

Supplementary Figure S1

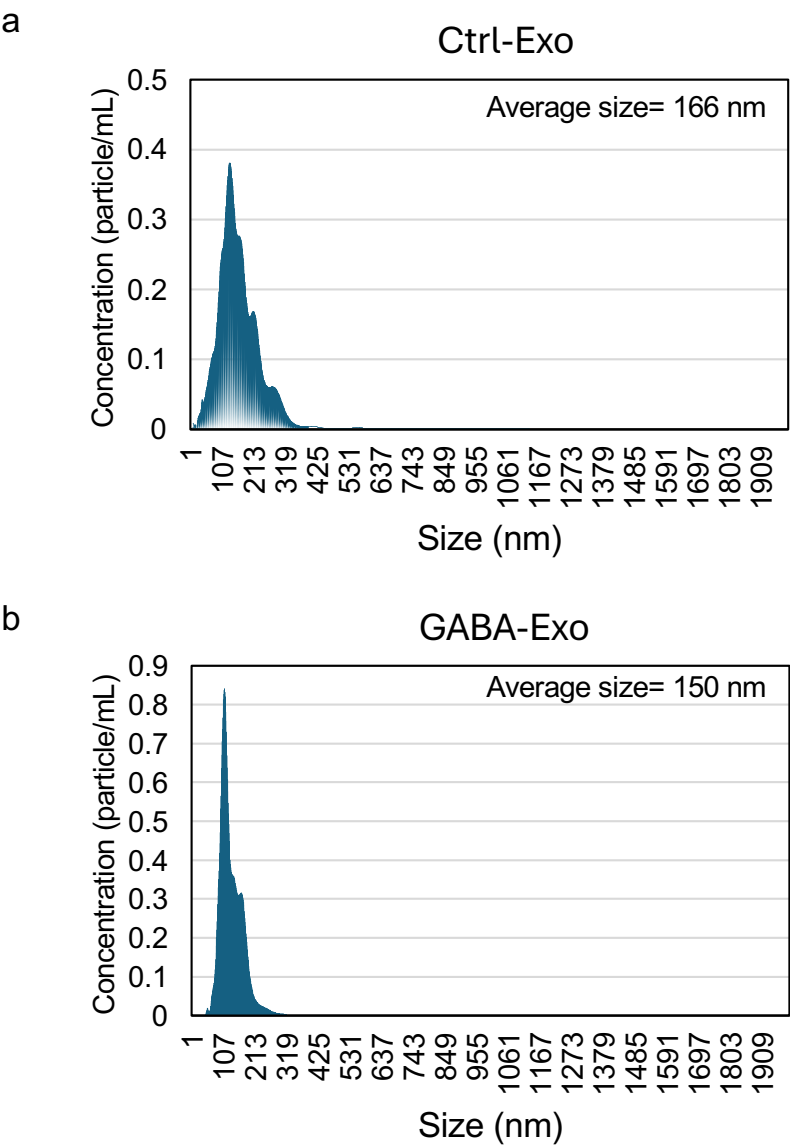


Figure S1. Size distribution of exosomes. Size distributions of plasma exosomes derived from Aged-Ctrl mice (a) and those from Aged-GABA mice (b) were analyzed by NanoSight (FUJIFILM). Particle size distribution was determined by nanoparticle tracking analysis (NTA), showing a typical exosomal size range.

