

Table S1. Phenotypic parameters of the human adipose tissue lipidomics study, including gender, age range, and BMI range, related to Figure 1.

Group	Parameter	Range	Mean
Non-obese (n=6)	Age (years)	45–66	55.5
	BMI (kg/m ²)	25.0–28.1	25.55
	Sex	5 male / 1 female	
Obese (n=6)	Age (years)	27–54	43.0
	BMI (kg/m ²)	38.0–47.3	43.98
	Sex	5 female / 1 male	

Table S2. Proteome data of 5XFAD mice with vehicle, Chow^{EVs}-PE^{low}, and HFD^{EVs}-PE^{high} administration, related to Figure 3H

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Table S3. Top pathway gene sets detected from the proteome signature of HFD^{EVs}-PE^{high} administrated 5XFAD mice, related to Figure 3H.

Category	Set Name	#Overlapped Proteins	#Queried Proteins	(Col C/Col D) %	Overlapped Protein IDs	#Member Proteins in Set	#Proteins in Category	Fold Enrichment	Over-representation p-values	Bonferroni	Benjamini	FDR
UP_KW_PTM	KW-0007-Acetylation	17	27	56.667	P34884, Q9D7A8, Q9CQ60, Q5U458, P70318, P14131, Q9QUM9, P01942, P0DP27, P60761, Q60829, Q8VED9, Q91XU3	3161	12816	2.552778657	7.08E-05	8.49E-04	9.20E-04	9.20E-04
GOTERM_CC_DIRECT	GO:0043209--myelin sheath	5	29	16.667	P02088, P12787, P01942, P34884, P0DP27	192	21179	19.01849856	1.13E-04	0.012915365	0.012998759	0.012772693
UP_KW_CELLULAR_COMPONENT	KW-0963-Cytoplasm	15	25	50.000	Q9CPX6, P34884, Q9D7A8, Q05BC3, Q9CQ60, Q8R071, Q9WV34, P70318, Q8R570, P16054, Q9QUM9, P0DP27, P60761, Q60829, Q91XU3	5081	17960	2.120842354	0.001965923	0.042369117	0.043250306	0.043250306
GOTERM_CC_DIRECT	GO:0098978--glutamatergic synapse	5	29	16.667	Q8R570, P16054, P60761, Q9WV34, Q60829	522	21179	6.995309816	0.004670479	0.416297162	0.268552538	0.263882059
GOTERM_CC_DIRECT	GO:0043025--neuronal cell body	5	29	16.667	Q8R570, P11627, Q0VGL4, P60761, Q60829	643	21179	5.678929587	0.009657305	0.672408371	0.370196683	0.36375848
UP_KW_BIOLOGICAL_PROCESS	KW-0561-Oxygen transport	2	14	6.667	P02088, P01942	10	11003	157.1857143	0.011757124	0.210642303	0.194218937	0.194218937
UP_SEQ_FEATURE	METAL:Iron (heme b distal ligand)	2	28	6.667	P02088, P01942	10	22511	160.7928571	0.011931979	0.799812458	0.541431373	0.541431373
UP_SEQ_FEATURE	METAL:Iron (heme b proximal ligand)	2	28	6.667	P02088, P01942	10	22511	160.7928571	0.011931979	0.799812458	0.541431373	0.541431373
GOTERM_BP_DIRECT	GO:0050996--positive regulation of lipid catabolic process	2	29	6.667	P09813, P16054	9	20094	153.9770115	0.012473852	0.981530462	1	1
GOTERM_BP_DIRECT	GO:0015671--oxygen transport	2	29	6.667	P02088, P01942	10	20094	138.5793103	0.013850538	0.988147989	1	1
GOTERM_MF_DIRECT	GO:0031720--haptoglobin binding	2	28	6.667	P02088, P01942	11	18713	121.512987	0.015761496	0.877186435	1	1
UP_SEQ_FEATURE	METAL:Iron (heme distal ligand)	2	28	6.667	P02088, P01942	14	22511	114.8520408	0.01666628	0.894822006	0.541431373	0.541431373
