The Metabolomic Bioenergetic Signature of Opa1-Disrupted Mouse Embryonic Fibroblasts Highlights Aspartate Deficiency

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Résumé en anglais	OPA1 (Optic Atrophy 1) is a multi-isoform dynamin GTPase involved in the regulation of mitochondrial fusion and organization of the cristae structure of the mitochondrial inner membrane. Pathogenic OPA1 variants lead to a large spectrum of disorders associated with visual impairment due to optic nerve neuropathy. The aim of this study was to investigate the metabolomic consequences of complete OPA1 disruption in Opa1 mouse embryonic fibroblasts (MEFs) compared to their Opa1 counterparts. Our non-targeted metabolomics approach revealed significant modifications of the concentration of several mitochondrial substrates, i.e. a decrease of aspartate, glutamate and α-ketoglutaric acid, and an increase of asparagine, glutamine and adenosine-5'-monophosphate, all related to aspartate metabolism. The signature further highlighted the altered metabolism of nucleotides and NAD together with deficient mitochondrial bioenergetics, reflected by the decrease of creatine/creatine phosphate and pantothenic acid, and the increase in pyruvate and glutathione. Interestingly, we recently reported significant variations of five of these molecules, including aspartate and glutamate, in the plasma of individuals carrying pathogenic OPA1 variants. Our findings show that the disruption of OPA1 leads to a remodelling of bioenergetic pathways with the central role being played by aspartate and related metabolites.
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