Supplementary Figure S2

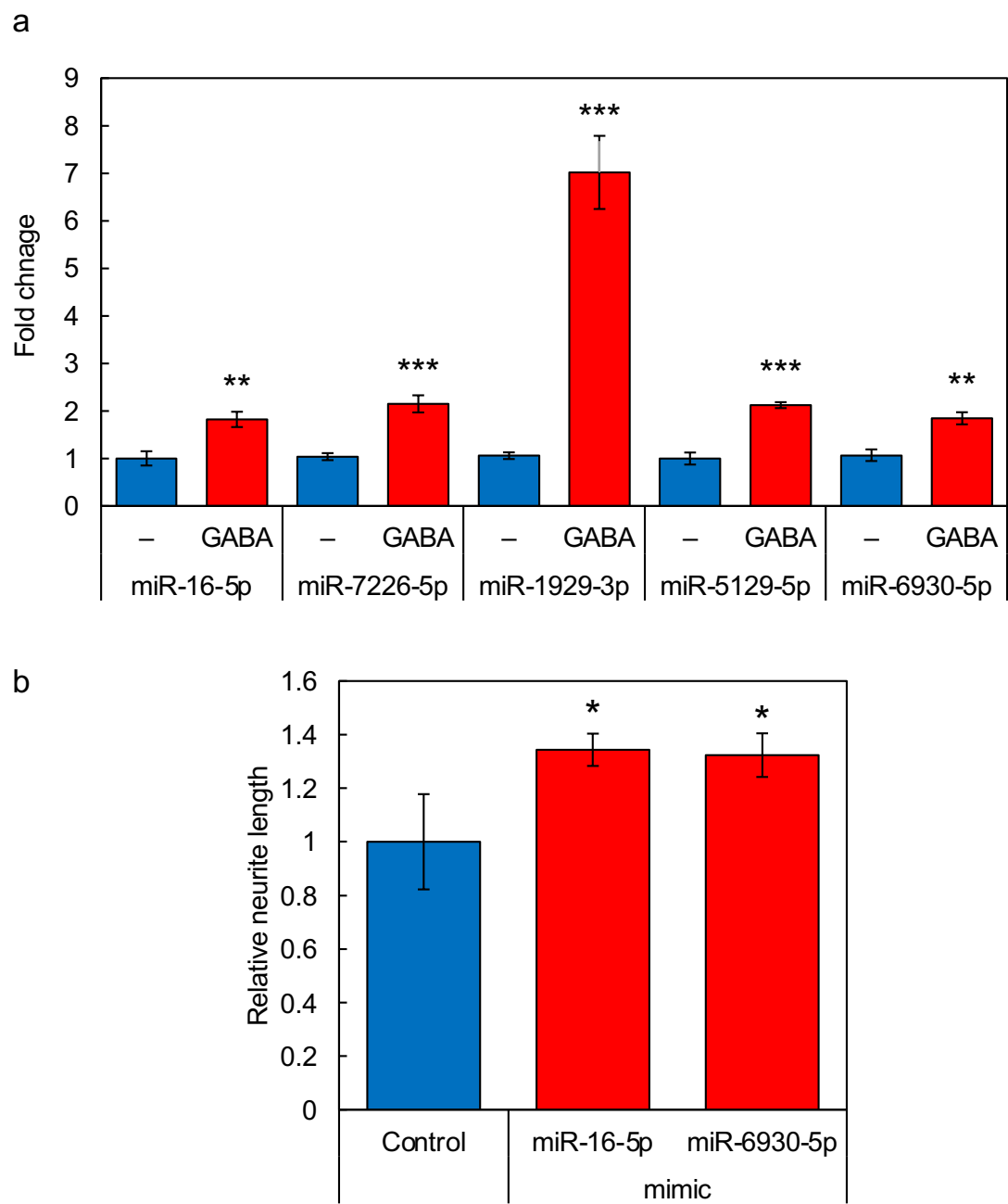


Figure S2. Expression and functional analysis of miRNA. a, Expression changes of selected miRNAs in exosomes derived from Aged-GABA mice (GABA) with those in exosomes derived from Aged-Ctrl mice (-). Total RNA in the exosomes was isolated using the miRNeasy Tissue/Cells Advanced Micro Kit (Qiagen). RT-qPCR was performed using the Mir-miRNA First-Strand Synthesis Kit (Takara) and TB Green Advantage qPCR Premix (Takara) according to the manufacturer's protocol. b, Neurite length in SH-SY5Y cells transduced with miR-16-5p mimic or miR-6930-5p mimic was determined by using the IN Cell Analyzer 2200.

