Analysis of Tau in neuron-derived extracellular vesicles

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Introduction: Recent Alzheimer's disease (AD) drug trials have highlighted a need for better diagnosis of study participants, and the development of biomarkers that can be used to monitor response to therapy. Measurement of tau and the amyloid beta-protein in cerebrospinal fluid (CSF) is unpopular with patients, and quantitation of amyloid by PET imaging is expensive. Thus, there is an urgent need for less costly and intrusive, and more widely available, blood-based biomarkers. Measurement of the tau and A in brain-derived blood-borne extracellular vesicles (EVs) should reflect changes occurring in the brain. In addition, EVs have been proposed to drive the spread of neurofibrillary tangles (NFTs) pathology in AD brains. Thus, measurement of tau in EVs may both facilitate biomarker development and provide insight on the molecular pathology of AD. Methods: We used differential centrifugation to isolate and characterize exosomes from cultured primary and iPSC-derived neurons (iNs), as well as from human CSF and plasma. Since the MTBR domain of tau is known to drive aggregation, we set out to determine whether MTBR-containing forms of tau are present in neural EVs. Results: In medium from 2 different iN lines, we detected MTBR-containing tau in exosomes at very low levels. Analysis of the exosomes pellet from CSF revealed low levels of tau, equivalent to ~0.1 pg per ml of CSF. As was evident with EVs from cultured neurons and CSF, neurally-derived exosomes from human plasma also contained aggregation-competent tau. Conclusions: Exosomes contain aggregated-competent tau, but further studies will be required to examine the potential for tau-containing exosomes to seed aggregation in the recipient cells.

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