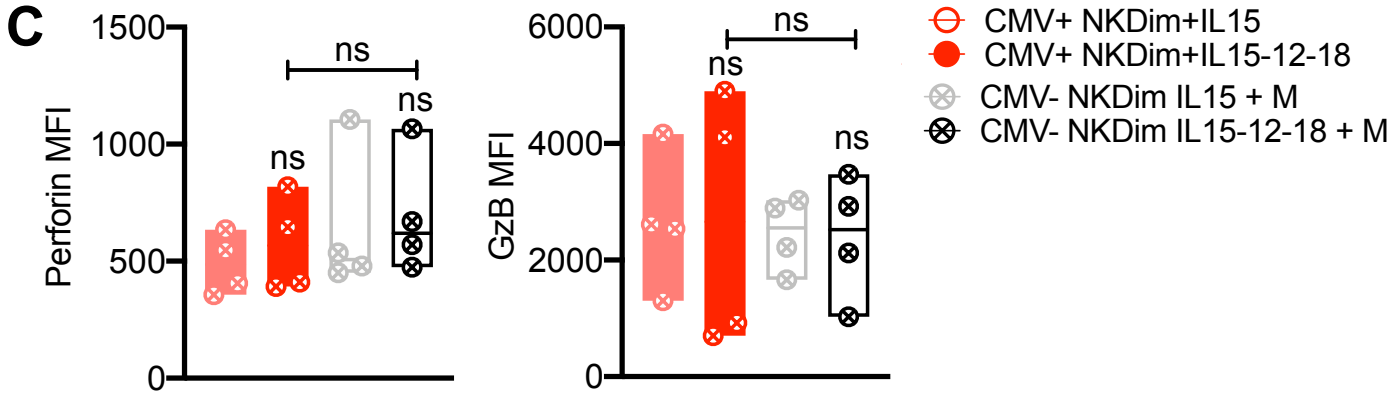
Supplementary 6



Supplementary 7







GLYCOLYSIS						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
ACSS1	35,10540569	38,5037208	49,09170249	31,3471319	53,41671978	61,67621843
ACSS2	1,404216228	0	0	1,492720567	4,217109456	4,934097474
ADH1A	0	0	0	0	0	0
ADH1B	0	0	0	0	0	0
ADH1C	0	0	0	0	0	0
ADH4	0	0	0	0	0	0
ADH5	35,10540569	44,16603268	43,31620808	43,28889643	36,54828195	48,10745037
ADH6	0	0	0	0	0	0
ADH7	0	0	0	0	0	0
ADPGK	22,46745964	21,51678515	28,87747205	17,9126468	15,46273467	25,90401174
AKR1A1	37,91383815	31,70894654	40,42846087	25,37624963	33,73687565	39,47277979
ALDH1A3	0	0	0	0	0	0
ALDH1B1	0	2,264924753	0	0	0	0
ALDH2	0	0	4,331620808	0	0	0
ALDH3A1	0	0	0	0	1,405703152	0
ALDH3A2	25,2758921	14,72201089	18,77035683	22,3908085	25,30265674	32,07163358
ALDH3B1	4,212648683	4,529849505	5,77549441	0	9,839922064	13,56876805
ALDH3B2	0	0	0	0	0	0
ALDH7A1	0	0	0	0	0	0
ALDH9A1	19,65902719	30,57648416	30,32134565	17,9126468	7,02851576	22,20343863
ALDOA	89,86983858	131,3656357	160,2699699	132,8521304	109,6448459	120,8853881
ALDOB	0	0	0	0	0	0
ALDOC	21,06324342	27,17909703	28,87747205	20,89808793	11,24562522	11,10171932
BPGM	12,63794605	28,31155941	17,32648323	25,37624963	11,24562522	9,868194948
DLAT	1,404216228	6,794774258	4,331620808	8,9563234	2,811406304	11,10171932
DLD	18,25481096	27,17909703	18,77035683	17,9126468	8,434218912	13,56876805
ENO1	171,3143798	164,2070446	255,5656277	198,5318354	206,6383633	228,2020082
ENO2	4,212648683	5,662311882	5,77549441	1,492720567	1,405703152	0
ENO3	7,02108113	5,66231188	10,1071152	5,97088226	4,21710945	1,23352436

