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Functional Profiling of a Circular RNA from the Huntingtin (HTT) Gene

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Abstract : Trinucleotide repeat disorders comprise ~20 severe, inherited human neuromuscular and neurodegenerative disorders, which are a result of an abnormal expansion of repetitive sequences in the DNA. The most common of these, Huntington's disease, results from the expansion of the CAG repeat region in exon 1 of the HTT gene via an unknown mechanism. Non-coding RNAs have been implicated in the initiation and progression of many diseases; thus, we focus on one circular RNA (circRNA) molecule arising from non-canonical splicing (back splicing) of HTT pre-mRNA. This circRNA and its mouse orthologue were transgenically overexpressed in human cells (SHSY-5Y and HEK293T) and mouse cells (Mb1), respectively. High-content imaging and flow cytometry demonstrated the overexpression of this circRNA reduces cell proliferation, reduces nuclear size independent of cellular size, and alters cell cycle progression. Analysis of protein by western blot and immunofluorescence demonstrated no change to HTT protein levels but altered nuclear-cytoplasmic distribution without impacting the expansion of the HTT repeat region. As these phenotypic and genotypic changes are found in Huntington's disease patients, these results may suggest that this circRNA may play a functional role in the progression of Huntington's disease.

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