MODULE 5.4
Summary

Chronic hyperglycemia can eventually lead to the development of retinopathy, characterized by vascular permeability changes.[1] This altered vascular permeability may lead to diabetic macular edema (DME), accumulation of fluid within the retina that, if left untreated, can lead to vision loss.[2] Diabetes acts on all retinal cell types including retinal vessels (endothelial), choroidal, Müller (glial), and neuronal cells.[3]

The retina is one of the most metabolically active tissues in the body and its oxygen demand is quite high.[4] Retinal hypoxia, which leads to the uncontrolled growth of new retinal blood vessels, is thought to play a role in the development of diabetic retinopathy (DR).5 A long-term animal model of diabetes (>6 years of diabetes) has demonstrated retinal hypoxia.[6]

DME is thought to be caused primarily by the breakdown of the inner blood-retinal barrier (BRB).[7] Breakdown of the BRB causes a shift in the balance of hydrostatic and oncotic pressure, resulting in the accumulation of fluid within the extracellular space and the development of macular edema.[8]

Some of the earliest changes seen histologically in the retinas of diabetic patients are adhesion of leukocytes to capillaries and accumulation of advanced glycation end products (AGEs).[9] These pathologic changes contribute to activation of inflammatory mediators and eventual endothelial cell (EC) death. The death of these (ECs) contributes to the breakdown of the BRB and can result in a state of ischemia. Breakdown of EC tight junctions also occurs.[7,10] The progression of DR is also associated with the loss of pericytes, which, in turn, may be caused by the accumulation of AGEs and by the effects of inflammatory mediators.[11,12]

Numerous retinal cell types are known to synthesize vascular endothelial growth factor (VEGF), including retinal pigment epithelium (RPE) cells, pericytes, ECs, glial cells, Müller cells, and ganglion cells.[13] VEGF is known to have several functions in the retina including neurotrophic and neuroprotective properties,[14-16] choroid fenestration,[16,17] EC protection,18 RPE integrity maintenance,[19] and oxidative stress protection.[20]

VEGF is also an important link between the neurodegenerative process that occurs in early stages of DR and the breakdown of the BRB.[21] The most important VEGF-mediated actions in the pathogenesis of DR are the breakdown of the BRB and angiogenesis.[22]

References

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