?-catenin aggregation in models of ALS motor neurons: GSK3? inhibition effect and neuronal differentiation

Pinto, Cristina

Medinas, Danilo B.

Fuentes-Villalobos, Francisco

Maripillán, Jaime

Castro, Ariel F.

Martínez, Agustín D.

Osses, Nelson

Hetz, Claudio

Henríquez, Juan P.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron death. A 20% of familial ALS cases are associated with mutations in the gene coding for superoxide dismutase 1 (SOD1). The accumulation of abnormal aggregates of different proteins is a common feature in motor neurons of patients and transgenic ALS mice models, which are thought to contribute to disease pathogenesis. Developmental morphogens, such as the Wnt family, regulate numerous features of neuronal physiology in the adult brain and have been implicated in neurodegeneration. ?-catenin is a central mediator of both, Wnt signaling activity and cell-cell interactions. We previously reported that the expression of mutant SOD1 in the NSC34 motor neuron cell line decreases basal Wnt pathway activity, which correlates with cytosolic ?-catenin accumulation and impaired neuronal differentiation. In this work, we aimed a deeper characterization of ?-catenin distribution in models of ALS motor neurons. We observed extensive accumulation of ?-catenin supramolecular structures in motor neuron somas of pre-symptomatic mutant SOD1 mice. In cell-cell appositional zones of NSC34 cells expressing mutant SOD1, ?-catenin displays a reduced co-distribution with E-cadherin accompanied by an increased association with the gap junction protein Connexin-43; these findings correlate with impaired intercellular adhesion and

exacerbated cell coupling. Remarkably, pharmacological inhibition of the glycogen synthase kinase-3? (GSK3?) in both NSC34 cell lines reverted both, ?-catenin aggregation and the adverse effects of mutant SOD1 expression on neuronal differentiation. Our findings suggest that early defects in ?-catenin distribution could be an underlying factor affecting the onset of neurodegeneration in familial ALS.