Supplementary Figure S3

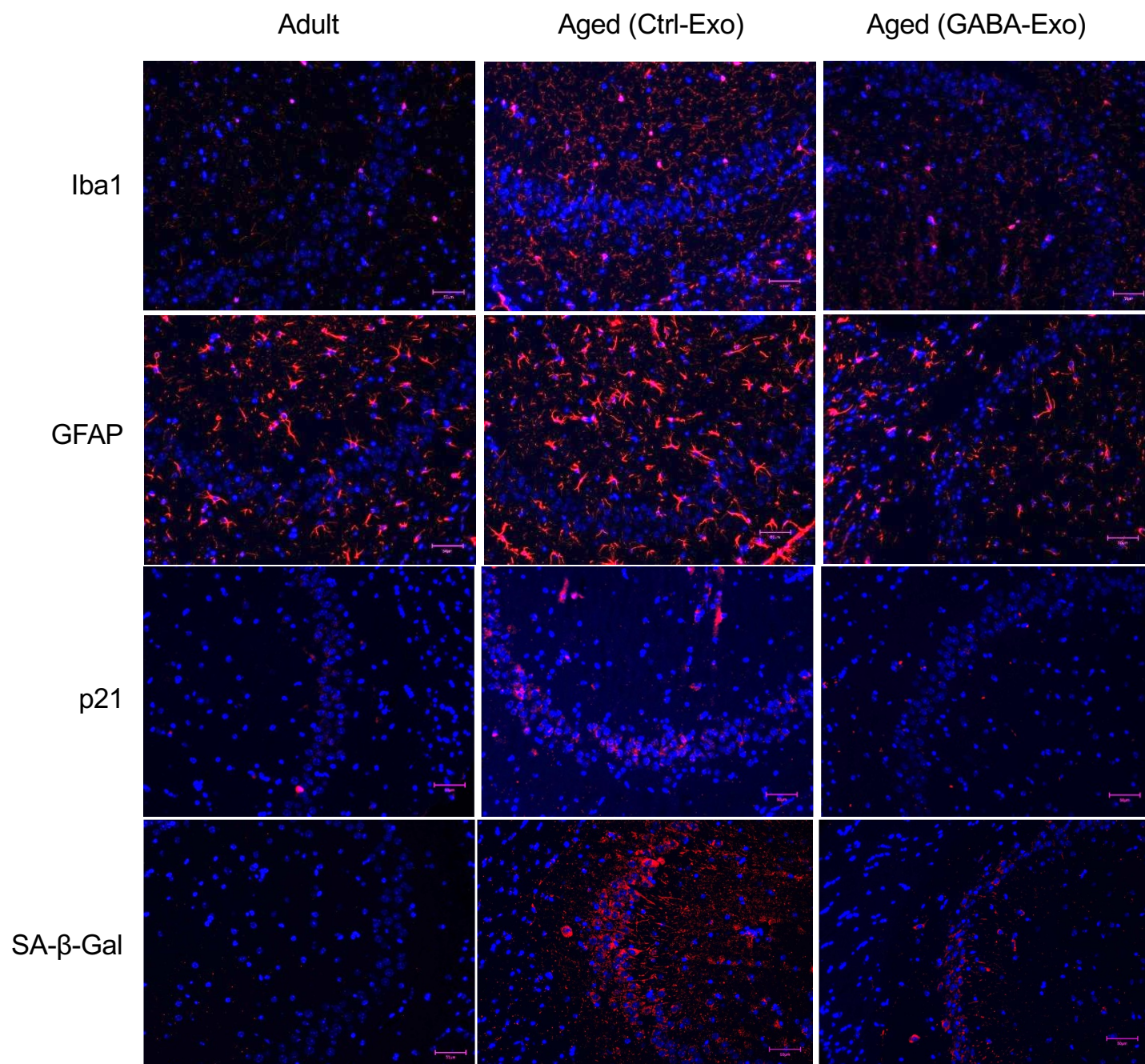


Figure S3. Effects of exosomes derived from GABA-ingested mice on hippocampus in aged mice. a, Brain sections (CA3) were incubated with primary antibody for anti-Iba1, anti-GFAP, anti-p21 and anti- β -galactosidase, and stained with Alexa Fluor 555.

