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Analysis of Extracellular Vesicles Interactomes of two Isoforms of Tau Protein via SHSY-5Y Cell Lines

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Abstract : Alzheimer's disease (AD) is a widespread dementing illness with a complex and poorly understood etiology. An important role in improving our understanding of the AD process is the modeling of disease-associated changes in tau protein phosphorylation, a protein known to mediate events essential to the onset and progression of AD. A main feature of AD is the abnormal phosphorylation of tau protein and the presence of neurofibrillary tangles. In order to evaluate the respective roles of the microtubule-binding region (MTBR) and alternatively spliced exons in the N-terminal projection domains in AD, we have constructed SHSY-5Y cell lines that stably overexpress four different species of tau protein (4R2N, 4R0N, N(E-2), N(E+2)). Since the toxicity and spreading of tau lesions in AD depends on the interactions of tau with other proteins, we have performed a proteomic analysis of exosome-fraction interactomes for cell lysates and media samples that were isolated from SHSY-5Y cell lines. Functional analysis of tau interactomes based on gene ontology (GO) terms was performed using the String 10.5 database program. The highest number of exosomes proteomes and tau associated proteins were found with 4R2N isoform (2771 and 159) in cell lysate and they have a high strength of connectivity (78%) between proteins, while N(E-2) isoform in the media proteomes has the highest number of proteins and tau associated protein (1829 and 205). Moreover, known AD markers were significantly enriched in secreted interactomes relative to lysate interactomes in the SHSY-5Y cells of tau isoforms lacking exons 2 and 3 in the N-terminal. The lack of exon 2 (E-2) from tau protein can be mediated by tau secretion and spreading to different cells. Enriched functions in the secreted E-2 interactome include signaling and developmental pathways that have been linked to a) tau misprocessing and lesion development and b) tau secretion and which, therefore, could play novel roles in AD pathogenesis.

Keywords : Alzheimer's disease, dementia, tau protein, neurodegenration disease
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