	9	2	2	7	6	9
FBP1	14,04216228	9,059699011	17,32648323	11,94176453	18,27414098	9,868194948
FBP2	0	0	0	0	0	0
G6PC	0	0	0	0	0	0
G6PC2	0	0	0	0	0	0
GALM	14,04216228	13,589548 52	31,76521926	10,44904397	8,434218912	16,03581679
GAPDH	681,0448705	706,6565229	655,5186156	631,4207997	570,7154797	615,5286599
GAPDHS	0	0	0	0	0	0
GCK	0	0	0	0	0	0
GPI	43,53070306	32,84140891	53,4233233	49,2597787	29,51976619	40,70630416
HK1	29,48854078	22,64924753	31,76521926	34,33257303	33,73687565	24,67048737
HK2	1,404216228	2,264924753	0	0	0	0
HK3	0	2,264924753	0	0	0	0
HKDC1	0	0	0	0	0	0
LDHA	150,2511364	185,7238297	170,3770851	182,1119091	186,9585192	198,5974233
LDHAL6A	0	0	0	0	0	0
LDHAL6B	0	0	0	0	0	0
LDHB	98,29513594	98,52422674	70,74980653	59,70882267	133,5417994	131,9871074
LDHC	0	0	7,219368013	1,492720567	0	0
PANK1	1,404216228	1,132462376	0	0	0	0
PCK1	0	0	0	0	0	0
PCK2	12,63794605	5,662311882	5,77549441	11,94176453	12,65132837	2,467048737
PDHA1	36,50962192	40,76864555	36,09684006	46,27433757	43,57679771	62,9097428
PDHA2	0	0	0	0	0	1,233524369
PFKM	0	3,397387129	4,331620808	0	2,811406304	2,467048737
PFKP	21,06324342	30,57648416	27,43359845	53,7379404	30,92546934	19,7363899
PGAM1	8,425297367	12,45708614	23,10197764	7,463602833	9,839922064	12,33524369
PGAM2	0	1,132462376	0	0	0	1,233524369
PGAM4	2,808432456	4,529849505	12,99486242	8,9563234	4,217109456	6,167621843
PGK1	85,6571898	131,365635	150,162854	102,997719	147,598831	136,921204

	9	7	7	1		9
PGK2	0	0	0	0	0	0
PGM1	14,04216228	23,7817099	17,32648323	11,94176453	11,24562522	12,33524369
PGM2	14,04216228	11,32462376	2,887747205	19,40536737	8,434218912	9,868194948
Oxidative Phosphorylation						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
ATP12A	0	0	0	0	0	0
ATP4A	0	0	0	0	0	0
ATP4B	0	0	0	0	0	0
ATP5E	318,7570837	403,156606	229,5759028	186,5900708	206,6383633	233,1361057
ATP5F1A	88,46562235	120,0410119	64,97431212	76,1287489	73,0965639	64,14326716
ATP5H	46,33913552	52,09326931	20,21423044	29,85441133	28,11406304	40,70630416
ATP5J	36,50962192	45,29849505	30,32134565	35,8252936	35,1425788	32,07163358
ATP5O	63,18973025	69,08020496	43,31620808	43,28889643	60,44523553	51,80802348
ATP5S	29,48854078	22,64924753	18,77035683	43,28889643	11,24562522	11,10171932
ATP6AP1	57,57286534	53,22573169	63,53043851	67,1724255	50,60531347	54,27507222
ATP6V0A1	0	0	0	0	0	2,467048737
ATP6V0A2	28,08432456	18,11939802	10,10711522	38,81073473	11,24562522	24,67048737
ATP6V0A4	0	0	0	0	0	1,233524369
ATP6V0B	91,27405481	67,94774258	75,08142734	83,59235173	75,90797021	55,50859659
ATP6V0C	230,2914614	203,8432277	294,5502149	244,8061729	380,9455542	440,3681996
ATP6V0D1	44,93491929	48,69588218	59,19881771	68,66514607	18,27414098	22,20343863
ATP6V0D2	0	0	0	0	0	0
ATP6V0E1	108,1246495	112,1137753	66,41818572	79,11419003	57,63382923	49,34097474
ATP6V0E2	14,04216228	13,58954852	25,98972485	14,92720567	33,73687565	17,26934116
ATP6V1A	32,29697324	9,059699011	14,43873603	20,89808793	22,49125043	9,868194948
ATP6V1B1	0	0	0	0	0	0
ATP6V1B2	9,829513594	18,11939802	4,331620808	7,463602833	2,811406304	2,467048737
ATP6V1C1	11,23372982	10,19216139	10,10711522	25,37624963	2,811406304	2,467048737

