

Integrative Multiomics Analysis Reveals a Coordinated Molecular Signature of Neuroresilience in human MAPT-knockout hiPSC-derived Neurons with relevance for Alzheimer's and Neurodegenerative Disease

Elnaz Amanzadeh Jajin

University of Cologne

Hans Zempel

`hans.zempel@uk-koeln.de`

University of Cologne

Research Article

Keywords: Alzheimer's Disease, MAPT knockout, Multiomics Integration, Neuroresilience, Proteomics, Transcriptomics

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11112521/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Transcriptome data provides a robust analytical viewpoint about cellular processes in Alzheimer's Disease (AD). Integrative multiomics analysis including transcriptome and proteome data elucidates the underlying mechanisms of this progressive disease. The microtubule-associated protein Tau (*MAPT*) is central to Alzheimer's disease (AD) pathogenesis. We demonstrated that Tau loss confers resistance to amyloid-beta ($A\beta$) toxicity in AD-relevant human glutamatergic neurons, but the active molecular reprogramming driving this neuroresilience remains poorly defined.

Methods

We employed an integrative multiomics approach, combining temporal transcriptomics (3h and 24h post- $A\beta$ exposure) with newly processed proteomic layers from terminally differentiated and electrophysiologically active human iPSC-derived neurons (WT vs. *MAPT*-Knockout (KO)). Analysis included DESeq2, WGCNA, and GSEA, followed by cross-layer integration to identify convergent molecular signatures and master regulators.

Results

Our analysis revealed a striking transcriptomic stagnation in WT neurons, which failed to mount an adaptive response to $A\beta$ stress. In contrast, *MAPT*-KO neurons exhibited a pre-established resilience signature characterized by profound baseline reprogramming. WGCNA identified a co-expression gene cluster (turquoise module, $r = 0.74$) strongly associated with the *MAPT*-KO phenotype and enriched in mitochondrial transport, autophagy, and synaptic homeostasis. Key hub genes including *SIM1*, *INPP5F*, and *AKR1C2* established a mitochondrial metabolic defense mechanism. Multiomics integration identified 27 core consensus hits (e.g., *COL17A1*, *PER3*, *ST3GAL6*) consistently preserved across both layers. Furthermore, transcription factor enrichment identified *KLF4* (Kruppel-like Factor 4), a key regulator of neuronal differentiation and metabolic adaptation, as the master regulator orchestrating this protective network.

Conclusion

These findings demonstrate that Tau deletion induces an active, multilevel gain-of-resilience rather than passive resistance. By identifying a *KLF4*-driven molecular signature, this study highlights novel therapeutic targets that could be leveraged to induce synthetic resilience in AD patients, protecting neurons from amyloid-induced bioenergetic and structural collapse.

Introduction

Alzheimer's disease (AD) ranks as the seventh leading cause of death worldwide among all diseases and medical conditions. Due to the higher diagnostic rates and aging populations, it accounts for a significantly higher mortality burden in developed regions, ranking among the top five leading causes of death in Europe and the United States. Dementia affects approximately 55 million people globally, with 10 million new cases diagnosed each year, a burden driven largely by population aging. As the most common cause of dementia, Alzheimer's disease directly claims 1.6 to 1.9 million lives - annually ¹. Researchers worldwide are actively investigating underlying mechanisms and putative therapeutic targets for this disease ².

Accumulation of (hyperphosphorylated) Tau and amyloid- β along with synapse loss and microtubules destabilization are considered as the main hallmarks of AD. While the accumulation of amyloid-beta ($A\beta$) plaques is considered the primary driver of AD pathology, clinical evidence and only partially successful amyloid-clearing therapies indicate that $A\beta$ plaques alone do not fully explain dementia progression ^{3,4}. Also, brain amyloid burden correlates weakly with the severity of memory loss in patients, though Tau protein pathological accumulation correlates strongly with cognitive decline ⁵. Neurofibrillary tangles composed of hyperphosphorylated Tau protein (encoded by the *MAPT* gene) show a strong correlation with synaptic impairment and neuronal loss ⁶. Under physiological conditions, Tau stabilizes axonal microtubules as a structural protein. Pathologically, however, it undergoes post-translational modifications, most notably hyperphosphorylation, causing its detachment from microtubules and missorting to dendrites which is related to the mitochondrial mislocalization ^{5,7,8}.

Although $A\beta$ accumulation and Tau missorting frequently co-occur in Alzheimer's disease, the precise mechanistic sequence and degree of their synergistic interaction remain incompletely understood. Crucially, emerging evidence indicates a non-linear interplay where Tau acts as an essential downstream mediator of $A\beta$ -induced toxicity. This is supported in *MAPT*-KO mouse models ^{9,10} and derived primary neurons ⁷, which demonstrate that Tau depletion attenuates $A\beta$ -driven synaptic dysfunction and bioenergetic collapse without requiring the clearance of $A\beta$ plaques itself.

Recently, the application of induced pluripotent stem cells (iPSCs) combined with CRISPR-Cas9 gene editing has revolutionized our understanding of AD pathogenesis. We demonstrated previously that *MAPT*-KO in human iPSC-derived neurons confers strong protection against $A\beta$ oligomer-induced toxicity, providing robust neuroprotection. Notably, we identified a distinct role for specific Tau isoforms, showing that the re-expression of the 1N4R Tau isoform in *MAPT*-KO neurons fully restores vulnerability to $A\beta$ and triggers synaptic dysfunction. These results reinforce Tau's role as an obligate mediator of $A\beta$ toxicity while highlighting the potential of isoform-specific therapeutic strategies targeting 1N4R function ^{11,12}.

Our current understanding of altered signaling cascades and protein-protein interactions in *MAPT*-KO cells is limited, underscoring the need for comprehensive multiomics analyses to elucidate pathway and

reprogramming conferring AD resistance. Critical questions persist: How do Tau-deficient neurons maintain structural and functional stable? Is this passive compensation or active genetic/proteomic reprogramming?

While the phenotypic resistance of *MAPT*-KO neurons was previously reported, this study provides a comprehensive multiomics framework by integrating matched transcriptomic and proteomic profiles derived from the same human iPSC-derived neuronal models. By pairing raw transcriptomic analysis with newly generated proteomic layers from identical cellular contexts, we delineate coordinated molecular signatures that transcend a single level of biological regulation. The main aim of this project is to identify unique molecular signatures in human neurons that exhibit resistance to AD pathology. Using this integrated approach, we show that *MAPT* knockout is not only associated with the structural alterations, but also it is related to a broad reprogramming of key cellular pathways, including response to endoplasmic reticulum (ER) stress. Our findings highlight the critical roles of genes such as *COL17A1*, *DEPDC1B*, *PER3*, *TNFRSF9*, and *ST3GAL6* in maintaining cellular homeostasis and synaptic stability in the absence of Tau. Altogether, these results propose novel and promising therapeutic targets that may mimic the Tau-deficient protective state in AD patients and facilitate the development of preventive therapeutic strategies.

Methods

RNA isolation and Quality Control

In this study, we used the WTC11 human induced pluripotent stem cell (hiPSC) line, harboring a doxycycline-inducible *Ngn2* transgene, to generate glutamatergic neurons. *MAPT* knockout (*MAPT*-KO) was generated using CRISPR-Cas9 genome editing, were performed as previously described¹³. Briefly, WT and *MAPT*-KO iPSCs were differentiated into glutamatergic neurons, and mature neurons were exposed to amyloid beta oligomers (A β O) or vehicle control prior to downstream transcriptomic analysis.

Total RNA was extracted from hiPSC neurons using the PureLink RNA Mini Kit (Thermo Fisher Scientific) according to the manufacturer's instructions, including chemical lysis, column-based purification, and elution in RNase-free water. RNA concentration and purity were assessed by spectrophotometry, and RNA integrity was verified using an automated electrophoresis system. Only samples with an RNA Integrity Number (RIN) greater than 8 was used for downstream RNA-seq analysis.

For gene expression validation, total RNA was reverse-transcribed into cDNA using the ProtoScript II First Strand cDNA Synthesis Kit (New England Biolabs). *MAPT* knockout efficiency and isoform expression levels were quantified by quantitative PCR (qPCR) using Power SYBR Green Master Mix on a StepOnePlus Real-Time PCR System (Applied Biosystems).

Whole transcriptome sequencing and re-analysis

Library preparation and sequencing

To gain novel mechanistic insights into Tau-mediated resilience, we revisited and re-analyzed the whole-transcriptome mRNA sequencing dataset from wild-type (WT) and *MAPT*-KO hiPSC-derived neurons at day 21 of differentiation¹³. Samples were collected 3- and 24-hours following exposure to 1 μ M A β oligomers (A β O) or vehicle control, using three independent biological replicates per condition. Library preparation and paired-end sequencing were conducted by Novogene (Cambridge, UK) on the Illumina NovaSeq 6000 platform to enable downstream differential expression analysis.

