INTERNEURONAL SPREADING OF TAU PATHOLOGY INVOLVES DENDRITIC TAU TRANSPORT, LOCALIZED MT LOSS AND SECRETION IN ASSOCIATION WITH FYN-POSITIVE VESICLES AND LC3 ACTIVATION

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Introduction: The interneuronal spreading of misprocessed human tau protein between live neurons in the vertebrate CNS has only very recently been recognized as such and its relevance to the systemic aspects of human tauopathy is not yet known. A key difficulty in the verification and characterization of interneuronal tau transfer in situ has been distinguishing cell-autonomous from intercellular pathogenic influences in transgenic tauopathy models.

Aims: To describe the involvement of fyn kinase and the autophagy protein LC3 in the secretion of tau from specific sites in the dendrites of ABCs in situ and its uptake into adjacent neuronal processes.

Methods: We use confocal imaging of tau-expressing neurons (ABCs) in a cell-autonomous in situ tauopathy model to characterize the phosphorylation, dendritic transport, secretion and uptake of secreted tau across synaptic connections and between adjacent neurons.

Results: Non MT-associated (9G3/12E8-positive) tau is processed via a degeneration-associated pathway featuring

1) tau localization to fyn/kinesin-positive vesicles,

2) transport of these to distal dendrites via a MT-mediated mechanism,

3) tau accumulation, induction of localized MT loss, and LC3 activation in distal dendrites, and

4) the release of tau to the ECF and its uptake by nearby neuronal processes in conjunction with the exocytosis of LC3 and fyn from tau-positive vesicles.

Conclusion: These results, along with our recent finding that tau secretion occurs via exosomes (Saman and Hall, 2011 Keystone Conference), suggest that tau-induced interference with autophagy-associated protein turnover could play a key role in the spread of tau-induced pathology between neurons in human tauopathies.