ATP6V1C2	0	0	1,443873603	0	0	0
ATP6V1D	14,04216228	27,17909703	7,219368013	10,44904397	2,811406304	4,934097474
ATP6V1E1	54,76443288	54,35819407	51,97944969	46,27433757	40,76539141	41,93982853
ATP6V1E2	0	0	4,331620808	0	0	1,233524369
ATP6V1F	133,4005416	143,8227218	141,4996131	137,3302921	98,39922064	104,8495713
ATP6V1G1	143,2300552	120,0410119	115,5098882	95,53411627	85,74789227	107,3166201
ATP6V1G2	64,59394648	62,2854307	109,7343938	59,70882267	56,22812608	80,17908396
ATP6V1G3	0	0	0	0	0	0
ATP6V1H	15,44637851	16,98693565	18,77035683	17,9126468	15,46273467	19,7363899
ATP8	25,2758921	16,98693565	43,31620808	49,2597787	15,46273467	48,10745037
BSG	92,67827103	107,5839258	76,52530094	76,1287489	77,31367336	43,1733529
COX10	7,021081139	9,059699011	7,219368013	2,985441133	2,811406304	7,401146211
COX11	14,04216228	18,11939802	18,77035683	8,9563234	32,3311725	24,67048737
COX15	14,04216228	5,662311882	10,10711522	8,9563234	5,622812608	7,401146211
COX17	26,68010833	74,74251684	27,43359845	31,3471319	11,24562522	20,96991427
COX2	53,36021666	63,41789308	51,97944969	58,2161021	54,82242293	64,14326716
COX4I1	634,705735	600,2050595	498,1363929	570,2192565	663,4918877	774,6533035
COX4I2	0	0	0	0	0	0
COX5A	56,16864911	80,40482872	53,4233233	71,6505872	82,93648597	86,3467058
COX5B	213,4408666	146,0876466	219,4687876	194,0536737	156,0330499	178,8610334
COX6A1	137,6131903	129,1007109	102,5150258	120,9103659	67,47375129	82,64613269
COX6A2	0	0	0	0	2,811406304	0
COX6B1	279,4390293	277,4532822	200,6984308	141,8084538	137,7589089	193,6633259
COX6B2	0	0	0	0	0	1,233524369
COX6C	88,46562235	106,4514634	50,53557609	64,18698437	32,3311725	49,34097474
COX7A1	0	0	0	0	0	0

COX7A2	43,53070306	90,59699011	18,77035683	28,36169077	39,35968826	29,60458485
COX7A2L	40,72227061	46,43095743	27,43359845	38,81073473	52,01101662	69,07736464
COX7B	50,5517842	87,19960298	33,20909286	37,31801417	18,27414098	32,07163358
COX7B2	0	0	0	0	0	0
COX7C	161,4848662	142,6902594	85,18854255	76,1287489	112,4562522	109,7836688
COX8A	314,544435	271,7909703	176,1525795	240,3280112	163,0615656	223,2679107
COX8C	0	0	0	0	0	0
CYC1	127,7836767	79,27236635	108,2905202	120,9103659	94,18211118	83,87965706
CYCS	98,29513594	97,39176437	62,08656491	76,1287489	50,60531347	75,24498648
ETFA	22,46745964	22,64924753	15,88260963	14,92720567	16,86843782	22,20343863
ETFB	106,7204333	84,93467823	108,2905202	98,5195574	113,8619553	93,74785201
FH	18,25481096	11,32462376	18,77035683	10,44904397	15,46273467	9,868194948
IDH2	50,5517842	47,56341981	62,08656491	65,67970493	42,17109456	33,30515795
LDHA	150,2511364	185,7238297	170,3770851	182,1119091	186,9585192	198,5974233
LHPP	15,44637851	7,927236635	24,54585124	13,4344851	19,67984413	0
MDH2	82,84875744	83,80221585	92,40791057	77,62146947	74,50226705	72,77793774
NDUFA1	146,0384877	150,6174961	92,40791057	83,59235173	37,9539851	50,57449911
NDUFA10	25,2758921	28,31155941	27,43359845	35,8252936	33,73687565	38,23925543
NDUFA11	102,5077846	124,5708614	108,2905202	98,5195574	127,9189868	139,3882536
NDUFA12	53,36021666	64,55035545	38,98458727	67,1724255	15,46273467	25,90401174
NDUFA13	162,8890824	144,9551842	144,3873603	217,9372027	143,3817215	198,5974233
NDUFA2	153,0595688	129,1007109	127,060877	122,4030865	99,80492379	130,7535831
NDUFA3	98,29513594	89,46452773	80,85692175	107,4758808	63,25664184	108,5501444
NDUFA4	73,01924384	63,41789308	30,32134565	64,18698437	29,51976619	30,83810921
NDUFA4L2	0	0	0	0	0	0
NDUFA5	35,10540569	27,17909703	17,32648323	20,89808793	16,86843782	12,33524369