Pseudoalignment and quantification

Raw FASTQ files were categorized into eight experimental groups: WT.CON.3, WT.AB.3, KO.CON.3, KO.AB.3, WT.CON.24, WT.AB.24, KO.CON.24, and KO.AB.24. Transcript abundance was quantified using Kallisto (v0.46.0) via pseudo-alignment against the human reference transcriptome (GRCh38). This quantification provided the transcript-level counts used as input for downstream statistical and differential expression analyses.

Statistical Analysis and Bioinformatics Framework

Differential expression analysis across the multi-factorial design (Genotype $\times$ Treatment) was conducted using the DESeq2 package (v1.40.2). To identify genes exhibiting statistically significant expression variation across experimental conditions, a generalized linear model (GLM) was fitted using the Likelihood Ratio Test (LRT). The statistical design incorporated technical covariates and interaction terms ($\sim$ Batch + Genotype + Treatment + Genotype: Treatment). The inclusion of batch covariates allowed us to control for potential technical variations, while the interaction term (Genotype:Treatment) evaluated genotype-specific transcriptomic responses to A β exposure relative to general treatment effects.

To handle count heteroskedasticity and normalize for library size, a Variance Stabilizing Transformation (VST) was applied to raw counts prior to exploratory data analysis, including Principal Component Analysis (PCA) and hierarchical clustering. For accurate effect size estimation, Log2 Fold Change (LFC) shrinkage was performed using the apeglm algorithm. Potential single-sample outliers were evaluated using Cook's distance as implemented in DESeq2. Multiple testing correction was performed using the Benjamini-Hochberg procedure, with genes defined as significantly differentially expressed (DEGs) at an adjusted p-value (FDR) < 0.05.

In addition to the global interaction model, a series of pairwise comparisons was conducted to evaluate treatment effects within each genotype separately. Specifically, A β -induced transcriptome changes were assessed independently in WT and *MAPT*-KO neurons. This stratified approach isolated A β -induced

stress responses from baseline variations associated with *MAPT* knockout, facilitating the identification of gene networks which may confer cellular resilience.

Weighted Gene Co-expression Network Analysis (WGCNA) and Identification of Key Modules

To evaluate co-expression patterns associated with *MAPT* deficiency and A β response, Weighted Gene Co-expression Network Analysis was performed using the WGCNA package. Count data were normalized, and low-abundance or low-variance transcripts were removed prior to network construction. Hierarchical clustering of samples was conducted to assess sample relationships and evaluate potential outliers. A soft-thresholding power (β) was selected based on the scale-free topology criterion, achieving an R^2 threshold > 0.8 . The resulting adjacency matrix was converted into a Topological Overlap Matrix (TOM), and co-expression modules were identified using the dynamic tree cut algorithm with a minimum module size of 30 genes.

Subsequently, a module eigengene (ME) was computed for each identified module to summarize its predominant expression trajectory across sample groups. MEs were correlated with experimental covariates (genotype and treatment) using Pearson correlation analysis to identify modules associated with the protective *MAPT*-KO phenotype. To determine the biological pathways represented by candidate modules, functional enrichment analysis was performed against Gene Ontology (GO) and KEGG database annotations. Finally, hub genes were defined based on high intramodular connectivity (high module membership, κ_{ME}), and their expression trajectories were further characterized across experimental conditions.

Proteomics Bioinformatic Pipeline and Differential Abundance Analysis

Differential protein abundance from mass spectrometry (MS) data was evaluated using the limma package in the R/Bioconductor environment. Raw protein intensities were log₂-transformed and normalized via global median centering to align intensity distributions across runs. To handle missing values, a two-step processing strategy was applied. First, proteins with greater than 20% missing values across the dataset were filtered out. Second, remaining missing values were imputed using the Minimum Detection (MinDet) method, assuming a Missing Not at Random (MNAR) mechanism typical for low-abundance features.

Differential abundance analysis was performed using linear models with Empirical Bayes (eBayes) variance moderation. P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure. p-values were adjusted for multiple testing using the Benjamini-Hochberg procedure. Differentially expressed proteins (DEPs) were defined at an adjusted p-value (FDR) < 0.05 and an

absolute log2 fold-change threshold of [e.g., $|\log_2\text{FC}| > 0.58$]. with differentially expressed proteins (DEPs) defined at an adjusted p-value (FDR) < 0.05 and a specified log2 fold-change threshold.

Integrative Multiomics Analysis and Functional Systems Biology

To integrate transcriptomic and proteomic profiles, a cross-platform concordant analysis was performed. Genes and their corresponding proteins were categorized as consensus hits if they met two criteria: (I) statistically significant differential abundance (FDR < 0.05) in both the RNA-seq and mass spectrometry datasets, and (II) a concordant direction of log2 fold-change. This dual-filtering approach was implemented to prioritize robust molecular features exhibiting coordinated regulation across transcriptional and translational layers in the *MAPT*-KO model.

Functional Enrichment and Master Regulator Prediction

To evaluate potential functional contexts associated with the consensus hits, Over-Representation Analysis (ORA) was performed using the clusterProfiler R package (v4.8.0). Consensus features were mapped against the Gene Ontology Biological Process (GO:BP) and KEGG databases to identify significantly enriched terms, with statistical significance was defined at a Benjamini-Hochberg (BH) adjusted p-value < 0.05 .

To identify potential transcription factors associated with the integrated target profile, transcription factor enrichment analysis was performed using the enrichR package. Downstream targets of candidate transcription factors were evaluated using the ChEA (2022) and TRRUST databases. Candidate transcription factors were prioritized using the combined score metric, which incorporates both the p-value and odds ratio. Finally, potential functional interactions and network topology among the consensus features were explored using the STRING database (v12.0), incorporating a high-confidence interaction score threshold (≥ 0.70).

Results

Experimental setup, Preprocessing and Quality Assessment of Transcriptomic Data

To elucidate the global molecular networks governing Tau-mediated neuroresilience against amyloid toxicity, we leveraged an isogenic human iPSC-derived neuronal model (WTC11 *Ngn2*-glutamatergic neurons) comprising wild-type (WT) and CRISPR-Cas9-edited *MAPT*-knockout (*MAPT*-KO) cohorts. Mature neurons (Day 21) were exposed to 1 μM amyloid-beta oligomers ($\text{A}\beta\text{O}$) or vehicle control for 3 hours and 24 hours, yielding eight distinct experimental conditions with three independent biological replicates per group ($n = 24$ total transcriptomic samples). To capture multi-layered regulatory dynamics, this setup was integrated with matching high-resolution quantitative proteomics profiling. A comprehensive quality control and statistical validation assessment was performed on the raw

transcriptomic data across all eight experimental groups. Analysis of total read counts revealed a high and consistent sequencing depth across all cohorts, providing a reliable foundation for comparative analysis.

To evaluate global transcriptomic variance, Principal Component Analysis (PCA) was performed on variance-stabilized counts. The PCA plot showed a clear primary separation based on genotype along PC1 (Fig. 1A). *MAPT*-KO samples from both 3h and 24h time points grouped closely together, indicating high consistency in the Tau-deficient transcriptome profile across time points. Concordance among biological replicates suggested that the observed variance reflected biological differences rather than technical noise. Additionally, gene-wise dispersion analysis demonstrated shrinkage of dispersion estimates toward the fitted trend line, indicating that variance was effectively stabilized across the multi-factorial design (Fig. 1B).

To evaluate the effectiveness of the normalization procedure, a density plot of gene expression distributions was generated (Fig. 1C). Prior to normalization, minor variations in counts distributions were present due to technical differences in library size. Following normalization, the expression density curves aligned closely across biological replicates and experimental conditions (WT and *MAPT*-KO, with or without A β). This alignment indicates that technical variation in sequencing depth was minimized, providing normalized count data suitable for downstream differential expression analysis.

To observe patterns among the most variable features, hierarchical clustering was performed on the top differentially expressed genes (DEGs) (Fig. 1D). The resulting dendrogram showed a primary separation between WT and *MAPT*-KO genotypes. Expression profiles of these top DEGs were consistent between the 3h and 24h time points in the *MAPT*-KO group, despite minor time-dependent fluctuations at the individual gene level. Specifically, while WT neurons displayed distinct transcriptional changes following A β exposure, *MAPT*-KO neurons maintained a profile closely aligning with their non-treated controls across both time points.

