COMBINED METABOLOMICS AND LIPIDOMICS ANALYSES OF FIBROBLASTS FROM ALS PATIENTS

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Introduction

- Genetic and environmental factors are associated with ALS but pathophysiology remains unknown in the majority of cases.

- Metabolic alterations and prominent role of lipid metabolism have been reported in ALS

- Previous findings from our group revealed metabolomics and lipidomics signatures of ALS, based on CSF samples and cellular models exploration.

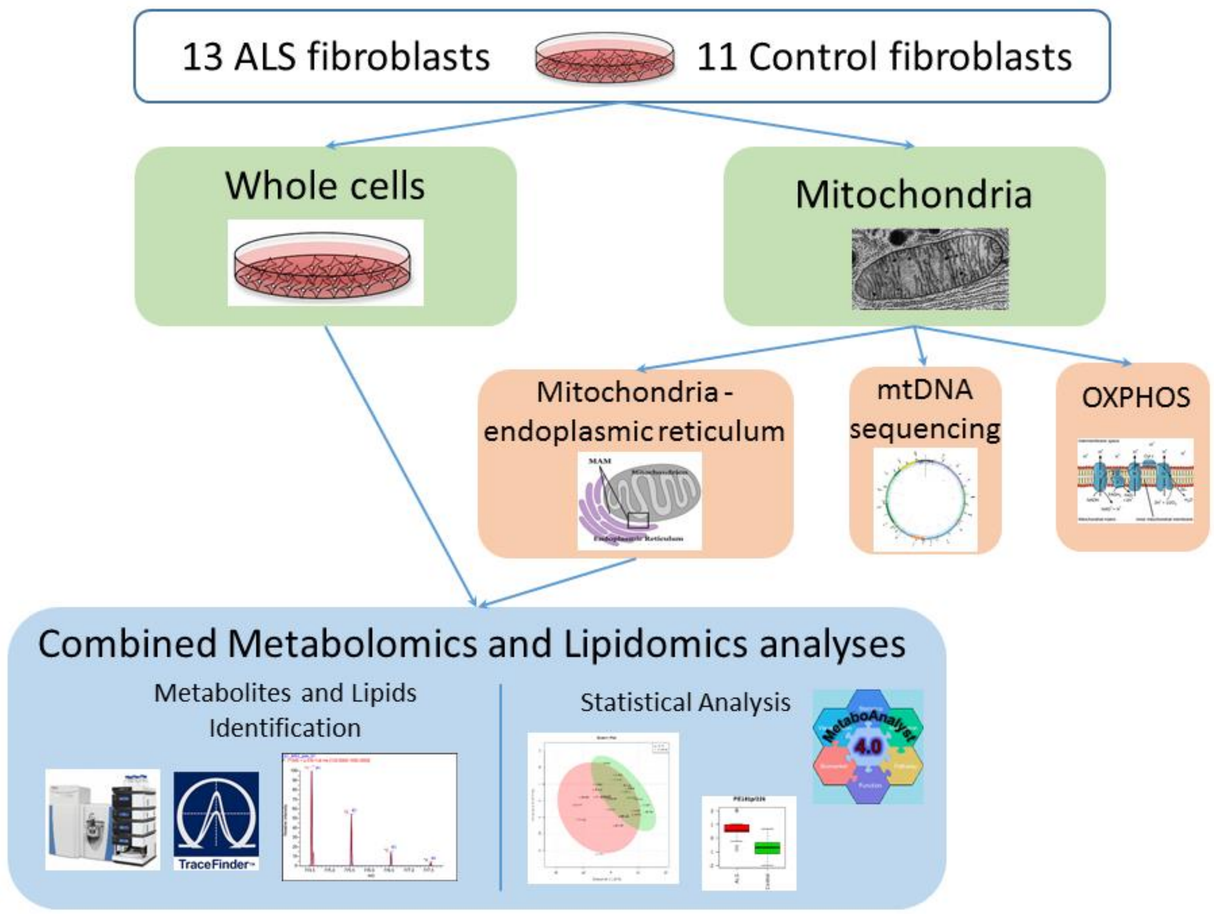
-Biological markers may provide a metabotype of ALS that could be helpful to deeply characterize patients

