Metabo-lipidomics of Fibroblasts and Mitochondrial-Endoplasmic Reticulum Extracts from ALS Patients Shows Alterations in Purine, Pyrimidine, Energetic, and Phospholipid Metabolisms

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Résumé en anglais	Amyotrophic lateral sclerosis (ALS) is characterized by a wide metabolic remodeling, as shown by recent metabolomics and lipidomics studies performed in samples from patient cohorts and experimental animal models. Here, we explored the metabolome and lipidome of fibroblasts from sporadic ALS patients (n = 13) comparatively to age- and sex-matched controls (n = 11), and the subcellular fraction containing the mitochondria and endoplasmic reticulum (mito-ER), given that mitochondrial dysfunctions and ER stress are important features of ALS patho-mechanisms. We also assessed the mitochondrial oxidative respiration and the mitochondrial genomic (mtDNA) sequence, although without yielding significant differences. Compared to controls, ALS fibroblasts did not exhibit a mitochondrial respiration defect nor an increased proportion of mitochondrial DNA mutations. In addition, non-targeted metabolomics and lipidomics analyses identified 124 and 127 metabolites, and 328 and 220 lipids in whole cells and the mito-ER fractions, respectively, along with partial least-squares-discriminant analysis (PLS-DA) models being systematically highly predictive of the disease. The most discriminant metabolomic features were the alteration of purine, pyrimidine, and energetic metabolisms, suggestive of oxidative stress and of pro-inflammatory status. The most important lipidomic feature in the mito-ER fraction was the disturbance of phosphatidylcholine PC (36:4p) levels, which we had previously reported in the cerebrospinal fluid of ALS patients and in the brain from an ALS mouse model. Thus, our results reveal that fibroblasts from sporadic ALS patients share common metabolic remodeling, consistent with other metabolic studies performed in ALS, opening perspectives for further exploration in this cellular model in ALS.
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