11 SEPT

2.00 P.M.
ROOM A205
POVO 1

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(GR)400 AND (PR)400 KNOCK-IN MICE RECAPITULATE C9ALS/FTD PATHOLOGY AND UNVEIL A CONSERVED NEUROPROTECTIVE HALLMARK OF C9ALS/FTD

A G4C2 repeat expansion in the C9orf72 gene is the most common genetic cause of ALS and FTD, collectively termed C9ALS/FTD. The presence of dipeptide repeat (DPR) proteins is a major pathogenic feature of C9ALS/FTD. The repeat expansion undergoes repeat-associated non-ATG initiated (RAN) translation leading to production of five distinct DPRs, including polyGR and polyPR. Despite numerous studies, the effects of DPRs in the endogenous context are not understood. Thus, there is an urgency for refined models to investigate the role of individual DPRs in vivo.
We generated the first DPR knock-in mouse models expressing 400 seamless GR or PR repeats driven by the endogenous mouse C9orf72 promoter. We observed that (GR)400 and (PR)400 mice expressed selectively their respective DPRs alongside a reduction of C9orf72. Intriguingly, we observed that (GR)400 mice exhibited cortical neuronal hyperexcitability. Notably, we did not detect cortical neuronal loss at the same time point, suggesting that neuronal hyperexcitability precedes neuronal loss. Additionally, we showed that DPR knock-in mice exhibited progressive rotarod impairment and age-dependent spinal motor neuron loss. These results confirmed that DPR knock-in mice recapitulate cardinal features of C9ALS/FTD.
Quantitative proteomics revealed increases in extracellular matrix (ECM) in (GR)400 and (PR)400 spinal cord. Interestingly, this ECM signature was conserved across different models and patient material. Our study proposed TGF-β1 to drive, at least in part, this ECM signature. Consistently, polyGR expression in i3Neurons was sufficient to induce TGF-β1 expression followed by COL6A1, used as representative ECM target.
Moreover, knock-down of the TGF-β1 or COL6A1 orthologues in Drosophila dramatically exacerbated eye degeneration in polyGR flies. Consistently, TGF-β1 and COL6A1 expression in C9 patient iPS cell-derived motor neurons significantly ameliorated glutamate-induced excitotoxicity.
In summary, we have generated and characterised the first C9orf72 knock-in mice that express 400 codon-optimised GR or PR repeats which recapitulate key features of C9ALS/FTD. Our investigation revealed a neuroprotective neuronal ECM signature conserved in C9ALS/FTD which may have broad relevance for ALS and other neurodegenerative diseases.

CIBIO EXTERNAL SEMINAR

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