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Multi-omics Integrative Analysis with Genome-Scale Metabolic Model Simulation Reveals Reaction Essentiality data in Human Astrocytes Under the Lipotoxic Effect of Palmitic Acid

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Abstract : Astrocytes play an important role in various processes in the brain, including pathological conditions such as neurodegenerative diseases. Recent studies have shown that the increase in saturated fatty acids such as palmitic acid (PA) triggers pro-inflammatory pathways in the brain. The use of synthetic neurosteroids such as tibolone has demonstrated neuro-protective mechanisms. However, there are few studies on the neuro-protective mechanisms of tibolone, especially at the systemic (omic) level. In this study, we performed the integration of multi-omic data (transcriptome and proteome) into a human astrocyte genomic scale metabolic model to study the astrocytic response during palmitate treatment. We evaluated metabolic fluxes in three scenarios (healthy, induced inflammation by PA, and tibolone treatment under PA inflammation). We also use control theory to identify those reactions that control the astrocytic system. Our results suggest that PA generates a modulation of central and secondary metabolism, showing a change in energy source use through inhibition of folate cycle and fatty acid β-oxidation and upregulation of ketone bodies formation.We found 25 metabolic switches under PA-mediated cellular regulation, 9 of which were critical only in the inflammatory scenario but not in the protective tibolone one. Within these reactions, inhibitory, total, and directional coupling profiles were key findings, playing a fundamental role in the (de)regulation in metabolic pathways that increase neurotoxicity and represent potential treatment targets. Finally, this study framework facilitates the understanding of metabolic regulation strategies, andit can be used for in silico exploring the mechanisms of astrocytic cell regulation, directing a more complex future experimental work in neurodegenerative diseases.

Keywords : astrocytes, data integration, palmitic acid, computational model, multi-omics, control theory
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