MODULE 5.3
Retinal Cell Types That Produce VEGF

The retina contains two types of glial cells: macroglia and microglia. The Müller cell is the most common macroglial cell type and is unique to the retina.[1] Shaped like a spindle, Müller cells expand across the entire retina. Müller cells are thought to have a key role in the pathogenesis of retinal microangiopathy in the diabetic eye because they produce factors that regulate blood flow, cell survival, and vascular permeability, and their processes surround all blood vessels in the retina.[2] The astrocyte is the less common type of macroglial cell. As it develops, the astrocyte travels along the optic nerve to reach the retina. Astrocytes form a monolayer at the inner limiting membrane.

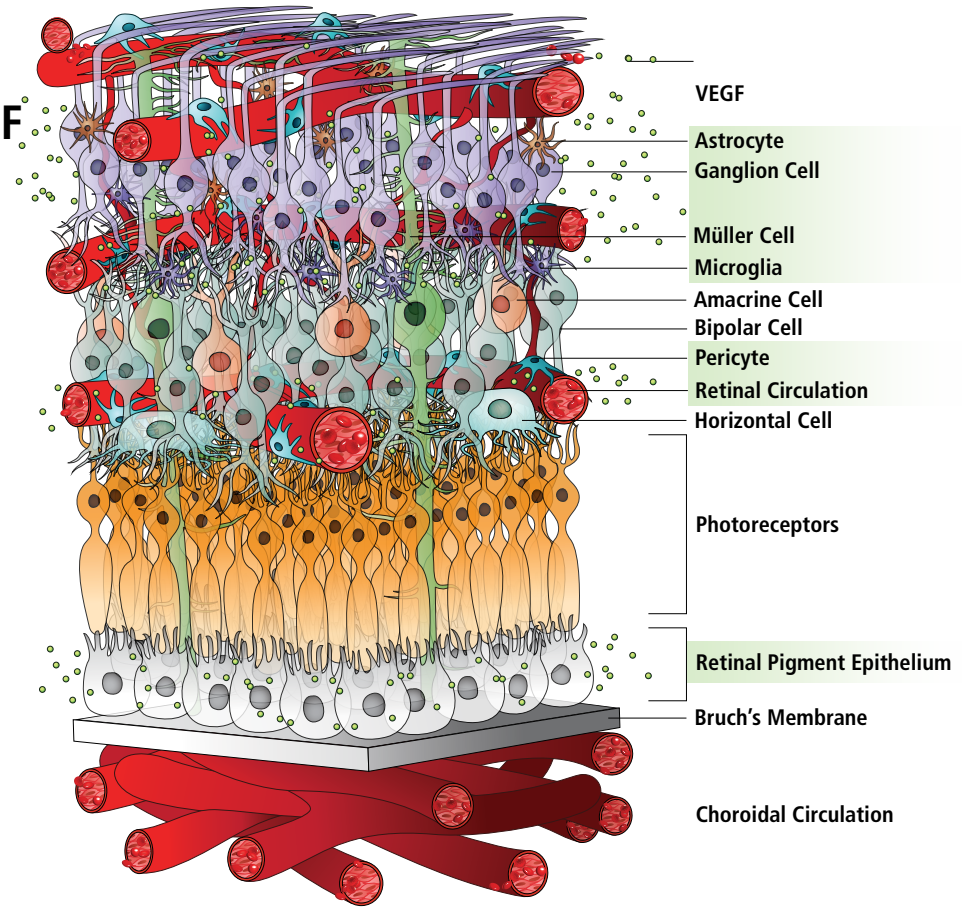
In vivo laboratory data have shown that astrocyte connexin-26 and -43 gene and protein expression decreases after 4 weeks of experimentally induced diabetes and before significant astrocyte loss.[3] During this same period, the retina became hypoxic. These data suggest astrocytes could play a key role in changes in retinal vasculature and inner retinal dysfunction in diabetes.

