IRE1 signaling exacerbates Alzheimer?s disease pathogenesis

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 Altered proteostasis is a salient feature of Alzheimer?s disease (AD), highlighting the occurrence of endoplasmic reticulum (ER) stress and abnormal protein aggregation. ER stress triggers the activation of the unfolded protein response (UPR), a signaling pathway that enforces adaptive programs to sustain proteostasis or eliminate terminally damaged cells. IRE1 is an ER-located kinase and endoribonuclease that operates as a major stress transducer, mediating both adaptive and proapoptotic programs under ER stress. IRE1 signaling controls the expression of the transcription factor XBP1, in addition to degrade several RNAs. Importantly, a polymorphism in the XBP1 promoter was suggested as a risk factor to develop AD. Here, we demonstrate a positive correlation between the progression of AD histopathology and the activation of IRE1 in human brain tissue. To define the significance of the UPR to AD, we targeted

IRE1 expression in a transgenic mous