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Report
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"Proteolysis of mitochondrial amyloid beta peptide of Alzheimer`s disease and its role in cellular homeostasis"

It has been proposed that in Alzheimer disease (AD) amyloid beta peptide (AB) aggregation is the major responsible of the neurodegenerative pathology and extensive neuronal death. Therefore can interfere the process of AB aggregation could be therapeutically useful. In the last years, two concepts gained relevance in AD physiopathology: AB degradation by proteases *in situ* to prevent cerebral AB accumulation and mitochondrial dysfunction is one of the early neuropathological events that precede extracellular AB deposition. Biochemical and genetics data support that: a-AB is produced inside mitochondria (mitAB); b-AB generated in the secretory pathway can translocate to mitochondria; c-insulin degrading enzyme (IDE) participates in cerebral AB catabolism; d- IDE presents two isoforms; the longest, IDE-Met1 translates from longer mRNA (L-IDE mRNA). IDE-Met1 might translocate to mitochondria. e- IDE expression and activity are down-regulated in AD.

The aim of the proposed investigation was to study the localization and regulation of human IDE-Met1 and evaluate its impact over mitochondrial AB levels and cellular homeostasis. We demonstrated *in vitro* that transcripcional regulation of L-IDE mRNA is mediated by the mitochondrial biogenesis pathway (transcription factors PGC1alpha and NRF-1). We also observed a fewer correlation among L-IDE, PGC1 alpha and NRF-1 mRNA levels on AD *post-mortem* brains, as compared to control. The silencing of IDE mRNA *in vitro* increased mitAB levels and declined mitochondria respiration. In contrast to this, the enhancement of L-IDE expression reverted the mitochondrial dysfunction mediated by mitAB accumulation. These results were published on: Transcriptional regulation of insulin-degrading enzyme modulates mitochondrial amyloid β (Aβ) peptide catabolism and functionality. Leal MC, Magnani N, Villordo S, Buslje CM, Evelson P, Castaño EM, Morelli L. J Biol Chem. 2013 May 3;288(18):12920-31.