Multi-omic analyses of hiPSC-derived astrocytes

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Astrocytes have a key role in brain development and functions and contribute to neurodegenerative disorders by various mechanisms, including metabolic alterations. They are also the major source of L-serine (L-Ser) in the brain, which is synthesized from the glycolytic intermediate D-3-phosphoglycerate through the phosphorylated pathway (PP), which comprises three enzymes: 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), phosphoserine phosphatase (PSP). L-Ser is the precursor of the two main co-agonists of the N-methyl-D-aspartate receptors, glycine and D-serine.

We generated human mature astrocytes from pluripotent stem cells (hiPSC) to study the changes occurring during astrocytes differentiation. By using an integrated multi-omics approach we studied differentiation from neural stem cells to 56-days-old astrocytes, showing that up to 30 days axon guidance processes, folate cycle, pyrimidine and amino acid metabolism were prevalent, along with sphingolipid synthesis and metabolites related to the serine pathway (published in Tripodi et al (2023) FEBS J 290(18) 4440-4464).

We have recently reported that the levels of the enzymes of the PP are increased in Alzheimer’s disease brains (previously published in Maffioli et al (2022) Cell Rep 40(10): 111271). Following this observation, we overexpressed PHGDH, PSAT or PSP in the hiPSC-derived astrocyte model and investigated metabolomic and proteomic changes following PP enzymes overexpression. Strikingly, significant alterations were apparent in the pathways directly linked to serine metabolism as well as on folate and nucleotide metabolism, and TCA cycle, suggesting a complex rewiring of the metabolism. These results provide a valuable model for developing potential novel approaches to address brain diseases, especially those linked to NMDA receptor alterations due to modification of serine concentration.

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