Exploring the correlation between bioenergetic profile and ALS pathogenesis in fibroblasts of TARDBP p.G376D mutation carriers

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Abstract:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the progressive degeneration of upper and lower motor neurons that leads to muscle weakness and atrophy.

The pathogenetic process remains largely unknown, ALS is a complex and multifactorial disease associated with a combination of environmental and genetic factors (i.e., *TARDBP* gene) and is classified into sporadic (sALS, 90% of cases) and familial (fALS, 10% of causes) types, depending on whether or not there is a family history of the disease. Both types share some common pathways, among which metabolic dysfunctions (i.e., hypermetabolism) that is recently under investigation.

Whithin the project of this study, we have characterized fibroblasts derived from healthy donors and carriers of the p.G376D mutation ($TARDBP^{G376D}$) belonging to an Apulian family. In particular, we collected fibroblasts from unrelated and related controls, an asymptomatic carrier, and from an ALS patient at two different time points (the first biopsy at 2 years from diagnosis and the second biopsy at 6 years from onset).

Given the lack of appropriate models and the difficulty in accessing nervous cells, we employed fibroblasts to model ALS, these primary cells share the same genetic background and recapitulate the metabolic dysfunctions observed in the central nervous system.

The aim of the thesis was to elucidate the differences between healthy individuals, healthy carriers and the ALS patient bearing the p.G376D mutation in order to point out possible protective mechanisms present in healthy carriers respect to patient, as well as possibly individuate molecular mechanisms of disease progression by comparing patient's cells over different disease stages.