To characterize the transcriptional dynamics driving Tau-mediated neuroresilience, pairwise differential expression analyses were conducted across experimental conditions. Direct comparisons between WT-Ctrl and *MAPT*-KO-Ctrl groups at both 3h and 24h identified substantial sets of differentially expressed genes (DEGs), reflecting immediate and sustained baseline transcriptomic reprogramming resulting from *MAPT* KO (Figs. 2A and 2B). In contrast to WT neurons, which failed to mount an adaptive response under chronic A β stress, *MAPT*-KO neurons exhibited a highly uniform transcriptomic profile following A β exposure (Figs. 2C and 2D). Comparisons reflecting purely temporal dynamics within control groups (e.g., WT-Ctrl3 vs. WT-Ctrl24) or cross-variable comparisons were shifted to the supplementary material, as they primarily reflect baseline maturation rather than stress-adaptive signaling. Based on this early transcriptomic stabilization, the 3-hour post-treatment time point was prioritized for downstream matched proteomic profiling to investigate early regulatory mechanics.

Identification of Co-Expression Modules Associated with MAPT Knockout and A β Response

Weighted Gene Co-expression Network Analysis (WGCNA) was performed to identify modules of co-expressed genes associated with genotype and treatment conditions across the dataset. Sample hierarchical clustering revealed no detectable outliers, confirming dataset suitability for network construction (Fig. 3A). A soft-thresholding power of 14 was selected to achieve a scale-free topology fit index ($R^2 > 0.8$), establishing the network framework for module detection (Fig. 3B).

Correlation analysis between experimental traits and identified co-expression modules revealed that the turquoise module exhibited a strong positive correlation with the *MAPT*-KO genotype ($r = 0.74$, $p < 0.001$). This correlation indicates a pronounced association between the transcriptomic profile of the turquoise module and Tau deletion. Functional enrichment analysis of the turquoise module using GO and KEGG databases identified significant over-representation in key cellular processes, including autophagy, mitochondrial transport, and the synaptic vesicle cycle (Fig. 3D). Additionally, pathways associated with neurodegenerative mechanisms and mTOR signaling were enriched within this module.

Genes exhibiting the highest intramodular connectivity within the turquoise module were identified as hub genes, including *HTR3A*, *INPP5F*, *SEMA3C*, and *SIM1*. Quantitative evaluation of these hub genes using violin plots demonstrated significantly higher expression levels in *MAPT*-KO neurons compared to the WT group ($p < 0.0001$). Elevated expression of these genes in *MAPT*-KO neurons was consistently maintained across both control and A β -treated conditions at both 3h and 24h time points (Fig. 3E).

Proteomic Profile Assessment and Identification of Differentially Expressed Proteins

To evaluate the global proteomic landscape, signal intensity distribution and normalization consistency were first assessed. Protein intensities exhibited a uniform distribution across biological replicates following normalization, confirming data suitability for downstream statistical testing (Fig. 4A). Principal Component Analysis (PCA) revealed clear partitioning of the neuronal proteome according to genotype (Fig. 4B). Principal Component 1 (PC1) accounted for 60.2% of the total variance, separating WT samples from *MAPT*-KO samples. This variance partitioning indicates a distinct proteomic profile associated with Tau deletion.

Differential expression analysis identified a subset of differentially expressed proteins (DEPs) based on statistical significance ($FDR < 0.05$). The volcano plot (Fig. 4C) illustrates upregulated proteins in the *MAPT*-KO group, including *LZTS1*, *NFATC3*, *ASB1*, *CAMK2A*, and *GDE1*. The increased abundance of these proteins in KO neurons reflects a distinct proteomic signature associated with the *MAPT*-KO genotype.

Furthermore, hierarchical clustering of the proteomic profiles demonstrated clear separation between WT and *MAPT*-KO biological replicates (Fig. 4D). Although the global correlation between the

transcriptome and proteome was modest, reflecting post-transcriptional and post-translational regulatory dynamics, a high degree of concordance was identified within specific functional modules. Proteins involved in extracellular matrix organization, complement activation, and vasculature development exhibited consistent directionality across both transcriptomic and proteomic layers. This concordant cross-omics alignment indicates a coordinated molecular response to *MAPT* deletion driven by a subset of consensus regulators.

To elucidate the coordinated biological pathways underlying the resilient phenotype in *MAPT*-KO neurons, we performed an integrative analysis of the transcriptomic and proteomic datasets.

Identification of Convergent Molecular Signatures Across Multi-Omics Layers

To evaluate the correlation between transcriptomic and proteomic profiles, an integrated scatter plot was constructed (Fig. 5A). The analysis identified concordantly upregulated and downregulated targets, representing consistent molecular markers associated with the *MAPT*-KO phenotype. To identify key targets exhibiting cross-layer agreement, transcriptomic and proteomic datasets were integrated into a consensus signature analysis (Fig. 5B). This assessment identified a subset of consensus hits displaying directionally consistent alterations at both mRNA and protein levels across genotypes, indicating a concordant regulatory response sustained from transcription to translation.

Functional characterization of these consensus hits through Gene Ontology (GO) enrichment analysis revealed overrepresented biological pathways, including the regulation of humoral immune responses and vasculature development (Fig. 5C). To evaluate candidate upstream regulatory elements driving this convergent signature, transcription factor (TF) enrichment analysis was performed. The analysis identified KLF4 (Kruppel-like Factor 4) as the top-ranked transcription factor based on statistical ranking (Combined Score = 259.9, Fig. 5D), target-enriching 5 out of the 7 consensus genes (*COL17A1*, *DEPDC1B*, *PER3*, *TNFRSF9*, and *ST3GAL6*). This target enrichment identifies KLF4 as a candidate regulatory hub within the consensus network.

Finally, protein-protein interaction (PPI) network analysis using the STRING database demonstrated functional connectivity among these targets, depicting structural and functional interactions within the consensus network (Fig. 5E). Together, these multiomics findings delineate a concordant transcriptomic and proteomic signature associated with KLF4-related pathway alterations in *MAPT* deficient neurons.

Discussion

The primary objective of this study was to elucidate the molecular mechanisms associated with cellular response patterns in *MAPT*-KO neurons, and also how the absence of Tau protein alters neuroprotective pathways upon amyloid-beta ($A\beta$) exposure. By integrating transcriptomic analysis with matched proteomic profiles, we conducted a systematic comparison between Wild-Type (WT) and *MAPT*-KO neurons under both control and $A\beta$ -treated conditions. Our results revealed that while WT neurons exhibit a relatively limited transcriptomic response to $A\beta$ exposure, while *MAPT*-KO neurons display a

distinct baseline molecular signature. This potentially protective state is characterized by baseline pathway shifts, associated with the candidate transcription factor KLF4, that align with normalized mitochondrial, synaptic, and metabolic profiles, suggesting an enhanced structural and functional tolerance to amyloid-induced stress.

At transcription level, multifactorial PCA revealed a clear divergence from conventional toxicological models: while WT neurons were anticipated to exhibit broad transcriptional shifts upon A β exposure, their profiles remained largely contiguous with their untreated controls. This constrained variance in WT neurons suggests a state of limited transcriptional reactivity, where the cells exhibit minimal immediate adaptation to amyloid stress within the evaluated timeframe. In contrast, *MAPT*-KO neurons displayed a substantial baseline shift relative to WT controls, characterized by the differential expression of high-confidence candidate genes, including *INPP5F*, *PER3*, and *SIM1*^{14,15}.

Specifically, the turquoise module represents the largest co-regulated gene network identified in our dataset and demonstrates a robust positive correlation with the *MAPT*-KO genotype ($r = 0.74$). This module shows significant enrichment in essential biological processes, including mitochondrial transport, organelle localization, and structural organization. By maintaining the co-expression of critical nuclear-encoded mitochondrial regulators under A β stress, this network suggests that Tau deletion stabilizes the physical and bioenergetic architecture of the cell, preventing the severe mitochondrial fragmentation and transport deficits typically triggered by amyloid toxicity. This indicates that the baseline regulatory shifts associated with Tau deletion may support a favorable structural configuration for mitochondria, potentially preserving pathway activity related to energy production under A β exposure. While WT neurons typically exhibit expression profiles indicative of mitochondrial disruption under amyloid stress, *MAPT*-KO neurons maintain the expression of hub genes involved in mitochondrial protein localization and transport. This baseline mitochondrial organization may help attenuate bioenergetic dysfunction, contributing to the sustained cellular and synaptic pathway integrity observed in *MAPT*-KO neurons under toxicological challenge^{16,17}.

Previous studies have shown that *MAPT* mutations lead to reprogramming in certain pathways such as apoptosis¹⁷, ROS production and mitochondrial function. However, the identified hub genes in the present study provide a candidate mechanistic link between Tau deletion and mitochondrial-metabolic pathway preservation upon exposure to A β which is reported for the first time based on our knowledge. *SIM1* (Single-minded homolog 1), which shows a substantial upregulation in *MAPT*-KO neurons, functions as a regulator of energy homeostasis and mitochondrial biogenesis¹⁸. Its elevation suggests that *MAPT*-KO neurons may possess an enhanced capacity to meet cellular energy demands during metabolic stress. Although a direct relationship between *SIM1* and tauopathies has not been previously established, prior studies suggest that *SIM1* and *SIM2* regulate molecules involved in the polarized growth of axons¹⁹. Based on these convergent observations, our findings indicate that *SIM1* may represent a novel candidate factor within the broader neuroprotective network activated in *MAPT*-deficient neurons.