NDUFA6	133,4005416	118,9085495	92,40791057	86,57779287	78,71937651	74,01146211
NDUFA7	74,42346007	62,2854307	38,98458727	43,28889643	47,79390717	54,27507222
NDUFA8	32,29697324	26,04663466	20,21423044	34,33257303	15,46273467	11,10171932
NDUFA9	15,44637851	21,51678515	24,54585124	22,3908085	19,67984413	20,96991427
NDUFAB1	44,93491929	36,23879604	24,54585124	34,33257303	47,79390717	38,23925543
NDUFB1	29,48854078	19,2518604	14,43873603	17,9126468	21,08554728	17,26934116
NDUFB10	119,3583794	100,7891515	109,7343938	173,1555857	88,55929857	115,9512906
NDUFB11	122,1668118	121,1734743	109,7343938	85,0850723	115,2676585	115,9512906
NDUFB2	228,8872451	225,3600129	124,1731298	195,5463942	74,50226705	83,87965706
NDUFB3	7,021081139	14,72201089	2,887747205	11,94176453	5,622812608	11,10171932
NDUFB4	58,97708157	90,59699011	60,64269131	37,31801417	35,1425788	56,74212095
NDUFB5	35,10540569	26,04663466	11,55098882	8,9563234	22,49125043	35,77220669
NDUFB6	60,38129779	87,19960298	21,65810404	40,3034553	40,76539141	38,23925543
NDUFB7	325,7781648	286,5129812	324,8715606	397,0636707	276,9235209	310,8481409
NDUFB8	207,8240017	194,7835287	235,3513972	150,7647772	172,9014877	245,4713493
NDUFB9	161,4848662	103,0540762	95,29565777	73,14330777	92,77640803	113,4842419
NDUFC1	23,87167587	29,44402179	44,76008168	25,37624963	9,839922064	18,50286553
NDUFC2	207,8240017	154,0148832	121,2853826	141,8084538	130,7303931	114,7177663
NDUFC2-KCTD14	117,9541631	83,80221585	60,64269131	76,1287489	61,85093869	53,04154785
NDUFS1	26,68010833	16,98693565	21,65810404	25,37624963	19,67984413	25,90401174
NDUFS2	26,68010833	31,70894654	46,20395528	14,92720567	14,05703152	28,37106048
NDUFS3	85,65718989	88,33206536	73,63755373	62,6942638	54,82242293	71,54441338
NDUFS4	16,85059473	10,19216139	11,55098882	11,94176453	9,839922064	19,7363899
NDUFS5	157,2722175	154,0148832	80,85692175	92,54867513	81,53078281	149,2564486
NDUFS6	134,804757	159,677195	112,622141	110,461321	126,513283	82,6461326

	9	1		9	7	9
NDUFS7	81,44454121	71,34512971	80,85692175	85,0850723	73,0965639	55,50859659
NDUFS8	99,69935217	98,52422674	109,7343938	128,3739687	192,5813318	150,489973
NDUFV1	137,6131903	125,7033238	140,0557395	155,2429389	179,9300035	144,3223511
NDUFV2	35,10540569	41,90110793	47,64782889	25,37624963	23,89695358	37,00573106
NDUFV3	22,46745964	16,98693565	23,10197764	20,89808793	26,70835989	14,80229242
NNT	11,23372982	14,72201089	14,43873603	16,41992623	7,02851576	13,56876805
OGDH	25,2758921	18,11939802	27,43359845	22,3908085	36,54828195	37,00573106
PARK7	165,6975149	139,2928723	164,6015907	147,7793361	118,0790648	123,3524369
PDHB	19,65902719	31,70894654	38,98458727	38,81073473	25,30265674	20,96991427
PDHX	1,404216228	4,529849505	7,219368013	8,9563234	4,217109456	3,700573106
PDK1	2,808432456	9,059699011	2,887747205	2,985441133	1,405703152	3,700573106
PDK2	7,021081139	11,32462376	15,88260963	23,88352907	7,02851576	6,167621843
PDK4	1,404216228	0	0	0	0	0
PPA1	21,06324342	23,7817099	37,54071367	26,8689702	37,9539851	65,37679153
PPA2	18,25481096	16,98693565	24,54585124	11,94176453	5,622812608	18,50286553
SCO1	8,425297367	6,794774258	7,219368013	17,9126468	8,434218912	2,467048737
SDHA	49,14756797	58,88804357	82,30079535	40,3034553	26,70835989	54,27507222
SDHB	40,72227061	47,56341981	59,19881771	58,2161021	43,57679771	64,14326716
SDHC	19,65902719	20,38432277	25,98972485	20,89808793	14,05703152	12,33524369
SDHD	36,50962192	30,57648416	10,10711522	16,41992623	9,839922064	20,96991427
SUCLG1	36,50962192	43,0335703	49,09170249	25,37624963	21,08554728	46,87392601
TCIRG1	140,4216228	150,6174961	142,9434867	152,2574978	331,7459439	323,1833846
UCP2	286,4601105	268,3935832	463,4834264	352,2820537	456,8535244	409,5300904
UQCR10	127,7836767	123,438399	56,3110705	91,05595457	29,51976619	70,31088901

