EFFECTS OF UBIQUILIN-1 TRANSCRIPT VARIANTS ON \( \gamma \)-SECRETASE ACTIVITY AND APP PROCESSING

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Introduction: Genetic alterations in ubiquilin-1 (UBQLN1) gene have been associated with Alzheimer's disease (AD) risk. Subsequent studies related to the functional role of ubiquilin-1 in the cellular processes relevant for AD pathogenesis, such as \( \gamma \)-secretase function and amyloid precursor protein (APP) processing, have revealed cell-type specific differences.

Aims: Here we have assessed the effects of the ubiquilin-1 transcript variants TV1 (full-length) and TV2 (lacking exon 8) on \( \gamma \)-secretase function and APP processing in SH-SY5Y cells stably over-expressing APP751.

Methods: SH-SY5Y-APP751 cells were transiently transfected with TV1, TV2 or control plasmids. Western blotting and \textit{in vitro} AICD generation assay were used to assess alterations in APP processing and \( \gamma \)-secretase activity, respectively.

Results: TV1 over-expression resulted in enhanced APP maturation and increased levels of APP C83 and C99. Furthermore, \textit{in vitro} AICD generation assay in TV1 over-expressing membrane fractions revealed a statistically significant \( \sim 1.7 \)-fold increase in the C83-normalized AICD levels. Over-expression of TV1 along with an additional \( \gamma \)-secretase substrate, leukocyte common antigen related phosphatase (LAR), resulted in a competition between APP and LAR for the \( \gamma \)-secretase-mediated cleavage. Over-expression of TV2 also augmented APP CTF levels, but to a lesser extent as compared to TV1. However, TV2 over-expression did not significantly increase AICD generation. Confocal microscopy did not reveal changes in the subcellular localisation of APP or presenilin-1 in TV1 or TV2 over-expressing cells.

Conclusions: Collectively, our data suggest that ubiquilin-1 alters \( \gamma \)-secretase activity and APP processing in SH-SY5Y cells and that ubiquilin-1 TVs exert differential effects on these processes.