Dissecting the role of serine in neurological disorders

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Abstract:

Introduction. Tau and beta-amyloid (Aβ) aggregation, mitochondria dysfunction, hypometabolism and inflammation are common features in Alzheimer's Disease (AD), the most known form of dementia worldwide. Progressive neurodegeneration, neuronal loss and brain atrophy in different brain areas, cause a mild to severe cognitive decline that afflicts AD patient's life. Among all the mediators of neurodegeneration in AD, astrocytes, which normally support neuronal metabolism, are reactive and may activate and proliferate around Aβ plaques. Astrocytes produce also serine, an important neurotransmitter that stimulates NMDA receptors (NMDARs), which are involved in synaptic transmission and brain plasticity. In AD brains, serine levels are lower than normal, thus compromising NMDARs function, leading to cellular excitotoxicity and synaptic dysfunctions. **Aim.** To assess the role of serine and related pathways in AD we performed proteomic and metabolomic analysis using LC-MS/GC-MS in two different models: i) we differentiated astrocytes from human neural stem cells (NSCs) and we maintained them in long-term cultures (56 days of differentiation); ii) we analyzed hippocampal brain tissues derived from males and females patients of AD. **Results.** Our preliminary results show that: i) hiPSC-derived astrocytes become mature around day30 from NSCs differentiation; metabolomic and proteomic analysis is still ongoing; ii) several metabolic pathways are altered in AD brains; interestingly, females present metabolic alterations that differ from males. **Conclusions.** Understanding AD pathophysiology is necessary for prevention and drug screening; although some analyses are still ongoing, our models are promising tools to investigate metabolic alterations in AD.