UQCR11	202,2071368	208,3730773	174,7087059	179,126468	160,2501593	186,2621797
UQCRB	77,23189253	97,39176437	40,42846087	47,76705813	66,06804814	41,93982853
UQCRC1	26,68010833	14,72201089	38,98458727	29,85441133	26,70835989	22,20343863
UQCRC2	81,44454121	75,87497922	83,74466895	64,18698437	85,74789227	90,0472789
UQCRFS1	56,16864911	62,2854307	59,19881771	43,28889643	53,41671978	64,14326716
UQCRH	102,5077846	139,2928723	63,53043851	77,62146947	59,03953238	72,77793774
UQCRHL	37,91383815	44,16603268	34,65296646	26,8689702	15,46273467	28,37106048
Pyruvate metabolism and TCA cycle						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
ACACA	5,616864911	5,662311882	8,663241616	16,41992623	5,622812608	4,934097474
ACACB	0	0	0	2,985441133	0	2,467048737
ACAT1	2,808432456	4,529849505	5,77549441	0	1,405703152	3,700573106
ACAT2	11,23372982	15,85447327	14,43873603	7,463602833	11,24562522	3,700573106
ACLY	19,65902719	36,23879604	17,32648323	28,36169077	15,46273467	14,80229242
ACO1	7,021081139	4,529849505	1,443873603	0	0	1,233524369
ACO2	35,10540569	33,97387129	34,65296646	41,79617587	33,73687565	19,7363899
ACOT12	0	0	0	0	0	0
ACSS2	1,404216228	0	0	1,492720567	4,217109456	4,934097474
ACYP1	19,65902719	16,98693565	20,21423044	10,44904397	14,05703152	18,50286553
ACYP2	9,829513594	15,85447327	5,77549441	19,40536737	5,622812608	7,401146211
ALDH1B1	0	2,264924753	0	0	0	0
ALDH2	0	0	4,331620808	0	0	0
ALDH3A2	25,2758921	14,72201089	18,77035683	22,3908085	25,30265674	32,07163358
ALDH7A1	0	0	0	0	0	0
ALDH9A1	19,65902719	30,57648416	30,32134565	17,9126468	7,02851576	22,20343863
CS	25,2758921	30,57648416	18,77035683	40,3034553	30,92546934	18,50286553
DLAT	1,40421622	6,79477425	4,33162080	8,9563234	2,81140630	11,1017193

	8	8	8		4	2
DLD	18,25481096	27,17909703	18,77035683	17,9126468	8,434218912	13,56876805
DLST	37,91383815	40,76864555	44,76008168	32,83985247	43,57679771	41,93982853
FH	18,25481096	11,32462376	18,77035683	10,44904397	15,46273467	9,868194948
GLO1	18,25481096	28,31155941	49,09170249	52,24521983	21,08554728	37,00573106
GRHPR	37,91383815	38,5037208	43,31620808	55,23066097	39,35968826	62,9097428
HAGH	30,89275701	39,63618317	27,43359845	52,24521983	29,51976619	38,23925543
IDH1	2,808432456	12,45708614	8,663241616	4,4781617	8,434218912	3,700573106
IDH2	50,5517842	47,56341981	62,08656491	65,67970493	42,17109456	33,30515795
IDH3A	7,021081139	3,397387129	2,887747205	4,4781617	2,811406304	6,167621843
IDH3B	65,99816271	89,46452773	119,841509	62,6942638	68,87945445	57,97564532
IDH3G	81,44454121	66,81528021	75,08142734	101,5049985	67,47375129	88,81375454
LDHA	150,2511364	185,7238297	170,3770851	182,1119091	186,9585192	198,5974233
LDHAL6A	0	0	0	0	0	0
LDHAL6B	0	0	0	0	0	0
LDHB	98,29513594	98,52422674	70,74980653	59,70882267	133,5417994	131,9871074
LDHC	0	0	7,219368013	1,492720567	0	0
LDHD	0	0	0	0	0	0
MDH1	80,04032498	74,74251684	44,76008168	50,75249927	43,57679771	62,9097428
MDH2	82,84875744	83,80221585	92,40791057	77,62146947	74,50226705	72,77793774
OGDH	25,2758921	18,11939802	27,43359845	22,3908085	36,54828195	37,00573106
OGDHL	0	0	0	0	0	0
PC	0	0	0	0	0	1,233524369
PCK1	0	0	0	0	0	0
PCK2	12,63794605	5,662311882	5,77549441	11,94176453	12,65132837	2,467048737
PDHA1	36,50962192	40,76864555	36,09684006	46,27433757	43,57679771	62,9097428
PDHA2	0	0	0	0	0	1,233524369
PDHB	19,6590271	31,7089465	38,9845872	38,8107347	25,3026567	20,9699142