Similarly, *AKR1C2* is implicated in the detoxification of reactive aldehydes and broader oxidative-stress defenses, pointing toward a protective role against A β -associated lipid peroxidation and mitochondrial damage^{20,21}. In support of this, Chen and colleagues reported that the *AKR1C* family plays key regulatory roles in neurosteroid metabolism and redox homeostasis²². Intriguingly, however, Zhao et al. identified *AKR1C2* as a ferroptosis-related hub gene in Alzheimer's brain tissues, correlating its elevation with disease progression²³, while others suggested its involvement in metabolic cell death biomarkers in Parkinson's disease²⁴. We propose that this apparent contradiction reflects a context-dependent regulatory outcome. In wild-type neurons under chronic amyloid stress, elevated *AKR1C2* expression likely represents a late-stage, incomplete compensatory response attempting to mitigate mounting lipid peroxidation. In contrast, within the pre-adapted metabolic and mitochondrial baseline of *MAPT*-deficient neurons, sustained *AKR1C2* activation may operate as a functional antioxidant node, effectively preventing ferroptotic signaling and reactive aldehyde buildup.

The upregulation of *PHOX2B* and *MAOA* (monoamine oxidase A) further underscores the baseline metabolic profile of *MAPT*-KO neurons. *PHOX2B* has previously been shown to be associated with neurodegenerative processes, though its precise mechanistic contribution in these contexts remains to be fully defined²⁵. In this regard, Fan and colleagues suggested that upregulation of *PHOX2B* contributes in maintenance of noradrenergic neurons function in adult rats brain and might have be useful as an anti-ageing therapeutic²⁶. *MAOA*, localized to the outer mitochondrial membrane, is conventionally involved in monoamine neurotransmitter degradation and redox balance, often serving as a marker of cellular metabolic state²⁷. When co-expressed alongside antioxidant regulators such as *AKR1C2*, the sustained expression of *MAOA* in *MAPT*-KO neurons may reflect a well-regulated oxidative microenvironment rather than unmitigated metabolic stress.

In parallel, *INPP5F*, a phosphoinositide phosphatase critical for endocytosis and synaptic vesicle recycling,^{28,29} displayed significant upregulation. Interestingly, elevated *INPP5F* expression has been identified in iPSC-derived neurons harboring the *TTC3* p.S1038C variant and positioned as a potential candidate risk gene in AD models³⁰. However, in *MAPT*-deficient neurons, *INPP5F* upregulation may instead support cellular tolerance by ensuring efficient vesicle-mediated transport and modulating inter-organelle dynamics, including endoplasmic reticulum-mitochondrial crosstalk and calcium signaling. Given its prominent differential expression across distinct disease models, *INPP5F* warrants further investigation as a context-dependent candidate regulator of neuronal integrity. Together, the distinct expression patterns of these metabolic and endocytic factors suggest a multi-tiered regulatory framework that helps mitigate the synaptic and bioenergetic vulnerabilities typically observed in wild-type neurons exposed to amyloid stress.

The concordance between transcript abundance and protein expression in *MAPT*-KO neurons, particularly for factors regulating humoral immune responses and complement pathway components, demonstrates a coordinated, multi-level molecular shift. Unlike WT neurons, which exhibit a limited capacity to mount such a synchronized response, *MAPT*-KO neurons maintain relative protein stability

even under A β stress. This cross-layer alignment suggests that the baseline molecular configuration of Tau-deficient neurons is not merely a transient transcriptional fluctuation, but reflects a sustained functional state that supports structural integrity, as evidenced by the preserved expression of extracellular matrix and signaling proteins such as COL17A1^{31,32}.

The candidate markers identified in our study, including *INPP5F*, *PER3*, *SIM1*, and *COL17A1*, collectively point toward a coordinated molecular profile characteristic of *MAPT*-KO neurons. *PER3*, a core component of the circadian clock network, is increasingly recognized for its role in modulating proteostasis and the cellular response to DNA damage³³. In line with our findings, Xie and colleagues demonstrated that *PER3* contributes in amelioration of depressive behaviors via regulation of NAD⁺ levels and mitochondrial function³⁴. Its elevated baseline expression in *MAPT*-KO neurons may contribute to the temporal coordination of protein quality control mechanisms. The constitutive upregulation of these factors in *MAPT*-KO neurons, contrasting with their constrained expression in WT cells under stress, indicates that *MAPT* deficiency is associated with a reconfigured basal signaling network. Rather than reflecting a passive consequence of Tau deletion, this phenotypic transition aligns with the activation of pathways that support cell membrane stability, optimize metabolic energy pathways, and preserve structural integrity, potentially mitigating the signaling cascades associated with amyloid-induced toxicity^{35,36}.

The culmination of our multiomics integration points toward the transcription factor *KLF4* as a candidate central regulator of the molecular phenotype observed in *MAPT*-KO neurons. Given *KLF4*'s established role as a Yamanaka factor (*OCT4*, *SOX2*, *KLF4*, *c-MYC*) during iPSC reprogramming and neuronal differentiation, it is critical to delineate whether its induction represents a developmental byproduct or a functional driver of A β resilience^{37,38}. On the other hand, Dhar and colleagues demonstrated that *KLF4* is an important TF for maintenance of brain endothelial homeostasis via eliminating proinflammatory and senescence programs³⁹. Noteworthy, the elevation of *KLF4* in our *MAPT*-KO neurons is strongly supported by recent human tissue-level transcriptomic analyses, which positioned *KLF4* as one of the few key drivers specifically distinguishing resilient brains from controls. This human in vivo evidence confirms that *KLF4* activation represents a genuine, pathophysiologically relevant resilience mechanism rather than a developmental byproduct of iPSC reprogramming⁴⁰. In addition, it has been shown that loss of *KLF4* is associated with disruption of circadian innate immune system as an underlying mechanism for ageing⁴¹. Collectively, these findings, coupled with the lack of differential expression among other Yamanaka factors, strongly suggest that *KLF4* operates independently of developmental lineage commitment, serving instead as an active orchestrator of cellular tolerance under toxic amyloid stress.

Altogether, regulating a significant subset of our convergent transcriptomic and proteomic hits, including *COL17A1* and *PER3*, *KLF4* appears to function as a key transcriptional node that maintains this baseline molecular state. While WT neurons exhibit a relatively constrained response to A β exposure, *MAPT*-KO neurons, within the context of *KLF4*-associated regulatory networks, sustain pathway stability aligned

with structural and metabolic preservation. This suggests that the observed tolerance in *MAPT*-deficient neurons is not merely a passive outcome of Tau loss, but may involve an active, adaptive transcriptional reconfiguration. Consequently, our findings highlight *KLF4* and its downstream target networks as potential targets for further investigation; modulating this molecular signature might offer pathways toward enhancing neuroprotective mechanisms in Tau-expressing neurons against amyloid-associated pathology^{42,43}.

In conclusion, this study provides an integrative perspective on the role of *MAPT* in neuronal stress responses and neuroprotection. By integrating transcriptomic and proteomic datasets, our findings indicate that *MAPT* deletion does not merely result in the absence of a tau-mediated pathology, but rather correlates with an active, multi-level adaptive state. Our analysis clarifies that while WT neurons exhibit a constrained transcriptional response upon amyloid stress, *MAPT*-KO neurons maintain a distinct baseline molecular configuration aligned with preserved homeostasis.

The identification of the *KLF4*-associated regulatory network, alongside a panel of 27 convergent multiomics candidates (such as *COL17A1*, *PER3*, and *INPP5F*), provides a detailed molecular signature of cellular endurance in *MAPT*-deficient neurons. These findings suggest that therapeutic strategies for Alzheimer's disease might benefit from pharmacologically recapitulating key elements of this Tau-independent resilience phenotype. By targeting central regulatory nodes such as *KLF4*, it may be possible to modulate molecular networks in vulnerable neurons to help preserve their structural and mitochondrial integrity, thereby supporting cellular tolerance against amyloid-associated pathology.

Declarations

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

Author Contribution

E.A.J. performed the bioinformatics, multiomics data processing, network modeling, and statistical analyses, prepared all figures, and wrote the main manuscript text. H.Z. conceptualized and supervised the study, provided resources, acquired funding, and critically revised the manuscript. All authors reviewed and approved the manuscript.