Under diabetic conditions, microglial cells, the main resident sentinel immune cells located in the inner part of the retina, are activated.[1] They then migrate to the subretinal space and release inflammatory cytokines that contribute to neuronal cell death.[5] The physiologic transcellular migration of activated microglia through the retinal pigment epithelial (RPE) cells in the retina is modulated by chronic elevated glucose.[6] This leads to the subretinal accumulation of activated microglia and/or macrophages. These activated microglial cells adjacent to blood vessels also have a key role in vasoregression, considered the vascular hallmark of the early stages of diabetic retinopathy (DR).[7]

A hallmark pathologic feature of early-stage DR is hyperglycemia-associated breakdown of the inner blood-retinal barrier (BRB), which begins with the loss of tight junctions (TJs) between adjacent microvascular endothelial cells (ECs).[8] This loosening of TJs in the BRB allows macromolecules to leak out. As BRB breakdown progresses, the basement membrane (BM) of the capillaries thickens and the capillaries become rigid.[9]

The loss of pericytes results in empty spaces on the walls of the retinal capillaries.[9] ECs try to repair the damaged vessel by proliferation on the inner vessel wall. At this stage, the disease is generally undetectable clinically. However, as the disease

Retinal Cell Types that Produce VEGF

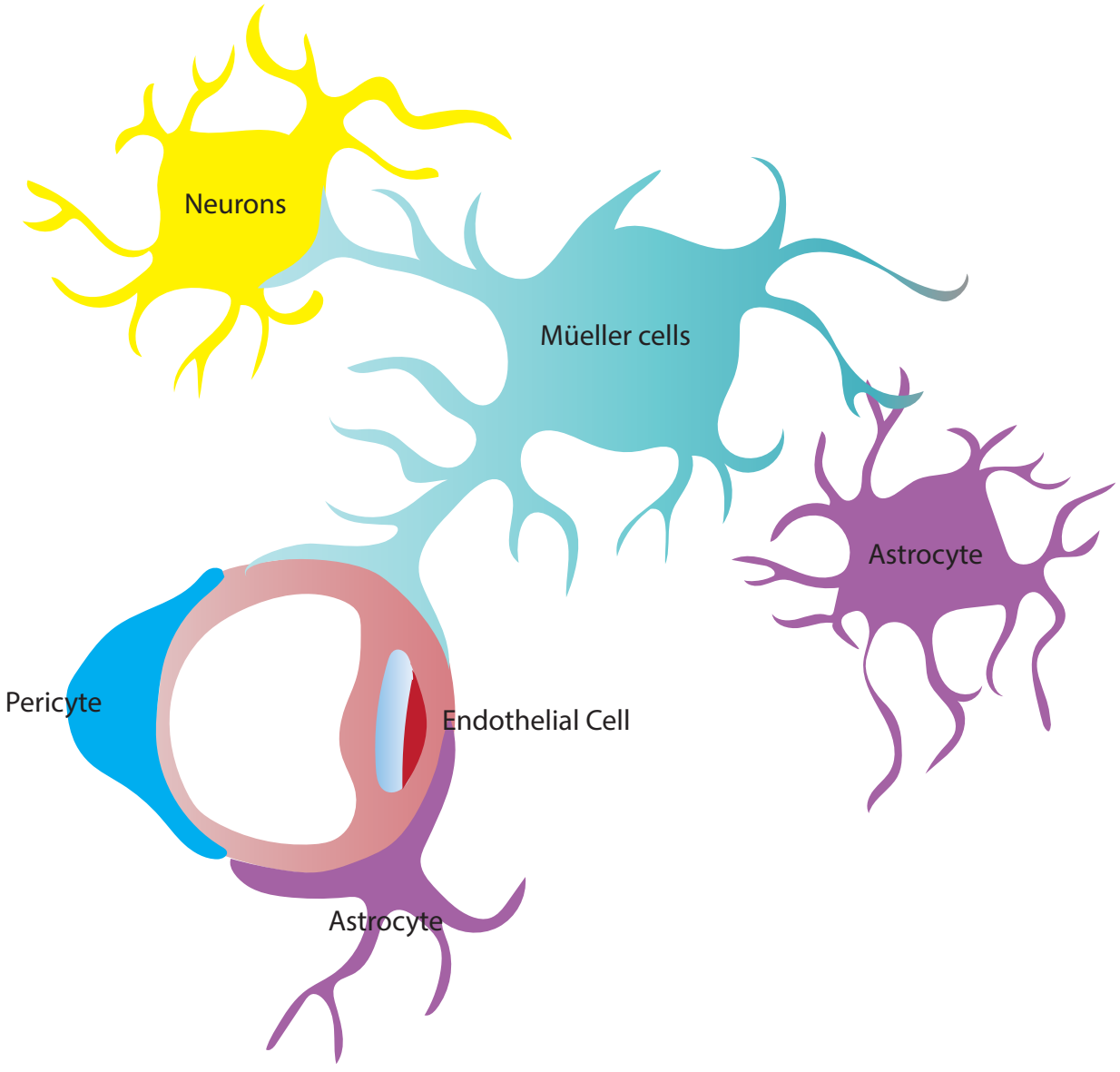


