Metabolic profiling of sporadic ALS patients: from fibroblasts to neurons and back

https://neurodegenerationresearch.eu/survey/metabolic-profiling-of-sporadic-als-patients-from-fibroblasts-to-neurons-and-back/

Principal Investigators

MANFREDI, GIOVANNI

Institution

WEILL MEDICAL COLL OF CORNELL UNIV

Contact information of lead PI
Country

USA

Title of project or programme

Metabolic profiling of sporadic ALS patients: from fibroblasts to neurons and back

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NIH (NINDS)

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

metabolic profile, Amyotrophic Lateral Sclerosis, Fibroblasts, Back, Bioenergetics

Research Abstract

? DESCRIPTION (provided by applicant): Sporadic ALS (sALS) includes by far the largest ALS patient population, but very little is known about the causes of the disease. Patients affected by

amyotrophic lateral sclerosis (ALS) have bioenergetic abnormalities, which can contribute to disease pathogenesis, and metabolic profiles could represent predisposing factors to develop ALS and affect disease course. Metabolic changes may also influence the response to therapeutics, and the lack of effective drugs for ALS may be in part attributable to insufficient understanding of metabolism as a disease modifier. To investigate energy metabolism we used a novel fluorimetric assay for mitochondrial membrane potential (MMP) and mitochondrial mass (MM), in primary sALS skin fibroblasts. We found that sALS patients have on average significantly increased membrane potential, which inversely correlates with disease onset. Furthermore, unbiased metabolomics studies identified unequivocal differences in intermediate metabolite profiles between ALS and control fibroblasts. To our knowledge, this is the first functional evidence in living cells that energy metabolism is altered in sporadic ALS. A major goal of the application is the identification of fibroblasts metabolism as a predictive factor for he evolution of ALS and for evaluating metabolic changes as disease modifiers. To this end, in aim 1, we propose to define a metabolite signature linked to energy metabolism in fibroblasts, in the extracellular medium, and in the plasma of the subjects from which skin biopsies were taken. We also propose to investigate the correlation of bioenergetic and metabolic parameters with disease status and progression. In aim 2, to understand if the changes in fibroblasts reflect a metabolic reprogramming affecting the cell types most involved in ALS, we will convert fibroblasts into induced pluripotent stem cells (iPSC) and then motor neurons, and study their bioenergetics and metabolic profiles. Importantly, to investigate if metabolic changes originate from genetic or epigenetic causes, we will determine if bioenergetic and metabolic changes persist or not after de-differentiation of iPSC followed by back-differentiation into fibroblasts.

Lay Summary
PUBLIC HEALTH RELEVANCE: Patients affected by amyotrophic lateral sclerosis (ALS) have impaired metabolism, which could contribute to disease pathogenesis. We have found that ALS skin fibroblasts have changes in mitochondrial metabolism. We are proposing to study whether metabolic alterations underlie disease mechanisms, using both fibroblasts and motor neurons derived from fibroblasts through induced pluripotent cells technology, and if metabolic alterations can be studied to predict disease progression and responsiveness to therapies.

Further information available at:

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Investments > €500k

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