	9	4	7	3	4	7
PKLR	0	0	0	0	0	0
PKM	40,72227061	62,2854307	56,3110705	49,2597787	44,98250086	60,44269406
SDHA	49,14756797	58,88804357	82,30079535	40,3034553	26,70835989	54,27507222
SDHB	40,72227061	47,56341981	59,19881771	58,2161021	43,57679771	64,14326716
SDHC	19,65902719	20,38432277	25,98972485	20,89808793	14,05703152	12,33524369
SDHD	36,50962192	30,57648416	10,10711522	16,41992623	9,839922064	20,96991427
SUCLA2	15,44637851	6,794774258	2,887747205	0	1,405703152	4,934097474
SUCLG1	36,50962192	43,0335703	49,09170249	25,37624963	21,08554728	46,87392601
SUCLG2	5,616864911	10,19216139	14,43873603	7,463602833	18,27414098	20,96991427
Mitochondria dynamics						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
PINK1	7,021081139	16,98693565	30,32134565	7,463602833	7,02851576	8,63467058
DNM1L	43,53070306	38,5037208	25,98972485	29,85441133	56,22812608	25,90401174
FIS1	64,59394648	66,81528021	76,52530094	89,563234	87,15359542	92,51432764
GDAP1	4,212648683	0	0	2,985441133	0	2,467048737
MFF	51,95600043	39,63618317	66,41818572	32,83985247	28,11406304	33,30515795
MIEF1	30,89275701	23,7817099	18,77035683	26,8689702	23,89695358	32,07163358
MIEF2	1,404216228	9,059699011	5,77549441	2,985441133	11,24562522	1,233524369
MTFP1	60,38129779	71,34512971	38,98458727	50,75249927	4,217109456	8,63467058
SH3GLB1	43,53070306	23,7817099	36,09684006	64,18698437	46,38820402	38,23925543
MFN1	8,425297367	9,059699011	2,887747205	0	2,811406304	11,10171932
MFN2	18,25481096	13,58954852	21,65810404	28,36169077	16,86843782	19,7363899
OPA1	15,44637851	10,19216139	12,99486242	8,9563234	5,622812608	8,63467058
PHB2	110,933082	97,39176437	128,5047506	101,5049985	113,8619553	111,0171932
PLD6	0	1,132462376	0	0	0	0
STOML2	16,8505947	12,4570861	12,9948624	16,4199262	14,0570315	24,6704873

	3	4	2	3	2	7
ACTB	717,5544924	765,5445664	1111,782674	809,0545471	413,2767267	386,0931274
ACTR10	21,06324342	33,97387129	12,99486242	28,36169077	22,49125043	27,13753611
ACTR1A	56,16864911	44,16603268	44,76008168	40,3034553	37,9539851	29,60458485
CAPZA1	40,72227061	36,23879604	34,65296646	40,3034553	26,70835989	49,34097474
DCTN1	36,50962192	49,82834456	50,53557609	44,781617	37,9539851	51,80802348
DCTN2	42,12648683	46,43095743	38,98458727	26,8689702	29,51976619	44,40687727
DCTN3	77,23189253	92,86191486	98,18340498	105,9831602	81,53078281	74,01146211
DCTN4	7,021081139	15,85447327	11,55098882	2,985441133	14,05703152	4,934097474
DCTN5	26,68010833	22,64924753	15,88260963	31,3471319	16,86843782	22,20343863
DCTN6	29,48854078	20,38432277	17,32648323	19,40536737	35,1425788	28,37106048
DYNC1H1	49,14756797	53,22573169	62,08656491	77,62146947	56,22812608	56,74212095
DYNC1I1	0	0	0	0	0	0
DYNC1I2	4,212648683	19,2518604	5,77549441	7,463602833	8,434218912	3,700573106
DYNC1LI1	22,46745964	16,98693565	18,77035683	13,4344851	29,51976619	30,83810921
DYNC1LI2	47,74335174	43,0335703	43,31620808	43,28889643	43,57679771	75,24498648
DYNLL1	89,86983858	96,25930199	36,09684006	49,2597787	30,92546934	30,83810921
DYNLL2	40,72227061	50,96080694	53,4233233	50,75249927	44,98250086	49,34097474
DYNLRB1	84,25297367	98,52422674	86,63241616	107,4758808	61,85093869	77,71203522
DYNLRB2	0	0	0	0	0	0
DYNLT1	61,78551402	89,46452773	77,96917454	82,09963117	75,90797021	62,9097428
DYNLT3	4,212648683	7,927236635	8,663241616	7,463602833	9,839922064	16,03581679
FEZ1	16,85059473	14,72201089	28,87747205	19,40536737	0	0
KIF1B	2,808432456	2,264924753	1,443873603	8,9563234	8,434218912	3,700573106
KIF5A	0	0	0	0	0	0
KIF5B	68,80659516	47,56341981	59,19881771	59,70882267	64,66234499	55,50859659
KIF5C	4,21264868	0	0	0	2,81140630	0