Acknowledgement

We thank Prof. Dr. Li Gan (Weill Cornell Medicine, NY, USA) for providing Ngn2-WTC11 iPSCs and Andrea Delle Vedove (Institute of Human Genetics, Cologne, Germany) for help with the ImageJ macro for calcium imaging analysis. We thank Lea Hund (University of Cologne) for supporting the off-target

sequencing of tau KO clones. We thank Prof. Dr. Florian Klein (Institute of Virology, University Hospital Cologne) for providing lentiviral vectors. Stem cell work was performed at the iPSC-Lab core facility of the CMMC (Cologne, Germany). We thank the CECAD Proteomics Facility for the analysis of proteome data. Our work is supported by the Else-Kröner-Fresenius-Stiftung, the DFG/GRC, Koeln Fortune Program/Faculty of Medicine, University of Cologne (all to H.Z.); a stipend from the Studienstiftung des Deutschen Volkes (to M.B.S.); and the Jürgen-Manchot-Stiftung (to C.C.). This work was supported by the large instrument grant INST 1856/71-1 FUGG by the German Research Foundation (DFG Großgeräteantrag). Partial support for Open Access funding by Project DEAL. We acknowledge support from Alzheimer Forschung Initiative e.V. for Open Access Publishing.

Data Availability

This study generates processed multiomics datasets (proteomics and integrated network analyses) and re-analyzes previously generated transcriptomic datasets from our hiPSC-derived neuronal models.

Code Availability

The custom R and Python scripts used for differential expression analysis, WGCNA co-expression network modeling, transcription factor enrichment, and multiomics integration will be made publicly available on GitHub upon publication.

Clinical Trial Number: Not applicable. This study is not a clinical trial.

Funding Declaration: There was no funding for this project.

Ethics, Consent to Participate, and Consent to Publish declarations: not applicable.

References

1. 2025 Alzheimer's disease facts and figures. *Alzheimer's & Dementia* 21, e70235 (2025).
2. Gustavsson A, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement.* 2023;19:658–70.
3. Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou SH. Reasons for Failed Trials of Disease-Modifying Treatments for Alzheimer Disease and Their Contribution in Recent Research. *Biomedicines.* 2019;7:97.
4. Haass C, Selkoe D. If amyloid drives Alzheimer disease, why have anti-amyloid therapies not yet slowed cognitive decline? *PLoS Biol.* 2022;20:e3001694.
5. Kametani F, Hasegawa M. Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. *Front Neurosci.* 2018;12:328460.

6. Leveille E, Ross OA, Gan-Or Z. Tau and MAPT genetics in tauopathies and synucleinopathies. *Parkinsonism Relat Disord.* 2021;90:142.
7. Zempel H, et al. Amyloid- β oligomers induce synaptic damage via Tau-dependent microtubule severing by TTL6 and spastin. *EMBO J.* 2013;32:2920–37.
8. Zempel H, Mandelkow EM. Linking Amyloid- β and Tau: Amyloid- β Induced Synaptic Dysfunction via Local Wreckage of the Neuronal Cytoskeleton. *Neurodegener Dis.* 2012;10:64–72.
9. Ittner LM, et al. Dendritic Function of Tau Mediates Amyloid- β Toxicity in Alzheimer's Disease Mouse Models. *Cell.* 2010;142:387–97.
10. Roberson ED, et al. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. *Science.* 2007;316:750–4.
11. Buchholz S et al. The tau isoform 1N4R confers vulnerability of MAPT knockout human iPSC-derived neurons to amyloid beta and phosphorylated tau-induced neuronal dysfunction. *Alzheimers Dement* 21, (2025).
12. Ng B et al. Tau depletion in human neurons mitigates A β -driven toxicity. *Molecular Psychiatry* 2024 29:7 29, 2009–2020 (2024).
13. Buchholz S, et al. The tau isoform 1N4R confers vulnerability of MAPT knockout human iPSC-derived neurons to amyloid beta and phosphorylated tau-induced neuronal dysfunction. *Alzheimer's Dement.* 2025;21:e14403.
14. Yarbro JM et al. Human and mouse proteomics reveals the shared pathways in Alzheimer's disease and delayed protein turnover in the amyloidome. *Nature Communications* 2025 16:1 16, 1533- (2025).
15. Al Kabbani MA, Köhler C, Zempel H. Effects of P301L-TAU on post-translational modifications of microtubules in human iPSC-derived cortical neurons and TAU transgenic mice. *Neural Regen Res.* 2024;20:2348.
16. de Veij Mestdagh CF, Smit AB, Henning RH, van Kesteren RE. Mitochondrial Targeting against Alzheimer's Disease: Lessons from Hibernation. *Cells.* 2023;13:12.
17. Korn L, et al. MAPT genotype-dependent mitochondrial aberration and ROS production trigger dysfunction and death in cortical neurons of patients with hereditary FTL. *Redox Biol.* 2022;59:102597.
18. Holder JL et al. Sim1 gene dosage modulates the homeostatic feeding response to increased dietary fat in mice. <https://doi.org/10.1152/ajpendo.00446.2003> 287, 105–113 (2004).
19. Marion JF, Yang C, Caqueret A, Boucher F, Michaud JL. Sim1 and Sim2 are required for the correct targeting of mammillary body axons. *Development.* 2005;132:5527–37.
20. Chen X et al. Exploring the roles of AKR1C1, AKR1C2, and AKR1C3 in the nervous system: Mechanisms and perspectives. *Exp Neurol* 397, (2026).
21. Rižner TL, Penning TM. Role of Aldo-Keto Reductase Family 1 (AKR1) Enzymes in Human Steroid Metabolism. *Steroids* 79. 10.1016/j.steroids.2013.10.012 (2013).

22. Chen X, et al. Exploring the roles of AKR1C1, AKR1C2, and AKR1C3 in the nervous system: Mechanisms and perspectives. *Exp Neurol*. 2026;397:115580.
23. Zhao H, et al. Identification ferroptosis-related hub genes and diagnostic model in Alzheimer's disease. *Front Mol Neurosci*. 2023;16:1280639.
24. Fu J et al. Exploring the mechanism of metabolic cell death-related genes AKR1C2 and MAP1LC3A as biomarkers in Parkinson's disease. *Sci Rep* 15, (2025).
25. Oswald F et al. The FOXP2-Driven Network in Developmental Disorders and Neurodegeneration. *Front Cell Neurosci* 11, (2017).
26. Fan Y, et al. Transcription factor Phox2 upregulates expression of norepinephrine transporter and dopamine β -hydroxylase in adult rat brains. *Neuroscience*. 2011;192:37–53.
27. Syed AU et al. Comparison of Monoamine Oxidase-A, A β Plaques, Tau, and Translocator Protein Levels in Postmortem Human Alzheimer's Disease Brain. *Int J Mol Sci* 24, (2023).
28. Nakatsu F, et al. Sac2/INPP5F is an inositol 4-phosphatase that functions in the endocytic pathway. *J Cell Biol*. 2015;209:85.
29. Cao M, Park D, Wu Y, De Camilli P. Absence of Sac2/INPP5F enhances the phenotype of a Parkinson's disease mutation of synaptojanin 1. *Proc. Natl. Acad. Sci. U. S. A.* 117, 12428–12434 (2020).
30. Cukier a-c HN et al. An Alzheimer's disease risk variant in TTC3 modifies the actin cytoskeleton organization and the PI3K-Akt signaling pathway in iPSC-derived forebrain neurons. <https://doi.org/10.1101/2023.05.25.542316> doi:10.1101/2023.05.25.542316.
31. Tsvetanov KA et al. Cellular signatures underlying functional resilience in presymptomatic frontotemporal dementia. *Brain* <https://doi.org/10.1093/BRAIN/AWAF443> (2025) doi:10.1093/BRAIN/AWAF443.
32. Andrés-Benito P et al. Deregulated Transcription and Proteostasis in Adult mapt Knockout Mouse. *Int J Mol Sci* 24, (2023).
33. Bertolesi GE et al. Interplay of Light, Melatonin, and Circadian Genes in Skin Pigmentation Regulation. *Pigment Cell Melanoma Res* 38, (2025).
34. Xie X, et al. Period3 modulates the NAD⁺-SIRT3 axis to alleviate depression-like behaviour by enhancing NAMPT activity in mice. *J Adv Res*. 2025;77:309–20.
35. Viola AU, et al. PER3 Polymorphism Predicts Sleep Structure and Waking Performance. *Curr Biol*. 2007;17:613–8.
36. Zhu W, et al. Inpp5f is a polyphosphoinositide phosphatase that regulates cardiac hypertrophic responsiveness. *Circ Res*. 2009;105:1240–7.
37. Yagi T et al. Establishment of induced pluripotent stem cells from centenarians for neurodegenerative disease research. *PLoS ONE* 7, (2012).
38. Drake SS et al. Cellular rejuvenation protects neurons from inflammation-mediated cell death. *Cell Rep* 44, (2025).