progresses, capillary occlusion and the appearance of small hemorrhages and yellow deposits (hard exudates) occur. These changes are followed by the loss of all cellular elements from the retinal microvessels and the development of abnormally dilated capillaries around the margins of areas with no capillary blood flow (ischemia). These microaneurysms (MAs) are the earliest clinically observable lesion of DR (nonproliferative DR). Without treatment, the disease often progresses into diabetic macular edema (DME). If the disease progresses, the nonproliferative DR may develop into the more severe form, known as preproliferative retinopathy. Ischemia and hypoxia can eventually lead to retinal neovascularization, which is the hallmark of proliferative retinopathy.[10] These new blood vessels are fragile and tend to hemorrhage. They can extend into the vitreous, and their fibrous proliferation into the retina can lead to traction retinal detachment, loss of visual acuity and contrast sensitivity, and ultimately to blindness.[10-14]

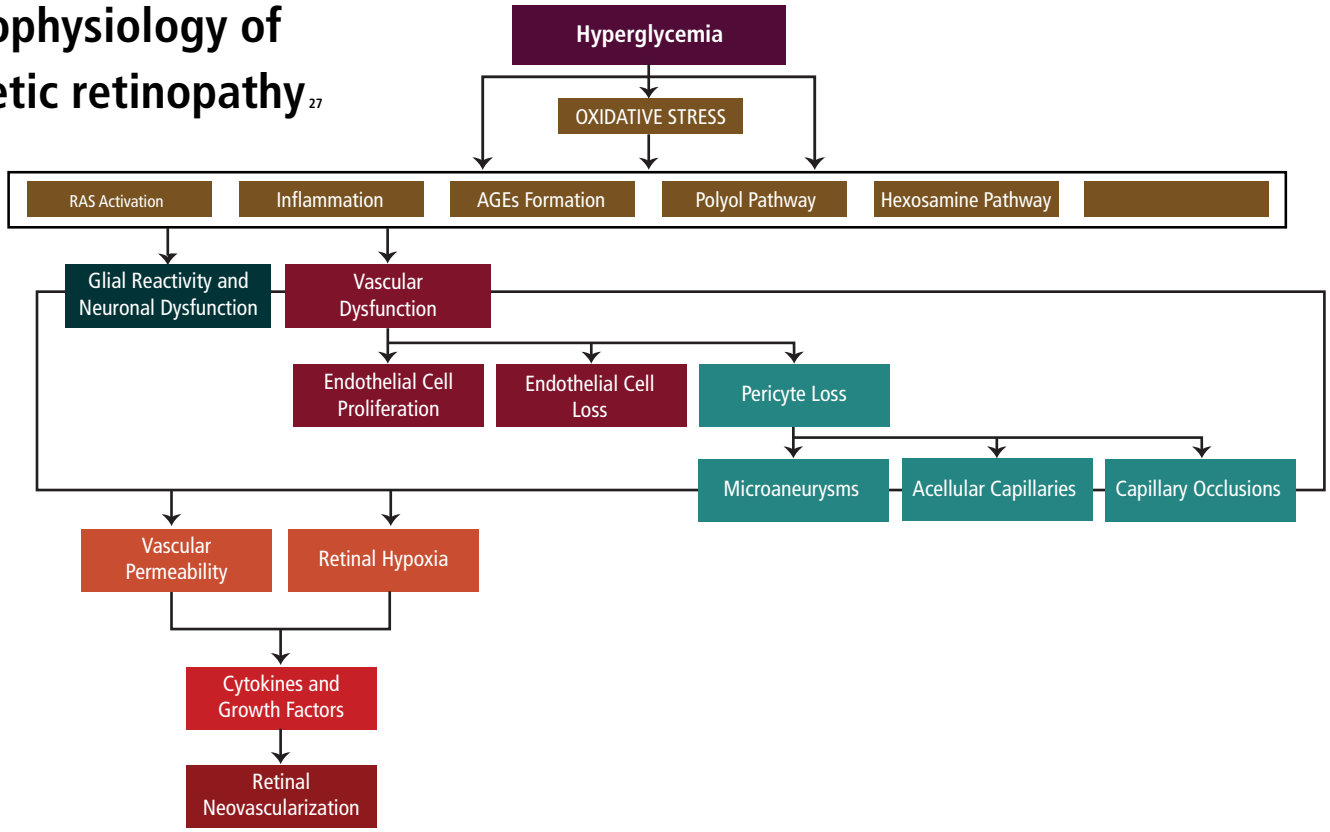
When hypoxia coincides with hyperglycemia, advanced glycation end products (AGEs) are formed.[9] The hyperglycemia-induced intracellular AGE precursors, cause pathologic changes in at least four ways: (1) direct intracellular glycation of proteins; (2) inhibition of enzymes responsible for protein degradation and lysosomal systems; (3) the intracellular AGE precursors can diffuse out of the cell and modify nearby cells, extracellular matrix, such as Bruch's membrane and choroidal capillary membranes; and (4) the intracellular AGE precursors can diffuse out of the cell to modify circulating proteins in the blood, which in turn activate AGE receptors (RAGEs) on proinflammatory cells, resulting in the production of inflammatory cytokines and/or growth factors.[9]

