

## **TNF $\alpha$ is Required for Late BRB Breakdown in Diabetic Retinopathy and it Promotes Hyperoxia-Induced Apoptosis in Retinal Vessels and Neurons**

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TNF $\alpha$  has been implicated in the pathogenesis of diabetic retinopathy (DR) and other ocular disorders, primarily through its pro-inflammatory activity. Blood-retinal barrier (BRB) breakdown is significantly increased 6 weeks after the induction of diabetes in C57BL6 mice by streptozotocin. Vascular permeability in the kidney is also increased in diabetic mice at this time. There is no difference in the integrity of the BRB in 6-week diabetic TNF $\alpha$  knockout (KO) mice compared to wild-type diabetic mice, but BRB breakdown is completely prevented in mice diabetic for 6 months in the absence of TNF $\alpha$ . This demonstrates that TNF $\alpha$  is required for later stage BRB breakdown associated with DR, but not for the early BRB breakdown. In addition, TUNEL and activated caspase-3 immunostaining showed that apoptosis is prevented or reduced in vessels in the inner and outer plexiform layers and in retinal ganglion cells, photoreceptors, and neurons in the inner nuclear layer in TNF $\alpha$ (KO) mice exposed to 75% oxygen for 2 weeks. This shows that TNF $\alpha$  inhibition protects retinal vascular cells in the inner and outer plexiform layers and retinal neurons from apoptosis associated with oxidative stress, which has been identified as a contributing factor in the development of age-related macular degeneration. These results suggest that TNF $\alpha$  inhibition could be beneficial for a variety of ocular disorders, particularly those associated with apoptosis and inflammation, such as DR and AMD.