ABSTRACT

THE ROLE OF SPHINGOLIPIDS IN RETINAL VASCULAR INTEGRITY

By

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Diabetic retinopathy is a vision-threatening microvascular complication of diabetes mellitus. The increase in the prevalence of diabetes in the population will most likely lead to a higher incidence of diabetic retinopathy (DR), a devastating complication with limited treatment options. Years of investigations have yet to yield a fully understood mechanism for the causes of vascular dysfunction in DR. Dyslipidemia, as well as hyperglycemia, is a major metabolic insult of diabetes and is positively correlated with the development of DR. The objective of this study is to provide a mechanistic link between retinal dyslipidemia in diabetes and retinal vascular pathology in DR. Our studies revealed two main pathways of sphingolipid metabolism involved in the development of DR. The first pathway leads to disruption of blood retinal barrier (BRB) and thus increased vascular permeability-- an early sign of DR. The second pathway plays a role in retinal endothelial damage and its defective repair.

First, we addressed the link between dyslipidemia and BRB using both in vitro and in vivo experiments. We demonstrated that diabetes induces down regulation of an essential retinal fatty acid elongase enzyme, Elongation of very long chain fatty acids-4 (ELOVL4), in the diabetic retina. Down regulation of ELOVL4 plays a crucial role in diabetes-induced blood retinal barrier dysfunction. Overexpression of ELOVL4 in retinal endothelial cells enhances barrier properties of retinal vasculature. Ceramides were found to co-localize with tight junction complexes. Lipidomic analysis of tight junction isolates revealed the presence of ELOVL4-produced VLC ceramides, notably, omega-linked acyl-ceramides that were previously identified only in the skin permeability barrier.

Second, we investigated the effect of dyslipidemia on the function of both cell types involved in revascularization; human retinal endothelial cells (HRECs) and circulating angiogenic cells

(CACs). We demonstrated that diabetes induces activation of acid sphingomyelinase (ASM), a key enzyme of sphingolipid metabolism in human retinal endothelial cells (HRECs) and human CD34+ CACs. Diabetes induced ASM upregulation has deleterious effect on both retinal endothelial cell and CD34+ CAC function. Diabetic HRECs with high ASM showed defective ability to form blood-vessel-like tubular structure and diabetic CD34+ CACs with high ASM showed defective incorporation into endothelial tubes formed by HRECs.

Taken together, these findings indicate that modulation of sphingolipid metabolism to normalize retinal vascular dysfunction and improve retinal vascular repair can represent a novel therapeutic strategy for treating DR.