















Figure S1 Inhibition of miR-4763-3p improves behavioral phenotyping in AD-MCI mice.

A: Volcano map of differentially expressed genes in serum non-coding RNA sequencing between AD patients and healthy controls, with red representing up-regulated genes in AD and blue representing down-regulated genes. $|\log_2FC| > 0.15$ and $p < 0.05$.

B: The MWM test was performed to analyze long-term memory. The frequency of occupancy of the target quadrant were measured (n = 10 per group).

C: The object recognition test was conducted to assess the spatial memory capacity. The frequency of exploration of objects were recorded (n = 10 per group).

D: The Y maze test was conducted to evaluate the spatial memory capacity. The frequency of exploration of the novel and familiar arms were recorded (n = 10 per group).

E: The Barnes maze test was performed to assess changes in cognitive ability. The path length (cm) to the target hole and the path length were recorded (n = 10 per group).

F: The motor ability of object recognition test exploration of objects were recorded.

Data are expressed as the mean \pm SEM of three independent experiments. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$.

Figure S2 Silencing of miR-4763-3p rescues the synaptic disorder in AD mice.

A: Golgi staining shows dendritic spine morphology injected with antagomir NC, antagomir, agomir, agomir NC. Scale bar, 200 or 50 μ m.

B, C: qRT-PCR analysis was performed to detect GLUR1 and GLUR2 in hippocampal homogenates from five different groups (n = 4).

D: The differential gene expression heatmap identified by RNA-seq for mice injected with the miR-4763-3p antagomir was significantly different from that for mice injected with the antagomir NC (AD-MCI-NC) (n = 3 per group).

E: The volcano plot shows a log₂-fold change on the x-axis and statistical

significance on the y-axis, with genes significantly different in abundance between mice injected with AD-MCI-NC and those injected with the miR-4763-3p antagomir.

The names of some differentially expressed genes are shown.

F: Volcano maps show differences in gene expression in hippocampal tissue after death between healthy controls and Alzheimer's patients.

G: GO enrichment analysis of differentially expressed genes. Data from GEO database (GSE173955).

Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure S3 MiR-4763-3p targets ATP11A.

A, B: Differences in the expression of *Atp11a* between WT (C57BL/6) and AD (AppNL-G-F) mice at different ages and in different brain regions. Data were taken from the Alzmap database.

C: RT-qPCR of the transfection efficiency of siATP11A.

D: RT-qPCR analysis of ATP11A expression in SH-SY5Y cells transfected with mimic NC, mimic, inhibitor, inhibitor NC and control.

E: Immunoblotting was evaluated the expression level of ATP11A in mouse hippocampal tissue from the antagomir NC, antagomir, agomir NC, and agomir groups.

F: Prediction of the binding sequence for miR-4763-3p and ATP11A using the RNAhybrid database.

G: Binding free energy of miR-4763-3p and ATP11A.

H, I: Plasmids were constructed according to the binding site between miR-4763-3p and wild-type ATP11A (ATP11A-WT); miR-4763-3p and mutant ATP11A (ATP11A-MUT).

Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure S4 The mechanism of miR-4763-3p/ATP11A/YY1 axis on cognitive

decline.

A-C: The Y maze test was conducted to assess spatial memory capacity. Frequency, distance in zone and duration of exploration of novel and familiar arms were recorded (n = 10 per group).

D-F: The object recognition tests were conducted to assess spatial memory capacity. The duration, distance in zone and frequency of exploration of novel object was recorded (n = 10 per group).

G, H: The morris water maze test was performed to analyze long-term memory. The duration and frequency of occupancy of the platform area was measured. The long-term memory performance of shATP11A mice was significantly reduced compared to NC mice. (n =10 per group).

I: Transcription factor network analysis for miR-4763-3p.

J: RT-qPCR was performed to detect YY1 expression levels in hippocampal tissues of Control and AD-MCI mice (n=4).

K: RT-qPCR was performed to detect the expression level of miR-4763-3p in SH-SY5Y transfected with NC or siYY1.

L: RT-qPCR was performed to detect the expression level of YY1 in SH-SY5Y transfected with mimic NC, mimic, inhibitor, inhibitor NC and control.

M: RT-qPCR was performed to detect the expression level of ATP11A in SH-SY5Y transfected with NC or siYY1.

Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure S5 MiR-4763-3p antagomir targets ATP11A to rescue early apoptosis.

A, B: Immunofluorescence staining of caspase 3 (green) in the CA1 and CA3 hippocampal regions of the mice brain from the five groups. Nuclei were stained with DAPI (blue). Scale bar, 100 μ m. The histograms show the relative expression of caspase 3.

C: Immunohistochemistry (IHC) staining for IL-6 and TNF- α in the mice brain from the five groups, scar bar, 50 μ m.

D, E: IL-6 and TNF- α positive areas were quantified after IHC assays (n=3).

F, G: RT-qPCR was performed to detect the expression level of IL-6 and TNF- α in brain tissue.