39. Dhar M et al. Endothelial KLF4 depletion drives age-related neurovascular dysfunction and neuropsychiatric impairment. *Proc. Natl. Acad. Sci. U. S. A.* 123, (2026).

40. Castanho I et al. Molecular hallmarks of excitatory and inhibitory neuronal resilience to Alzheimer’s disease. *Mol Neurodegener* 20, (2025).

41. Blacher E, et al. Aging disrupts circadian gene regulation and function in macrophages. *Nat Immunol.* 2022;23:229–36.

42. Qin S, Zhang C-L. Role of Kruppel-like factor 4 in neurogenesis and radial neuronal migration in the developing cerebral cortex. *Mol Cell Biol.* 2012;32:4297–305.

43. Cheng Z et al. The Role of KLF4 in Alzheimer’s Disease. *Front Cell Neurosci.* 12, (2018).

Figures

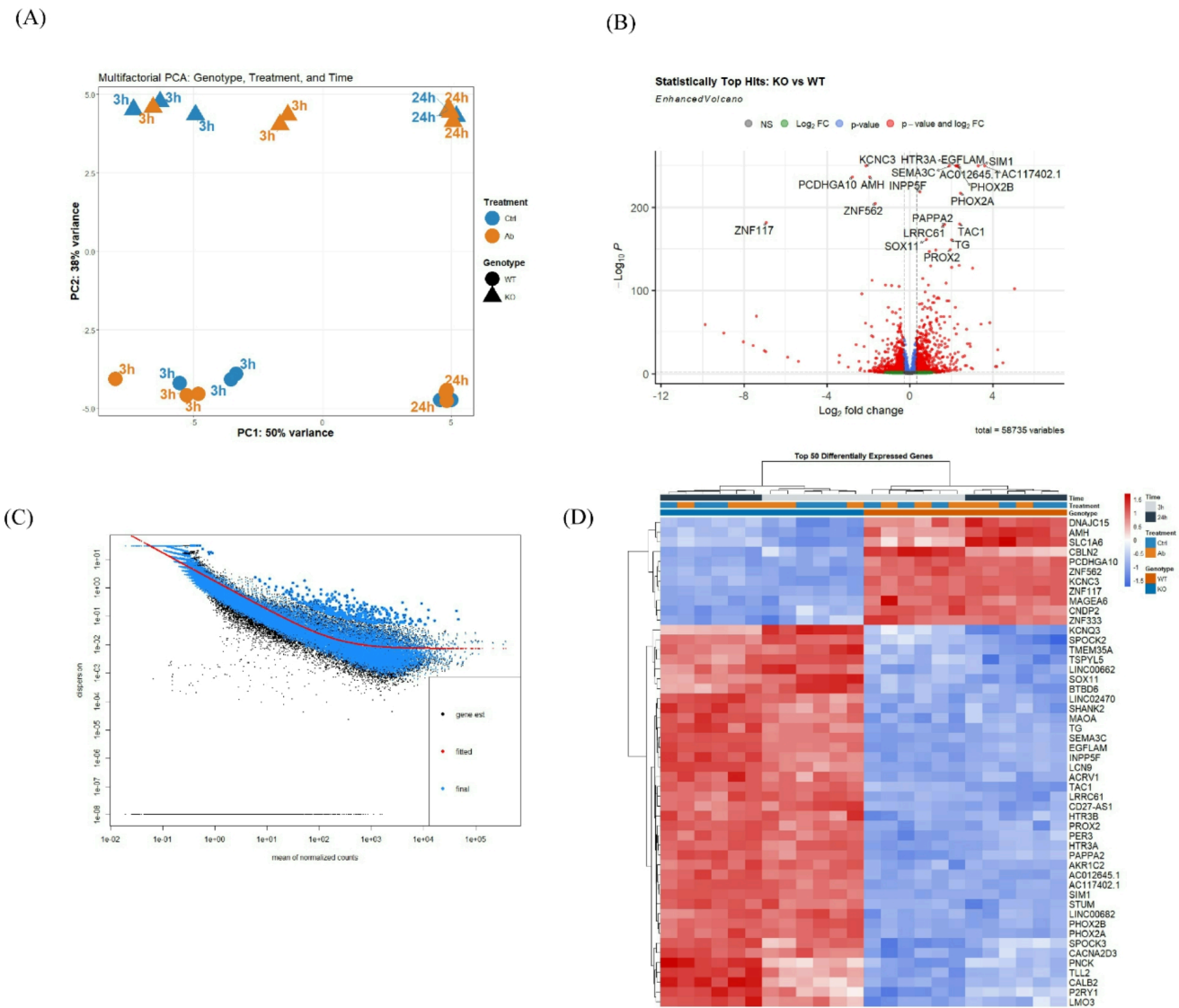


Figure 1

Global Transcriptomic Landscape and Statistical Quality Control of RNA-seq Data. (A) Multi-factorial PCA displaying variance across genotype, treatment, and time points. PC1 accounts for 50% of the total transcriptomic variance, driving the separation between WT (circles) and *MAPT*-KO (triangles) genotypes, while PC2 accounts for 38% of the variance. Samples cluster consistently with their biological groups across time points (3h and 24h). (B) Volcano Plot of Differentially Expressed Genes (DEGs): Differential expression analysis comparing *MAPT*-KO and WT neurons. Red points represent statistically significant genes meeting thresholds for both adjusted p -value and $\log_2$ fold change ($|\log_2\text{FC}| > 1, -\log_{10}P$). Top ranked upregulated and downregulated genes are labeled. (C) Gene-wise Dispersion Plot: Assessment of the DESeq2 statistical modeling across normalized mean counts. Shrinkage of gene-specific dispersion estimates (black dots) toward the fitted trend line (red line) to yield final estimates (blue dots) illustrates variance stabilization across the multi-factorial design. (D) Hierarchical Clustering Heatmap: Heatmap depicting the top 50 differentially expressed genes across all biological replicates annotated by Genotype, Treatment, and Time (3h vs. 24h). Dendrogram clustering shows primary division driven by genotype, highlighting consistent baseline expression patterns in *MAPT*-KO groups relative to WT controls.

