Multi-omic data integration approach identifies microglial epigenetic-induced metabolic alterations during Alzheimer's disease

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Abstract

Background: Genetics alone can explain only 5% of Alzheimer's disease (AD) cases. Altered homeostasis is a common feature in AD. Here, we used a multi-omic data integration approach to identify metabolic biomarkers under epigenetic influence in the microglia.

Methods: We performed PubMed literature text mining to establish AD endophenotypes. Using microglial ATAC-seq and RNA-seq data from the FreshMicro Study (matched 30 controls and 37 AD samples), we performed differential gene expression/accessibility analysis and, separately, mapped expression data on a human genome-scale metabolic network, based on gene-protein-reaction rules, using iMAT [1] and MOOMIN [2] tools to identify altered metabolic processes. Concurrently, gene co-expression networks were constructed from RNA-seq data using WGCNA [3] and MEGENA [4], followed by enrichment analysis to identify endophenotype-enriched gene modules. Using a metabolite-centric network topological analysis approach, we extracted the significantly affected metabolic subnetwork to identify metabolites with high network influence during AD.

Results: We identified 2/12 and 3/69 gene modules by WGCNA and MEGENA, respectively, which were enriched for AD endophenotypes such as amyloidosis, neuroinflammation, oxidative stress, proteostasis and vascular dysfunction. These endophenotype gene modules were linked with transport, nicotinate and nicotinamide, beta oxidation, fatty acid activation and androgen metabolism related reactions. Importantly, in ATAC-seq versus RNA-seq, we found common perturbations of bile acid and transport reactions and distinct perturbation of pyruvate metabolism from ATAC-seq data. Network analysis revealed high betweenness centrality for apoB100 metabolite in addition to asparagine, tyrosine, and methionine amino acids from RNA-seq. In contrast, from ATAC-seq, we identified cofactor metabolites such as FADH2 and FAD, and lipid metabolites such heneicosanoyl-CoA, ceramide and dihydroceramide pool and GA2.

Conclusion: We established a unique metabolic role of epigenetic programme in the microglia during AD. The identified multi-omic networks will be instrumental in elucidating novel epigenome-wide AD biomarkers and network-based drug repurposing analysis.

Keywords: Epigenetics, Alzheimer's disease, multi-omics, metabolic networks, biomarker.

References

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