Modeling Familial Danish Dementia: Implications for the amyloid hypothesis of Alzheimer´s disease

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Background: Familial Danish Dementia (FDD) is a neurodegenerative disease with cerebral deposition of Dan-amyloid (ADan), neuroinflammation, and neurofibrillary tangles - hallmark characteristics remarkably similar to those in Alzheimer´s disease (AD). We have generated transgenic mouse models of FDD that recapitulate the deposition of ADan throughout the brain as well as the associated amyloid angiopathy, microhemorrhage, neuritic dystrophy, and neuroinflammation seen in Danish patients. Furthermore, ADanPP tg mice are impaired in the Morris water maze and exhibit increased anxiety in the open field. Objective: To advance our understanding of disease pathogenesis and that of amyloid hypotheses in general, we have used this model of non-ABeta amyloidosis to investigate whether ADan, ABeta, and Tau participate in similar disease-related pathways. Methods: ADanPP tg mice were cross-bred to models that exhibit ABeta-amyloidosis and Tau tangle formation. Offspring from these crosses were analysed for changes in beta-amyloid plaque and Tau tangle formation using histochemical and biochemical methods. Results: When crossed with TauP301S mice, ADan accumulation induced neurofibrillary lesions, in all aspects similar to the Tau lesions observed in crosses between beta-amyloid depositing mice and TauP301S mice. While these observations argue for shared mechanisms of downstream pathophysiology for the sequence-unrelated ADan and ABeta peptides, the lack of co-deposition of these peptides in crosses of ADan- and ABeta-depositing APPPS1 mice also points to distinguishing properties of the two peptides. Conclusions: Our results suggest that different proteins prone to amyloid formation can drive strikingly similar pathogenic pathways in the brain. Further investigation of common disease pathways is likely to shed light on key upstream therapeutic targets.

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