

P066 Dying to survive: Increased Akt activation with loss of PTEN and Akt are features of Alzheimer's disease pathogenesis
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The serine-threonine kinase Akt plays a central role in controlling brain growth, differentiation and survival, and is negatively regulated by the phosphatase PTEN, which dephosphorylates the major Akt activator, the lipid PtdIns (3, 4, 5)P₃. This work detected a disease-stage related loss of Akt protein and increased activity of Akt, with hyperphosphorylation of many Akt substrates, including Ser214 and the Thr212/Ser214 tau sites, in the brains of individuals with AD compared to non-disease controls. PTEN protein levels were significantly decreased (47%, p<0.001) in the same AD brains, and striking differences in the subcellular distribution of PTEN were detected in AD hippocampal neurons compared to control neurons. Together this work suggests that PTEN loss, and progressively impaired PTEN function may cause aberrant and possibly pathogenic Akt activation in AD. We are thus now developing pharmacological and molecular approaches to determine the relationship between PTEN loss, Akt overactivation and AD tau and β -amyloid pathologies. In *in vitro* studies, we show that inhibition of PTEN activity in SH-SY5Y cells, using low concentrations of dipotassium bisperoxo(5-hydroxypyridine-2-carboxyl)oxovanadate compounds, results in a significant increase in Akt activation and Akt substrate phosphorylation, and also importantly in significantly increased Ser214 tau phosphorylation compared to unphosphorylated tau. We have also suppressed PTEN protein expression using siRNA in these cells, and this approach is also being used to understand the role of the PTEN/Akt pathway in AD.