

**P065** Are Shortfalls in the Cell Cycle and Tau-Regulating Protein Pin1 a Susceptibility Factor for Neurodegeneration and Ageing?  
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The peptidyl-prolyl *cis-trans* isomerase Pin1 modulates the activity of a range of proteins involved in the cell cycle, transcription, translation, endocytosis, apoptosis and cytoskeletal stability via binding p-Ser/Thr-Pro motifs. Isomerisation of such p-peptidyl-prolyl bonds by Pin1, at the interface of specific kinase/phosphatase activities, provides a novel signalling mechanism regulating dephosphorylation of specific targets in subcellular compartments. Thereby, Pin1 modulates a range of cellular activities. We have demonstrated apparent neuronal Pin1 deficits in AD and frontotemporal dementias. This may be a susceptibility factor as others have shown the following: Pin1 depletion causes apoptosis; patterns of AD pathology correlate with regions of lower Pin1 expression in normal brain; Pin1 knockout mice suffer neurodegeneration; and Pin1 can ameliorate p-tau pathology by isomerising p-tau, facilitating its trans-specific dephosphorylation and restoring its ability to stabilise cytoskeletal integrity. Our observation that even in normal neurons nuclear Pin1 deficits increase with age, correlating with Pin1 re-localisation to lipofuscin accumulations, suggests that neuronal Pin1 shortfalls may be a susceptibility factor for neurodegeneration and ageing.