Supplementary Figure S4

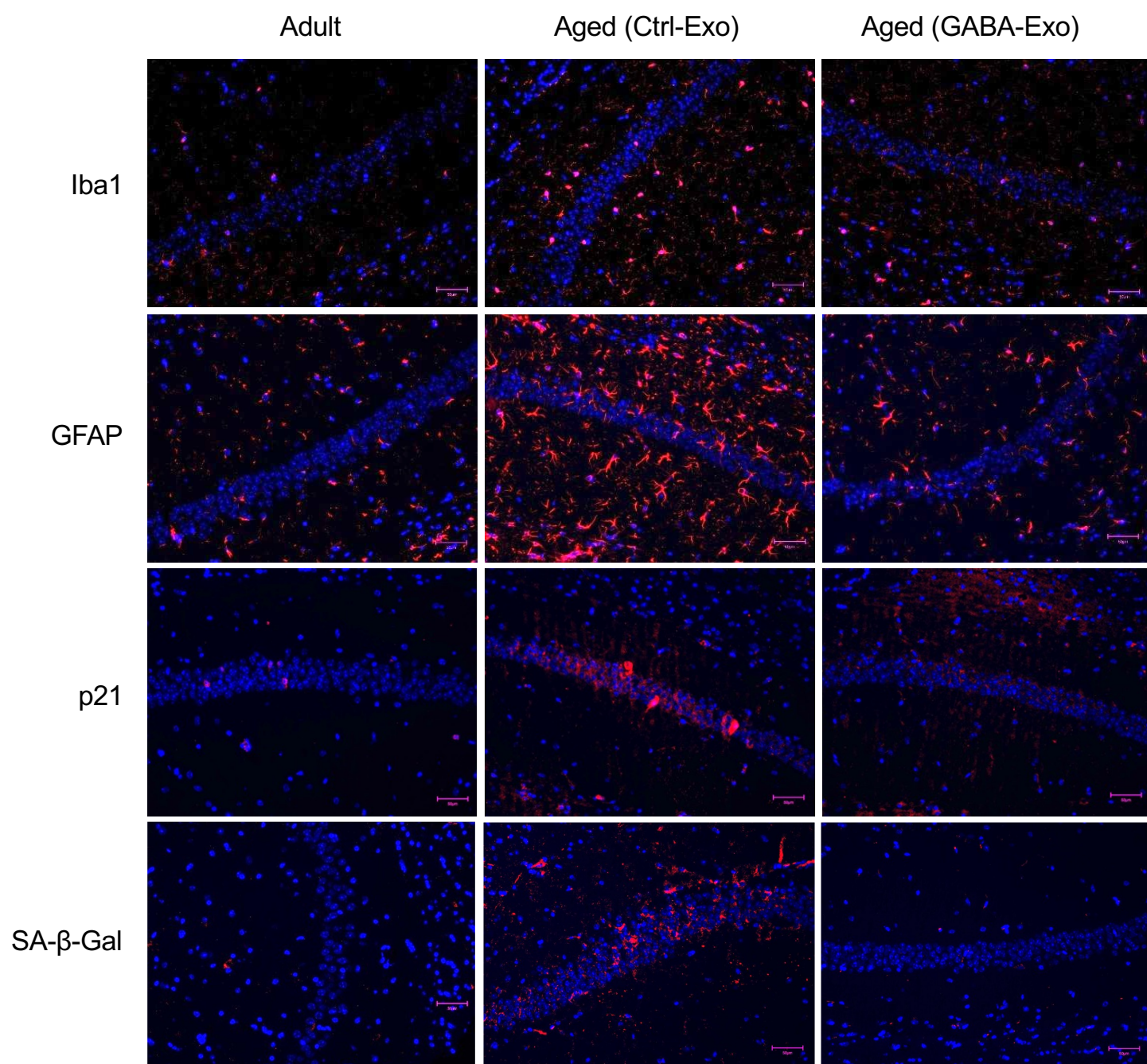


Figure S4. Effects of exosomes derived from GABA-ingested mice on hippocampus in aged mice. a, Brain sections (CA1) were incubated with primary antibody for anti-Iba1, anti-GFAP, anti-p21 and anti- β -galactosidase, and stained with Alexa Fluor 555.

Supplementary Figure S5