GOTERM_CC_DIRECT	GO:0005833--hemoglobin complex	2	29	6.667	P02088, P01942	13	21179	112.3554377	0.017055956	0.861703412	0.386744271	0.380018284
KEGG_PATHWAY	mmu05012:Parkinson disease	4	20	13.333	Q8BK30, P12787, P0DP27, Q9QUM9	264	8992	6.812121212	0.017117142	0.788573966	0.77130599	0.77130599
KEGG_PATHWAY	mmu04070:Phosphatidylinositol signaling system	3	20	10.000	P0DP27, Q8R071, Q91XU3	96	8992	14.05	0.017140133	0.7890186	0.77130599	0.77130599
UP_SEQ_FEATURE	DOMAIN:GLOBIN	2	28	6.667	P02088, P01942	15	22511	107.1952381	0.017846438	0.910455468	0.541431373	0.541431373
GOTERM_CC_DIRECT	GO:0031838--haptoglobin-hemoglobin complex	2	29	6.667	P02088, P01942	14	21179	104.3300493	0.01835627	0.881232349	0.386744271	0.380018284
UP_KW_BIOLOGICAL_PROCESS	KW-0813-Transport	7	14	23.333	P02088, Q8BK30, P09813, Q9JKD3, Q9CPX6, P01942, Q91XL9	2006	11003	2.742522433	0.019421894	0.324471233	0.194218937	0.194218937
GOTERM_MF_DIRECT	GO:0043177--organic acid binding	2	28	6.667	P02088, P01942	14	18713	95.4744898	0.020018395	0.930694781	1	1
UP_SEQ_FEATURE	METAL:Iron (heme proximal ligand)	2	28	6.667	P02088, P01942	17	22511	94.58403361	0.020202663	0.935097993	0.541431373	0.541431373
GOTERM_CC_DIRECT	GO:0031966--mitochondrial membrane	3	29	10.000	P12787, P0DP27, P60761	170	21179	12.88782961	0.021117223	0.914092899	0.386744271	0.380018284
INTERPRO	IPR000971:Globin	2	30	6.667	P02088, P01942	16	20908	87.1166667	0.021970888	0.893945286	0.739686579	0.739686579
INTERPRO	IPR009050:Globin-like	2	30	6.667	P02088, P01942	16	20908	87.1166667	0.021970888	0.893945286	0.739686579	0.739686579
INTERPRO	IPR012292:Globin, structural domain	2	30	6.667	P02088, P01942	16	20908	87.1166667	0.021970888	0.893945286	0.739686579	0.739686579
GOTERM_MF_DIRECT	GO:0005344--oxygen transporter activity	2	28	6.667	P02088, P01942	16	18713	83.54017857	0.022846472	0.952675048	1	1
UP_KW_PTM	KW-0597-Phosphoprotein	22	27	73.333	P12787, Q9D7A8, Q0VGL4, Q9CQ60, Q8R071, Q5U458, Q9WV34, Q91XL9, P70318, P14131, P16054, Q9QUM9, P01942, P0DP27, P60761, Q60829	7742	12816	1.348833204	0.023504848	0.248305979	0.152781515	0.152781515
GOTERM_CC_DIRECT	GO:0044327--dendritic spine head	2	29	6.667	P60761, Q60829	18	21179	81.14559387	0.023540956	0.935402796	0.386744271	0.380018284
GOTERM_BP_DIRECT	GO:0035556--intracellular signal transduction	4	29	13.333	P16054, Q8Z268, P60761, Q60829	450	20094	6.15908046	0.024139846	0.999578059	1	1
GOTERM_BP_DIRECT	GO:1900242--regulation of synaptic vesicle endocytosis	2	29	6.667	Q9JKD3, P0DP27	18	20094	76.98850575	0.024797597	0.999659486	1	1
UP_KW_LIGAND	KW-0349-Heme	3	11	10.000	P02088, P12787, P01942	174	6582	10.31661442	0.027197929	0.240994601	0.27197929	0.27197929
GOTERM_BP_DIRECT	GO:0098869--cellular oxidant detoxification	2	29	6.667	P02088, P01942	20	20094	69.28965517	0.027515998	0.99985984	1	1

