The Revitalized Tau Hypothesis on Alzheimer's Disease

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Many hypotheses have been raised regarding the pathophysiology of Alzheimer's disease (AD). Because amyloid beta peptide (A?) deposition in senile plaques appears as a late, nonspecific event, recent evidence points to tau phosphorylation and aggregation as the final common pathway in this multifactorial disease. Current approaches that provide evidence in favor of neuroimmunomodulation in AD and the roles of tau pathological modifications and aggregation into oligomers and filamentous forms are presented. We propose an integrative model on the pathogenesis of AD that includes several damage signals such as A? oligomers, oxygen free radicals, iron overload, homocysteine, cholesterol and LDL species. These activate microglia cells, releasing proinflammatory cytokines and producing neuronal degeneration and tau pathological modifications. Altered and aggregated forms of tau appear to act as a toxic stimuli contributing to neurodegeneration. Recent findings provide further support to the