NUB1 modulation of tau aggregation

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Background: The NEDD8 ultimate buster 1 (NUB1) reduces synphilin1-positive inclusions in a cell model of Parkinson's disease by directly binding both synphilin-1 and the proteasome. Proteins conjugated with the ubiquitin-like modifiers NEDD8 or FAT10 are targeted by NUB1 for their proteasomal degradation. Recently, NEDD8 has been found to decorate neurofibrillary tangles (NFT) in Alzheimer's disease. The aim of this study is to elucidate the role of NUB1 in tau aggregation. **Methods:** Human neuroblastoma SK-N-SH cells lacking endogenous tau were transiently transfected with GFP-tagged tau and glycogen synthase kinase (GSK) 3β, treated with proteasome inhibitors prior to quantification of eGFP-tau positive inclusions. To determine the effect of NUB1 on GFP-tau aggregation, cells were transfected with the optimized quantity of GFP-tau, GSK3β and increasing amounts of NUB1 and treated with a vehicle (DMSO) or proteasome inhibitor. The percentage of transfected cells with GFP-tau inclusions were counted independently of the quantity of NUB1 co-transfected. A filter-trap assay and western blotting were performed to further characterise the mechanism of NUB1-mediated reduction in intracellular GFP-tau inclusions. **Results:** The co-transfection of GSK3β with GFP-tau in the presence of proteasome inhibition significantly increased the percentage of transfected cells with GFP-tau inclusions. Transfection of increasing amounts of NUB1 significantly decreased the percentage of transfected cells with GFP-tau inclusions in a concentration-dependent manner and this effect is seen in the presence or absence of proteasome inhibition. Filter trap assays revealed that NUB1 reduced GFP-tau levels in a GSK3β dependent manner, and western blotting furthermore indicated that NUB1 alters the levels or phosphorylation status of GSK3β. **Conclusions:** These data suggest that NUB1 is a potential regulator of tau aggregation. NUB1 could reduce tau aggregation via a direct interaction with tau or via a GSK3β-dependent pathway.