GOTERM_CC_DIRECT	GO:0005737--cytoplasm	16	29	53.333	Q9CPX6, P34884, Q9D7A8, Q05BC3, Q9CQ60, Q8R071, Q9WV34, P70318, Q8R570, P14131, P16054, Q9QUM9, P0DP27, P60761, Q60829, Q91XU3	7357	21179	1.588278581	0.031379973	0.974434982	0.451087105	0.443242112
GOTERM_CC_DIRECT	GO:0005829--cytosol	11	29	36.667	P14131, P09813, P16054, Q9Z268, Q9CPX6, P34884, Q9QUM9, Q9D7A8, Q05BC3, Q91XU3, Q91XL9	4193	21179	1.915910754	0.036580125	0.986234431	0.46741271	0.459283793
GOTERM_MF_DIRECT	GO:0019825--oxygen binding	2	28	6.667	P02088, P01942	26	18713	51.40934066	0.036869377	0.992978252	1	1
GOTERM_BP_DIRECT	GO:0042744--hydrogen peroxide catabolic process	2	29	6.667	P02088, P01942	29	20094	47.78596908	0.03965864	0.999997422	1	1
KEGG_PATHWAY	mmu01100:Metabolic pathways	8	20	26.667	Q8BK30, Q921H8, P12787, P34884, Q9CQ60, P70699, Q8R071, Q91XU3	1620	8992	2.220246914	0.041092213	0.97709575	1	1
GOTERM_BP_DIRECT	GO:0048821--erythrocyte development	2	29	6.667	P02088, P01942	32	20094	43.30603448	0.0436736	0.99999932	1	1
KEGG_PATHWAY	mmu05010:Alzheimer disease	4	20	13.333	Q8BK30, P12787, P0DP27, Q9QUM9	383	8992	4.695561358	0.044762284	0.983780721	1	1
GOTERM_BP_DIRECT	GO:0043278--response to morphine	2	29	6.667	P16054, Q60829	34	20094	40.75862069	0.046341242	0.99999972	1	1
GOTERM_MF_DIRECT	GO:0004601--peroxidase activity	2	28	6.667	P02088, P01942	40	18713	33.41607143	0.05617629	0.999515162	1	1
GOTERM_BP_DIRECT	GO:0001975--response to amphetamine	2	29	6.667	P0DP27, Q60829	42	20094	32.99507389	0.056940234	0.999999992	1	1
GOTERM_CC_DIRECT	GO:0030017--sarcomere	2	29	6.667	P0DP27, Q9QUM9	46	21179	31.75262369	0.059101473	0.99909339	0.656928143	0.645503305
GOTERM_BP_DIRECT	GO:0010811--positive regulation of cell-substrate adhesion	2	29	6.667	P16054, P11627	46	20094	30.12593703	0.062197043	0.999999999	1	1
GOTERM_CC_DIRECT	GO:0022627--cytosolic small ribosomal subunit	2	29	6.667	P14131, P01942	49	21179	29.8085855	0.062836605	0.999426199	0.656928143	0.645503305
UP_KW_DOMAIN	KW-0677--Repeat	9	17	30.000	P70318, Q8R570, P16054, P11627, Q9Z268, P0DP27, Q05BC3, Q9WV34, Q91XL9	4487	15344	1.810406534	0.064858862	0.521756818	0.600807656	0.600807656
GOTERM_BP_DIRECT	GO:0030073--insulin secretion	2	29	6.667	P16054, Q0VGLJ4	49	20094	28.28149191	0.066121095	1	1	1
GOTERM_MF_DIRECT	GO:0015485--cholesterol binding	2	28	6.667	P09813, Q91XL9	49	18713	27.27842566	0.068390487	0.999913129	1	1
GOTERM_BP_DIRECT	GO:0046854--phosphatidylinositol phosphorylation	2	29	6.667	Q8R071, Q91XU3	52	20094	26.64986737	0.070029312	1	1	1
GOTERM_MF_DIRECT	GO:0044877--macromolecular complex binding	4	28	13.333	P02088, Q9JKD3, P01942, P34884	677	18713	3.948723359	0.072514584	0.999951634	1	1
KEGG_PATHWAY	mmu05022:Pathways of neurodegeneration - multiple diseases	4	20	13.333	Q8BK30, P12787, P0DP27, Q9QUM9	471	8992	3.818259023	0.074167855	0.99902747	1	1
GOTERM_BP_DIRECT	GO:0048167--regulation of synaptic plasticity	2	29	6.667	Q0VGLJ4, Q8R071	58	20094	23.89298454	0.077798485	1	1	1
UP_SEQ_FEATURE	METAL:Calcium 4	2	28	6.667	Q9Z268, P0DP27	68	22511	23.6460084	0.07848004	0.999982476	1	1
KEGG_PATHWAY	mmu05143:African trypanosomiasis	2	20	6.667	P02088, P01942	39	8992	23.05641026	0.079343947	0.999412826	1	1
GOTERM_CC_DIRECT	GO:0014069--postsynaptic density	3	29	10.000	Q8R570, P60761, Q9WV34	363	21179	6.035622685	0.082713359	0.999951238	0.792669692	0.778884132
UP_KW_CELLULAR_COMPONENT	KW-0206--Cytoskeleton	5	25	16.667	P16054, P0DP27, Q05BC3, Q8R071, Q9WV34	1271	17960	2.826121164	0.085538188	0.860156388	0.940920063	0.940920063
GOTERM_CC_DIRECT	GO:0005739--mitochondrion	6	29	20.000	Q8BK30, Q921H8, P16054, P12787, Q9D7A8, Q9U458	1880	21179	2.330777696	0.097225063	0.999992208	0.860067865	0.845110163

