Multi-omics network integration across disease progression in myotubular myopathy

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Résumé

X-linked myotubular myopathy (XLMTM) is a rare and severe form of centronuclear myopathy (CNM) caused by loss-of-function mutations in Myotubularin 1 (MTM1). Previous studies have used network-based integration to combine different layers of omics with public knowledge bases into a multilayer network, revealing both pathogenic and protective pathways in XLMTM. However, the analyses overlooked the temporal dynamics of disease progression across developmental stages. Moreover, the coordinated impact of transcriptomic and proteomic changes on downstream metabolic alterations remains poorly understood. To address this, we performed longitudinal transcriptomic and proteomic analyses in the tibialis anterior muscle of Mtm1-/y mice at embryonic, early, and late developmental stages. These analyses revealed temporal dysregulation at the pathway level, with coordinated changes in gene and protein expression across stages. Notably, pathway-level overlap between transcriptomic and proteomic layers highlighted convergent molecular alterations, emphasizing the need for time-resolved integrative approaches to capture disease progression. Building on these findings, we propose a temporal multi-omics network framework that integrates transcriptomic, proteomic, metabolomic, and lipidomic datasets across developmental stages. Transcriptomic and proteomic profiles are modelled as a time-resolved multiplex network, in which each stage represents a distinct layer and is connected by directed temporal edges. Metabolomic and lipidomic data collected at the late stage are incorporated via pathway-based bipartite connections linking genes, proteins, and metabolites. Network propagation using Random Walk with Restart (MultiXRank), seeded from Mtm1 in the early stage, enables the topological and functional prioritization of molecular features and pathways and potentially captures the dynamic disease trajectories. Overall, this provides a comprehensive view of disease progression, facilitates identification of candidate biomarkers, and highlights potential therapeutic targets for XLMTM.

Mots-Clés: Centronuclear myopathy, MTM1, Multi, omics integration, Temporal dynamics, MultixRank, Metabolomics, Lipidomics, Transcriptomics, Proteomics

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