

AB039. BMP9 signaling maintains endothelial integrity and prevents hyperglycemia-induced retinal vascular permeability

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Background: The maintenance of a quiescent retinal vascular endothelial barrier is paramount for tissue supply and homeostasis to ensure visual function. Chronic hyperglycemia in diabetes causes structural and functional alterations of the endothelium that are accelerated by the production of several mediators such as VEGF. The disturbance of interendothelial junction stability leading to retinal hyperpermeability is one of the changes leading to diabetic macular edema (DME) that can occur at any stage of diabetic retinopathy. Advances in our understanding of the pathophysiological mechanisms of DME have enabled effective new therapies such as anti-VEGF's, which are however associated with non-negligible side effects. The discovery of endothelium-specific protective targets that could restore retinal endothelial quiescence could provide a therapeutic alternative. Signaling mediated by BMP9 circulating protein via its endothelium-specific receptor ALK1, is known for its role in the maintenance of vascular quiescence. However, its ability to protect the endothelium and prevent vascular permeability has not been tested in the context of diabetes.

Methods: We investigated BMP9/ALK1 signalling pathway in the hyperglycemic endothelium and its effect on retinal permeability in a type 1 diabetes mouse model. Hyperglycemic endothelial cells and tissue were extracted to evaluate BMP9/ALK1 signaling. BMP9 overexpression was achieved using adenoviral vectors. Retinal permeability was measured using miles assay.

Results: We found that BMP9/ALK1 signaling was inhibited in hyperglycemic endothelial cells and blood vessels of diabetic (DB) mice, and that this loss of function was directly associated with retinal hyperpermeability. Molecularly, inhibition of this pathway triggers the activation of the VEGFR2/SRC pathway reducing interendothelial adhesion junctions. Conversely, the activation of ALK1 by sustained BMP9 overexpression in DB mice enabled the restoration of physiological permeability by regulating the levels and localization of interendothelial junctions, in part by limiting the action of VEGF signalling. We also observed that BMP9 overexpression demonstrated a regulating effect of blood glucose levels in DB mice. Our results showed that BMP9 significantly ameliorates glucose control over a 4-week span in DB mice and that this regulation was mediated primarily via the ALK3 receptor inhibiting gluconeogenic gene expression and hepatic glucose production and hence hyperglycemia.

Conclusions: Together, our data show that BMP9 acts on several levels to safeguard endothelial integrity preventing retinal hyperpermeability in DB mice. The effects are mediated by its endocrine effect by directly stabilizing the endothelial barrier through Alk1 and its hypoglycemic paracrine/autocrine action in the liver through Alk3. Thus, BMP9 could be used in the development of future therapeutic alternatives against several vascular diseases involving edematous complications.

Keywords: Diabetes; vascular permeability; activin receptor

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