Table S4. Gene markers used for cell type annotation in snRNA-seq analysis.

Cell type	Genes
Neuron	Syt1, Snap25, Grin1
Excitatory Neuron	Slc17a7, Camk2a, Nrgn
Inhibitory Neuron	Gad1, Gad2
Astrocyte	Aqp4, Gfap
Endothelial cell	Flt1, Cldn5
Microglia	Cd74, Csf1r, C3
Oligodendrocyte	Mbp, Mobp, Plp1
Oligodendrocyte Progenitor Cells	Pdgfra, Vcan, Cspg4

Table S5. COMPASS results ranking subsystems by the corresponding reaction counts in 5XFAD brains treated with engineered EVs (PE^{high}-EVs vs . PE^{low}-EV

No.	Subsystems	NumberOfReactions
1	Transport, extracellular	2007
2	Exchange/demand reaction	1279
3	Fatty acid oxidation	1226
4	Eicosanoid metabolism	445
5	Transport, mitochondrial	426
6	Nucleotide interconversion	271
7	Transport, endoplasmic reticular	270
8	Transport, peroxisomal	210
9	Unassigned	182
10	Bile acid synthesis	177
11	Tyrosine metabolism	173
12	Transport, lysosomal	151
13	Transport, golgi apparatus	150
14	Fatty acid synthesis	147
15	Miscellaneous	133
16	Transport, nuclear	125
17	Vitamin A metabolism	112
18	N-glycan synthesis	110
19	Arachidonic acid metabolism	108
20	Androgen and estrogen synthesis and metabolism	98
21	Tryptophan metabolism	98
22	Steroid metabolism	95
23	Urea cycle	93
24	Keratan sulfate degradation	92
25	Phosphatidylinositol phosphate metabolism	84
26	Sphingolipid metabolism	83
27	Cholesterol metabolism	81
28	Glycerophospholipid metabolism	81
29	Valine, leucine, and isoleucine metabolism	67
30	Folate metabolism	66
31	Inositol phosphate metabolism	64
32	Pentose phosphate pathway	62
33	Keratan sulfate synthesis	59
34	Chondroitin sulfate degradation	55
35	Methionine and cysteine metabolism	53
36	Glycolysis/gluconeogenesis	52
37	Purine catabolism	52
38	Glycine, serine, alanine and threonine metabolism	51
39	Arginine and Proline Metabolism	49
40	Pyrimidine catabolism	47
41	Blood group synthesis	46
42	Chondroitin synthesis	45
43	Starch and sucrose metabolism	42
44	Fructose and mannose metabolism	37
45	Pyruvate metabolism	36
46	Aminosugar metabolism	35
47	Linoleate metabolism	35
48	Heparan sulfate degradation	33
49	Vitamin D metabolism	33
50	Citric acid cycle	32

No.	Subsystems	NumberOfReactions
51	Pyrimidine synthesis	32
52	Vitamin E metabolism	32
53	NAD metabolism	28
54	Tetrahydrobiopterin metabolism	28
55	Lysine metabolism	26
56	Alanine and aspartate metabolism	23
57	Glutamate metabolism	22
58	Glutathione metabolism	21
59	CoA synthesis	20
60	Histidine metabolism	20
61	Purine synthesis	20
62	Vitamin C metabolism	20
63	Galactose metabolism	18
64	Selenoamino acid metabolism	18
65	Propanoate metabolism	17
66	Glyoxylate and dicarboxylate metabolism	16
67	N-glycan degradation	16
68	Cytochrome metabolism	15
69	O-glycan synthesis	15
70	C5-branched dibasic acid metabolism	14
71	Heme synthesis	14
72	Ubiquinone synthesis	14
73	beta-Alanine metabolism	13
74	Glycosphingolipid metabolism	13
75	Limonene and pinene degradation	13
76	Phenylalanine metabolism	13
77	Triacylglycerol synthesis	13
78	Vitamin B6 metabolism	13
79	Biotin metabolism	12
80	Dietary fiber binding	12
81	Taurine and hypotaurine metabolism	11
82	CoA catabolism	8
83	Oxidative phosphorylation	8
84	Vitamin B2 metabolism	8
85	ROS detoxification	7
86	Squalene and cholesterol synthesis	7
87	Alkaloid synthesis	6
88	Thiamine metabolism	6
89	Butanoate metabolism	5
90	Hyaluronan metabolism	5
91	Nucleotide sugar metabolism	5
92	Cysteine Metabolism	4
93	D-alanine metabolism	4
94	Lipoate metabolism	4
95	Vitamin B12 metabolism	4
96	Nucleotide salvage pathway	3
97	R group synthesis	3
98	Heme degradation	2
99	Stilbene, coumarine and lignin synthesis	2

Table S6. Key resources table, related to Methods.

	REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies and Probes	Guinea pig polyclonal anti-Perilipin-2	CiteAb	Cat# 20R-AP002 RRID: AB_1282475
	Rabbit polyclonal anti- β -Amyloid	Abcam	Cat# ab2539 RRID: AB_303141
	Mouse monoclonal anti- β -Amyloid, 1-40	Biolegend	Cat# SIG-39140 RRID: AB_10175638
	Mouse monoclonal anti- β -Amyloid (21F12), 1-42	Absolute antibody	Cat# Ab02391-3.0
	Rabbit polyclonal anti- β -Amyloid (21F12), 1-42	Absolute antibody	Cat# Ab02391-23.0
	Mouse monoclonal anti- β -Actin	Signalway	Cat# 21800
	Rabbit monoclonal anti-APP (6E10)	Novus Biologicals	Cat# NBP2-62566 RRID: AB_2917960
	Mouse monoclonal anti-tau (BT2)	Invitrogen	Cat# MN1010 RRID: AB_10975238
	Mouse monoclonal anti-p-tau (Thr181) (AT270)	Invitrogen	Cat# MN1050 RRID: AB_223651
	Mouse monoclonal anti-p-tau (Ser202 Thr205) (A	Invitrogen	Cat# MN1020 RRID: AB_223647
	Rabbit monoclonal anti-p-tau (Ser396)	Abcam	Cat# ab156623
	Mouse monoclonal anti- β -III Tubulin	Santa Cruz Biotechnology	Cat# sc-80005 RRID: AB_2210816
	Streptavidin, Alexa Fluor 647™ conjugate	Thermo Fisher Scientific	Cat# S21374 RRID: AB_2336066
	Duramycin-LC-Biotin	Polysciences	Cat# 25690-100
	Rabbit polyclonal anti-NFAT1 (D43B1)	Cell Signaling	Cat# 5861
	Oregon Green™ 488 BAPTA-1, AM	Thermo Fisher Scientific	Cat# O6807
	ER-Tracker™ Red (BODIPY™ TR Glibenclamide	Thermo Fisher Scientific	Cat# E34250
	NeuN Polyclonal Antibody	Thermo Fisher Scientific	Cat# PA5-143567
	NFkB p65 Polyclonal Antibody	Thermo Fisher Scientific	Cat# 51-0500
	SREBP1 Polyclonal Antibody	Thermo Fisher Scientific	Cat# PA1-337
	Mouse monoclonal anti-APP (22C11)	Thermo Fisher Scientific	Cat# 14-9749-82
	Rabbit polyclonal anti-BACE1	Thermo Fisher Scientific	Cat# PA1-757
	Goat polyclonal anti-RAB5	antibodies.com	Cat# A121672
Chemicals, peptides, and recombinant proteins	Ethanolamine (Etn)	Sigma-Aldrich	Cat# E9508-25 ML
	Ebsulfur	Medchemexpress	Cat# HY-128170
	Choline	Sigma-Aldrich	Cat#7017
	Ebselen	Sigma-Aldrich	Cat# E3520-25 MG
	Ivermectin	Sigma-Aldrich	Cat# I8898
	MG 624	Sigma-Aldrich	Cat# M3184-5 MG
	Ro 90-7501	Tocris	Cat# 2408
	Pentamidine isethionate salt	Sigma-Aldrich	Cat# P0547-250MG
	CP-339818	Sigma-Aldrich	Cat# C2499-5MG
	Leflunomide	Sigma-Aldrich	Cat# L5025
	Retinoic acid	Sigma-Aldrich	Cat# R2625
	Tegaserod maleate	Sigma-Aldrich	Cat# 189188-57-6
	Methylene Blue	Sigma-Aldrich	Cat# M9140
	Stem Cell Dissociation Reagent	ATCC	Cat# ACS-3010
	Cell Basement Membrane	ATCC	Cat# ACS-3035
	DMEM/F12 medium	Gibco/Life	Cat# 11320-033
	RPMI Medium 1640	Technologies	Cat# 11875-119
	DMEM (high glucose)	Gibco	Cat# CM002-050
	HEPES Buffer Solution (1 M)	GenDEPOT	Cat# CA011-010
	Penicillin/Streptomycin/Amphotericin B	Lonza	Cat# 17-745E
	Dulbecco's Phosphate Buffered Saline	Lonza	Cat# 17-512Q
	PBS pH 7.2	Gibco	Cat# 20012-027
	ReNcell Neural Stem Cell Freezing Medium	EMD Millipore	Cat# SCM007
	Matrigel	Corning	Cat# 356230
	Bovine Serum Albumin	Sigma-Aldrich	Cat# A2153
	DAPI	Cellomics Technology	Cat# 1860586
	SuperScript® VILO™ Master Mix	Invitrogen	Cat# 11755050
	Itaq™ Universal SYBR	Bio-Rad	Cat# 1725121
	Normal Donkey Serum	Jackson	Cat# 017-000-121
	LipidTOX™ Deep Red	Thermo Fisher Scientific	Cat# H34477
	BODIPY™ 558/568-C ₁₂	Thermo Fisher Scientific	Cat# D3835
	ETNK2 recombinant protein	Mybiosource	Cat# MBS140838
	Hydrogen peroxide solution, 30 % (w/w) in H ₂ O	Sigma-Aldrich	Cat# H1009
	BAY 11-7082	Sigma-Aldrich	Cat# 196870
	Fatostatin	Sigma-Aldrich	Cat# AMBH6FD841CF
	DiIC18(3)	Invitrogen	Cat# #D3911
	Digitonin	Sigma-Aldrich	Cat# D141

