

Transcriptomic Analysis of Trichostatin A Treatment Identifies Candidate Genes Associated with Alzheimer’s Disease

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Cross-dataset transcriptomic analyses identified GPC4 as the strongest candidate gene associated with TSA-mediated transcriptional restoration across Alzheimer's disease datasets, with additional support for MEGF10, PHLDB2, and S1PR1, an AGORA-nominated AD target.

BACKGROUND

CROSS-DATASET INTERSECTION ANALYSIS

GO ENRICHMENT OF TSA-RESCUED GENES

Alzheimer's disease (AD) lacks disease-modifying therapies. Previous work from our group demonstrated that the HDAC inhibitor trichostatin A (TSA) reduces amyloid-beta (Aβ) accumulation in iPSC-derived cortical neurons. Here, we used cross-dataset transcriptomic analyses to identify candidate genes associated with TSA-mediated restoration signatures across independent AD datasets.

Intersection analysis of TSA-responsive genes across independent AD datasets

Left: overlap between TSA-treated neurons and postmortem AD neuron datasets.

Right: overlap between TSA-treated neurons and iPSC-derived AD models.

Intersections represent genes **upregulated by TSA and downregulated in AD**.

Gene Ontology (GO) enrichment of intersected TSA-rescued genes.

Left: Biological Process (BP). Right: Molecular Function (MF). Enriched terms were associated with pathways relevant to AD, including neuronal development, transcriptional regulation, and extracellular matrix function.

CANDIDATE GENE EXPRESSION

CONCLUSIONS

FUTURE DIRECTIONS

GPC4

Heparan sulfate proteoglycan involved in synapse development and neuron-glia signaling

S1PR1

sphingosine-1-phosphate receptor involved in immune signaling and neuroinflammation

- TSA treatment was associated with reversal of AD-associated gene expression.
- GPC4**, with additional support for **MEGF10**, **PHLDB2**, and **S1PR1**, emerged as prioritized candidate genes.
- TSA-responsive genes were enriched for biological pathways associated with AD.

- Experimentally validate candidate genes identified through transcriptomic analyses.
- Investigate the biological roles of **GPC4**, **MEGF10**, **PHLDB2**, and **S1PR1** in AD.
- Evaluate the therapeutic relevance of TSA-regulated pathways.

METHODS

TSA DIFFERENTIAL EXPRESSION

UpSet analysis of TSA and Aβ differential expression

Candidate genes were prioritized from the intersection of genes **upregulated by TSA and downregulated by Aβ** for downstream cross-dataset analyses.

Brain region (top) and single-cell (bottom) expression of GPC4

Enriched in astrocytes and other glial populations, suggesting potential relevance to Alzheimer's disease

Brain region (top) and single-cell (bottom) expression of S1PR1

Enriched in immune-associated cells, supporting its potential role in neuroinflammation and nomination as an AGORAAD target

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CONTACT & REFERENCES

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