Neurocellular ER Stress Response in Alzheimer's Disease and Related Dementias (ADRD) Risk

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Background: Alzheimer's Disease (AD) pathology, characterized by neurodegeneration, amyloid-β (Aβ) plaques, and intracellular tangles of hyperphosphorylated Tau, starts in the entorhinal cortex and then spreads to the hippocampus and cerebral cortex. The presence of AD pathology in the hippocampus is strongly correlated with cognitive decline. The hippocampus is also one of the major sites of adult neurogenesis in the brain and accumulating evidence now suggests that adult hippocampal neurogenesis (AHN) that occurs throughout life (albeit declining with age) is essential for cellular homeostasis and hippocampus-dependent cognitive functions, and is severely impaired in ADRD patients. However, the causation of impaired AHN in ADRD patients and its contribution to ADRD-related cognitive decline remains poorly understood. Studies of postmortem AD brain showed elevated levels of endoplasmic reticulum (ER) stress. While the accumulation of Aβ and intracellular neurofibrillary tangles may primarily contribute to ER stress by disruption of Ca^{2+} and protein homeostasis and the resulting unfolded protein response (UPR) potentially alters AHN by mechanisms yet to be fully understood.
Methods: To study the ER stress-associated neurocellular response and its effects on neurocellular homeostasis and neurogenesis, we performed ER stress challenge using Thapsigargin (TG), a specific inhibitor of sarco/endoplasmic reticulum Ca2+ ATPase (SERCA), on induced pluripotent stem cell (iPSC) derived neural stem cells (NSCs) of two individuals of our Mexican American Family Study (MAFS). We have previously shown that our iPSC-derived NSCs are transcriptionally akin to dorsal neuroepithelium that give rise to the majority of the central nervous system and are a relevant cell type to study developmental and adult neurogenesis. Both pre- and post-ER stress-challenged NSCs were multi-dimensionally phenotyped by quantitative high-content screening and genome-wide mRNA sequencing (mRNAseq) analysis.
Results: The high-content phenotypic analysis of the pre- and post-ER stress-challenged NSCs shows evidence of upregulated UPR, a decline in NSC proliferation, an increase in apoptosis, and cellular oxidative stress in post-ER stress-challenged NSCs. A total of 2,300 genes were significantly (moderated *t* statistics FDR corrected *p*-value ≤ 0.05 and Fold Change absolute ≥ 2.0) differentially expressed (DE) between pre- and post-ER stress-challenged NSCs. The DE genes showed significant enrichment in protein export, DNA replication, protein processing in ER, cell cycle, and apoptosis KEGG pathways. All three UPR-associated (PERK, ATF6, and IRE1) pathways were significantly upregulated. Due to the short G1 phase, activated NSCs rely on higher expression of CDT1 and CDC6 licensing factors and MCM complex for timely DNA duplication during the cell cycle, ER stress-induced activation of UPR down-regulated CDT1 licensing factor and MCM complex genes in ER stress-challenged NSCs and induced G1 phase cell cycle arrest. The ER stress-challenged NSCs also showed activation of CHOP-mediated apoptosis and down-regulation of neurotransmitter homeostasis and synaptic plasticity-associated genes.
Conclusions: Overall our results suggest that ER stress-associated attenuation of NSC self-renewal, increased apoptosis, and dysregulated neurotransmitter homeostasis and synaptic plasticity plausibly affect hippocampal neurogenesis and causation of ADRD.