Progress Report: Diacomp
Charles E Alpers, PI.
Characterization of a New Model of Diabetic Retinopathy."
Oct. 28, 2013

Progress

We have succeeded in adapting ultra-high sensitive optimal new OMAG for use in the eyes of mice. We have completed an initial set of studies, as proposed in this grant, Diabetic BTBR ob/ob mice, known to have morphology advanced diabetic nephropathy by 18 week of age, underwent retinal imagery at age 20 weeks. Parameters studied included thickness of retinal layers, measurement of retinal capillary density in both the inner and outer plexiform layers, and measurement of total retinal blood flow rate, mice were then sacrificed. Correlative histopathology of retina isolated after sacrifice was performed.

Key findings of this study were that no differences in retinal capillary density could be detected in either IPL or OPL of diabetic BTBR ob/ob mice when compared to WT controls. Corresponding pathology showed loss of vascular cell nuclei (pericyte and endothelial), resulting in a cellular capillary segments which are thought to be an early manifestation of DR, but also did not show proliferation of neovessels into the pre-retinal space (a critical feature of advanced DR). Vascular microaneurysm, another key feature of advanced DR, was likewise not detected.

A potentially important observation, but currently of uncertain pathophysiologic significance, was significantly decreased in retinal blood flow in diabetic mice dw WT controls (2.63 + 0.23 ul/min vs. 3.05 + 0.20 ul/min, $p<0.05$). An anatomic basis for this difference was not identified.

A manuscript detailing these findings has been submitted and a revision requested from the journal; the abstract of this submission is included below:

Abstract

Purpose: To evaluate early diabetes-induced changes in retinal thickness and microvasculature in type II diabetic mouse model using optical coherence tomography/optical microangiography (OCT/OMAG).

Methods: 22 week old obese BTBR mice (OB, n=10) and wild type control mice (WT, n=10) were used. Three-dimensional data volumes were captured with a spectral domain OCT system using an ultrahigh sensitive (UHS) OMAG scanning protocol for 3D volumetric angiography of retina and for measurement of total retinal blood flow (RBF) rate. The thickness of nerve fiber layer (NFL) and NFL to inner plexiform layer (IPL) were measured and compared between OB and WT mice. The linear capillary density within intermediate and deep capillary layers was calculated as the number of capillaries crossed by a 500 μm line. Total retinal blood flow (RBF) rate was evaluated using *en face* Doppler approach. These quantitative measures were statistically analyzed between the OB and WT mice.

Results: The thickness from NFL to IPL was approximately 10% thinner in OB mice ($p<0.01$). 3D depth-resolved OMAG angiography revealed the first *in vivo* tri-dimensional model of mouse retinal microcirculation. No obvious difference in the capillary vessel density for both intermediate and deep capillary layers was found between normal and obese mice. The total RBF rate was however 13% ($p<0.05$) lower in obese mice than that in WT mice.

Conclusions: We conclude that, compared with the wild-type, there is reduction in NFL-IPL thickness and total RBF rate in the obese BTBR mice as revealed by OCT/OMAG. OMAG

provides a unprecedented capability for high-resolution depth-resolved imaging of mouse retinal microvasculature which may play vital role for detecting early microvessel abnormality such as microaneurysms.