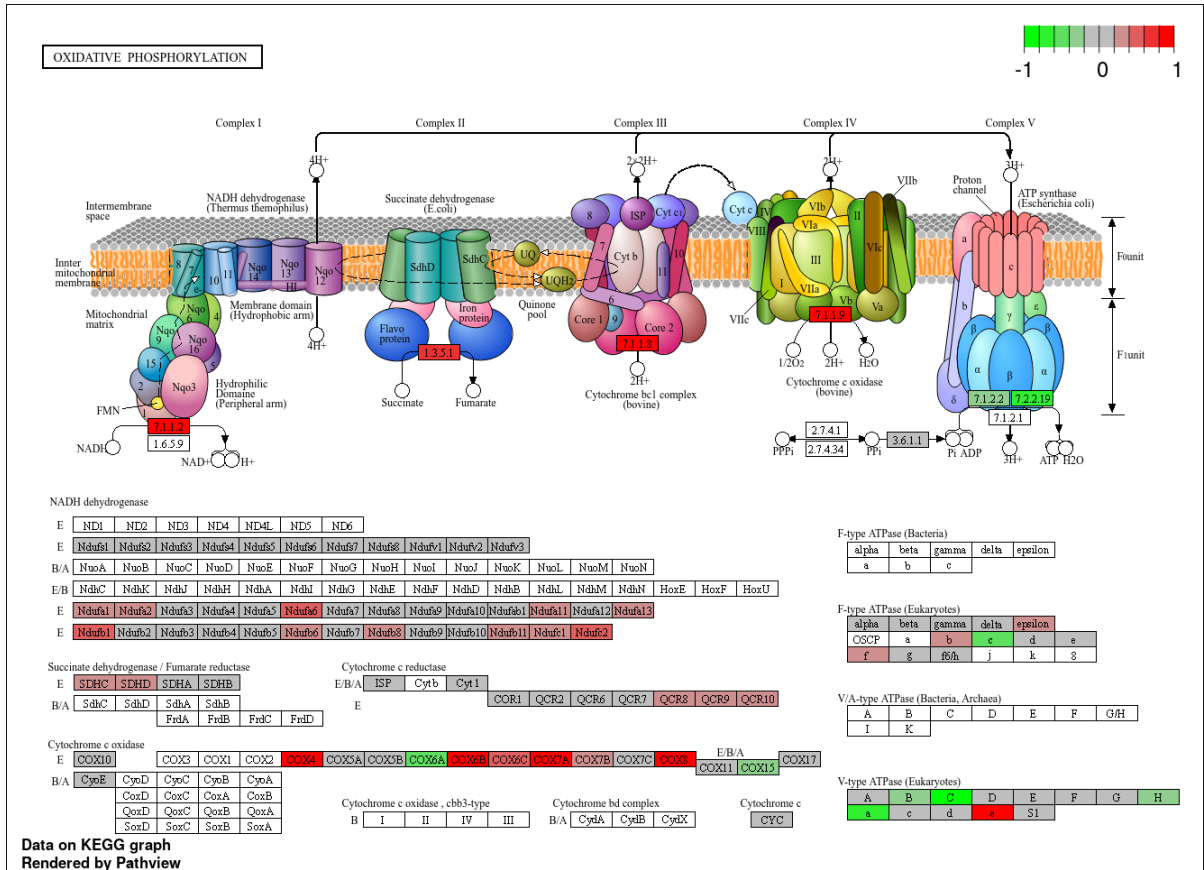


Figure S5. Comprehensive analysis of gene expression in the hippocampus. RNA-seq analysis revealed a change in gene expression in the hippocampus of Aged (GABA-Exo) compared with that of Aged (Ctrl-Exo). Many of the differentially expressed genes were involved in the oxidative phosphorylation pathway.