H, I: IL-34 expression in miR-antagomir and AD-MCI-NC sequencing data(H); IL-34 expression level in five groups was detected by qPCR(I).

Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Figure S6 MiR-4763-3p antagomir targets ATP11A to rescue apoptosis in neurons

A-C: Flow cytometry analysis of PS exposure in SH-SY5Y cells transfected with the miR-4763-3p inhibitor and siATP11A.

D-H: Flow cytometry analysis of the apoptotic rate of SH-SY5Y cells transfected with the miR-4763-3p inhibitor or siATP11A. The histogram shows the percentage of early and late apoptotic cells.

I, J: The histograms show the relative protein expression of PTSS1 and caspase 3. Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Figure S7 MiR-4763-3p antagomir/ATP11A increases autophagic flux in neurons.

A: IF staining of SQSTM1 (green) in the hippocampal region of mice brain from the antagomir NC, antagomir, agomir NC, and agomir groups. Nuclei were stained with DAPI (blue). Scale bar, 50 μ m.

B-G: Western blot analysis of autophagy flux markers in SH-SY5Y cell transfected mimic, mimic NC, inhibitor, inhibitor NC and control groups (B, C); NC, siATP11A (D, E) and inhibitor, siATP11A and inhibitor co-transfected with siATP11A (F, G).

Data are expressed as the mean \pm SEM of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure S8 miR-4763-3p antagomir/ATP11A inhibits the PI3K/AKT/mTOR signaling pathway to mediate crosstalk between autophagy and apoptosis

RT-qPCR analysis of mTOR, PI3K, AKT, Beclin1, and Bcl2 mRNA expression. GAPDH served as an internal reference gene. Data are expressed as the mean \pm SD

of three independent experiments. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$.

Table S1: List of PCR and qPCR primers used in this study

Primers for qPCR (Name ID-human)	
U6-F	TGGAACGATACAGAGAAGATTAGCA
U6-R	TATGGAACGCTTCACGAATTTGC
GAPDH-F	GGAGCGAGATCCCTCCAAAAT
GAPDH-R	GGCTGTTGTCATACTTCTCATGG
ATP11A-F	CAAACAGGGTTATGAAGACTGGC
ATP11A-R	TGCCGTGCTGAATGAAATGAA
Caspase3-F	GAAATTGTGGAATTGATGCGTGA
Caspase3-R	CTACAACGATCCCCTCTGAAAAA
PTDSS1-F	GCAAGTGGAGGACATCACCAT
PTDSS1-R	TCATCCCTGGTAAAGGCGAAG
GLUR1-F	CGAGCTTTCCCGTTGATACAT
GLUR1-R	CATTCAGATGAGACCCGACCT
GLUR2-F	TCTGCCACTTGTAATGGTCAATG
GLUR2-R	GGTATGCAAACCTTGTCCCATTGA
YY1-F	ACGGCTTCGAGGATCAGATTC
YY1-R	TGACCAGCGTTTGTTC AATGT
BCL2-F	GGTGGGGTCATGTGTGTGG
BCL2-R	CGGTT CAGG TACTCAGTCATCC
LC3B-F	AAGGCGCTTACAGCTCAATG
LC3B-R	CTGGGAGGCATAGACCATGT
SQSTM1-F	GACTACGACTTGTGTAGCGTC
SQSTM1-R	AGTGTCCGTGTTT CACCTTCC
TNF- α -F	GACGTGGAAC TGGCAGAAGAG
TNF- α -R	TTGGTGGTTTGTGAGTGTGAG
IL-6-F	TAGTCCTTCTACCCCAATTTCC
IL-6-R	TTGGTCCTTAGCCACTCCTTC
MTOR-F	TCCGAGAGATGAGTCAAGAGG
MTOR-R	CACCTTCCACTCCTATGAGGC
AKT-F	AGCGACGTGGCTATTGTGAAG
AKT-R	GCCATCATTCTTGAGGAGGAAGT
Beclin1-F	GGTGTCTCTCGCAGATTCATC
Beclin1-R	TCAGTCTTCGGCTGAGGTTCT
PI3K-F	CCACGACCATCATCAGGTGAA
PI3K-R	CCTCACGGAGGCATTCTAAAGT

