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Editorial

Tau in Alzheimer's Disease

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Editorial

Alzheimer's disease (AD) is the most common neurodegenerative disorder worldwide characterized by decline in memory and progressive loss of cognitive function [1-2]. The hallmarks of AD are aggregation of beta-amyloid (Aβ) peptide (known as senile plaques) and accumulation of neurofibrillary tangles composed of hyperphosphorylated forms of the microtubule associated protein tau [3-4]. Definitive diagnosis is only possible based on histological investigation of the brain at autopsy by detecting extracellular plaques containing Aβ peptides and intracellular neurofibrillary tangles [5].

Tau proteins are mainly neuronal and play a role in microtubule polymerization. In the adult human brain, there are six isoforms of tau, which are generated by alternative splicing of exons 2, 3 and 10 a primary transcript of a single gene located on chromosome 17. The length of their sequences varies from 352-441 amino acids. In AD, phosphorylation of tau protein is unquestionably abnormal. The hyperphosphorylation and aggregation of tau lead to neuronal loss in AD.All of the six tauisoforms are hyperphosphorylated and aggregated into PHF [6-9]. Several studies have confirmed that tau is the major component of neurofibrillary tangles that positively correlate with neurodegeneration and cognitive decline in AD. Neurofibrillary degeneration of abnormally hyperphosphorylated tau not only occurs in AD brain but is also seen in a family of related neurodegenerative diseases, called tauopathies, such as fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) caused by tau mutations, Pick disease, corticobasal degeneration, dementia pugilistica, and progressive supranuclear palsy [7,10-13].

The combination of cerebrospinal fluid (CSF) biomarkers and imaging has been investigated extensively for a number of years. It can provide an increased diagnostic accuracy. Researchers conducted, in this area, focus on analysis based on blood and CSF.The combination of decreased amyloid Aβ42, increased T-Tau and phosphorylated tau P-Tau in CSF can distinguish groups with MCI who convert later to AD with high sensitivity, specificity and predictive values. Recently, these biomarkers have been defined as specific markers for pre-clinical AD [14-16]. Novel PET/SPECT probes for the imaging of tau have been developed. Several compounds including [18F] THK-523, [18F]THK-5105, [18F]T807, [18F]T808, and [11C]PBB3 were tested clinically. The results showed their feasibility for imaging tau aggregates for the diagnosis of AD [17]. Mutations of Tau are correlated to several neurodegenerative disorders. Recently, the Tau mutation A152T was selected as a novel risk factor for frontotemporal dementia spectrum disorders and AD. *In vitro* Tau-A152T shows a decreased binding to microtubules and a reduced tendency to form abnormal fibers in mouse model expressing human full-length Tau with this mutation (hTau40AT) [18].

Cells incubated in the absence of glucose reveal a significant increase in tau phosphorylation at epitopes Ser202/ Thr205 and Ser404, which was associated with a selective activation of the P38 mitogen-activated protein kinase. These studies highlight a new mechanism whereby glucose deprivation can modulate AD pathogenesis by affecting tau phosphorylation and suggest that this pathway opens new therapeutic target for AD [19]. The exposition to oligomeric Aβ, Tau becomes mislocalized (missorted) into the somatodendritic compartment, a feature reminiscent of incipient AD. Missorting of Tau correlates with a loss of synapses, most expressed in dendrites containing high amounts of Tau. This highlights a link between the mislocalization of Tau and the cognitive decline revealed in mouse models of AD and in AD cases [20]. In a recent study methylthioninium chloride (methylene blue dye) has been found to disaggregate PHF *in vitro*, reduce the number of tau aggregates in tau transgenic mice, and show significant inhibition of cognitive impairment in a PHASE II double blind clinical trial in AD patients [21-22].

Targeting tau phosphorylation will require a greater understanding on how site-specific tau phosphorylation alters its function. Inhibition of abnormal hyperphosphorylation of tau offers a promising therapeutic target for AD and related tauopathies.

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