The Identification and Validation of Novel Targets and Pathways of Alzheimer's Disease Through Integrated System Approaches

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Alzheimer’s Disease (AD) is a neurodegenerative disorder with no current effective therapies. Synaptojanin 1 (synj1) is a novel target as lowering its expression can be beneficial for AD. Nimodipine lowers synj1 and improves cognitive function, but its effects are not persistent. Therefore, nimodipine structural derivatives were developed with one compound (Cpd #9) showing sustained effects. This project aims to understand the mechanisms of action of nimodipine and Cpd #9 and to determine why Cpd #9 is superior. Using a self-developed pipeline and a published pipeline, the transcriptomic data of mouse brains treated with vehicle, nimodipine or Cpd #9 was processed. Among the top Differentially Expressed Genes (DEGs) between nimodipine and Cpd #9, 15 overlapped between both pipelines. It was found that a large amount of DEGs were associated with immune system processes. Three DEGs were prioritized because of their enrichment in brain immune cells, microglia. Further validation in mouse brains and microglial cell cultures treated with vehicle, nimodipine, or Cpd #9 identified changes in expression in ATP13A2 only by Cpd #9. This result suggests that the superior effects of Cpd #9 may be driven through its target: ATP13A2. Therefore this study opens a new direction for future drug development as ATP13A2 may serve as a possible novel therapeutic target for AD.

Awards Won:
Third Award of $1,000