**EXPRESSION OF ALZHEIMER’S DISEASE-ASSOCIATED PROTEIN UBIQUILIN-1 DECREASES SER51 PHOSPHORYLATION OF EIF2Α AND CHOP LEVELS UNDER ER-STRESS**

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**Introduction:** Previous genetic and functional studies have suggested that ubiquilin-1 plays a role in Alzheimer's disease (AD) pathogenesis by e.g. altering amyloid precursor protein (APP) processing. Ubiquilin-1 also has a pivotal role in the unfolded protein response (UPR), a stress condition implicated in AD pathogenesis. Interestingly, amyloidogenic APP processing is initiated by BACE1, whose translation is induced by increased Ser51 phosphorylation of eIF2α under stress conditions.

**Aims:** Here we have investigated whether ubiquilin-1 affects UPR after tunicamycin- or thapsigargin-induced endoplasmic reticulum (ER)-stress by assessing the downstream stress markers, such as the Ser51 phosphorylation of eIF2α and C/EBP homologous protein (CHOP) levels.

**Methods:** ER-stress was induced by treating human neuroglioma H4 cell clones stably over-expressing full-length ubiquilin-1 or control plasmid with tunicamycin (5 µg/ml) or thapsigargin (10 nM). Western blotting was used to assess the Ser51 phosphorylation status of eIF2α and C/EBP homologous protein (CHOP) levels.

**Results:** H4 cells stably over-expressing ubiquilin-1 showed reduced Ser51 phosphorylation of eIF2α and decreased CHOP levels when compared to control cells after tunicamycin induced ER-stress. Thapsigargin treatment also robustly decreased CHOP levels in ubiquilin-1 over-expressing H4 cells, but did not affect Ser51 phosphorylation status of eIF2α. Due to the ubiquilin-1-induced reduction of Ser51 phosphorylation of eIF2α under ER-stress, the effects on BACE1 expression will be examined in detail using a BACE1 cDNA construct encompassing endogenous 5’ and 3’ UTRs.

**Conclusions:** These findings suggest that expression of the AD-associated protein ubiquilin-1 alleviates ER-stress, partially by decreasing eIF2α phosphorylation, which in turn may reduce amyloidogenic processing of APP.