OC39: HUMMR Acts as a "roadblock" for mitochondrial transport in Alzheimer's disease

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Introduction: Alterations in axonal transport of mitochondria play a critical role in Alzheimer's disease (AD) neuropathology; however, the molecular mechanisms involved remain unexplored (Li et al., 2009).

Objectives: To unveil the role of the hypoxia up-regulated mitochondrial movement regulator [HUMMR - a protein that favors the anterograde movement of mitochondria in a hypoxia-inducible factor 1 (HIF-1)-dependent process (Li & Rempe, 2014)] on defective mitochondrial trafficking during the course of AD pathology.

Materials and Methods: Using human post-mortem brain cortex and hippocampus from AD subjects and rodent model and differentiated SH-SY5Y cells exposed to A $_{1-42}$, and respective controls, we evaluated HIF-1 and HUMMR protein levels and mRNA by Western blotting and RT-PCR, respectively, and mitochondrial function and dynamics by fluorimetry and confocal microscopy.

Results and Discussion: A progressive reduction in HIF-1 and HUMMR protein levels and mRNA was observed with increasing AD Braak stage. Consistently, AD rodent model also presented a decrease in HUMMR protein levels in the brain cortex. Notably, differentiated SH-SY5Y cells treated with high levels of A $_{1-42}$ exhibit a marked reduction in HUMMR protein levels, altered mitochondrial trafficking and distribution and loss of synaptic integrity.

Conclusion: Loss of HUMMR during AD progression contributes to the mitochondrial traffic jam that characterizes this disease. Furthermore, HUMMR may represent a feasible therapeutic target to minimize mitochondrial trafficking deficits and axonal and synaptic degeneration associated to AD.

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