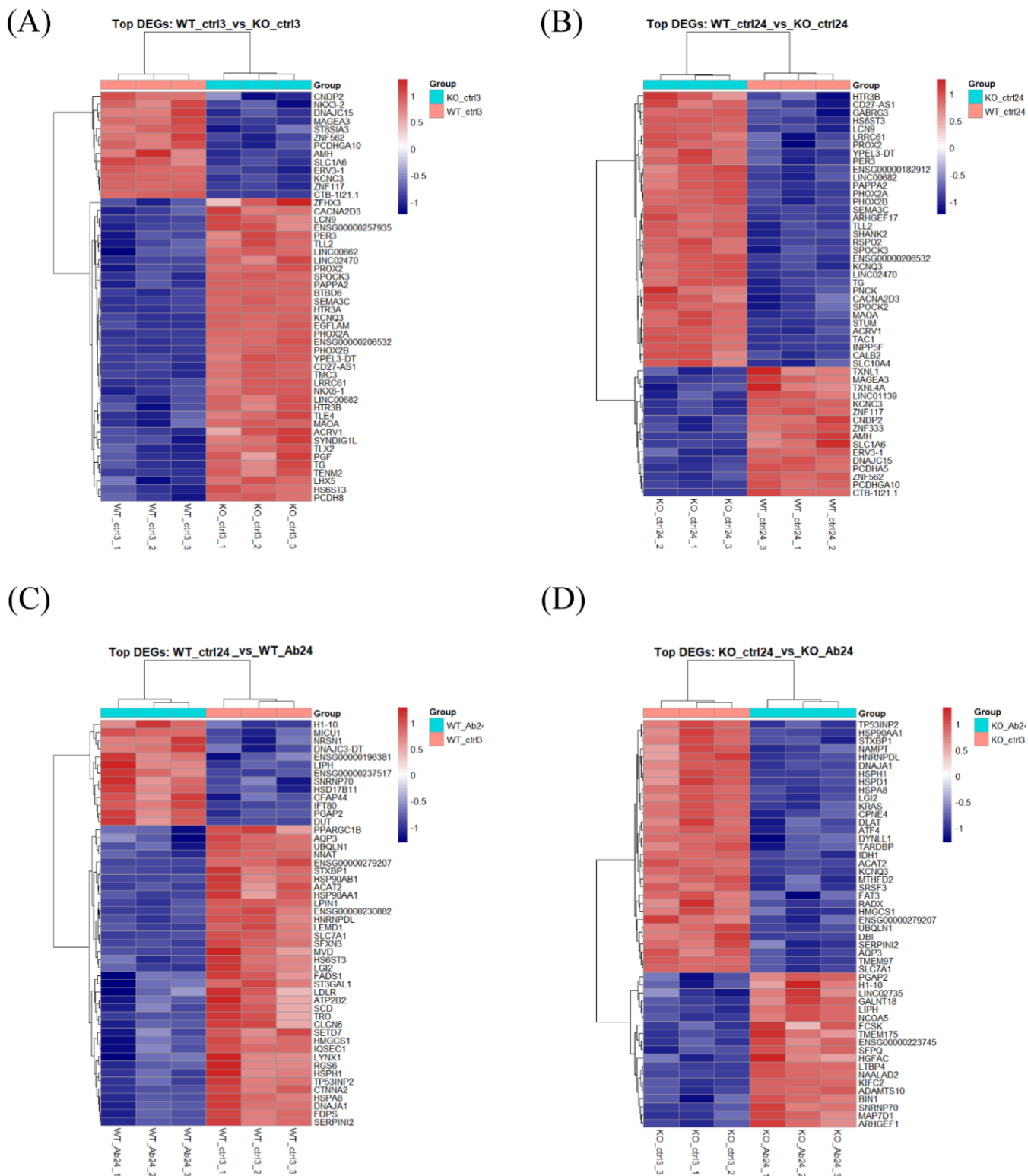


Figure 2

Differential Expression Analysis and Transcriptional Responses Across Genotypes and Treatment Conditions. Hierarchical clustering heatmaps depicting the top differentially expressed genes (DEGs) across primary pairwise comparisons (n = 3 independent biological replicates per group). **(A, B)** Pairwise comparisons evaluating baseline genotype differences between wild-type control (WT_ctrl) and *MAPT*-knockout control (KO_ctrl) neurons at **(A)** 3 hours and **(B)** 24 hours post-vehicle treatment, showing

sustained transcriptomic reprogramming driven by *MAPT* deletion. **(C)** Pairwise comparison of WT neurons under control versus 24-hour A β oligomer exposure (WT_ctrl24 vs. WT_Ab24), demonstrating extensive transcriptomic alterations induced by amyloid stress. **(D)** Pairwise comparison of *MAPT*-KO neurons under control versus 24-hour A β exposure (KO_ctrl24 vs. KO_Ab24), highlighting relative expression stability and preserved baseline profiles under toxic challenge. Color intensity represents the Z-score of normalized read counts, with red indicating higher relative expression and blue indicating lower relative expression.

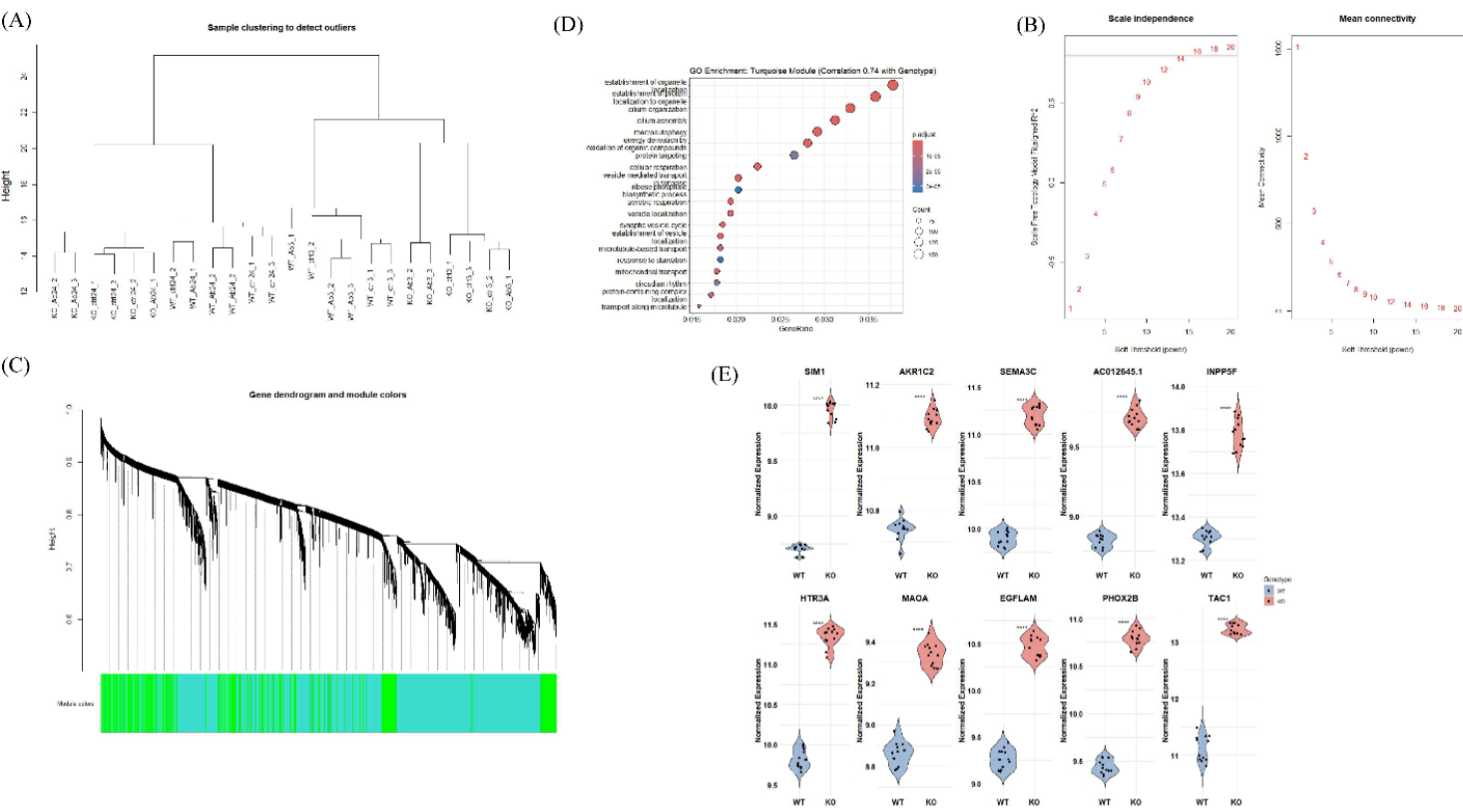


Figure 3

WGCNA Identification of Co-Expression Modules and Functional Pathways Associated with *MAPT* Knockout. **(A)** Hierarchical clustering of transcriptomic profiles using Euclidean distance. The dendrogram demonstrates dataset quality with no detectable sample outliers. **(B)** Evaluation of network topology scale-free fit index (left) and mean connectivity (right) across various soft-thresholding powers. A power of 14 was selected ($R^2 > 0.8$). **(C)** Hierarchical clustering dendrogram of genes based on topological overlap, with color bands indicating identified co-expression modules (including the Turquoise module). **(D)** Gene Ontology (GO) functional enrichment analysis for the Turquoise module, which exhibits a strong positive correlation with the *MAPT*-KO genotype ($r = 0.74$). Enriched biological processes include macroautophagy, mitochondrial transport, and synaptic vesicle cycle. Dot size corresponds to gene count, and color indicates adjusted p -value. **(E)** Violin plots illustrating normalized expression levels of representative hub genes (e.g., *SIM1*, *INPP5F*, *SEMA3C*, *HTR3A*) comparing WT and

MAPT-KO neurons across conditions. Expression levels are consistently elevated in *MAPT*-KO neurons (**** $p < 0.0001$, Student's *t*-test).