		holo-Transferrin	Sigma-Aldrich	Cat#T0665
Critical commercial assays		Mouse IFN- γ ELISA Kit, Extra sensitive	Invitrogen	Cat# BMS609
		Mouse TNF- α ELISA Kit, High sensitive	Invitrogen	Cat# BMS607HS
		Mouse Granzyme B ELISA Kit	Invitrogen	Cat# BMS6029
		Phosphatidylethanolamine Assay Kit	Abcam	Cat# 241005
		Pierce TM BCA Protein Assay Kit	ThermoFisher	Cat# 23225
		ADP-Glo TM Kinase Assay kit	Promega	Cat# V6930
		SimpleChIP [®] Enzymatic Chromatin IP Kit	Cell Signaling Technology	Cat# 9002
		RNeasy Plus Mini Kit	QIAGEN	Cat# 74134
		In Situ Cell Death Detection Kit, Fluorescein	Roche	Cat# 11684795910
		Chromium Next GEM Single Cell 3' Kit v3.1	10X Genomics	Cat#1000269
		Chromium Nuclei Isolation with Rnase Inhibitor K	10X Genomics	Cat#1000494
		Dual Index Kit TT Set A 96 rxns	10X Genomics	Cat#1000215
		Chromium Next GEM Chip G Single Cell Kit	10X Genomics	Cat#1000127
Experimental models: Cell lines		DO-11-10 Cells	Dr. Xiang H.-F. Zhang (BCM)	N/A
		VM Human Neural Stem Cell Lines	EMD Millipore	Cat# SCC008
		HEK293-APP695-WT cell line	KYINNO BIOTECHNOLOGY	Cat#KC-0146
		Human peripheral blood CD8+ T cells, Frozen	STEMCELL	Cat#70027
Experimental Models: Organisms		Mouse: C57BL/6J	The Jackson Laboratory	Strain # 000664
		Mouse: 3xTg	The Jackson Laboratory	Strain # 004807
		Mouse: 5XFAD	The Jackson Laboratory	MMRRC Strain # 034848
Software and algorithms		FlowJo	BD Biosciences	RRID:SCR_008520
		GraphPad Prism 9	GraphPad	http://www.graphpad.com
		Adobe Illustrator	Adobe [®]	http://adobe.com
		Fiji (Image J)	Zulu OpenJDK	http://imagej.nih.gov/ij/
		RAWGraphs 2.0	Open source	http://app.rawgraphs.io
		MetaboAnalyst 5.0	NIH – Canada Research Chair	http://metaboanalyst.ca/
		UALCAN	PMID: 35078134	http://ualcan.path.uab.edu/
		Agora	National Institute on Aging	http://agora.adknowledgeportal.org
		GEPiA2	Zhang Lab	http://gepia2.cancer-pku.cn/
		NeuriteIQ	PMID: 22277654	N/A

Table S7. RT-qPCR and ChIP-qPCR primers, related to quantitative PCR (qPCR) part in Methods.

