Developing Approaches to Protect from Proliferative Diabetic Retinopathy

Diabetic Complications Consortium Pilot & Feasibility Project
Andrius Kazlauskas, PhD; PI
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The paragraph below outlines the original goals of the proposal. I am pleased to report that we made substantial progress. Since writing this proposal we discovered that conditioned medium (CM) from high glucose (HG) treated primary retinal endothelial cells contained the same activity that was present in vitreous from patients with proliferative diabetic retinopathy (PDR); like PDR vitreous, HG CM inhibited LPA (lysophosphatidic acid)-mediated regression of retinal neovessels. This is an important discovery because it eliminated two major challenges inherent to PDR vitreous, namely limited availability and heterogeneity. We focused our efforts on identifying the agent in HG CM that is responsible for inducing unresponsiveness to LPA-mediated regression. Although these studies have not been completed, we identified a number of candidates, which provide intriguing insights and opportunities for managing patients afflicted with PDR.

We recently reported that diabetes (DM) activates the RSE (ROS, SFK, Erk) pathway in retinal endothelial cells and thereby antagonizes a signaling enzyme that is required for LPA-mediated regression. This proposal's working hypothesis is built upon these previous findings and posits that PDR vitreous induces unresponsiveness to LPA by engaging the RSE pathway. The following 3 specific aims will test this hypothesis.

1. **Determine whether PDR vitreous activates the RSE pathway.**

2. **Investigate whether pharmacologically targeting members of the RSE pathway overcomes PDR vitreous-induced non-responsiveness to LPA.**

3. **Same as Aim 2, except use a molecular approach.**