Increased microhemorrhages induced by acute and chronic hypertension in a mouse model of cerebral amyloidosis

Intracerebral hemorrhage (ICH) is a subtype of stroke with high morbidity and mortality, accounting for about 15% of all deaths from stroke. Hypertension as well as Cerebral Amyloid Angiopathy (CAA) are major risk factors for ICH, however, interplay between the two are not fully understood. To gain insight on the effect of vascular amyloid and hypertension in stroke development, we developed a mixed pathology, CAA and hypertension, mouse model.

Acute and chronic hypertension-induced spontaneous intracerebral hemorrhage in 15 month-old Tg2576 mice

(A) Systolic blood pressure in Tg2576 mice and nTg littermates after acute/chronic hypertension (HT), evaluated 14 days after initiation of hypertension. (B) Kaplan-Meier plot showing accelerated appearance of signs of stroke in Tg vs nTg mice (n = 8-21). (C) Examples of hypertension-induced cerebral hemorrhage.

Increased microhemorrhages induced by acute and chronic hypertension in Tg2576 mice

(A) Representative image of extracellular vesicles, observed in real time under Brownian Motion. (B) Size distributions of extracellular vesicles derived from human vascular endothelial cells using NTA technology. (C) An assay demonstrating measurable protein in extracellular vesicles after purification. (D) Western blot detection of CD9 tetraspanin, a protein marker for extracellular vesicles.

Extracellular Vesicles as potential biomarkers for neurodegeneration

Secreted extracellular vesicles (EVs) are secreted from many cell types, including neurons and endothelial cells that border blood vessels in the brain. Within the past decade, research on EVs has discovered diverse biological functions ranging from mediators of cell-to-cell communication to shuttling proteins, mRNAs & microRNAs between cells. In addition, extracellular vesicles loaded with aggregated proteins may be involved with the spread of amyloid and tau neuropathology in the AD brain.

Schematic Illustration of Isolation and Characterization

Confocal laser microscopy of endothelial cells (red), amyloid (blue), and PICALM (green) demonstrating the co-localization of PICALM and CAA in blood vessels in an Alzheimer’s disease brain tissue.

APOE ε4 and PICALM may interact to exacerbate neurodegeneration in the aging human brain

Representative western blot (A) and quantitative results (B) showing how the ApoE 4 genetic variation reduces expression of PICALM in AD brains. Tissue amounts of GAPDH were used as loading controls. Effect of PICALM genetic variation on CAA in AD brains shows a trend towards an increase in CAA in the cases homozygous for the PICALM risk variant when compared with cases homozygous for the non-risk variant (C).

PICALM Future Directions

Further research will be done on a larger sample set to further characterize the effects of the PICALM AD risk and non-risk variants on amyloid plaques, cerebral amyloid angiopathy (CAA), and inflammation. In addition, we will determine if the APOE4 variant reduces PICALM protein levels in the brain.

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PICALM co-localizes with CAA in blood vessels in Alzheimer’s disease brain tissue

Recent genetic studies have identified new AD risk genes that are important for cellular uptake or transport across biological membranes. One example of this involves the blood brain barrier (BBB) that is critically important for efficient transport of molecules in and out of the central nervous system (CNS). Genetic changes in phosphatidylinositol-binding clathrin assembly protein (PICALM), have been identified with increased risk for AD, and PICALM is involved in transporting molecules across the BBB. PICALM mediated dysfunction in this process may result in clogging of the pervascular space potentially contributing to increased vascular amyloid.

Contribution of the PICALM AD risk variant on cerebral amyloid angiopathy in human brain

We have begun investigating extracellular vesicles as potential biomarkers for AD pathogenesis.