Deciphering the interplay between the unfolded protein response and metabolic defects in Down syndrome neuropathology

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Protein homeostasis (proteostasis) is essential for normal brain function and the unfolded protein response (UPR) holds a key role in its preservation. A maladaptive response, such as chronic UPR activation, provides a link between deficits in molecular chaperones, accumulation of misfolded proteins, increased oxidative stress and neurotoxicity. We recently reported that the dysregulation of the PERK branch of the UPR leads to aberrant proteostasis contributing to the progression of Alzheimer-like signatures in Down syndrome (DS) brain. In addition, our studies support the notion that in DS brain insulin resistance (BIR) and mitochondrial defects advance in parallel to faulty proteostasis and are associated with cognitive decline.Our study aimed to understand the pronicity of DS phenotype in developing defect of proteostasis under aberrant metabolic stimuli and to unravel the role of trisomic genes in exacerbating the toxic partnership between BIR and UPR. We treated primary cortical neurons and astrocytes with a cocktail of insulin and palmitic acid (IPA), to mime BIR, demonstrating the de-regulation of the PERK/eIF2a axis, which resulted in the reduction of protein translation and of antioxidant responses.Subsequently, we administered IPA-treated cells with UPR targeting agents showing its rescue, the amelioration of metabolic defects and the decrease of oxidative stress.Following data on lymphoblastoid cells isolated from DS patients demonstrated that IPA-induced activation of PERK is an early and toxic mechanism that precedes and triggers redox imbalance, tau and Aβ accumulation. Currently, we investigated the role of BIR and UPR in DS mice subjected to high fat diet (HFD). Collected data suggest that HFD in DS mice is related with poor cognition and with the development of BIR and the chronic de-regulation of the PERK/eIF2a axis. Additional studies are ongoing in our laboratory to fully clarify the mechanisms linking metabolic defects and aberrant proteostasis.

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