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REVIEW

Mechanistic Insights into Pathological Changes in the Diabetic Retina

Implications for Targeting Diabetic Retinopathy

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Increasing evidence points to inflammation as one of the key players in diabetes-mediating adverse effects to the neuronal and vascular components of the retina. Sustained inflammation induces biochemical and molecular changes, ultimately contributing to retinal complications and vision loss in diabetic retinopathy. In this review, we describe changes involving metabolic abnormalities secondary to hyperglycemia, oxidative stress, and activation of transcription factors, together with neuroglial alterations in the diabetic retina. Changes in biochemical pathways and how they promote pathophysiologic developments involving proinflammatory cytokines, chemokines, and adhesion molecules are discussed. Inflammation-mediated leukostasis, retinal ischemia, and neovascularization and their contribution to pathological and clinical stages leading to vision loss in diabetic retinopathy (DR) are highlighted. In addition, potential treatment strategies involving fibrates, connexins, neuroprotectants, photobiomodulation, and anti-inflammatory agents against the development and progression of DR lesions are reviewed. The importance of appropriate animal models for testing novel strategies against DR lesions is discussed; in particular, a novel nonhuman primate model of DR and the suitability of rodent models are weighed. The purpose of this review is to highlight our current understanding of the pathogenesis of DR and to summarize recent advances using novel approaches or targets to investigate and inhibit the retinopathy. *(Am J Pathol 2016, ■: 1–11; http://dx.doi.org/10.1016/j.ajpath.2016.08.022)*

Q5 Diabetic retinopathy (DR) is a major complication of diabetes and is the leading cause of visual impairment and blindness among working-age adults.[1] Patients with DR may lose sight as a result of the development of diabetic macular edema and/or proliferative diabetic retinopathy.

The progression of advanced DR can be inhibited by laser-induced photocoagulation,[2] but this procedure may destroy parts of the retina. Intravitreal injections of anti–vascular endothelial growth factor therapies[3–5] or corticosteroids[6,7] can also appreciably diminish retinal neovascularization and retinal edema, but these injections require frequent visits to a physician and have only transitory beneficial effects in approximately half of treated patients.[3] Use of corticosteroids may have adverse effects, leading to cataract formation and increased intraocular pressure in a significant number of patients[8]; therefore, its clinical use is limited.

The early stages of DR can be inhibited by improvement of glycemic control using either insulin or oral agents,[9,10] but this control remains difficult or impossible for many diabetics to achieve and maintain. Thus, there has been considerable effort to identify specific pharmacological targets to inhibit the development of retinopathy. Inhibitors of protein kinase C, aldose reductase (AR), nonenzymatic glycation, and vascular endothelial growth factor comprise just a few of the

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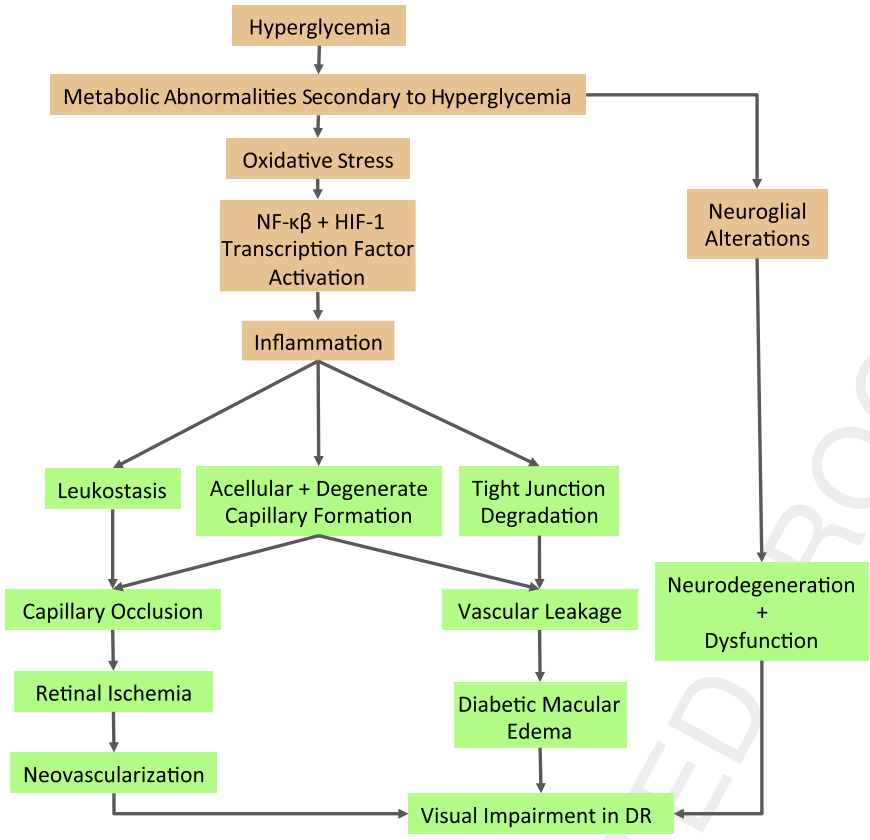

