

P010 Expression of the APP intracellular domain (AICD) potentiates ER stress mediated apoptosis

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Altered processing of the Amyloid Precursor Protein (APP) plays a pivotal role in the pathogenesis of Alzheimer's disease. Recent research has revealed an interesting biological function for the APP intracellular domain (AICD), the short APP C-terminal region which generated by γ - and/or ϵ -secretase cleavage. In a manner analogous to the Notch signalling pathway, AICD binds to several co-factors involved in the regulation of transcription, in particular Fe65, Tip60 and CP2. Upon interaction with its co-factors, AICD becomes stabilised, enabling its nuclear translocation where it has been implicated in the regulation of several genes. In the present study we have established human SH-EP neuroblastoma cell lines stably and inducibly expressing AICD to investigate the ability of AICD to modulate cell death pathways. We found that AICD overexpression was specifically associated with increased sensitivity to treatment with the ER stressors, thapsigargin (1 μ M) and tunicamycin (1 μ M), as assessed by DEVDase assay. In contrast, levels of apoptosis induced by more generalised apoptotic stimuli (Staurosporine and TNF- α I) were unaffected by AICD expression. Induction of the ER stress marker, Grp78, was unaltered by AICD expression implying that AICD potentiates ER stress-induced cell death downstream or independent of the initial ER stress response. Our data suggests that altered levels of AICD expression may increase the susceptibility of neurons to ER stress mediated cell death and contribute to the pathogenesis of Alzheimer's disease.