p-374

Friday

Testing RNA Aptamers in an animal model with TDP-43 pathology

Li Niu

TAR DNA-binding protein 43 (TDP-43) is a highly conserved nuclear RNA/DNA-binding protein involved in the regulation of RNA processing. TDP-43 has been identified as a major pathogenic protein in frontotemporal lobar degeneration (FTLD) with ubiquitin-positive, tau-negative inclusions with or without amyotrophic lateral sclerosis (ALS). Strikingly, ~97% of the ALS and ~45% of all FTLD cases involve TDP-43 pathology. FTLD and ALS actually share some common clinical, neuropathological and genetic features. Among them, dysregulation of glutamate ion channels, particularly AMPA receptor-subtype, which is known to cause excitotoxicity, has been implicated in both FTLD and ALS from preclinical and clinical studies. Furthermore, in an ALS animal model study, it has been shown that TDP-43 cytoplasmic aggregation is triggered by AMPA receptor-mediated Ca2+ entry. In the current study, we have tested a novel class of AMPA receptor RNA inhibitors or RNA aptamers in a transgenic mouse model where AMPA receptors are exclusively dysregulated. We found that infusion of these RNA aptamers was capable of rescuing disease phenotypes as evidenced by the increase of both the size and the number of motor neurons. The motor function of these mice was also improved. More importantly, these positive changes are linked to the increase of nuclear fraction of TDP-43 in the aptamer-treated mice. These AMPA receptor aptamers have been isolated using systematic evolution of ligands by exponential enrichment (SELEX). Our results show that these AMPA receptor RNA aptamers may be useful as a potential therapeutic option for treatment of FTLD by targeting glutamatergic pathway.

Conflicts of interest

None