Evaluation of the metabolic profile of fibroblasts carrying the L145F mutation in the superoxide dismutase 1 gene

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Abstract:
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by the loss of upper and lower motor neurons (MNs) at the spinal or bulbar level. MNs loss determines skeletal muscle paralysis and leads to patients' death, mostly by respiratory failure, 3-5 years after symptoms onset, and no effective treatment is available. ALS is a multifactorial disease caused by both environmental and genetic factors. The majority (90-95%) of ALS forms are classified as sporadic (sALS), while about 10% of cases are associated with mutations in specific genes (familial, fALS). Among the numerous defective genes associated with ALS, SOD1 (Cu/Zn superoxide dismutase-1) is the first and the most extensively studied gene. Mutant SOD1 can adopt multiple misfolded conformation, loose the correct coordination of metal binding, decrease the structural stability and form aggregates. Thus, the characterization of common conformational alterations of ALS-associated mutant SOD1 should be particularly challenging. In our work we focused our attention on the L145F mutation, typical of Mediterranean countries, sharing peculiar clinical features. Even though SOD1 mutations usually lead to motor neuron degeneration through a gain of toxic function, it has been shown that this mutation causes a reduced SOD1 activity; moreover, it affects anti-oxidative defense. In this preliminary study of the mutation, we analyzed phenotypic peculiarities in fibroblasts derived from a 48-year-old female patient, by evaluating the impact on protein conformation, alterations of proliferation rate, oxidative stress response and bioenergetic metabolism by using Seahorse Analysis.