THE ROLE OF AUTOPHAGY AND THE UPR IN THE DEVELOPMENT OF ALZHEIMER DISEASE IN A MOUSE MODEL OF DOWN SYNDROME NEUROPATHOLOGY

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Down syndrome (DS) is the most frequent chromosomal abnormality that causes intellectual disability. The neuropathology of DS is complex and includes development of Alzheimer disease (AD). The accumulation of amyloid beta (Aβ)-peptide in DS brain can be observed as early as 8–12 years of age. Interestingly, the incidence of dementia typically does not increase until adults with DS are over the age 50 years. Within this context, it has been suggested that DS may serve as a model for the study the early molecular events in the pathogenesis and progression of AD neuropathology. The alteration of mammalian target of rapamycin (mTOR)/ autophagy axis, increased levels of oxidative stress and endoplasmic reticulum (ER) and its associated Unfolded protein response (UPR) are emerging as major common themes in neurodegenerative disorders such Down Syndrome neuropathology. We focus on the disturbance of mTOR signaling that leads to the alteration of autophagy and the abnormal accumulation of aggregated and unfolded/misfolded proteins and the UPR that is a protective mechanism that acts to restore proteostatsis in the face of a misfolded protein load. The UPR facilitates this restoration of normal ER function through joint activation of three ER stress sensors : IRE1, ATF6 and PERK each of wich activates its own distinct signaling pathway. A sustained uncontrolled ER stress can promote the activation of proapoptotic signaling pathways, such as those observed in neurodegenerative disorders.