Early and Selective Activation and Subsequent Alterations to the Unfolded Protein Response in Down Syndrome Mouse Models

Lanzillotta C.

Tramutola A.

Meier S.

Schmitt F.

Barone E.

Perluigi M.

Di Domenico F.

Abisambra J.F.

Down syndrome (DS) is the most common chromosomal disorder and the leading genetic cause of intellectual disability in humans, which results from the triplication of chromosome 21. DS individuals have an increased risk of developing Alzheimer's disease (AD)-like pathology and dementia by the age of 40 due to the triplication of several genes involved in the formation of amyloid plaques and tau tangles. Further, DS and AD are characterized by the aberrant accumulation of unfolded/misfolded proteins resulting from over-burdened protein quality control systems. The accumulation of misfolded proteins in the endoplasmic reticulum (ER) triggers a cellular stress response called the unfolded protein response (UPR). Long-term activation of the UPR mediates neuronal dysfunction in AD. We hypothesized that the UPR is impacted in a mouse model of DS. To test this, we performed gene and protein expression analysis of ER stress markers in the Ts65Dn mouse model of DS at 3, 9, and 18 months. We identified activation of the PERK pathway in Ts65Dn DS mice at 3 months of age compared to euploid controls. We also determined that the early and overt UPR activation decreased with age, the UPR signal was significantly reduced by 18 months. Our data suggest that UPR activation in DS mouse models occurs early before consistent brain neurodegeneration and might be an essential contributor to dys-proteostasis.

Down syndrome

eif2 alpha

PERK

Ts65Dn

unfolded protein response

protein kinase

protein kinase RNA like endoplasmic reticulum kinase

unclassified drug

Ddit3 protein, mouse

growth arrest and DNA damage inducible protein 153

PERK kinase

protein kinase R

age

animal experiment

animal model

animal tissue

Article

brain degeneration

controlled study

Down syndrome

endoplasmic reticulum stress

female

gene expression

male

mouse

mouse model

nonhuman

priority journal

protein expression

protein homeostasis

unfolded protein response

aging

animal

disease exacerbation

disease model

Down syndrome

gene expression profiling

hippocampus

metabolism

physiology

time factor

transgenic mouse

unfolded protein response

Aging

Animals

Disease Models, Animal

Disease Progression

Down Syndrome

eIF-2 Kinase

Female

Gene Expression Profiling

Hippocampus

Male

Mice, Transgenic

Time Factors

Transcription Factor CHOP

Unfolded Protein Response