Investigating the Functional Impacts of Metabolic Disease Associated Immune-Vascular Interactions in Alzheimer's Disease

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Background and Hypothesis:

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder with undefined etiology and is the fifth leading cause of death worldwide. AD pathology is characterized by amyloid-beta (Aβ) plaques. Previous work demonstrated that alterations in the microvasculature are some of the earliest recognizable changes in AD, and that most patients with dementia have mixed vascular pathologies. We investigated the functional impacts of metabolic disease associated immune-vascular perturbation on the underlying mechanisms of AD.

Methods:

Adult male Lepr^{db}/J (db/db) were obtained from the Jackson Laboratory. Activated microglia and brain vessel density levels were assessed using immunofluorescence. Cerebral microvessels were isolated for RNA examination using qPCR, and FACS-based analysis of brain endothelial cells. Immunofluorescence of hAβ42 transport in microvessels were observed via confocal microscope. Quantification of images were performed using Fiji (NIH) software.

Results:

Db/db mice brains displayed higher levels of activated microglia with increased soma area and decreased circularity ($p<0.05$). This confirms early vascular stress leads to increased immune cell activation. Brain vessel density analysis revealed a non-statistically significant trend with decreased density in db/db mice. Given that functional changes occur before structural changes, we shifted our examination to the microvasculature. Brain microvessels were isolated and validated and both qPCR and FACS results demonstrated increased levels of inflammatory mediators and cell adhesion molecules in db/db mice ($p<0.05$), confirming microvessel dysfunction and neuroinflammation. Finally, quantification of luminal area fluorescence demonstrated decreased hAβ42 transport in db/db mice ($p<0.01$), validating functional disturbance in the cerebral microvasculature.

Conclusion and Impact:

The vascular risk factors of metabolic disease can lead to dysfunction and inflammation in cerebral microvasculature, causing accelerated progression of AD. Our results emphasize the contributory role of cerebral small vessel health in the origin and evolution of AD and present an opportunity for novel development of surrogate biomarkers and therapeutic treatments.