INVESTIGATION OF WNT SIGNALING FACTORS IN POSTMORTEM BRAIN OF ALZHEIMER DISEASE

Jeroen Hoozemans

Department of Pathology, VU university medical center, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands

Alzheimer's disease (AD), the most common form of dementia, is a chronic neurodegenerative disease causing progressive impairment of memory and other cognitive functions. Apart from the loss of synapses and neurons, Alzheimer's disease is characterized at the neuropathological level by neurofibrillary tangles (NFTs), and extracellular aggregates of amyloid β (Aβ) protein. The major component of the intracellular NFTs is hyperphosphorylated tau, a microtubule stabilizing protein. So far it is elusive how amyloid pathology and NFT formation in AD are functionally related.
We and others have previously shown that increased expression of cyclins, cyclin dependent kinases (CDKs) and their inhibitors can be detected in neuronal cells localized in affected areas of the AD brain. The presence of these cell-cycle proteins precedes the formation of degenerative lesions, and it is therefore suggested that an uncoordinated expression of cell-cycle proteins and the consequent breach of cell-cycle checkpoints in post-mitotic cells could be a primary mechanism by which neurons undergo degeneration. The Wnt pathway is one of the signaling pathways involved in the regulating of cell cycle protein expression. Dickkopf-1 (DKK-1), an extracellular protein, negatively modulates the canonical Wnt pathway, and is increased in AD brain. Also glycogen synthase kinase 3β (GSK-3β) mediates Wnt signalling and its kinase activity is increased in AD brain facilitating the phosphorylation of tau protein and the formation of neurofibrillary tangles. In this study we analysed the expression of DKK-1 and GSK-3β in different stages of AD pathology. DKK-1 expression and GSK-3β are localized in pretangle neurons, suggesting their early involvement in AD pathology. In addition, DKK-1 is localized in reactive astrocytes associated with neuritic plaques. These findings indicate that the Wnt pathway might be involved in reactivation of the cell cycle in neurons and the formation of neurofibrillary tangles during AD pathogenesis.