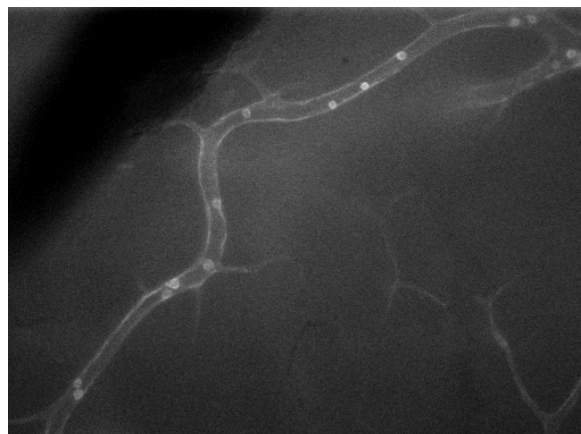




# Mechanisms of the Development of Diabetic Retinopathy

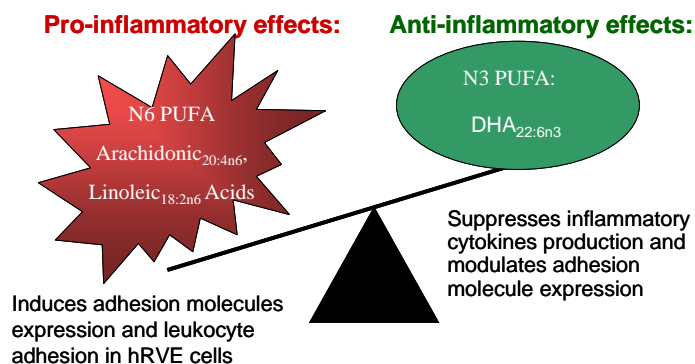
Julia V. Busik, Ph.D.

Diabetic retinopathy is one of the most disabling diabetic complications with both type 1 and type 2 diabetic patients being affected by the disease. Diabetic retinopathy is a leading cause of blindness in adults. Despite the progress made in the last decade in understanding of the molecular mechanisms of the disease, diabetic retinopathy is still neither preventable nor curable. Early diabetic retinopathy has been recognized as a low-grade chronic inflammatory disease involving induction of specific adhesion molecules followed by increased leukocyte attachment and transmigration into the vascular intima (Fig. 1). The individual molecular steps leading to inflammation in the retina are not well resolved, but likely involve



**Fig. 1.** Leukocyte adhesion in rat retinal vasculature.

hyperglycemia and dyslipidemia associated with diabetes mellitus. We have demonstrated that n6 fatty acids (linoleic<sub>18:2n6</sub> and arachidonic<sub>20:4n6</sub>) have a pro-inflammatory effect and the major n3 polyunsaturated fatty acid (PUFA) in the retina, docosahexaenoic acid (DHA<sub>22:6n3</sub>), has a pronounced anti-inflammatory effect on human Retinal Vascular Endothelial cells. The ongoing study in my laboratory also demonstrated that diabetes induced a decrease in DHA<sub>22:6n3</sub> in the plasma and the retina with a shift toward a higher n6 to n3 PUFA ratio in animal model. The hypothesis of this study is that the **diabetes induced decrease in DHA<sub>22:6n3</sub> with a concomitant increase in the n6 to n3 PUFA ratio promotes basal and cytokine induced adhesion molecules expression, leukocyte adhesion and, finally, development of the anatomic lesions of diabetic retinopathy (Fig. 2).**



**Fig. 2. The Ying and Yang of fatty acid regulation of inflammation.** Increase in n6-to-n3 ratio in diabetic retina shifts the balance towards pro-inflammatory state.

Two major approaches are used in the laboratory. First, we use animal models of type 1 and type 2 diabetes to determine the changes in plasma and retinal lipid profiles induced by the disease. We then apply dietary supplementation with n3 fatty acids to alter diabetes induced changes in the fatty acid profiles as a route to prevent or reduce the development of diabetic retinopathy.

Animal studies provide critical *in vivo* information on dyslipidemia induced changes in the diabetic retina. To determine the precise retinal specific biochemical mechanisms of the diabetes induced changes we use primary cultures of human Retinal Vascular Endothelial (hRVE) cells as a model. Three major pathways are studied in these cells (a) production of oxidized lipids; (b) regulation of transcription factors; and (c) modification of lipid raft structure and/or components by n3 and n6 fatty acids as a route of regulation of basal and cytokine induced adhesion molecule expression and subsequent leukocyte adhesion.

1. Chen, W., D. B. Jump, M.B. Grant, W.J. Esselman, and J.V. Busik (2003) Dyslipidemia, but not hyperglycemia, induces inflammatory adhesion molecules in human retinal vascular endothelial cells. *Inv. Ophthalm. Vis. Sci.* 44(11): 5016-22.
2. Chen, W., W. Esselman, D. Jump and J. Busik (2005) "Anti-Inflammatory Effect of Docosahexaenoic Acid (DHA) on Cytokine Induced Adhesion Molecule Expression in Human Retinal Vascular Endothelial Cells" (2005) *Inv. Ophthalm. Vis. Sci.* 46(11):4342-7