In vitro disease modeling of Amyotrophic Lateral Sclerosis: an iPS TALE(N)

Alessandro Rosa, Jessica Lenzi, Riccardo De Santis, Valeria de Turris and Irene Bozzoni

Induced Pluripotent Stem Cells (iPSCs) provide an opportunity to model in vitro neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), a fatal condition caused by loss of motoneurons (MNs). Several ALS-linked genes have been recently discovered. In the case of the RNA-binding factor FUS, most in vitro studies rely on cell lines in which the mutated protein is overexpressed. Such systems do not recapitulate the complexity of the MN and its microenvironment. Here, we describe the derivation of iPSCs carrying ALS mutations in the FUS gene. Our iPSCs collection includes lines derived by reprogramming from patients (FUS-R514S and FUS-R521C) or raised by TALEN-directed mutagenesis (FUS-P525L). iPSC-derived MNs provided an in vitro model to study the behavior of the mutant proteins in the appropriate cellular and genetic background. We show that aberrant cytoplasmic localization of mutated FUS, an hallmark of the pathology, was recapitulated in iPSC-derived MNs. Increased oxidative stress is thought to play a role in ALS pathogenesis. In our system, mutated FUS is aberrantly recruited into stress granules upon different kinds of stress. Moreover, iPSCs can be differentiated into other cell types relevant to ALS, such as muscle cells. Therefore, the iPSC system presented here represents a suitable model for investigating the role of FUS mutations in ALS ethiopathogenesis.