The role of variant (v)U1 snRNAs in development and disease.

https://www.neurodegenerationresearch.eu/survey/the-role-of-variant-vu1-snrnas-in-development-and-disease/

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United Kingdom

Title of project or programme

The role of variant (v)U1 snRNAs in development and disease.

Source of funding information

MRC

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3.0

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)|Neurodegenerative disease in general

Keywords
Research Abstract

Our recent discovery of a large family of non-coding variant U1 small nuclear (sn) RNAs, (vU1s) which, like U1 snRNA (U1), can regulate recognition of splicing and polyadenylation signals in pre-mRNA, has uncovered new mechanisms controlling gene expression in human cells. vU1 genes are most highly-expressed in human embryonic stem cells (hESCs), in dedifferentiated cancer cell lines and the cells of patients with neurodegenerative disease, including Spinal

Muscular Atrophy (SMA) and down-regulated upon differentiation. Thus, vU1s may play key roles in hESCs and early development and mis-regulation of these RNAs could cause disease. We have shown that, like U1, one of the vU1s-vU1.8 is complexed with proteins in an snRNP. While some proteins are common to U1 and vU1.8 snRNPs, others are associated only with vU1.8, including DIS3L2, mutations in which cause Perlman Syndrome. The composition of snRNPs containing other vU1s has not been investigated. In addition, the direct pre-mRNA targets of any vU1 snRNP have not been identified. The proposed research aims to further characterize the composition of the vU1.8 snRNP, which is found in HeLa cells and hESCs and the hESC-specific vU1.20 snRNP and to identify the direct targets of these RNPs using immunoprecipitation and RNA-seq. In addition, the role of DIS3L2 in the vU1 snRNPs will be investigated using immunoprecipitation, siRNA-mediated knockdown and analysis of DIS3L2 enzymatic activity. The role of vU1s in ESC maintenance and pluripotency will be investigated by knock down and over-expression of vU1s in hESCs. In addition, the expression of the full range of vU1s will be analysed by qRT-PCR in cells from patients with SMA and Parkinson's disease to determine whether mis-regulation of these RNAs is a common occurrence in neurological disease. The proposed research will help to elucidate the roles vU1s play in human gene regulation and may yield insights into the molecular basis of human disease.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

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Neurodegenerative disease in general, Spinal muscular atrophy (SMA)

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