

Research Project

Intracellular cholesterol homeostasis in tauopathies: role of the ER-mitochondria coupling

Third-party funded project

Project title Intracellular cholesterol homeostasis in tauopathies: role of the ER-mitochondria coupling

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Organisation / Research unit

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Status Completed

Tau protein aggregation is a hallmark of Alzheimer's disease (AD) brains and additional tauopathies including frontotemporal lobar degeneration (FTLD). Substantial evidence has been linking Tau to neurodegeneration, but the mechanisms are still incompletely understood. Strikingly, Tau impacts mitochondrial function, leading to neurotoxicity. Mitochondria are coupled with the endoplasmic reticulum (ER) via the mitochondria-associated ER membranes or MAMs. An upregulation of MAMs function is observed in amyloid β -related AD models, impairing calcium homeostasis as well as cholesterol metabolism, leading to neuronal death. Interestingly, the influence of Tau on the ER-mitochondria axis remains elusive until today. Preliminary data show that abnormal Tau disturbs intracellular cholesterol homeostasis, especially cholesterol transport to mitochondria.

Therefore, we hypothesize that abnormal Tau protein impacts on the ER-mitochondria interaction, leading to a disturbed cholesterol homeostasis and a defect of cholesterol import into mitochondria. The specific aims of this project are to test this concept and to study in more details the impact of abnormal Tau protein on intracellular cholesterol homeostasis and mitochondrial transport.

For this approach, we will use a multi-step process, combining pharmacological and molecular biology as well as microscopy techniques. We aim to dissect a novel fundamental mechanism and to study the ER-mitochondria axis as a potential target in AD. The project has ramifications for additional neurodegenerative diseases such as Parkinson's disease as well as amyotrophic lateral sclerosis with associated temporal dementia (ALS/FTD) that also have been linked with damaged ER-mitochondria associations.

Financed by

University of Basel

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Published results

4634649, Demetrius, Lloyd A.; Eckert, Anne; Grimm, Amandine, Sex differences in Alzheimer's disease: metabolic reprogramming and therapeutic intervention, 1043-2760 ; 1879-3061, Trends in Endocrinology & Metabolism, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4634657, Grimm, Amandine, Impairments in Brain Bioenergetics in Aging and Tau Pathology: A Chicken and Egg Situation?, 2073-4409, Cells, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

4634660, Szabo, Leonora; Eckert, Anne; Grimm, Amandine, Insights into Disease-Associated Tau Impact on Mitochondria, International Journal of Molecular Sciences, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

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