Gene	Sequence	Source
mEtnk1 (<i>Eki1</i>) -FWD	GCTGTTACAGATGGGATCACAAAC	Modified from PMID: 34234346
mEtnk1 (<i>Eki1</i>) -RVS	TTGCCGTAAATCCTCACCAGAACTAC	Modified from PMID: 34234346
mPcyt2 -FWD	TGGTGCGATGGCTGCTATG	PMID: 34234346
mPcyt2 -RVS	CCCTTATGCTTGGCAATCTCC	PMID: 34234346
mPcyt1a -FWD	TGGATGCACAGAGTTGAGCTAAAGTC	Modified from PMID: 34234346
mPcyt1a -RVS	TGGCTGCCGTAAACCAACTG	PMID: 34234346
mSelenoi (<i>Ept1</i>) -FWD	TCCTACTCCTGACATACTTCGACCC	Modified from PMID: 34234346
mSelenoi (<i>Ept1</i>) -RVS	CCACGACAATCCAAACCCAG	PMID: 34234346
mEtnk2 -FWD	GCTTCAGCGTCACGGTGG	This paper*
mEtnk2 -RVS	AATAGCTTGTGGTGATGCCGTC	This paper*
mCept1 -FWD	GCTGGCAGTGATTGGAGGAC	This paper*
mCept1 -RVS	CACCACCTGTGAAGATTACACGG	This paper*
mPdcd1 (<i>Pd-1 Cd279</i>) -FWD	ACCCTGGTCATTCACTTGGG	PMID: 34234346
mPdcd1 (<i>Pd-1 Cd279</i>) -RVS	CATTTGCTCCCTCTGACACTG	PMID: 34234346
mCxcr3 (<i>Cd183</i>) -FWD	GGTAGCTCGAACTTACCCGTAAC	This paper*
mCxcr3 (<i>Cd183</i>) -RVS	GCAGCTAAGGCACAGTAATGGTG	This paper*
mCxcr5 -FWD	ATGAACCTACCCACTAACCCCTGG	PMID: 34234346
mCxcr5 -RVS	TGTAGGGGAATCTCCGTGCT	PMID: 34234346
mLag-3 (<i>Cd223</i>) -FWD	GTCCCATCACGTACAACCTCAAGG	This paper*
mLag-3 (<i>Cd223</i>) -RVS	GGAGTCCACTTGGCAATGAGC	This paper*
mLy108 (<i>Cd352</i>) -FWD	AAGCGTGCTTCCAACTGGC	Origene
mLy108 (<i>Cd352</i>) -RVS	GCAGCATGTGGATGAGTTACCC	Origene
mRgs16 -FWD	ATCCGATCAGCCACCAACTG	This paper*
mRgs16 -RVS	GAAGCAACTGGTAGTGGCAGCTTC	This paper*
mTigit -FWD	CGGAGCCACAGGAATGGAAC	This paper*
mTigit -RVS	CCTGTGGGTCAGCATAGTCATCTT	This paper*
mTim-3 (<i>Cd366</i>) -FWD	CCGCCTCTGGACTGCCAC	This paper*
mTim-3 (<i>Cd366</i>) -RVS	TGAGGTTGCCAAGTGACATATCACATAG	This paper*
mNfat1 -FWD	ACTTCACAGCGGAGTCCAAGGT	Origene
mNfat1 -RVS	GGATGTGCTTGTTCGATACTCG	Origene
mNfat2 -FWD	GGTGCCCTTTGCGAGCAGTATC	Origene
mNfat2 -RVS	CGTATGGACCAGAATGTGACGG	Origene
mNr4a1 -FWD	GTGCAGTCTGTGGTGACAATGC	Origene
mNr4a1 -RVS	CAGGCAGATGTACTTGCGCTT	Origene
mNr4a2 -FWD	CGCCGAAATCGTTGTCAGTACTG	This paper*
mNr4a2 -RVS	TCGGCTTCGAGGGTAAACGAC	This paper*
mNr4a3 -FWD	CCGAAACCGATGTCACTACTGC	This paper*
mNr4a3 -RVS	CTCCTGTTGTAGTGGGCTCTTTGG	This paper*
mTox -FWD	AAGATGGCGCACTGCTCTCC	This paper*
mTox -RVS	ATGCTTGCTGCTGTCTGATG	This paper*
mTox2 -FWD	GAAGCTGCCAAGAAGGAGTACCTG	This paper*
mTox2 -RVS	GGTTGCTGAGTGTTCTTGGC	This paper*
mTnfr -FWD	GAGAAAGTCAACCTCCTCTCTG	This paper*
mTnfr -RVS	GAAGACTCCTCCCAGGTATATG	This paper*
mGzmb (<i>Ctla-1</i>) -FWD	GATTGCTCTAGGACAGGTGGCA	This paper*
mGzmb (<i>Ctla-1</i>) -RVS	GTTGTCACAGCATGGTGGCAG	This paper*
mIfn γ -FWD	AAGACAATCAGGCCATCAGCAAC	This paper*
mIfn γ -RVS	CCTGTGGGTTGTTGACCTCAAAC	This paper*
mAtg3 -FWD	ACACGGTGAAGGGAAGGC	PMID: 25383539
mAtg3 -RVS	TGGTGGACTAAGTGATCTCCAG	PMID: 25383539
mAtg4a -FWD	GCTGGTATGGATTCTGGGGAA	PMID: 25383539
mAtg4a -RVS	TGGGTTGTCTTTTGTCTCTCC	PMID: 25383539
mAtg4b -FWD	CATCCATCAGATAGCGCAA	PMID: 25383539
mAtg4b -RVS	TGATTTCTCCATCACCACA	PMID: 25383539
mAtg4c -FWD	AGATGAAAGCAAGATGTTGCCT	PMID: 25383539
mAtg4c -RVS	CCCTGTAGGTCAGCCATATTCTA	PMID: 25383539
mAtg4d -FWD	GTCAAAGTATGGTTGGGCAGTT	PMID: 25383539
mAtg4d -RVS	TGTCACCCTCTCCCTCGAAAT	PMID: 25383539
mAtg7 -FWD	TGCCTATGATGATCTGTGTC	PMID: 25383539
mAtg7 -RVS	CACCACTGTTATCTTTGTCC	PMID: 25383539
mH2-d1 -FWD	GCTCTGAAATGTCTCTCCGAGATTG	This paper*
mH2-d1 -RVS	ACAGGGAACATCAGACAAATGTTGTG	This paper*
mH2-k1 -FWD	CAGGCTGGTGAAGCAGAGAGAC	This paper*
mH2-k1 -RVS	TTCAAGGTCTGCTGTGATGGG	This paper*
mTbx21 -FWD	GGAGCCCAAGCCATTACAG	This paper*
mTbx21 -RVS	GACATATAAGCGGTTCCCTGGC	This paper*
mGata3 -FWD	TGCGTGAGGAGTCTCCAAGTG	This paper*
mGata3 -RVS	ATGGGATCCGATTCACTGGT	This paper*
mFox3 -FWD	TCGCCTACTTCAGAAACCACCC	This paper*
mFox3 -RVS	CAAAATCATCTACGGTCCCACTGC	This paper*
mIL6 -FWD	TCTATACCACTTCACAAGTCGGAGG	This paper
mIL6 -RVS	CTGCAAGTGCATCATCGTTGTTC	This paper
mNrf1 -FWD	GGAGCTCTATCATGGCAGCG	This paper
mNrf1 -RVS	ACCAGATCCAGAGTGGTGTC	This paper

