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Project title: Role of Molecular Chaperones in Alzheimer's Disease

Introduction/Objectives: Alzheimer's disease (AD) is characterized by intracellular neurofibrillary tangles of the tau protein and extracellular senile plaques of the A β peptide within the neocortex and hippocampus. The protein aggregates leading to the formation of these pathological inclusions interfere with normal cellular functions and cause neuronal death and degeneration. Molecular chaperones are proteins that normally prevent protein aggregation by assisting in the proper folding of other proteins. Here, we investigated the role of two molecular chaperones, namely Hsp25 and α B-crystallin, in the development of A β plaques in AD mouse models and in humans.

Methods: We used two distinct transgenic mouse models of AD – Tg2576 and APP/PS1 along with age-matched wild-type controls. Mice were euthanized, perfusion fixed with formalin and, their brains were embedded in paraffin. Ten micron thick tissue sections were cut and mounted on a slide. A β plaques were visualized using Congo Red and Thioflavine S. Immunohistochemical localization of Hsp25 and α B-crystallin in relation to A β plaques was carried out. Similar histological studies were carried out with paraffin sections of human AD and non-AD control hippocampus obtained from commercial sources.

Results: Hsp25 consistently localized to the periphery of A β plaques in the mouse brain and in human AD hippocampus. However, despite greater levels, α B-crystallin did not show this same colocalization pattern in either tissue.

Summary/Discussion: Our results suggest that Hsp25 and α B-crystallin may play distinct roles in the formation of A β plaques. While Hsp25 appears to co-localize with the periphery of plaques, α B-crystallin does not. Since the distribution of these molecular chaperones are similar in mice and humans, our results show that mouse models are useful to elucidate the role of molecular chaperones in plaque formation in AD. Future studies will be necessary to find the cellular source of Hsp25 in extracellular A β plaques and to examine the importance of Hsp25 in neuronal death.