Multi-omics study of intracellular transport defects impacting focal adhesion in myotubular myopathy in mice

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Résumé

X-linked myotubular myopathy (XLMTM) is rare and a severe form of centronuclear myopathy (CNM) caused by the loss-of-function mutations in *Myotubularin 1* (*MTM1).* Previous studies have reported significant impairments in focal adhesion dynamics and integrin intracellular localization in 8 weeks *Mtm1*−/y mice. However, the underlying causes of these defects and their progression across different disease stages remain poorly understood. To address this, we performed transcriptomic and proteomic analyses on the *Mtm1*−/y mouse model at pre-symptomatic (E18.5), early (2w) and late (7w) developmental stages. Our results reveal that the pathways related to intracellular transportation, integrin activation and recycling, vesicle trafficking, and extracellular matrix (ECM) organization were consistently altered. An early upregulation of caveolin-dependent endocytosis and ECM components along with impaired fast recycling of integrins, were observed. These findings were confirmed by measuring the mRNA and protein expression. This ultimately led to the intracellular accumulation of active β1-integrin at the late disease stage. In silico analyses further indicated that these defects occur at the early endosomal level due to the absence of MTM1 and not at the late endosomal stage. Additionally, in-vitro studies have validated the overexpression of slow recycling transporter and caveolins during the later stages of disease progression.
Overall, these findings suggest that major defects in various intracellular transport systems have impact on the dysregulation of focal adhesion and cytoskeleton dynamics. This highlights intracellular transporters as a strong promising therapeutic targets for restoring cellular homeostasis at early disease stages in *Mtm1KO* mouse models.

Mots-Clés: Myotubularin 1 (MTM1), Intracellular transport, Integrin signalling, Extracellular Matrix (ECM), Multi, omics

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