ALZHEIMER DISEASE

Neuron

Microglia

Phagophore

Modulation of gene expression
Induction of apoptosis

Oxidative phosphorylation

Mitochondria

ATP depletion
Fall in mitochondrial membrane potential
Increased ROS

Apoptosis

Cell death

Protein processing in endoplasmic reticulum

ER stress

Protein oxidation
Mitochondrial dysfunction
Apoptosis
DNA damage
Inflammation
Lipid peroxidation

Antioxidant responses
Amino acid metabolism

Reduction in LTP

Impairment of autophagy

Autophagy

Beclin 1 deficiency

ULK complex
PI3K complex
ATG5-ATG12-ATG16 conjugate
LC3-PE

ATG2

ATG14

NRBF2

VPS15

VPS34

PI3P

WIP1

TUBA

TUBB

Kinesin1

Anterograde Cargo

Axon transport defects

Neurofibrillary tangles (NFTs)

(Tau-P_{in})

Wnt signaling pathway

β-catenin

CK1ε

CK2

CK1δ

CK1γ

CK1ζ

CK1η

CK1θ

CK1ι

CK1j

CK1k

CK1l

CK1m

CK1n

CK1o

CK1p

CK1q

CK1r

CK1s

CK1t

CK1u

CK1v

CK1w

CK1x

CK1y

CK1z

CK1aa

CK1ab

CK1ac

CK1ad

CK1ae

CK1af

CK1ag

CK1ah

CK1ai

CK1aj

CK1ak

CK1al

CK1am

CK1an

CK1ao

CK1ap

CK1aq

CK1ar

CK1as

CK1at

CK1au

CK1av

CK1aw

CK1ax

CK1ay

CK1az

CK1ba

CK1bb

CK1bc

CK1bd

CK1be

CK1bf

CK1bg

CK1bh

CK1bi

CK1bj

CK1bk

CK1bl

CK1bm

CK1bn

CK1bo

CK1bp

CK1bq

CK1br

CK1bs

CK1bt

CK1bu

CK1bv

CK1bw

CK1bx

CK1by

CK1bz

CK1ca

CK1cb

CK1cc

CK1cd

CK1ce

CK1cf

CK1cg

CK1ch

CK1ci

CK1cj

CK1ck

CK1cl

CK1cm

CK1cn

CK1co

CK1cp

CK1cq

CK1cr

CK1cs

CK1ct

CK1cu

CK1cv

CK1cw

CK1cx

CK1cy

CK1cz

CK1da

CK1db

CK1dc

CK1dd

CK1de

CK1df

CK1dg

CK1dh

CK1di

CK1dj

CK1dk

CK1dl

CK1dm

CK1dn

CK1do

CK1dp

CK1dq

CK1dr

CK1ds

CK1dt

CK1du

CK1dv

CK1dw

CK1dx

CK1dy

CK1dz

CK1ea

CK1eb

CK1ec

CK1ed

