Zebrafish disease models for hnRNP A mutations in ALS

Acronym:
hnRNP A proteins in ALS

Principal Investigator:
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Summary of the research project

Amyotrophic Lateral Sclerosis (ALS) is a devastating disease, and currently the development of therapies is limited by the poor understanding of the disease-causing molecular mechanisms. A pathological hallmark in ALS is the depletion of heterogeneous nuclear ribonucleoproteins (hnRNP) such as TDP-43 or FUS from the nucleus and their aggregation in the cytoplasm. Just recently, the same protein mislocalisation was described in ALS and another ALS-type myopathy (IBMPFD/ALS) for mutant hnRNP A1 and hnRNP A2B1 (1).

The mislocalised hnRNP proteins imply two distinct pathomechanisms (Figure 1), which are currently under debate:

1) in disease state, the physiological function of hnRNP proteins could be lost or reduced, impairing various cellular processes essential for cell survival such as transcription, splicing, transport, and translational regulation.

2) the cytoplasmic aggregates of hnRNP proteins could convey toxicity, e.g. by sequestering essential RNAs and proteins to inclusions.

Each pathomechanism by itself or in combination could be responsible for the neurodegeneration seen in ALS patients.
Patients carrying the recently identified mutations in hnRNP A1 and hnRNP A2B1 develop ALS with the typical pathological hallmarks of nuclear depletion and cytoplasmic aggregation (1). We therefore chose the two hnRNP A genes to model both pathomechanisms in zebrafish in vivo. We include hnRNP A3 for disease modelling in our study, since it binds to transcripts of the hexanucleotide repeat expansion of C9orf72, the most frequent cause of ALS (2). Moreover, it is detected in cytoplasmic aggregates while it is depleted from nuclei in patients with a C9orf72 hexanucleotide repeat expansion (2).

We will generate suitable disease models by genetically manipulating the hnRNP A gene family in zebrafish to identify the pathomechanism of the ALS-associated mutations in hnRNP A1 and hnRNP A2B1.

HnRNP A proteins are highly conserved across species (Figures 2 and 3) allowing a relevant analysis for clinical research.

Our work will describe the consequences of the ALS-causing mutations in hnRNP A1 and hnRNP A2B1 to unravel the pathomechanism on a molecular level. Once we understand the pathogenesis of ALS, we can design better potential therapeutic strategies. Furthermore, having a genetic zebrafish disease model for ALS opens the possibility to perform large unbiased chemical screens to identify therapeutic compounds that rescue or improve the mutant phenotype hold the potential to serve as an ALS therapy.

Relevant research articles for this project are:

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Her 5 most relevant publications:


