Pathogenic mechanism of the C9orf72 expanded hexanucleotide repeat mutation in neurodegeneration

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Pathogenic mechanism of the C9orf72 expanded hexanucleotide repeat mutation in neurodegeneration

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Research Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are devastating neurodegenerative diseases that form two ends of a complex disease spectrum. Aggregation of RNA binding proteins is one of the hallmark pathological features of ALS and FTDL, and suggests perturbance of the RNA metabolism in their aetiology. In 95% of all ALS and 60% of FTLD patients the aggregating protein is TDP-43, thus defining the major part of the

disease spectrum as TDP-43 proteinopathies. However, only a very small percent of aggregation is caused by TDP-43 mutations. Therefore, the main questions in the field are what makes ‘normal’ TDP-43 aggregate in ALS and FTLD and what is the role of perturbed RNA metabolism in these diseases. Recent identification of the disease-associated expansions of the intronic hexanucleotide repeat GGGGCC (G4C2) in the C9orf72 gene further substantiates the case for RNA involvement. This hexanucleotide repeat expansion mutation (HREM) has turned out to be the single most common genetic cause of ALS and FTLD and also presents itself as TDP-43 proteinopathy. HREM may enable the formation of complex DNA and RNA structures, changes in RNA transcription and processing and formation of toxic RNA foci, which may sequester and inactivate RNA binding proteins. This complexity is furtherer increased by the fact that expanded repeat is also transcribed in the antisense direction forming the CCCCGG (C4G2) repeat. According to some reports the antisense HREM transcript is even more abundant than the sense transcript. Additionally, the transcribed expanded repeats from both directions can undergo repeat-associated non-ATG-initiated (RAN) translation resulting in accumulation and aggregation of a series of dipeptide repeat proteins. Finally, HREM may also lead to haploinsufficiency of the C9orf72 protein. As it is a newly discovered protein it has not been well characterized to date. There are very recent publications linking it to endosomal trafficking. Of importance, it has also been recently reported that C9orf72 protein associates with RNA binding proteins. As C9orf72 repeat expansion is the biggest single contributing cause of TDP-43 proteinopathies, it is very important to resolve which of the possible mechanism of pathogenicity are leading to the TDP-43 proteinopathy. Therefore, increased characterization and understanding of these mechanisms is a pre-requirement in order to find ways of delaying onset or progression of ALS and FTLD. Thus, this project aims to contribute to the understanding of the pathological role of expanded hexanucleotide repeat in the gene C9orf72 with the focus on RNA toxicity and characterization of the C9orf72 protein.Recent publications, including ours, have identified a set of proteins that bind to the (G4C2)n RNA and colocalize with RNA foci, therefore in the proposed project we will focus on the disease relevance of the antisense transcript and characterization of the C9orf72 protein in light of its association with RNA binding proteins. The disease relevance of these findings will be tested on inducible pluripotent stem cells containing C9orf72 mutations and postmortem CNS brain and spinal cord tissue from ALS and FTLD patients with C9orf72 mutations.

Further information available at:

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