Neurovascular damage and inflammation in the brains of nonhuman primates fed an atherogenic diet

Peter Hecker [1] • Lei Cai, PhD [2] • Donna Wilcock, PhD [3] • Elizabeth Head, PhD [3] • Ryan Temel, PhD [4]

[1]Pharmacology and Nutritional Sciences, University of Kentucky • [2]Saha Cardiovascular Center and Department of Pharmacology and Nutritional Sciences, University of Kentucky • [3]Sanders-Brown Center of Aging and Department of Pharmacology and Nutritional Sciences, University of Kentucky • [4]Saha Cardiovascular Research Center and Department of Pharmacology and Nutritional Sciences, University of Kentucky

Age- and lifestyle-dependent cerebrovascular lesions are associated with reduced cognition and vascular dementia. Studying the vascular contributions to cognitive impairment and dementia (VCID) has been hampered from a lack of large animal translational models. Our lab is studying atherosclerosis progression and regression in male cynomolgus monkeys fed a high-fat/high-cholesterol diet. After 20 months on this atherogenic diet, a subset of monkeys are switched to standard nonhuman primate “chow” diet for six months and are concomitantly treated with vehicle or a microRNA-33 antagonist (anti-miR-33). We hypothesize that anti-miR-33 treatment will create more stable atherosclerotic plaques by increasing cholesterol efflux from foam cells and dampening inflammation in the vessel wall. While our initial interest was atherosclerosis in the coronary arteries, we have recently turned our attention to atherosclerosis in the brain vasculature. Evaluation of the circle of Willis (COW) reveals atherosclerotic lesions in major branch points of the large arteries and a rust-like staining that likely denotes hemosiderin deposition in the perivascular space due to a loss of integrity in the blood brain barrier (BBB). Immunohistochemistry (IHC) on arterial sections has begun and will allow us to characterize both atherosclerotic and hemosiderin-like lesions along with BBB integrity. With an understanding that small vessel disease (SVD) is the most prevalent pathology underlying VCID we have also started to examine brain sections from the monkeys. Preliminary IHC data shows increased microglia and astrocyte activation around small vessels from a monkey fed atherogenic diet versus a control animal fed chow only. In the near future, we plan to pair MRI analysis of hypoperfusion and white matter lesions (WML) with histology and IHC assessments of WML, cerebral amyloid angiopathy, and astrocyte endfeet engagement with the vasculature. Although much work remains to be done, we are optimistic that we have created a unique and important translational VCID model that will facilitate future research linking hypercholesterolemia and atherosclerosis to neurovascular function and cognition.