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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 transcriptional 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
3;288(18):12920-31.