Multi-Omics Integrative Analysis Coupled to Control Theory and Computational Simulation of a Genome-Scale Metabolic Model Reveal Controlling Biological Switches in Human Astrocytes under Palmitic Acid-Induced Lipotoxicity

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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-inflammatorypathways in the brain. The use of synthetic neurosteroids such as tibolone has demonstrated neuro-protective mechanisms. However, broad studies with a systemic point of view on the neurodegenerative role of PA and the neuro-protective mechanisms of tibolone are lacking. 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 applied a control theory approach to identify those reactions that exert more control in the astrocytic system. Our results suggest that PA generates a modulation of central and secondary metabolism, showing a switch 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 of metabolic pathways that may increase neurotoxicity and represent potential treatment targets. Finally, the overall framework of our approach facilitates the understanding of complex metabolic regulation, and it can be used for in silico exploration of 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

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