Clinical studies have shown that the concentrations of AGEs in serum,[15-17] skin,[18] and cornea[19] correlate with the onset or

The Retinal Neurovascular Unit[4]



Pathophysiology of diabetic retinopathy[27]



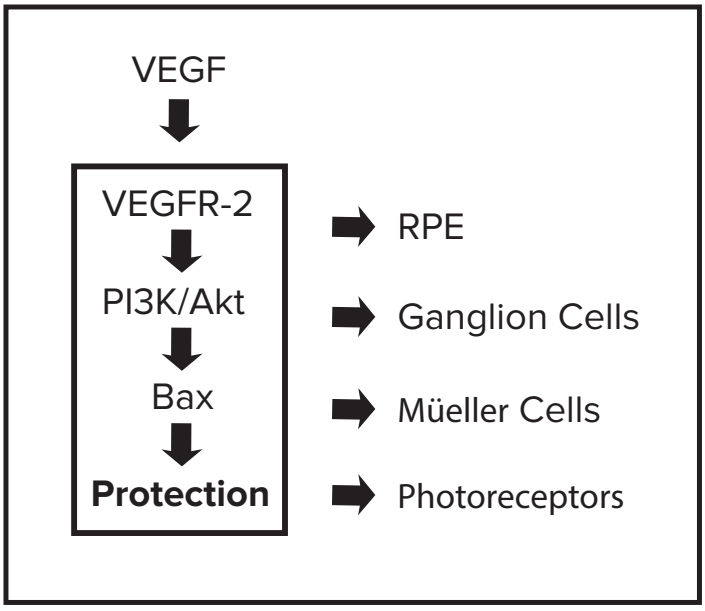
severity of DR. Exposure to AGEs results in several deleterious effects on the retinal vessels, including increasing vasopermeability, neovascularization, and evocation of proinflammatory pathways, etc. Studies have demonstrated that exposure to AGEs, as well as other stimuli including protein kinase C isoform activation, inflammation, and retinal ischemia, causes significant upregulation of vascular endothelial growth factor (VEGF),[20,21] which increases vascular permeability and induces DR-related neovascularization. As a pathophysiologic hallmark of DR, the direct damage of excessive vasopermeability to the retinal microvasculature is the dysfunction of the inner BRB.[22] The increased levels of adhesion molecules on the surface of retinal microvascular ECs can activate proinflammatory pathways. In conjunction with an enhanced stickiness and reduced deformability of blood-borne leukocytes in the diabetic state, this can lead to a marked leukocyte adhesion to retinal vascular endothelium that precipitates capillary occlusion, vascular cell death, and, finally, DR.[23-26]

Numerous retinal cells synthesize VEGF, including RPE cells, pericytes, ECs, glial cells, Müller cells, and ganglion cells.[28] There is also evidence that VEGF has significant neurotrophic and neuroprotective properties.[29-31] VEGF is known to have several functions in the retina, including:

- Fenestration of the choroid[31, 32]
- EC protection[33]
- Neuroprotection (protects photoreceptors)[31]
- Survival and maintenance of RPE integrity[34]
- Müller cell protection[31]
- Oxidative stress protection[35]

VEGF is also an important link between the neurodegenerative process that occurs in early stages of DR and the breakdown of the BRB.[1] The most important VEGF-mediated actions in the pathogenesis of DR are the breakdown of the BRB and angiogenesis.[36]

VEGF provides a protective effect in cells of the retina.[37]



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