UNIVERSITÀ DEGLI STUDI DI MILANO

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

Dissecting nuclear and axonal transport defects in ALS patient-derived iPSC-motoneurons

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Aim

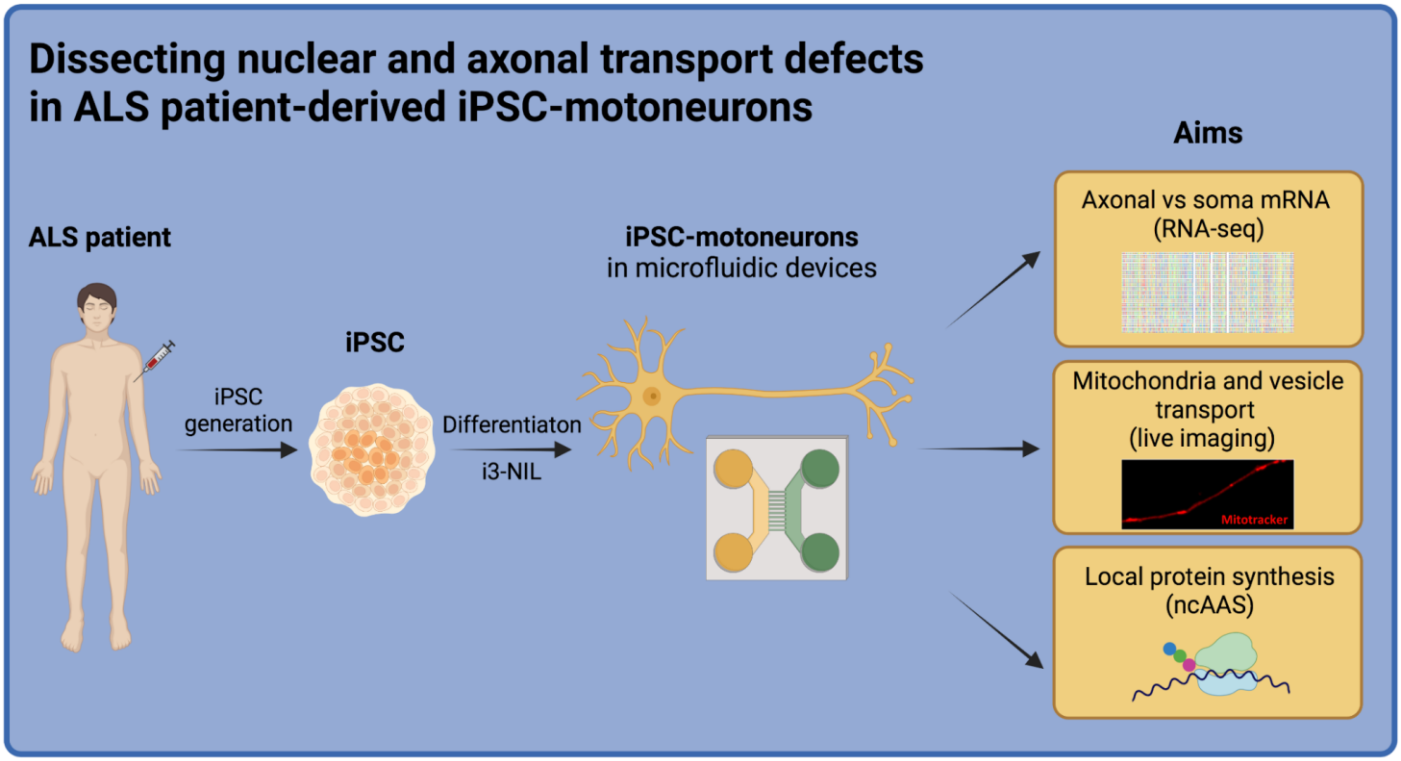
Aim of the project is to investigate the nuclear-cytoplasmic trafficking and axonal transport in human motoneurons obtained from reprogrammed iPSC of patients suffering of amyotrophic lateral sclerosis (ALS).

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. Among the causative genes, *C9orf72* and *TARDBP* represent the most frequently mutated ones and are involved in regulating RNA metabolism at different levels, from splicing to mRNA transport and local translation. The pathomechanisms associated to these two genes in ALS have been mostly investigated in rodent primary neurons or post-mortem brains. Patient-derived iPSC motoneurons represent a suitable disease cell model to study how mutant *C9orf72* and *TARDBP* genes promote neurodegeneration.

Study design

iPSC lines from mutant *C9orf72* and *TARDBP* ALS patients have already been established in the lab and are available for the project. The inducible i3-system with the NIL (Neurogenin2-Islet1-Lim-homeobox3) cassette will be utilized to differentiate motoneurons in a more reproducible and fast manner. iPSC-motoneurons will be grown in microfluidic devices to separate the axonal compartment and to study transport of different cargoes (RNA granules, mitochondria, vesicles) and local protein synthesis in axons using specific techniques.



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