	3				4	
RANBP2	23,87167587	23,7817099	14,43873603	19,40536737	25,30265674	18,50286553
RHOT1	14,04216228	15,85447327	11,55098882	10,44904397	11,24562522	29,60458485
RHOT2	110,933082	112,1137753	109,7343938	122,4030865	64,66234499	88,81375454
SNPH	5,616864911	3,397387129	0	5,970882267	0	0
SYBU	0	0	0	0	0	0
TRAK1	8,425297367	14,72201089	11,55098882	4,4781617	9,839922064	19,7363899
TRAK2	11,23372982	6,794774258	10,10711522	13,4344851	25,30265674	28,37106048
FA Metabolism						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
ACAA1	58,97708157	64,55035545	66,41818572	53,7379404	67,47375129	76,47851085
ACAA2	57,57286534	41,90110793	41,87233448	43,28889643	19,67984413	23,436963
ACACA	5,616864911	5,662311882	8,663241616	16,41992623	5,622812608	4,934097474
ACACB	0	0	0	2,985441133	0	2,467048737
ACADL	0	0	0	0	0	0
ACADM	11,23372982	7,927236635	5,77549441	10,44904397	9,839922064	8,63467058
ACADS	21,06324342	27,17909703	31,76521926	32,83985247	15,46273467	22,20343863
ACADSB	7,021081139	10,19216139	8,663241616	16,41992623	8,434218912	7,401146211
ACADVL	120,7625956	108,7163881	124,1731298	107,4758808	81,53078281	66,6103159
ACAT1	2,808432456	4,529849505	5,77549441	0	1,405703152	3,700573106
ACAT2	11,23372982	15,85447327	14,43873603	7,463602833	11,24562522	3,700573106
ACOX1	7,021081139	5,662311882	5,77549441	4,4781617	8,434218912	6,167621843
ACOX3	5,616864911	2,264924753	4,331620808	4,4781617	2,811406304	1,233524369
ACSBG1	0	0	0	0	0	0
ACSBG2	0	0	0	0	0	0
ACSL1	5,616864911	6,794774258	2,887747205	4,4781617	2,811406304	7,401146211
ACSL3	12,63794605	13,58954852	18,77035683	8,9563234	21,08554728	14,80229242
ACSL4	9,829513594	9,059699011	4,331620808	8,9563234	2,811406304	9,868194948

ACSL5	32,29697324	29,44402179	15,88260963	17,9126468	15,46273467	16,03581679
ACSL6	0	0	0	1,492720567	16,86843782	17,26934116
ADH1A	0	0	0	0	0	0
ADH1B	0	0	0	0	0	0
ADH1C	0	0	0	0	0	0
ADH4	0	0	0	0	0	0
ADH5	35,10540569	44,16603268	43,31620808	43,28889643	36,54828195	48,10745037
ADH6	0	0	0	0	0	0
ADH7	0	0	0	0	0	0
ALDH1B1	0	2,264924753	0	0	0	0
ALDH2	0	0	4,331620808	0	0	0
ALDH3A2	25,2758921	14,72201089	18,77035683	22,3908085	25,30265674	32,07163358
ALDH7A1	0	0	0	0	0	0
ALDH9A1	19,65902719	30,57648416	30,32134565	17,9126468	7,02851576	22,20343863
CPT1A	112,3372982	115,5111624	93,85178417	85,0850723	47,79390717	44,40687727
CPT1B	16,85059473	6,794774258	8,663241616	8,9563234	18,27414098	6,167621843
CPT1C	0	0	0	0	0	0
CPT2	12,63794605	7,927236635	1,443873603	19,40536737	7,02851576	3,700573106
CYP4A11	0	0	0	0	0	0
CYP4A22	0	0	0	0	0	0
ECHS1	33,70118947	39,63618317	49,09170249	31,3471319	49,19961032	30,83810921
ECI1	50,5517842	37,37125842	40,42846087	28,36169077	85,74789227	62,9097428
ECI2	15,44637851	11,32462376	17,32648323	11,94176453	16,86843782	13,56876805
EHHADH	0	0	0	1,492720567	0	0
FASN	33,70118947	19,2518604	23,10197764	22,3908085	9,839922064	20,96991427
GCDH	2,808432456	10,19216139	12,99486242	19,40536737	14,05703152	17,26934116
HADH	7,021081139	11,32462376	10,10711522	5,970882267	8,434218912	30,83810921
HADHA	78,63610876	88,33206536	85,18854255	74,63602833	95,58781433	94,98137638
HADHB	29,48854078	39,63618317	34,65296646	17,9126468	60,44523553	43,1733529
MCAT	1,40421622	1,13246237	4,33162080	14,9272056	5,62281260	3,70057310