Table S2: List of PCR and qPCR primers used in this study

Primers for qPCR (Name ID-mouse)	
PI3K-F	ACACCACGGTTTGGACTATGG
PI3K-R	GGCTACAGTAGTGGGCTTGG
AKT-F	ATGAACGACGTAGCCATTGTG
AKT-R	TTGTAGCCAATAAAGGTGCCAT
MTOR-F	CACCAGAATTGGCAGATTTGC
MTOR-R	CTTGGACGCCATTTCCATGAC
GAPDH-F	AGGTCGGTGTGAACGGATTG
GAPDH-R	GGGGTCGTTGATGGCAACA
ATP11A-F	GCTTACTACATTGGCCAGATT
ATP11A-R	AGGCTGGTACATGGTCTTGAA
Caspase3-F	ATGGAGAACAACAAAACCTCAGT
Caspase3-R	TTGCTCCCATGTATGGTCTTTAC
PTDSS1-F	GCAGGACTCTGAGCAAGGATG
PTDSS1-R	GGCGAAGTACATGAGGCTGAT
GLUR1-F	TCCCCAACAATATCCAGATAGGG
GLUR1-R	AAGCCGCATGTTCTGTGATT
GLUR2-F	TTCTCCTGTTTTATGGGGACTGA
GLUR2-R	CACTCTCGATGCCATATACGTTG
YY1-F	CAGTGGTTGAAGAGCAGATCAT
YY1-R	AGGGAGTTTCTTGCCTGTCAT
BCL2-F	GTCGCTACCGTCGTGACTTC
BCL2-R	CAGACATGCACCTACCCAGC
LC3B-F	TTATAGAGCGATAACAAGGGGGAG
LC3B-R	CGCCGTCTGATTATCTTGATGAG
SQSTM1-F	AGGATGGGGACTTGGTTGC
SQSTM1-R	TCACAGATCACATTGGGGTGC
TNF- α -F	CCCTCACACTCAGATCATCTTCT
TNF- α -R	GCTACGACGTGGGCTACAG
IL-6-F	TAGTCCTTCCTACCCCAATTTCC
IL-6-R	TTGGTCCTTAGCCACTCCTTC
Beclin1-F	ATGGAGGGGTCTAAGGCGTC
Beclin1-R	TCCTCTCCTGAGTTAGCCTCT

Table S3: List of PCR and qPCR primers used in this study

Primers for CHIP-qPCR (Name ID)	
ATP11A-0kb-F	GCTGCTGCATTGTCAACCAA
ATP11A-0kb-R	GGGTGAGACATGTTGTCGGT
ATP11A -(+0.5kb)-F	CTGGGACCCTGGCTGAAAC
ATP11A -(+0.5kb)-R	CTTCTCTCTCCCCGTCGGTC
ATP11A -(+4kb)-F	TCCAGCTGACTTCGGTGAAC
ATP11A -(+4kb)-R	CTGGAGGGGAAATGGCTCAG
ATP11A -(+3kb)-F	TGTGGGTCCCTAGACACCTT
ATP11A -(+3kb)-R	TGTCCCCCTCCCAAGATGAA
ATP11A -(+5kb)-F	ACATAGCTGAGTCCCTGGGT
ATP11A -(+5kb)-R	TCCACACCATGCTCAGTGTC
ATP11A -(3kb)-F	AGGTTAGAGAATGGCCTGCG
ATP11A -(3kb)-R	CCTAGGTGACCATCTCCCCA
ATP11A -(5kb)-F	GAAACGGAGCCAATGATCGC
ATP11A -(5kb)-R	CACACCCATCCTGAGACACC

Table S4: The sequences of siRNAs

(Name ID)	Target sequence
SiATP11A-#1-F	GCAUAGGUGUCAUCGGCAATT
SiATP11A-#1-R	UUGCCGAUGACACCUAUGCTT
SiATP11A-#2-F	GACGUUUGGAACGCUGGUAUU
SiATP11A-#2-R	AAUACCAGCGUCCAAACGUC
SiATP11A-#3-F	CCAGAGGAUGUACUACGUGUU
SiATP11A-#3-R	AACACGUAGUACAUCUCUGG

Table S5: miR-4763-3p agomir/antagomir sequence information list

(Name ID)	Target sequence
miR-4763-3p antagomir	CCCGCCAGCACCAGCCCCUGCCU
miR-4763-3p agomir	AGGCAGGGGCUGGUGCUGGGCGGG

Table S6: List of Antibodies used in this study

Antibody	Company	Cat. No.	Species
p-PI3K	Cell Signaling Technology	4228T	Rabbit
p-PI3K	Abways	CY6428	Rabbit
PI3K	Proteintech	67644-1-Ig	Mouse
p-AKT	Abways	CY6569	Rabbit
AKT	Abways	CY5561	Rabbit
mTOR	Abways	CY8744	Rabbit
p-mTOR	Abways	CY5996	Rabbit
Bcl2	ABclonal	A19693	Rabbit
Beclin1	ABclonal	A21191	Rabbit
Caspase3	ABclonal	A0214	Rabbit
YY1	Cell Signaling Technology	46395S	Rabbit
IL-6	ABclonal	A21264	Rabbit
TNF-α	ABclonal	A11534	Rabbit
NeuN	Abcam	ab177487	Rabbit
Iba1	Abcam	ab178846	Rabbit
Annexin V	Abways	CY6721	Rabbit
SQSTM1	ABclonal	A19700	Rabbit
β-Amyloid(1-42)	ABclonal	A24422	Rabbit
beta Tubulin	Bioss	bsm-33034M	Mouse
ATP11A	Invitrogen	PA5-20995	Rabbit
beta Actin	Abways	AB2001	Mouse
IgG	ABclonal	AC011	Mouse
GAPDH	Abways	AB0036	Rabbit
Vinculin	Abways	CY5164	Rabbit