Structural and functional roles of exosomal nanovesicles in the formation, release and synaptotoxicity of amyloid proteins

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Structural and functional roles of exosomal nanovesicles in the formation, release and synaptotoxicity of amyloid proteins

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Research Abstract
Alzheimer’s disease (AD), the most common neurodegenerative disease, is a serious threat to the autonomy, mobility, and overall functionality of aging persons worldwide. Although the etiology of AD remains incompletely defined, over a decade of investigation increasingly implicates oligomers of the amyloid-ß (Aß) peptide as the primary toxic molecular species responsible for the disease. Several studies support a robust correlation between Aß oligomer

concentration and the extent of synaptic loss and severity of cognitive impairment, and Aß oligomers also trigger abnormalities of the microtubule-associated protein tau, which is associated with irreversible neuronal damage. The revised amyloid cascade hypothesis stipulates that when Aß is generated, by ß and ?-secretase cleavage of amyloid precursor protein (APP), the non-toxic Aß monomers rapidly form soluble, toxic Aß oligomers, which are then converted to relatively non-toxic insoluble Aß fibril plaques that are deposited extracellularly. However, much is unknown about the “strain” of Aß (oligomers, fibrils, post-translationaly modified forms) that is toxic and also the subcellular location, cellular basis of Aß oligomerization and the mechanism of Aß release from cells remains largely unknown. These mechanisms may also explain the characteristic spreading of Aß pathology throughout the brain, and could lead to new therapeutic approaches. Recently we showed that exosomes, endocytically derived nanovesicles, carry Aß peptides out of the cell and to contain the enzymatic machinery required to generate these peptides from APP (1). This suggests that Aß-associated with lipidic vesicles could confer toxicity as well be seeds for amyloid formation. The overarching goal of this proposal it to demonstrate that exosomes are a major way to shuttle amyloids out of the cell, and that exosome-associated amyloids contribute to AD pathology by enhancing formation of Aß aggregates.
By combining chemical biology tools, biophysical and structural biology, cell biology and neuroscience, we propose to explore the role of the exosomal nanovesicles in the formation of amyloid aggregates, making it a truly interdisciplinary project.
The subcellular mechanisms governing exosomal-Aß biogenesis and secretion will be addressed using immunofluorescence and electron microscopy in concert with a novel fluorescently labeled ?-secretase inhibitor. The proteins involved in exosomal release will be investigated using an RNAi silencing screen and the application of various knock out cell lines. The role of exosomes in nucleating amyloid aggregation will be monitored using in vitro aggregation assays and the pathological consequences of exosomal-Aß will be examined in vivo by assaying plaque propagation after intracerebral injection of exosomal-Aß in AD mouse models, and by examining tau phosphorylation and synaptic functionality after exosomal-Aß treatment. The expected results will clarify the role of exosomes in amyloid pathology propagation and define the rules for exosomal-Aß biogenesis and release from neurons.

Further information available at:

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