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## The Neurotoxic Aggregation of Tdp-43 Can Be Modulated by Trodusquemine

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TAR DNA-binding protein 43 (TDP-43) protein exhibits a tendency for mislocalization from the nucleus to the cytoplasm, resulting in the formation of aberrant inclusions, which represent a key feature in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). The natural aminosterol trodusquemine (TRO) has been reported to modulate the aggregation and to suppress the toxicity of several proteins involved in neurodegeneration. This study aims to elucidate the impact of TRO on TDP-43 aggregation, cytotoxicity and dynamics, using in vitro systems and NSC-34 motoneuron-like cells. TRO modulates the aggregation kinetics of FL-TDP-43, as it was shown through turbidity assays, Dynamic Light Scattering and confocal microscopy, and reduces TDP-43 accumulation in NSC-34 motor neuron-like cells, restoring cell viability, as revealed from confocal microscopy and MTT reduction test. TRO was also shown to influence the structural and dynamic properties of TDP-43 aggregation taking advantage of FRAP and Raman Spectroscopy. Overall, our results highlight the ability of TRO to prevent and modulate TDP-43 aggregation and toxicity, putting forward TRO as a new potential therapeutic candidate for TDP-43-associated proteinopathies. This study was supported by NextGenerationEU, PRIN 2022 PNRR, CUP «B53D23028100001», project P20225ZPYH to R.C. and M.B.).