Objectives

Exploration of fibroblast metabolism from ALS patients in order to better understand metabolic dysregulation in ALS

1) Metabolomics and lipidomics of the entire fibroblasts
2) Metabolomics, lipidomics and genomics focused on mitochondria

Materials and Methods



Results

Whole cell extracts

126 metabolites identified and 328 lipids detected
with variation <30% in quality controls

Mitochondria – endoplasmic reticulum extracts

135 metabolites identified and 220 lipids detected
with variation <30% in quality controls

Specific mitochondria explorations

OXPHOS

* No difference in basal respiration between ALS and control fibroblast
* **Significant lower non-phosphorylative** respiration in ALS cells

→ **higher respiration due to mitochondria mtDNA sequencing**

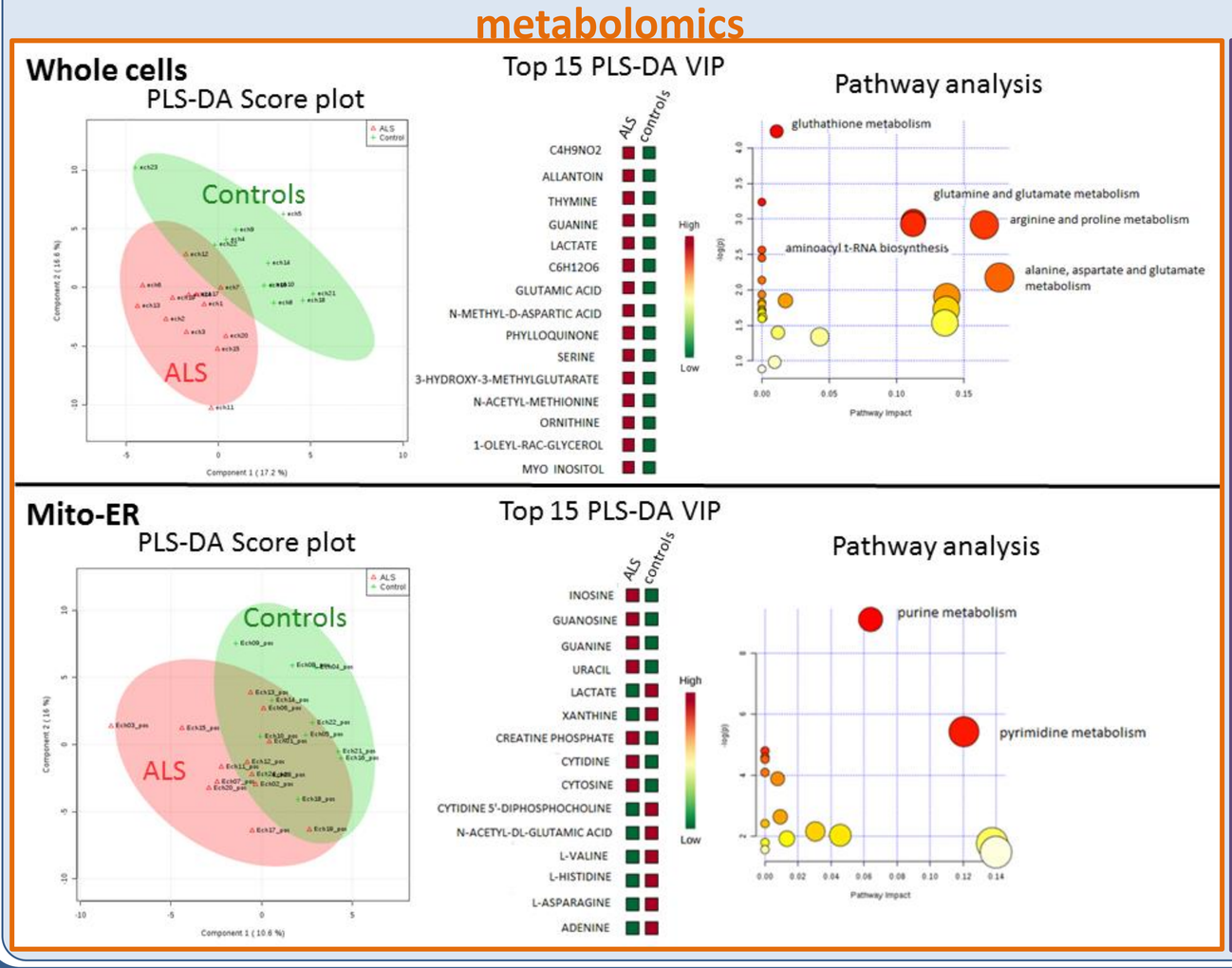
∞

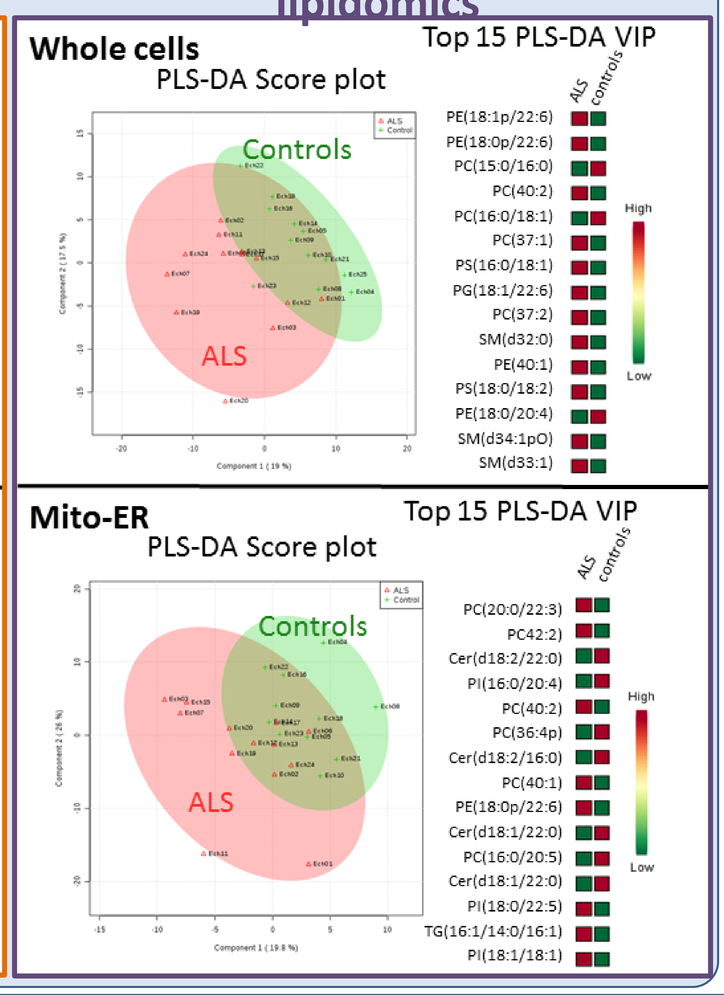
mtDNA of ALS

* fibroblasts seemed to have many similarities with mtDNA of controls
* **Higher global heteroplasmy level**

→ **impact on epigenetic of mtDNA?**

Specific metabolomics and lipidomics signatures in ALS whole cells and mito-ER extracts





Discussion-Conclusion

- First analysis **combining metabolomics and lipidomics** in fibroblasts from sporadic ALS patients
- Modification of purine and pyrimidine metabolism, increase of plasmalogens (ether phospholipids) → **Involvement of oxidative stress**
- Disturbance of ceramide and sphingomyelin metabolism, increase of phosphatidylcholine (PC) levels → **Involvement of inflammatory processes**
- Increase of mitochondrial respiration associated with increase of quinone level, increase of phosphocreatine and modification of hexose and lactate concentration → **Disturbance of energy metabolism**
- Open perspective of functional, genomic and transcriptomic approaches focused on metabolites identified in this study and help to better understand mechanisms of the disease