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Abstract

New insights on signaling pathways deregulated in LAP1-deficient cells: a proteomics study

Cátia D. Pereira [1], Guadalupe Espadas [2,3], Filipa Martins [1], Anne T. Bertrand [4], Laurent Servais [5,6], Eduard Sabidó [2,3], Odete A. B. da Cruz e Silva [1] and Sandra Rebelo [1,*]

[1] Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, 3810-193 Aveiro, Portugal; daniela.pereira@ua.pt (C.D.P.); samartins@ua.pt (F.M.); odetecs@ua.pt (O.A.B.-d.C.S.)
[2] Centre de Regulació Genòmica (CRG), Barcelona Institute of Science and Technology (BIST), 08003 Barcelona, Spain; guadalupe.espadas@crg.eu (G.E.); eduard.sabido@crg.eu (E.S.)
[3] Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain
[4] Sorbonne Université, INSERM UMRS 974, Center of Research in Myology, Institut de Myologie, 75013 Paris, France; a.bertrand@institut-myologie.org
[5] MDUK Oxford Neuromuscular Center, University of Oxford, Oxford, United Kingdom; laurent.servais@paediatrics.ox.ac.uk
[6] Neuromuscular Reference Center, University Hospital Liège & University of Liège, 4000 Liège, Belgium
* Correspondence: srebelo@ua.pt; Tel.: +351-924-406-306

Abstract: Mutations in genes encoding nuclear envelope (NE) proteins, despite being rare, represent a major threat to cell homeostasis by compromising nuclear integrity and function as well as nucleocytoplasmic communication. In the last decade, several diseases have been associated to mutations in the *TOR1AIP1* gene that codes for lamina-associated polypeptide 1 (LAP1), a NE protein ubiquitously expressed in human tissues. Although this is suggestive of an important physiological role of LAP1, it remains unclear which cellular activities are regulated by this protein. To address this, we investigated the molecular repercussions of its deficiency in patient-derived skin fibroblasts carrying a pathological LAP1 mutation (p.E482A), previously reported in a case of severe dystonia, cerebellar atrophy and cardiomyopathy. Using liquid chromatography with tandem mass spectrometry (LC–MS/MS), a quantitative proteome analysis was performed to identify up-/downregulated proteins in LAP1 E482A fibroblasts relative to age-matched control fibroblasts. A subsequent functional characterization of the LC–MS/MS-identified differentially expressed proteins using bioinformatics tools unraveled various signaling pathways/biological processes potentially deregulated in LAP1 E482A fibroblasts, such as DNA repair, neurodevelopment and myogenesis, among others. This work sheds light on dysfunctional molecular mechanisms in LAP1-deficient cells, which will contribute to a better understanding of LAP1's physiological relevance for the maintenance of cell homeostasis and, hopefully, allow to uncover potential therapeutic targets for LAP1-associated pathologies.

Keywords: LAP1; DNA repair; neurodevelopment; myogenesis

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