gofar Comitato RUDI Onlus
Friedreich's Ataxia Research

"Comparative analysis of FA patient iPSC-derived retinal, sensory and cortical neurons and reactivation of the silenced Frataxin gene with an epigenetic approach"

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Friedreich's ataxia (FA) is an inherited neurodegenerative disease that causes the development of progressive ataxia of the gait and limbs, dysarthria, loss of tendon reflexes, pyramidal signs and scoliosis accompanied by cardiomyopathy and diabetes mellitus. In some cases, patients show hearing impairment and significant loss of vision due to optic atrophy. Most studies on the pathological mechanisms of this disease have focused on the degeneration of the cerebellar and dorsal ganglia sensory neurons. Much less is known on the underlying causes of visual dysfunction and degeneration in retinal neurons. Our group generated reprogrammed stem cells (iPSCs) from 2 patients with moderate or severe neurological symptoms of AF caused by, respectively, a short or larger expansion of the GAA trait in the Frataxin gene. In this project iPSC cells will be differentiated into neurons of the retina, sensory dorsal ganglia and cerebral cortex to study the pathological changes in cells and mitochondria. This comparative analysis will allow us to understand the progression and dynamics of the pathological processes in different neuronal classes that are more sensitive (dorsal ganglia sensory neurons and retinal neurons) or more resistant (neurons of the cerebral cortex) to the inactivation of the Frataxin gene. The second part of the project is aimed at the generation of "gene editing" systems with the Cas9 protein with the aim of reactivating the silenced Frataxin gene through epigenetic mechanisms. With this modality it is possible to remove the chromatin modifications that silence the gene, inducing the reactivation of its promoter and the re-expression of the gene. This strategy has the advantage of activating the endogenous gene with its own levels of expression, thus avoiding side effects caused by overexpression of the gene that can likely occur with traditional gene therapy approaches. The effectiveness of this system will be assessed by the ability to reactivate the Frataxin gene in patient fibroblasts and in the mouse model of the disease. It will also be investigated whether Frataxin reactivation will be able to recover and to what extent the cellular and mitochondrial defects present in patients' iPSCs.
This project aims to acquire new knowledge on the pathological mechanisms of FA by using patient stem cells for generating various classes of neurons differently affected by the disease. In addition, new molecular tools will be developed that can be used to reactivate the silenced Frataxin gene in disease and thus become a new precision medicine therapeutic option for AF.

Tipo ricerca: studio pre-clinico
Costo globale del Progetto 320.000 €, durata 2 anni (Aprile, 2022 – Aprile, 2024)