AB010. Promotion of BMP9/ALK1 quiescence signaling for the prevention of diabetic macular edema (DME)

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Background: Sight-threatening diabetic macular edema (DME) is caused by increased microvascular permeability. While few direct vascular targeting strategies are available, VEGF pathway inhibition has shown to be effective in reducing retinal vascular leakage but is associated with non-negligible side effects. Thus, more options are needed. Vascular specific Activin-like kinase receptor type I (ALK1) pathway and its circulating ligand Bone morphogenetic protein-9 (BMP9) is known for its potent quiescent and stabilizing effect on the vasculature. However, little is known about this pathway in the context of microvascular permeability associated with diabetes. We hypothesize that BMP9/ALK1 pathway is inhibited in diabetic (DB) retinas leading to vascular destabilization and leakage and that its activation could re-establish proper vascular endothelial barrier functions (EBF).

Methods: The effect of hyperglycemia (i.e., HG >10 mM of D-glucose) on Alk1 signaling was evaluated *in vitro* by subjecting endothelial cells (EC) to increasing concentrations of D-glucose (5, 11, 25 mM) and *in vivo* using DB mice (Streptozotocin-induced diabetes). The contribution of Alk1 signaling on EBF was evaluated using Evans Blue permeation in inducible endothelial specific Alk1 KO mice. To evaluate the potential protective effects of BMP9/Alk1 signaling on EBF, BMP9 overexpression was achieved using adenoviral delivery in DB mice. Statistical-One-Way ANOVA or Student's *t*-test was used.

Results: Endothelial tissue from DB mice showed a significant inhibition of BMP9/ALK1-canonical Smad1,5,8 quiescence signaling (DB n=5; CTL n=4; P<0.01), which was associated with reduced expression of target genes (JAG1, Id1,3, Hey1,2 & HES). Moreover, we showed that retinal hyperpermeability associated with diabetes was exacerbated in Alk1 heterozygote mice (n=4–9/group; P<0.0001). Finally, we demonstrated that activation of Alk1 signaling in ECs prevented vascular permeability induced by HG, both *in vitro* (n=3; P=0.009) and *in vivo* (n=4–9/group; P<0.0001).

Conclusions: Consistent with our hypothesis, vascular stability and quiescence induced by BMP9-ALK1 signaling is inhibited in the DB/HG endothelium which could be an important factor in vascular leakage leading to DME. Our results show that activation of this pathway could offer a therapeutically interesting future option to slow down the onset of DME.

Keywords: Diabetes; retinopathy; diabetic macular edema (DME); vascular permeably

doi: 10.21037/aes.2018.AB010

Cite this abstract as: Akla N, Viallard C, Gil CL, Przemyslaw S, Larrivée B. Promotion of BMP9/ALK1 quiescence signaling for the prevention of diabetic macular edema (DME). Ann Eye Sci 2018;3:AB010.