# Regulation of ephrinB2-dependent angiogenesis by PS1 in normal and AD

https://neurodegenerationresearch.eu/survey/regulation-of-ephrinb2-dependent-angiogenesis-by-ps1-in-normal-and-ad/

**Principal Investigators**

GEORGAKOPOULOS, ANASTASIOS

**Institution**

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

Regulation of ephrinB2-dependent angiogenesis by PS1 in normal and AD

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 1,700,272.48

**Start date of award**

01/01/2004

**Total duration of award in years**

2

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

gamma secretase, cadherin 5, EphB4 Receptor, angiogenesis, Vascular System

**Research Abstract**
?DESCRIPTION (provided by applicant): Evidence in the last decade implicates cerebral microvasculature abnormalities in the genesis of AD neuropathology. Additional literature shows

that the EphB4/ephrinB2 system is an important regulator of the development and function of the vascular system. Binding of the extracellular sequence of EphB4 receptor to its transmembrane ligand ephrinB2 protein on the surface of endothelial cells of blood vessels, stimulates angiogenesis and growth of new vessels from existing vasculature. Furthermore, in vitro assays show that treatment of ephrinB2expressing endothelial cells with the extracellular domain of EphB4 stimulates cell sprouting and tube formation, processes considered crucial initial steps in angiogenesis, while transgenic mouse experiments indicate that the intracellular (cytoplasmic) domain of ephrinB2 protein is necessary for ephrinB2-dependent angiogenesis. We found that EphB4 stimulates the metalloproteinase (MP) and PS/?-secretase processing of ephrinB2 producing cytosolic peptide ephrinB2/CTF2 and that the EphB4-induced sprouting and tube formation of endothelial cells depends on ?-secretase activity. These observations raise the possibility that the endothelial EphB4/ephrinB2 system regulates angiogenesis through PS/?-secretase. In support of this hypothesis, we obtained data that peptide ephrinB2/CTF2 stimulates sprouting of endothelial cells in vitro. Recent literature shows that a crucial step in angiogenic factor-induced angiogenesis is formation of complexes between Raf1/ Rok-? and Vascular Endothelial cadherin (VE-cadherin) and we made the novel observation (preliminary data) that treatment of endothelial cell cultures with EphB4 increases these angiogenic complexes. Together, our observations suggest that PS1/?-secretase may affect angiogenesis by regulating processing of transmembrane protein ephrinB2, a critical step in EphB4-induced angiogenesis. Here we propose to explore the mechanisms via which the EphB4/ephrinB2 and PS1/?-secretase systems interact to promote endothelial cell sprouting and angiogenesis and to examine whether any of these mechanisms are altered in Alzheimer disease (AD) brains. Furthermore, we and others reported that PS1 familial AD (FAD) mutations may affect the epsilon (?) cleavage of PS1/?-secretase substrates thus decreasing production of CTF2 peptides including ephrinB2/CTF2 (see Significance). Thus, we will ask whether PS1 FAD mutants alter the EphB4/ephrinB2-dependent angiogenesis.

## Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer Disease (AD) brains show severe defects in the vascular system. It is believed these defects impair neuronal health and function because they restrict transport of nutrients and oxygen to neurons. Research in the last decade showed that protein ephrinB2 regulates development and function of the vascular system and we discovered that Presenilin1 (PS1), a factor important to familial AD, interacts with ephrinB2 and regulates it vascular functions. This application examines the mechanisms by which PS1 and ephrinB2 regulate the vascular system with the ultimate aim of discovering methods to correct defects of brain vasculature.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
N/A