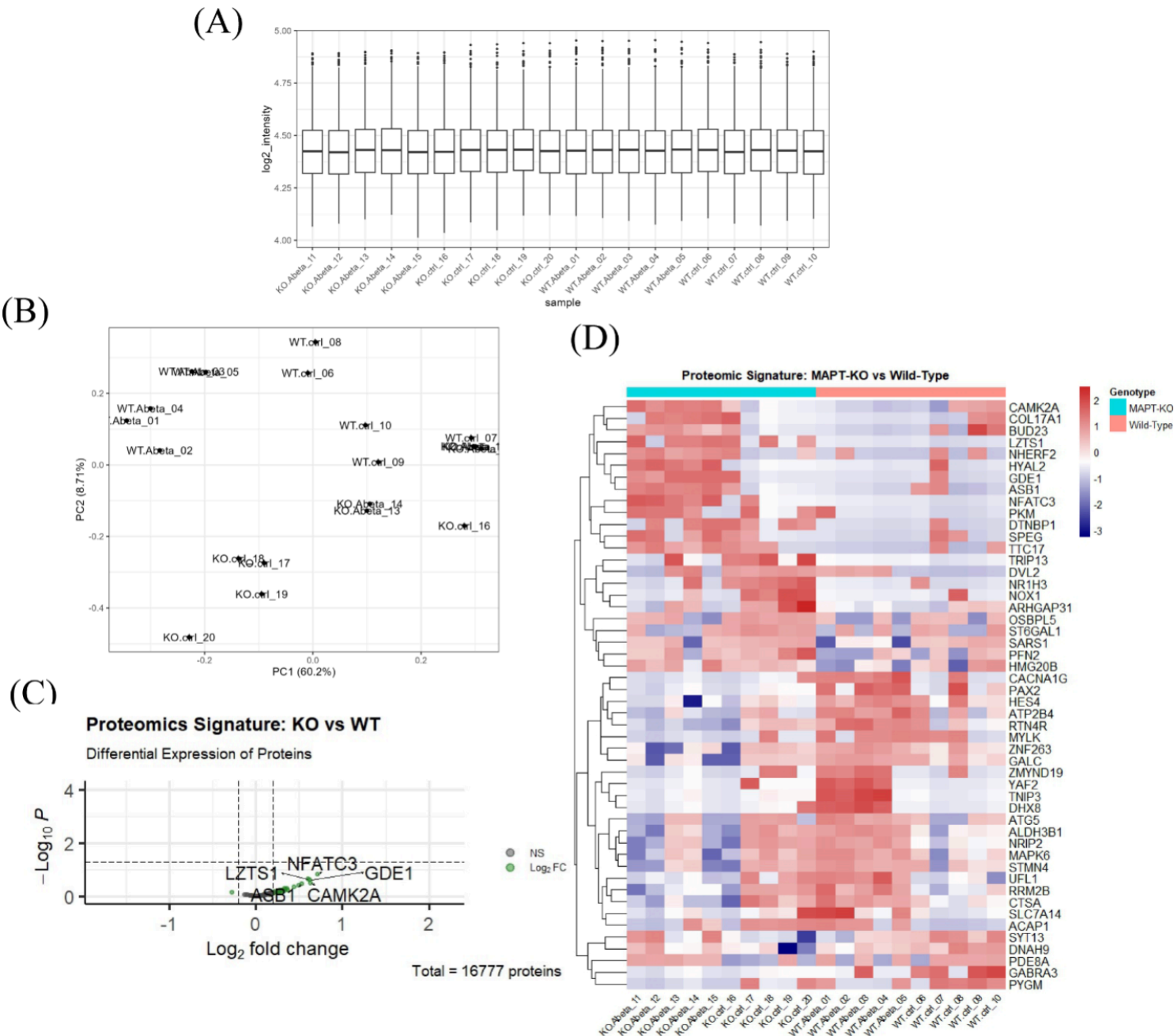


Figure 4

Proteomic Profiling and Identification of Differentially Expressed Proteins. (A) Signal intensity distribution box plots displaying $\log_2$ -transformed protein intensities across biological replicates following normalization. (B) PCA of global proteomic profiles. PC1 (60.2%) demonstrates primary sample variance partitioning between Wild-Type and *MAPT*-KO neurons, while PC2 (8.71%) captures secondary variance. (C) Volcano plot illustrating differentially expressed proteins (DEPs) comparing *MAPT*-KO versus Wild-Type groups. The horizontal axis represents $\log_2$ fold change, and the vertical axis indicates statistical significance ($-\log_{10} P$ -value). Top candidate DEPs (including *LZTS1*, *NFATC3*,

ASB1, *CAMK2A*, and *GDE1*) are labeled. Total analyzed proteins (N = 16,777) are indicated.

(D) Hierarchical clustering heatmap of top differentially expressed proteins ranked by statistical significance (*p*-value). Biological replicates cluster by genotype (*MAPT*-KO vs. Wild-Type). Color intensity represents the Z-score of normalized protein abundance, ranging from blue (lower relative expression) to red (higher relative expression).

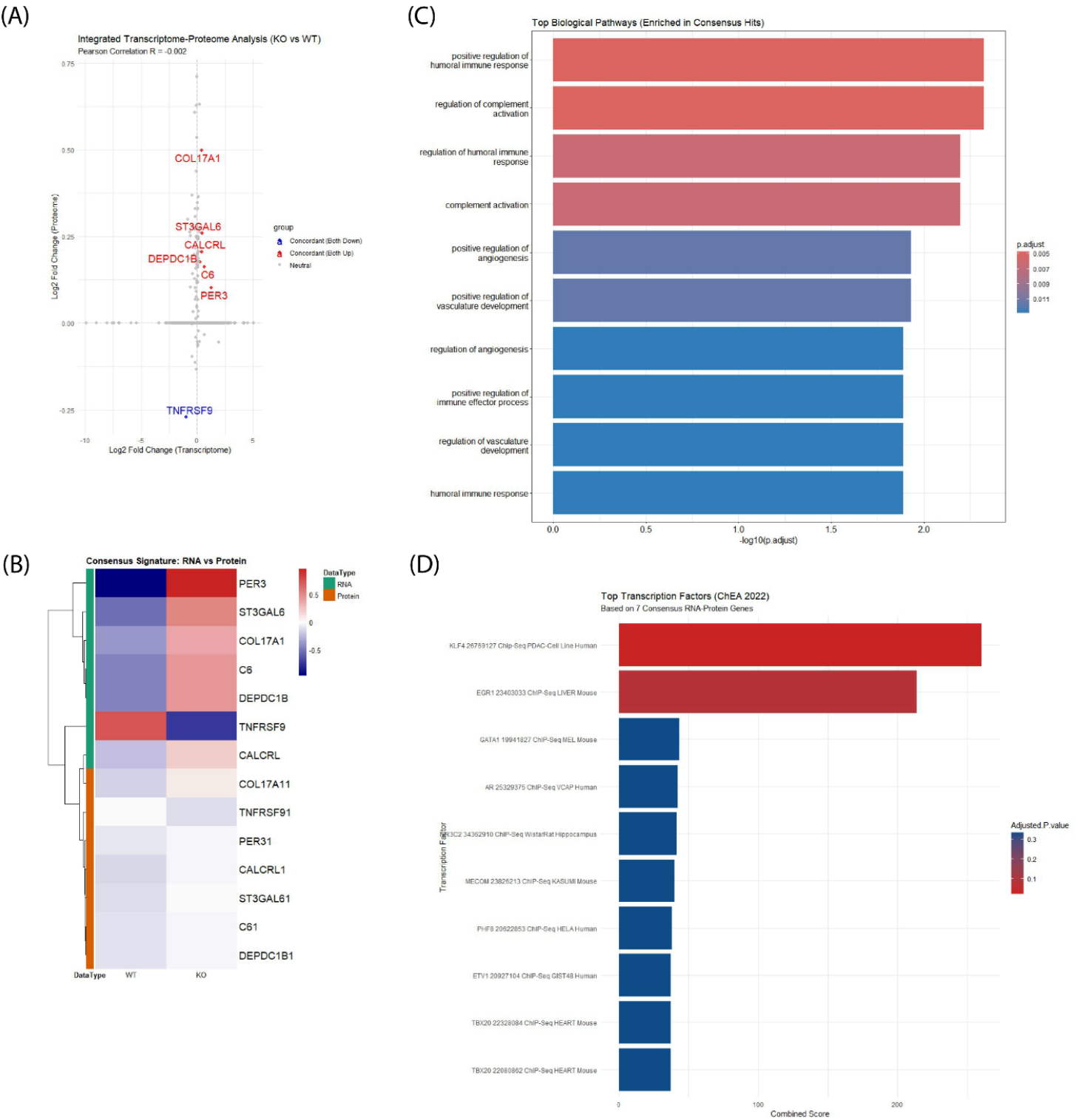


Figure 5

Integrated Multiomics Analysis and Identification of Upstream Transcription Factors.

(A) Integrated transcriptome-proteome scatter plot comparing log₂ fold change values at the transcript level (x-axis) versus the protein level (y-axis) between *MAPT*-KO and Wild-Type neurons ($R = -0.002$). Red dots highlight concordantly upregulated targets (Concordant Both Up: *COL17A1*, *ST3GAL6*, *CALCRL*, *DEPDC1B*, *C6*, *PER3*), blue dots indicate concordantly downregulated targets (Concordant Both Down: *TNFRSF9*), and gray dots denote non-concordant or neutral targets. **(B)** Consensus signature heatmap displaying relative abundance across transcriptomic (RNA, green bar) and proteomic (Protein, orange bar) layers for WT and *MAPT*-KO conditions. Color intensity corresponds to normalized Z-score values ranging from blue (lower relative expression) to red (higher relative expression). **(C)** Gene Ontology (GO) enrichment analysis of consensus targets. Bar lengths denote statistical significance calculated as $-\log_{10}$ adjusted *P*-value), highlighting pathways including humoral immune response and vasculature development. **(D)** Transcription factor enrichment analysis (ChEA 2022) of consensus hits. Candidate upstream regulators are ranked by Combined Score (x-axis), with color intensity indicating adjusted *P*-values. KLF4 is identified as the top-ranked candidate regulator.