Figure 1 Effects of hyperglycemia (HG) on biochemical pathways and inflammation in diabetic retinopathy (DR) pathogenesis. In the HG condition, metabolic abnormalities secondary to hyperglycemia contribute to neuroglial alterations that can lead to neurodegeneration and dysfunction. Increased oxidative stress can promote NF-κB and hypoxia-inducible factor (HIF)-1 activation. In addition, increased activity of proinflammatory cytokine, chemokine, and adhesion molecule can result in tight junction degradation and acellular capillary formation. Leukostasis contributes to capillary occlusion and can lead to retinal ischemia. Diabetes-induced macular edema, and neovascularization, all significant pathological events in DR. The **orange boxes** represent stages leading to the development of retinal vascular lesions; **green boxes**, pathological and clinical stages leading to vision loss in DR.

candidates that have been investigated as therapeutic targets against DR, but anti−vascular endothelial growth factor therapy has been unique among pharmacological approaches in showing efficacy in diabetic patients. Therapies developed for conditions other than diabetes or retinopathy, such as blood pressure medications[11] and fibrates,[12] also are reported to have beneficial effects on DR, although again only in a subset of diabetic patients. Thus, available therapies for DR are not equally effective in all patients.

Targets of DR Lesions for Which Treatment Is Needed

Major causes of clinically significant vision loss due to diabetes are generally accepted to be vascular in origin and include retinal edema and preretinal lesions, such as neovascularization, fibrovascular membranes, and hemorrhages. Vascular permeability, local ischemia, and preretinal neovascularization thus have a clear relationship to visual impairment in DR, and are appropriate targets for DR treatment.

Retinal neurons also are adversely affected in diabetes. They become dysfunctional, as evidenced by diabetes-induced changes in electroretinogram, contrast sensitivity, visual acuity, and color sensitivity, and these defects can impair the quality of vision. However, whether the functional defects or the death of retinal neurons contributes to clinically meaningful loss of vision in diabetes is not yet clear. Although many publications attribute the adverse effects of diabetes to neurodegeneration, it is not clear that cell death is the culprit, as opposed to less obvious metabolic or functional defects within remaining neurons. Thus, retinal neurons also might be a therapeutic target to inhibit the retinopathy and accompanying visual impairment or loss. More important, evidence is accumulating that a specialized kind of retinal neuron (photoreceptors) plays an important role in the diabetes-induced degeneration of retinal capillaries, which can subsequently lead to retinal neovascularization. These topics are discussed below.

Mechanisms Implicated in the Pathogenesis of DR

Although hyperglycemia has been demonstrated to initiate the pathology of DR, appreciable evidence suggests that oxidative stress and inflammatory changes in the retina play critical steps in the pathogenesis of the hyperglycemia-induced retinopathy (Figure 1). Recently, proinflammatory [F1] lipids,[13] epigenetic and epigenomic modifications,[14] insulin dysregulation,[15] and β-cellulin signaling,[16] which initiate and contribute to DR pathogenesis independently from hyperglycemic condition, have been identified.

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