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Functional analysis of a potential RAN translation regulator in *C9orf72* FTLD/ALS

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Patients with *C9orf72*-related FTLD/ALS have an abnormally extended GGGGCC repeat sequence in intron of the gene. This repeat is transcribed and translated into dipeptide repeat (DPR) proteins via repeat associated non-AUG (RAN) translation. DPR toxicity is thought to contribute to the neurodegeneration of *C9orf72* FTLD/ALS. While several groups have proposed potential regulators of *C9orf72* RAN translation, the detailed mechanism of RAN translation is still largely unknown. Revealing more detailed mechanisms of RAN translation is necessary for development therapeutic treatment.

We identified a potential regulator of RAN translation. In this poster, we call the regulator "TR1 (Translation regulator 1)". We applied a cellular model of *C9orf72* FTLD/ALS exogenously expressing 80 repeats of tandem GGGGCC. siRNA-mediated knockdown of TR1 significantly decreased the expression of one of the DPR proteins poly-GA expression level. Oppositely, overexpression of TR1 increased poly-GA expression level. Mutagenesis analysis revealed TR1 regulates poly-GA RAN translation via its intrinsic activity. Puromycin incorporation assay supported that TR1 preferentially regulates poly-GA RAN translation over conventional translation.

In conclusion, we revealed that TR1 stimulates poly-GA expression through its intrinsic activity. Currently we are investigating whether TR1 also regulates the other DPR such as poly-GP or poly-GR expression levels. Suppression of DPR expression levels via reduction or inhibition of TR1 would have a therapeutic potential for *C9orf72* FTLD/ALS.

Conflicts of interest

None to declare.