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Heterogeneity in tau spreading among tauopathies; the place of extracellular vesicles

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In AD, PSP, AGD and PiD, the progression of neurodegeneration follows a hierarchical progression which is specific to a tauopathy. This could be linked to a prion-like propagation where seed-competent tau species spread from cell-to-cell. Extracellular vesicles (EV) represent a unique intercellular vehicle for transferring pathological species from one population to another one. They have selectivity in terms of the target cell that could explain the differing cell vulnerability seen in tauopathies. Here, we compare the vesicle's mediated transmission of tau pathology that are present within brain derived fluid of patients with various tauopathies.

Brain extracts were obtained from the Lille Neurobank. EVS were characterized (EM, nanotracking analyses, mass spectrometry, biochemistry). Tau in BD-EVs (brain-derived enriched-EV) was evaluated by ELISA and EM. Seeding mediated by BD-EVs was tested in a cellular seeding assay or after BD-EVs injection into the hippocampus of tau transgenic mice, tau lesions were quantified (MC1 and AT100).

Whereas the vesicles concentration and the tau content did not differ among the tauopathies and controls, we observed considerable heterogeneity in their seeding capacities. The most striking evidence was coming from AD where the BD-EVs clearly contain pathological species that can induce tau lesions *in vivo*. For PSP and PiD patients, a weak FRET signal was observed which was consistent with neuropathology.

Together, our results support the hypothesis that BD-EVs, participate in the prion-like propagation of tau pathology but especially in AD. There may be implications for diagnostic and therapeutic strategies especially in PSP disease for instance.

Conflicts of interest

N/A