Elucidating Mechanisms & Impacts of Age-related Alterations in Blood-CNS Barriers: A Transcriptome Study of the Aging Blood-brain Barrier & the Dry Age-related Macular Degeneration Retina

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Causal relationships have been established between blood-brain barrier (BBB) & inner blood-retina barrier (iBRB) dysfunction and many age-related CNS disorders. However, mechanisms governing age-related barrier dysfunction and its impacts on neural tissues are unexplored. This study used machine learning and biostatistics to characterize brain endothelial transcriptomes of African green monkeys across their lifespans and retinal transcriptomes of mice subject to a model of dry age-related macular degeneration (AMD)—an age-related form of blindness—induced by iBRB hyperpermeability. Pathway and coexpression network analyses of brain endothelial transcriptomes provided the first molecular indication of premature brain endothelial aging and established plausible mechanisms for age-related BBB dysfunction as well as chronic, endothelial dysfunction-driven, pan-neurological disease risk beginning in adulthood. Investigations of retinal transcriptomes detailed temporal changes in dry AMD gene expression signatures for the first time. Disease progression culminated in downregulation of GABAergic signaling, the first evidence of a transcriptional link between barrier dysfunction and hypoinhibition. Deconvolution analyses identified correlations between disease and proportions of retinal cell types, suggesting that horizontal cells degenerate in dry AMD. Overall, these findings help unravel the endothelial contribution to age-related CNS disease. Based on both the endothelial and retinal RNA-seq analyses, putative therapeutic mechanisms are proposed. By clarifying age-related changes in brain endothelial cell function and resultant changes in neural tissues, this study provides a path towards prevention and treatment for an array of neurological and ophthalmological diseases.

Awards Won:

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