hypothesized that tau perturbs the cellular program that maintains terminal neuronal differentiation. Based on RNA-sequencing, we identified prospero as the most differentially expressed and downregulated transcript in tau transgenic flies. Prospero regulates genes that promote and maintain terminal neuronal differentiation. At the protein level, prospero is significantly reduced in tau transgenic flies at 10 days old. We find that over stabilization of f-actin or over-expression of moesin, a cytoskeletal protein known to participate in tumor progression and metastasis, depletes prospero. Using genetically manipulated prospero target genes we find a connection to neurodegeneration. These targets include a PKC, tep4, and knot-suggesting that broad cellular processes are affected by this reduction. Overall, our findings suggest that pathological tau causes cell cycle re-entry by disrupting transcription factors governing terminal neuronal differentiation as well as over-stabilization of f-actin being the driving loss of terminal neuronal differentiation and casually associated with neuronal death.

MICRORNA REGULATORS OF THE SENESCENCE TRANSCRIPTOME

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Cellular senescence is a state of indefinite growth arrest triggered in response to sublethal stresses such as telomere shortening, DNA damage, oxidative injury, oncogene activation, and hypoxia. Compared with proliferating cells, senescent cells are enlarged, display heterochromatic DNA foci, and express distinct subsets of proteins, including the enzyme β-galactosidase (β-gal). Previously, we identified transcriptome signature of senescent cells. We asked if these transcripts might be regulated by microRNAs (miRNAs). To address this question, we identified six miRNAs (miR-129-5p, -19a-3p, -128-3p, -124-3p, -340-5p, and -27b-3p) as potential regulators of subsets of transcripts differentially expressed during senescence. RT-qPCR analysis indicated that miR-129-5p, -19a-3p, -128-3p, -124-3p, and -340-5p were downregulated in senescent cells. We modulated these miRNAs in proliferating WI-38 fibroblasts and found that miRNA antagomirs did not show significant changes in β-gal activity. Interestingly, however, overexpression of miR-124-3p or miR-340-5p increased β-gal activity. We conclude that despite the decrease of miR-124-3p and miR-340-5p in senescent cells, their overexpression enhanced senescence as indicated by β-gal activity. Future analyses will focus on the mechanisms through which these miRNAs induce senescence and their physiologic and pathologic impacts in vivo.

TRANSGENIC MOUSE MODELS OF ALZHEIMER'S DISEASE

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Alzheimer's disease is a progressive brain disease that slowly destroys memory and thinking skills. Alzheimer's is characterized by an increase in Aβ plaques , and tau tangles. Neurons in the brain have axons covered in myelin sheath that connect microglia and astrocytes. The myelin sheath is composed of about 70% lipid composition; Sulfatide contributing to 30% overall. Sulfatide changes the morphology of primary microglia to their activated form. To study the role of microglia activation and sulfatide levels, three different mouse models were created: APP KI mice, CST Whole Body Ko mice, and cCST (conditional) KO. In order to create the genotype of the APP KI mice, a breeding mouse line was created. The APP KI gene had to be introduced in Plp1-Cre and cCST KO crossed mice to receive a working mouse model. During the duration of breeding for the APP KI mice, a preliminary experiment was performed on the CST KO mice. These mice were given the PLX3397 diet with the aim to remove the microglia and to see the effect of Aβ plaques. The PLX3397 will reduce the microglia targeting the CSF1R. After consuming the diet, the mice were harvested to collect tissues from the brain and spinal cord. Lipidomics and immunohistology were performed. In conclusion, we will continue the breeding of the CST flox/flox / Plp1-Cre / APP KI mice, and the drug dosage and treatment to be used in our APP KI mice will be based on preliminary data from our CST mice.

THE ROLE OF CAPRIN-1 PROTEIN DYSREGULATION IN SYNAPSE DECLINE LEADING TO PROGRESSION OF TAUOPATHIES

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Many neurodegenerative diseases are characterized by accumulation of proteins such as tau, a microtubule stabilization protein. Toxic tau forms tangles and affects neuronal synapse function, an early step of neurodegeneration. To focus on synapse function, we highlighted Caprin-1 protein. Through gene ontology, Caprin-1 is related to RNA granule proteins, important for transport and local translation in dendrites. Caprin-1 is of interest for neurodegeneration because it is a memory related protein, transports mRNA in RNA granules, and knock out mice demonstrate memory deficits. As we age, the performance of local translation in the dendrites is compromised and leads to synapse dysfunction. We hypothesize Caprin-1 binds to Tau and becomes disrupted. This leads to the dissolution of RNA granules, inhibition of mRNA transport in dendrites, suppression of translation, and failure of synapse. Early western blot data showed reduced Caprin-1 in PS19 Tau+, supporting our model that Caprin-1 is disrupted in disease models. Through immunohistochemistry, we investigated the localization of Caprin-1 in the mouse hippocampus. We observed Caprin-1 localization to dendrites of CA1 neurons in the hippocampus. Furthermore, Caprin-1 exhibited colocalization with Rps6, an RNA granule marker. This suggests Caprin-1 associates with RNA granules in mouse hippocampus. Finally, we investigated the localization of Caprin-1 in human iPSC-derived neurons. Similar to the mouse hippocampus, we observed localization of Caprin-1 to dendrites of human neurons. In future directions, we will examine whether pathogenic tau alters the association of Caprin-1 with RNA granules and the mechanisms by which pathogenic tau negatively effects synapse function.