Structure of Triplet Repeat mRNA in Neurodegenerative Disease

https://neurodegenerationresearch.eu/survey/structure-of-triplet-repeat-mrna-in-neurodegenerative-disease/

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USA

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Structure of Triplet Repeat mRNA in Neurodegenerative Disease

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5

The project/programme is most relevant to:

Huntington's disease

Keywords
Research Abstract

Triplet nucleotide repeat expansion mutations cause progressive and lethal neurodegenerative diseases such as Huntington’s Disease (HD) and Spinocerebellar ataxia type 2 (SCA2). Although many mechanisms have been proposed to explain the pathological effects of triplet repeat expansion mutations, the molecular basis for these diseases remains elusive. Most research has focused on the toxic effects of expanded polyglutamine proteins encoded by CAG

repeats. However, triplet repeat RNA has recently been shown to be toxic to neurons and to contribute to disease. This research will use a new X-ray footprinting technique to visualize the abnormal structure of the expanded huntingtin mRNA in living neuronal cells. The first aim is to determine the structures of normal and expanded RNA in unstressed and stressed cells that mimic the neurotoxic effects of HD. Comparisons of different triplet repeat mRNAs will identify sequences that readily form neurotoxic RNA structures. The second aim is to investigate how interactions between triplet repeat RNA and cellular proteins contribute to neurotoxicity. In addition, a tool compound that binds CAG RNA repeats will be tested for its ability to block abnormal mRNA structures. The third aim is to determine whether the structures of triplet repeat complexes and their effect on the mRNA interactome account for the varied sensitivity of neurons to triplet repeat mutations. This first application of X-ray footprinting to mRNAs in cells will link the three-dimensional structures of mRNAs with the pathology of triplet repeat diseases, and determine how small molecule tool compounds disrupt these structures in live cells. The long-term goal is to identify a structural signature of RNA-protein interactions that predict neurotoxicity and that can be targeted by new therapies.

Lay Summary
Neurodegenerative diseases such as Huntington’s and spinocerebellar ataxias are caused by an inherited mutation in which the affected gene contains many extra copies of the three bases CAG. This research will use a new X-ray footprinting technique to visualize how CAG repeats alter the mRNA structure in living cells. The goal is to understand how abnormal CAG RNA harms neurons, and whether disrupting abnormal RNA structures can delay or prevent deterioration of the brain.

Further information available at:

Types:
Investments > €500k

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