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Presenilin1 fad mutants impair angiogenic functions of vegfr2 in brain endothelial cells.

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Abstract

Alzheimer's disease (AD) is a multifactorial and progressive neurodegenerative disease where cerebrovascular abnormalities are commonly observed. Brain vascular alterations occur before the appearance of neuropathology in animal AD models. Various factors, including decreased sprouting angiogenesis, can cause the reduction in capillary density observed in AD brains. Angiogenesis is a reparative function of the brain in response to toxic insults and is regulated by endothelial cells (ECs) and angiogenic factors such as the Vascular Endothelial Growth factor (VEGF); impairment in this function would render the brain vulnerable to toxic insults and lead to neurodegeneration. The purpose of this study is to examine the effects of Presenilin1 (PS1) mutants linked to familial AD (FAD) in the VEGFinduced angiogenic signaling and functions of brain endothelial cells. Methodology and Theoretical Orientation: Primary cortical endothelial cells (pCECs) from brains of wild-type (WT) and knock-in (KI) mice expressing either PS1 M146V or PS1 I213T FAD mutant in heterozygous state were isolated and cultured. These mice constitute a "humanized" FAD model having the same genotype as human FAD patients. We performed in vitro angiogenesis assays including sprouting on beads, cell migration and tube formation using pCEC cultures. Processing of VEGFR2 was detected in HEK293 cells overexpressing VEGFR2 in the presence or absence of VEGF-A and γ-secretase inhibitor (RO4929097). The same processing was also analyzed by western blotting in PS1 M146V and I213T mutant pCECs treated with VEGF-A. The role of γ-secretase in VEGF-induced formation of angiogenic complexes between VEcadherin and Rok-α kinase was detected in the presence or absence of RO4929097 with immunoprecipitation and western blotting. VEGF-induced phosphorylation of signaling molecules downstream of VEGFR2 such as ERK1/2 and Akt kinases and PLCγ1 was also examined in WT and both PS1 FAD mutant pCECs by western blotting. Findings: We found that VEGFR2 is processed by γ-secretase and that this processing together with VEGF-induced sprouting, tube formation, migration and angiogenic complexes between VE-cadherin and Rok-α kinase are decreased in the presence of γ-secretase inhibitor or by PS1 FAD mutants. Furthermore, the VEGF-induced phosphorylation of ERK1/2, Akt and PLCγ1 is decreased in PS1 FAD mutant pCECs. Conclusion & Significance: Our findings show that VEGFR2 is processed by γ-secretase, which promotes VEGF-induced angiogenic functions of brain ECs through activation of VEGFVEGFR2 downstream signaling. Our data also show that PS1 FAD mutants decrease both the VEGFR2 processing by γ-secretase and the VEGF-induced angiogenic signaling and functions of brain endothelial cells, providing a mechanism via which FAD mutants affect brain angiogenesis and promote neurodegeneration.

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Biography

Anastasios Georgakopoulos is a Professor at the Center for Molecular Biology and Genetics of Neuro degeneration, department of Psychiatry at the Icahn School of Medicine at Mount Sinai, New York. He has extensive experience in research on the role of Presenilin1(PS1)/γ-secretase system on the function of various cell systems including neuronal and endothelial cells. PS1 mutants have been linked to the pathogenesis of Familial Alzheimer's Disease (FAD). He has been working exclusively on the molecular biology of WT and mutant PS1 for over 24 years. He was the first to show that PS1 localizes at Cadherin-based adherens junctions at cell-cell contact sides and synapses. In addition, he found the interaction of PS1 with substrates of γ-secretase such as E- and N-cadherins and ephinB ligands and EphB receptors and the physiological role that these interactions have. He has published several articles on the above subjects. His laboratory studies mechanisms of VEGF/VEGFR2 and ephrinB/EphB-mediated angiogenesis and neuroprotection and the role that PS1/γ-secretase system has on their regulation aiming to discover methods to effectively treat and prevent neurodegenerative disorders like Alzheimer's Disease

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