	8	6	8	7	8	6
OLAH	0	0	0	0	0	0
Steroids Metabolism						
Gene	**NKDim**	**NKDim**	**NKDim**	**NKDim**	**NKBr**	**NKBr**
AKR1C1	1,404216228	0	2,887747205	0	0	0
AKR1C2	4,212648683	0	0	2,985441133	0	1,233524369
AKR1C3	117,9541631	103,0540762	88,07628976	94,0413957	4,217109456	3,700573106
AKR1C4	1,404216228	0	0	0	0	0
AKR1D1	0	0	0	1,492720567	0	0
CEL	2,808432456	0	0	0	0	0
COMT	23,87167587	49,82834456	43,31620808	31,3471319	30,92546934	33,30515795
CYP11A1	0	0	0	0	0	0
CYP11B1	0	0	0	0	0	0
CYP11B2	0	0	0	0	0	0
CYP17A1	0	0	0	0	0	0
CYP19A1	0	0	0	0	0	0
CYP1A1	0	0	0	0	0	0
CYP1A2	0	0	0	0	0	0
CYP1B1	0	0	0	0	0	0
CYP21A2	2,808432456	2,264924753	0	2,985441133	4,217109456	0
CYP24A1	0	0	0	0	0	0
CYP27B1	0	0	0	0	0	0
CYP2E1	2,808432456	0	0	1,492720567	7,02851576	2,467048737
CYP2R1	7,021081139	4,529849505	8,663241616	0	5,622812608	11,10171932
CYP3A4	0	0	0	0	0	0
CYP3A5	0	0	0	0	0	0
CYP3A7	0	0	0	0	0	0
CYP3A7-CYP3A51P	0	0	0	0	0	0
CYP51A1	26,68010833	16,98693565	10,10711522	22,3908085	18,27414098	13,56876805
CYP7A1	0	0	0	0	0	0
CYP7B1	0	0	0	0	0	0
DHCR24	2,808432456	5,662311882	8,663241616	1,492720567	1,405703152	0
DHCR7	2,808432456	6,794774258	0	8,9563234	8,434218912	1,233524369
DHRS11	2,808432456	2,264924753	0	2,985441133	4,217109456	6,167621843
EBP	61,78551402	77,00744159	59,19881771	71,6505872	35,1425788	34,53868232
FDFT1	46,33913552	36,23879604	56,3110705	32,83985247	19,67984413	33,30515795
HSD11B1	0	0	0	0	0	0
HSD11B2	0	0	0	0	0	0

HSD17B1	1,404216228	5,662311882	2,887747205	4,4781617	1,405703152	4,934097474
HSD17B12	14,04216228	16,98693565	18,77035683	10,44904397	23,89695358	12,33524369
HSD17B2	0	0	0	0	0	0
HSD17B3	0	0	0	0	0	0
HSD17B6	0	1,132462376	0	2,985441133	0	0
HSD17B7	16,85059473	10,19216139	12,99486242	11,94176453	7,02851576	16,03581679
HSD17B8	8,425297367	5,662311882	11,55098882	7,463602833	8,434218912	12,33524369
HSD3B1	0	0	0	0	0	0
HSD3B2	0	0	0	0	0	0
LIPA	35,10540569	27,17909703	17,32648323	28,36169077	9,839922064	16,03581679
LRTOMT	4,212648683	2,264924753	2,887747205	0	1,405703152	3,700573106
LSS	30,89275701	29,44402179	44,76008168	43,28889643	11,24562522	9,868194948
MSMO1	7,021081139	4,529849505	8,663241616	10,44904397	2,811406304	4,934097474
NSDHL	7,021081139	9,059699011	2,887747205	4,4781617	4,217109456	11,10171932
SC5D	11,23372982	5,662311882	1,443873603	4,4781617	11,24562522	3,700573106
SOAT1	26,68010833	23,7817099	8,663241616	16,41992623	14,05703152	13,56876805
SOAT2	0	1,132462376	0	0	0	0
SQLE	15,44637851	12,45708614	8,663241616	4,4781617	15,46273467	12,33524369
SRD5A1	15,44637851	12,45708614	8,663241616	4,4781617	15,46273467	12,33524369
SRD5A2	0	0	0	0	0	0
SRD5A3	4,212648683	6,794774258	2,887747205	7,463602833	2,811406304	7,401146211
STS	1,404216228	2,264924753	2,887747205	1,492720567	2,811406304	0
SULT1E1	0	0	0	0	0	0
SULT2B1	0	0	0	0	0	0
TM7SF2	21,06324342	13,58954852	15,88260963	5,970882267	7,02851576	3,700573106
UGT1A1	0	0	0	0	0	0
UGT1A10	0	0	0	0	0	0
UGT1A3	0	0	0	0	0	0
UGT1A4	0	0	0	0	0	0
UGT1A5	0	0	0	0	0	0
UGT1A6	0	0	0	0	0	0
UGT1A7	0	0	0	0	0	0
UGT1A8	0	0	0	0	0	0
UGT1A9	0	0	0	0	0	0
UGT2A1	0	0	0	0	0	0
UGT2A2	0	0	0	0	0	0
UGT2A3	0	0	0	0	0	0
UGT2B10	0	0	0	0	0	0

UGT2B11	0	0	0	0	0	0
UGT2B15	0	0	0	0	0	0
UGT2B17	0	0	0	0	0	0
UGT2B28	0	0	0	0	0	0
UGT2B4	0	0	0	0	0	0
UGT2B7	0	0	0	0	0	0