ND79 | Metabotropic glutamate receptor type 5 effects on ALS progression

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron (MN) death, whose aetiologyis not clear, although glutamate(Glu)-mediated excitotoxicity represents one major cause. Group I metabotropic glutamate receptors (mGluR1 and mGluR5) may be implicated in ALS, since they are largely over-expressed during disease progression and involved in altered cellular processes. In this scenario, we recently demonstrated that mGluR1 and mGluR5 at Glu synapses produces abnormal Glu release and that knocking-down mGluR1 in SOD1G93A mice significantly prolongs survival and ameliorates disease progression. To study the function of mGluR5 in ALS, we investigated the effects of the genetic down-regulation of mGluR5 (SOD1G93AmGluR5+/-) or its ablation (SOD-1G93AmGluR5-/-) in SOD1G93A mice. SOD1G93AmGluR5+/-mice showed delayed disease onset and prolonged survival probability, accompanied by spinal motoneuron preservation, decreased astrocyte and microglia activation, and normalization of the excessive cytosolic [Ca2+]I and Glu release. Unexpectedly, motor skills were improved in male SOD1G93AmGluR5+/- mice only. SOD1G93AmGluR5-/- mice presented a more evident amelioration of all disease features, including motor skills, both in males and females. These results represent a proof of concept supporting the idea that mGluR5 represents a useful target for promising pharmacological treatment in ALS.

Keywords: Animal model, Degeneration

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ND80 | TDP-43 and R loops relation in Amyotrophic Lateral Sclerosis

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R loops are three-stranded nucleic acid structures composed by a RNA-DNA hybrid and displaced single-stranded DNA which accumulation can induce genomic instability in several neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). The prevention or repair of R loop associated DNA damage is mediated by TDP-43, that once mutated is involved in ALS through formation of cytoplasmic aggregates containing inert RNA and associated proteins, called stress granules. R loops presence was measured in lymphoblastoid cell lines (LCLs) derived from a mutated TDP-43 ALS patient (mutTDP43), a sporadic ALS (sALS) patient and a healthy control (Ctrl) by flow cytometry, revealing their significant accumulation in mutTDP43 LCLs. Co-localization of R loops with TDP-43 and stress granules was investigated by immunofluorescence, showing a strong segregation of R loops with TDP43 and stress granules in the perinuclear area of mutTDP43 LCLs. Co-immunoprecipitation (Co-IP) confirmed the obtained data, demonstrating relevant TDP-43 and R loops interaction in whole lysate of mutTDP43 LCLs in comparison with chromatin fraction. We can hypothesize from the obtained data that translocation of mutated TDP-43 in cytoplasmic cellular compartment can lead to co-localization with R-loops and segregation in cytoplasmic stress granules.

Keywords: Molecular biology, Degeneration, Protein aggregation

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