ROLE OF AMYLOID-β PRECURSOR PROTEIN IN MAINTAINING VASCULAR STABILITY AND BLOOD BRAIN BARRIER INTEGRITY IN RESPONSE TO STRESS FACTORS

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Introduction: Beta-amyloid (Aβ) peptide accumulation is the main hallmark of neurovascular disorders such as Cerebral Amyloid Angiopathy (CAA) and Alzheimer's disease (AD). Aβ is a short hydrophobic peptide generated by cleavage of the Amyloid Precursor Protein (APP), a ubiquitous transmembrane glycoprotein abundantly expressed in the cerebrovascular endothelium. In physiological conditions, APP is cleaved by different secretases through two main proteolytic pathways: the amyloidogenic and non-amyloidogenic processing. Two decades of research on compounds that chronically target the amyloidogenic processing have led to unsuccessful clinical trials, and yet the normal function of APP and in particular the exact role of endothelial APP in cerebrovascular/cardiovascular homeostasis is unknown. A number of physiological roles have been attributed to APP and its non-amyloidogenic processing products, some of which impact neurovascular development and function. In the brain, impairment of vascular endothelial function plays an essential role in initiation and progression of vascular disease that ultimately leads to the neuronal death and cognitive demise. Thus, the maintenance of vascular stability is crucial in preventing hemorrhagic strokes in CAA and in limit neuronal atrophy in AD.
This study aims to 1) define molecular mechanisms and signal transduction pathways responsible for endothelial function of APP; 2) identify contributions of APP to cerebrovascular homeostasis *in vivo*.

Material and methods: Human umbilical vascular endothelial cells (HUVECs) were transfected with small interfering RNAs (siRNAs) targeting APP mRNA. Endothelial functions were assessed under both normal conditions and upon angiogenic growth factors (VEGF and bFGF) stimulation. MTT cell proliferation assays, scratch assays, immunofluorescence staining and western blot analyses were used to examine the effects of APP knockdown on HUVEC growth, survival, and migration and on the angiogenesis molecular signaling.

Results: Transfected HUVEC cells demonstrated significant inhibition of cell migration in the scratch assay. Western-blot analysis revealed a dysfunction of angiogenic growth factors signaling.

Conclusion: our preliminary results suggest that intact expression and processing of APP is required for normal endothelial function. The identification of the molecular mechanisms responsible for vasoprotective properties of endothelial APP may have an impact on clinical efforts to preserve and protect healthy cerebrovasculature in patients at risk for development of cerebrovascular disease and dementia including AD and CAA.