Cell cycle changes and the unfolded protein response in Alzheimer's disease: opposite effects?

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Increased expression of cyclins, cyclin dependent kinases and their inhibitors can be detected in neuronal cells localized in affected areas of the brain of patients with Alzheimer's disease (AD). Although the cause and the role of the neuronal cell cycle changes remain unclear, a role for cell cycle proteins in neuronal regenerative mechanisms has been suggested.
In this study the relation between cell cycle protein expression in AD and protein misfolding is evaluated. AD is characterized by the aggregation of amyloid β and hyperphosphorylated tau protein. It is still elusive how the accumulation of these abnormal proteins could lead to neurodegeneration in AD. Proposed mechanisms of toxicity include inhibition of the ubiquitin-proteasome system and induction of apoptosis.
Cyclin D1, cyclin E and phosphorylated retinoblastoma protein in neurons are increased in neurons at an early stage of AD pathology. We have compared these data with the occurrence of protein misfolding as measured by the expression of BiP (GRP78), a molecular chaperone located in the endoplasmic reticulum (ER). BiP is known to be upregulated during the unfolded protein response (UPR), a cellular mechanism for dealing with an accumulation of unfolded proteins. It appears that BiP is increased expressed in AD patients at relatively late stages of AD pathology. These results suggest a negative correlation between cell cycle changes and the UPR in AD. Additional in vitro experiments show that the UPR has direct negative effects on cell cycle progression. Our data show that protein misfolding and aggregation in AD could negatively influence the proposed regenerative role of cell cycle proteins in AD neurons.

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