Molecular mechanisms of TDP-43 mediated neurodegeneration

https://www.neurodegenerationresearch.eu/survey/molecular-mechanisms-of-tdp-43-mediated-neurodegeneration/

Principal Investigators

Dr F Hirth

Institution

King's College London

Contact information of lead PI
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United Kingdom

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Research Abstract

Tar DNA binding protein of 43 kDa (TDP-43) has been identified as the major disease protein present in cytoplasmic inclusions in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD), as well as in other neurodegenerative disorders including Alzheimer’s, Parkinson’s and Huntington’s disease, thereby defining a novel proteinopathy. Dominant missense mutations in the encoding TARDBP gene characterise both familial and sporadic cases of ALS and FTLD, and recent studies in Drosophila, zebrafish and mice reveal that both loss and toxic gain of TDP-43 function contribute to disease onset and progression. TDP-43 proteinopathy is associated with synaptic defects which precede behavioural abnormalities and progressive age-related neurodegeneration. However, the molecular

mechanisms underlying neurodegeneration remain elusive. Our hypothesis is, and our preliminary data suggest, that TDP-43 regulates dSarm/Sarm1 and Hiw/mycBP2 that mediate an active autodestruction program causing dying back-like neurodegeneration. Here we propose to use animal and cell culture models to test this hypothesis and to dissect the molecular mechanisms by which TDP-43 regulate dSarm/Sarm1 and Hiw/mycBP2. We also aim to identify ways to rescue disease formation in a Drosophila model of TDP-43 related neurodegeneration, and to translate these findings into the human disease condition by detecting RNA/protein changes for human homologues of the autodestruction pathway. Given that TDP-43 proteinopathy characterises several neurodegenerative disorders, including dementia, the expected findings will be of general relevance and application as they likely identify novel biomarkers and therapeutic targets for TDP-43 related neurodegeneration.

Further information available at:

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