CK1ee

CK1ef

CK1eg

CK1eh

CK1ei

CK1ej

CK1ek

CK1el

CK1em

CK1en

CK1eo

CK1ep

CK1eq

CK1er

CK1es

CK1et

CK1eu

CK1ev

CK1ew

CK1ex

CK1ey

CK1ez

CK1fa

CK1fb

CK1fc

CK1fd

CK1fe

CK1ff

CK1fg

CK1fh

CK1fi

CK1fj

CK1fk

CK1fl

CK1fm

CK1fn

CK1fo

CK1fp

CK1fq

CK1fr

CK1fs

CK1ft

CK1fu

CK1fv

CK1fw

CK1fx

CK1fy

CK1fz

CK1ga

CK1gb

CK1gc

CK1gd

CK1ge

CK1gf

CK1gg

CK1gh

CK1gi

CK1gj

CK1gk

CK1gl

CK1gm

CK1gn

CK1go

CK1gp

CK1gq

CK1gr

CK1gs

CK1gt

CK1gu

CK1gv

CK1gw

CK1gx

CK1gy

CK1gz

CK1ha

CK1hb

CK1hc

CK1hd

CK1he

CK1hf

CK1hg

CK1hh

CK1hi

CK1hj

CK1hk

CK1hl

CK1hm

CK1hn

CK1ho

CK1hp

CK1hq

CK1hr

CK1hs

CK1ht

CK1hu

CK1hv

CK1hw

CK1hx

CK1hy

CK1hz

CK1ia

CK1ib

CK1ic

CK1id

CK1ie

CK1if

CK1ig

CK1ih

CK1ii

CK1ij

CK1ik

CK1il

CK1im

CK1in

CK1io

CK1ip

CK1iq

CK1ir

CK1is

CK1it

CK1iu

CK1iv

CK1iw

CK1ix

CK1iy

CK1iz

CK1ja

CK1jb

CK1jc

CK1jd

CK1je

CK1jf

CK1jg

CK1jh

CK1ji

CK1jj

CK1jk

CK1jl

CK1jm

CK1jn

CK1jo

CK1jp

CK1jq

CK1jr

CK1js

CK1jt

CK1ju

CK1jv

CK1jw

CK1jx

CK1jy

CK1jz

CK1ka

CK1kb

CK1kc

CK1kd

CK1ke

CK1kf

CK1kg

CK1kh

CK1ki

CK1kj

CK1kk

CK1kl

CK1km

CK1kn

CK1ko

CK1kp

CK1kq

CK1kr

CK1ks

CK1kt

CK1ku

CK1kv

CK1kw

CK1kx

CK1ky

CK1kz

CK1la

CK1lb

CK1lc

CK1ld

CK1le

CK1lf

CK1lg

CK1lh

CK1li

CK1lj

CK1lk

CK1ll

CK1lm

CK1ln

CK1lo

CK1lp

CK1lq

CK1lr

CK1ls

CK1lt

CK1lu

CK1lv

CK1lw

CK1lx

CK1ly

CK1lz

CK1ma

CK1mb

CK1mc

CK1md

CK1me

CK1mf

CK1mg

CK1mh

CK1mi

CK1mj

CK1mk

CK1ml

CK1mm

CK1mn

CK1mo

CK1mp

CK1mq

CK1mr

CK1ms

CK1mt

CK1mu

CK1mv

CK1mw

CK1mx

CK1my

CK1mz

CK1na

CK1nb

CK1nc

CK1nd

CK1ne

CK1nf

CK1ng

CK1nh

CK1ni

CK1nj

CK1nk

CK1nl

CK1nm

CK1nn

CK1no

CK1np

CK1nq

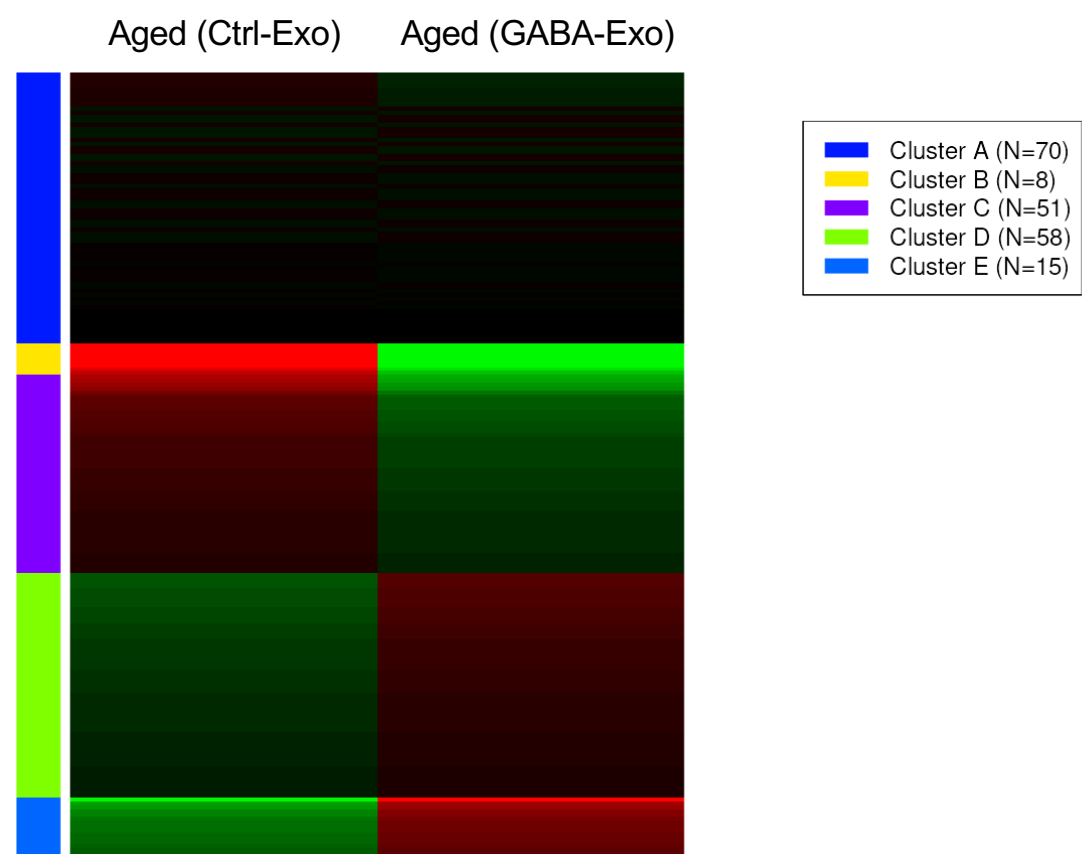
CK1nr

CK1ns

CK1nt

Figure S6. Comprehensive analysis of gene expression in the hippocampus. RNA-seq analysis revealed a change in gene expression in the hippocampus of Aged (GABA-Exo) compared with that of Aged (Ctrl-Exo). Many of the differentially expressed genes were involved in the Alzheimer's disease pathway.

Supplementary Figure S7



Cluster	p-value	Genes	Pathway
A	0.008	10	Modification-dependent macromolecule catabolic process
E	0.002	2	Positive regulation of glycogen biosynthetic process
E	0.003	2	Regulation of calcineurin-mediated signaling
E	0.003	2	Glycogen biosynthetic process
E	0.003	2	Glucan biosynthetic process
E	0.003	2	Regulation of glucan biosynthetic process
E	0.003	2	Regulation of polysaccharide metabolic process
E	0.003	2	Calcineurin-NFAT signaling cascade
E	0.003	2	Regulation of calcineurin-NFAT signaling cascade
E	0.003	2	Calcineurin-mediated signaling
E	0.003	2	Positive regulation of glucose metabolic process
E	0.003	2	Inositol phosphate-mediated signaling
E	0.004	2	Glycogen metabolic process
E	0.004	2	Cellular glucan metabolic process
E	0.004	2	Cellular polysaccharide biosynthetic process
E	0.004	2	Glucan metabolic process

Figure S7. Comprehensive analysis of gene expression in the hippocampus. RNA-seq analysis revealed a change in gene expression in the hippocampus of Aged (GABA-Exo) compared with that of Aged (Ctrl-Exo). Differential gene expression and pathway analyses were performed using the integrated iDEP web application (ver. 2.01, <http://bioinformatics.sdstate.edu/idep/>, accessed on February 1, 2024) .