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A monocarboxylate transporter modifies C9orf72 repeat expansion toxicity

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A hexanucleotide repeat expansion within the C9orf72 gene (C9) is the primary genetic cause of Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD). Toxicity in neurons at least partly results from the production of dipeptide repeat proteins (DPR) which are translated via non canonical non- ATG initiated translation. To try to understand the mechanisms leading to neuronal death we have developed a Drosophila melanogaster model expressing 36 hexanucleotide repeats (36R). This model displays neuronal toxicity and a shortened lifespan. We have carried out a large scale genetic screen and identified a number of suppressors of toxicity. We are now characterising one of these, a monocarboxylate transporter.
The monocarboxylate transporter we have identified, when over-expressed, leads to a substantial rescue of toxicity and to a reduction in the levels of the toxic peptides associated with the repeats. This transporter can import lactate and pyruvate, two known suppressors of histone deacetylases (HDACs).
We are in the process of understanding how this rescue is mediated and whether modulation of HDACs is a mediator of this rescue.

Conflicts of interest

None