Is there a biochemical or molecular switch from healthy to symptomatic phenotype in Amyotrophic Lateral Sclerosis?

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BACKGROUND

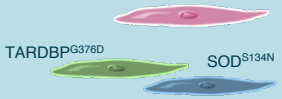
ALS is a fatal neurodegenerative disease, characterized by the loss of MNs[1].10% of ALS cases are associated with mutations in specific genes (familial, fALS) and patients display diverse phenotypic expression patterns and may exhibit different progression rate. Although the effects of the mutations are not completely clear, they share some common pathways: glutamate excitotoxicity, structural and functional **abnormalities of mitochondria**, **oxidative stress**, intracellular aggregates, activation of microglia.

AIMS

Comparison between **healthy and symptomatic fibroblasts with mutations in SOD1[2] and TARDBP[3]** genes to investigate the existence of a molecular or biochemical switch **from sane to affected phenotype**, thanks to phenotypical, biochemical, and molecular analysis.

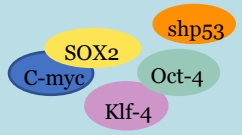
EXPERIMENTAL PLAN

1) Analysis of putative metabolic pathways altered in ALS : cell proliferation, oxydative stress, antioxidant defense and bioenergetics

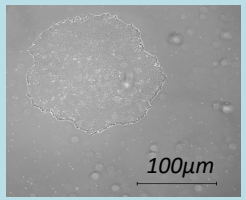


Fibroblasts

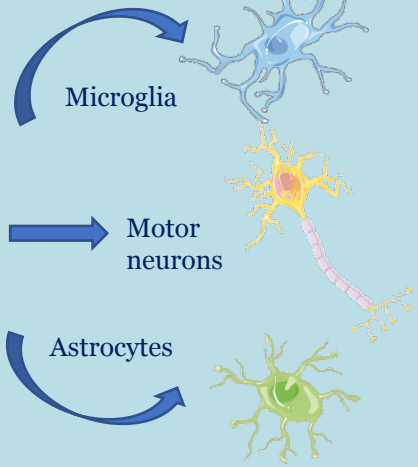
2) Production of disease-relevant cell phenotypes



Reprogramming factors



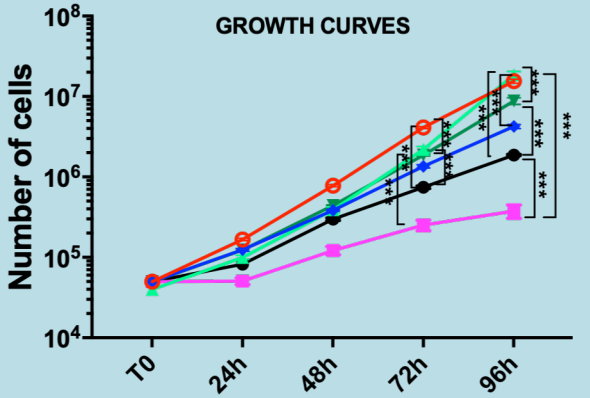
hiPSCs



3) In vitro co-culture systems

REFERENCES
1) Rowland LP, et al.,Shneider NA. (2001). Amyotrophic lateral sclerosis. N Engl J Med;
2) Huai, J., & Zhang, Z. (2019). Structural properties and interaction partners of familial ALS-associated SOD1 mutants. Frontiers in Neurology;
3) Mitsuzawa, S. *et al.* (2018). TARDBP p.G376D mutation, found in rapid progressive familial ALS, induces mislocalization of TDP-43. ENeurologicalSci.

RESULTS



*Symptomatic mutated fibroblasts show a **higher proliferation rate** compared to controls and healthy mutated cell lines (p value: *p<0,05; **p<0,01;***p<0,001).*

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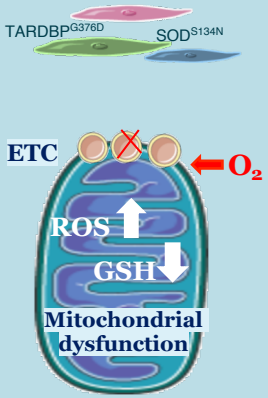
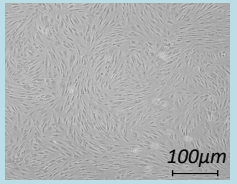
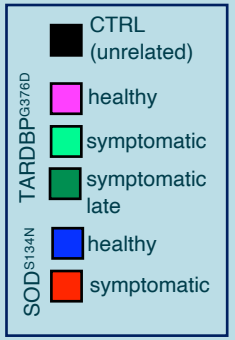
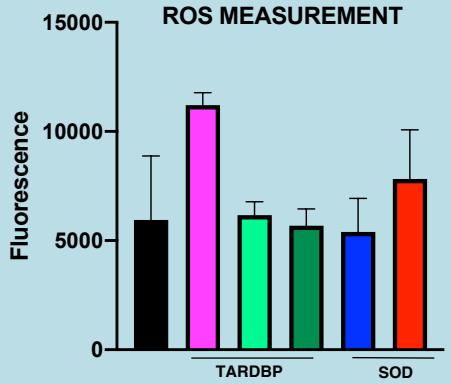
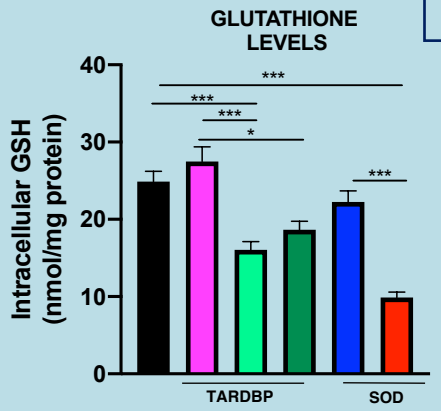


Attempt to compensate for the deleterious effect of the mutated proteins?









*Although there are **no significant differences in ROS levels**, **healthy individuals have higher GSH levels** compared to symptomatic ones and this could represent a protective mechanism (p value: *p<0,05; **p<0,01;***p<0,001).*

NEXT STEPS: Seahorse analysis to study bioenergetic parameters (Glycolysis VS OXPHOS), since the normal process of ETC is perturbed in ALS patients, causing less production of ATP.