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Alanine rich dipeptide repeat proteins sequester arginine rich dipeptide repeat proteins in a cellular model of *C9orf72*

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A hexanucleotide repeat expansion in the *C9orf72* gene is the most common genetic cause of frontotemporal dementia and motor neuron disease. Carriers present with both conditions concurrently, so they are considered a continuum. The RNA from the hexanucleotide expansion is translated by repeat associated non-ATG (RAN) translation; producing five dipeptide repeat (DPR) proteins. These are the alanine rich polyAP and polyGA, the arginine-rich polyGR and polyPR, and polyGP. Previous *in vitro* studies show that the arginine-rich DPRs are toxic because they localise to the nucleolus, causing nucleolar stress. However, preliminary research showed sequestration of polyGR by polyGA when they were co-expressed in HeLa cells, *Drosophila* and human neurons. Our aim was to determine whether alanine-rich DPR proteins sequester arginine-rich DPR proteins when the two are co-expressed *in vitro*. This was investigated using alternative coding sequences for the DPR proteins, cloned into mCherry-tagged plasmids. Next, two DPR proteins with different fluorescent tags were co-transfected into HeLa cells and the subcellular locations of the DPR proteins were visualised using immunofluorescence. Our results showed cytoplasmic co-localisation of the arginine-rich DPRs with polyGA. This was replicated 3 times in HeLa cells and once in SH-SY5Y cells. Co-transfection, but no colocalisation, was seen when two alanine-rich or two arginine-rich DPR proteins were co-expressed. Overall, our findings suggest that the arginine-rich DPRs are sequestered by polyGA in the cytoplasm, meaning they are unlikely to cause nucleolar stress. This demonstrates that single transfections of DPR proteins may not be a good model to study DPR protein function or toxicity.

Biography

Katherine Radcliffe conducted this original research whilst inculating and studying MRes Translational Medicine at the University of Manchester. She has just graduated from Manchester Medical School and is due to start as an FY1 doctor in August. This research earned her the best poster prize within her course and she has presented posters at multiple conferences including a European Congress whilst studying.

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