UNIVERSITÀ DEGLI STUDI DI MILANO

D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

Patient-derived iPSC to dissect pathomechanisms with 2D and 3D models of ALS motoneuron disease

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Aim

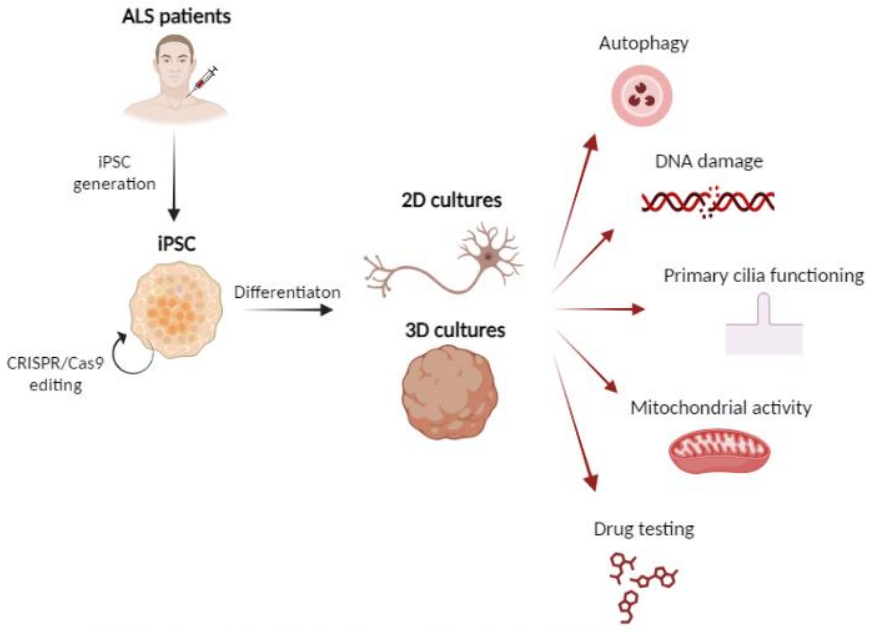
Aim of the project is to exploit iPSC from patients suffering from amyotrophic lateral sclerosis (ALS) to investigate pathomechanisms associated to neurodegeneration and to test potential therapeutic strategies in 2D motoneuronal cultures and 3D cerebral organoids

Rationale

ALS is a neurodegenerative disease characterized by the progressive death of upper and/or lower motoneurons with a multifactorial etiology in the majority of cases (90%) and a recognized inheritance in familial cases (10%) with more than 30 causative genes identified so far. In vitro modeling of ALS and neurodegenerative disorders is challenging because of the inability to establish human neuronal cultures, but iPSC (induced plutipotent stem cells) reprogrammed from patients' somatic cells now allow to obtain differentiated neuro-glial cells and brain organoids retaining the individual's genetic background. These These iPSC-based models therefore represent suitable disease models to study the pathomechanisms driving the neurodegenerative process in ALS.

Study design

iPSC lines from familial ALS patients, isogenic controls or healthy individuals have already been established in the lab and are available for the project to be differentiated into motoneurons and brain organoids according to already optimized protocols. In these 2D and 3D iPSC-derived disease models mitochondrial functionality, response to stress and DNA damage, autophagy and cilia functioning will be investigated using a variety of molecular and cell biology techniques. Potential therapeutic strategies will be also tested to rescue the observed defects.



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