

Amyloid and Tau in Neurodegeneration

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Background and Hypothesis:

Familial British dementia (FBD) and familial Danish dementia (FDD) are two autosomal dominant neurodegenerative diseases caused by mutations in the BRI₂ gene. FBD and FDD are characterized by widespread cerebral amyloid angiopathy (CAA), parenchymal amyloid deposition, and neurofibrillary tangles. Previous studies have shown that accumulation of Danish amyloid peptide (ADan) induces hyperphosphorylation of tau and cell cytotoxicity; however, progress in our understanding of the interaction between ADan and tau has been hindered by the lack of antibodies against ADan. In addition, whether the British amyloid peptide (ABri) has a similar effect on tau phosphorylation remains unknown. The main goals of our project are to generate monoclonal antibodies against ADan and to test whether the ABri peptide induces hyperphosphorylation of tau and cell cytotoxicity.

Experimental Design or Project Methods:

A peptide homologous to the C-terminus of the ADan peptide was used to immunize 5 mice. Serum samples were tested from mice with high ELISA titers and the best 2 animals were used for cell fusion. Cell culture supernatants were screened by ELISA, western blot and immunohistochemistry. ABri peptides were used as negative controls.

HEK cells expressing human tau were used to assess the interaction between ABri and tau. We performed immunocytochemistry and Western blot analysis to investigate tau phosphorylation.

Results:

A total of 11 clones tested positive by western blot. 3 clones tested positive for ABri and were discarded. 5 clones were tested by immunohistochemistry. 3 of the positive clones will be used for subcloning to complete clonality. Work in progress on the interaction between ABri and tau will determine whether ABri induces tau hyperphosphorylation in cell culture.

Conclusion and Potential Impact:

Our work will provide novel tools to study the interaction between amyloid and tau in neurodegenerative diseases and may uncover possible new targets for pharmaceutical intervention in tauopathies.