mLef1-FWD	GCCACCGATGAGATGATCCC	This paper
mLef1-RVS	TTGATGTCGGCTAAGTCGCC	This paper
mTcf7-FWD	CAATCTGCTCATGCCCTACC	This paper
mTcf7-RVS	CTTGCTTCTGGCTGATGTCC	This paper
mBcl6-FWD	TGTGTAAGGCAAACCTGTCAGC	This paper
mBcl6-RVS	GCAACCTGTCAAGTCAGAACTTCTGC	This paper
mI7r-FWD	GCCCATCTCCACTTCCTCAGTACTG	This paper
mI7r-RVS	CATTTGGTTGTCGATGGAAGGG	This paper
m36b4 -FWD	GAAACTGCTGCCTCACATCCG	This paper
m36b4 -RVS	GCTGGCACAGTGACCTCACAC	This paper

The primers with "*" means that the primers were modified from Origene.

ChIP-qPCR primers

Gene	Sequence
hSREBF1 F1	GCGTTTAATTAAGGCCAAGG
hSREBF1 R1	GTTTTCAGGAGTGGCCTCAT
hSREBF1 F2	AGCCCAGGCCCTTATTTC
hSREBF1 R2	AGTGTGCTTTTGGGTCAAGGA
hETNK F	GACCGGAGGCGAGAAA
hETNK R	TCTCGGAGAAAATTCCTGTT