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Inflammation and Diabetic Retinopathy

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1. Introduction

Diabetic retinopathy (DR) is the leading cause of blindness in working-age individuals. There is increasing evidence that established risk factors for DR, including duration of diabetes, hyperglycemia, and hypertension, only explain a limited amount of the variance in the risk of DR. Furthermore, the underlying pathogenesis of DR remains inadequately understood. Diabetes causes metabolic and physiologic abnormalities in the retina, and these changes suggest a role for inflammation in the development of DR. These changes include up regulation of isoforms of nitric oxide synthase (iNOS), cyclooxygenases (COX)-2, intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor (VEGF), nuclear factor kappa B (NF-κB), increased production of nitric oxide, prostaglandin E2, interleukin (IL)- 1β, and cytokines, as well as increased permeability and leukostasis.

Using selective pharmacologic inhibitors or genetically modified animals, an increasing number of therapeutic approaches have been identified that significantly inhibit development of at least the early stages of diabetic retinopathy, especially occlusion and degeneration of retinal capillaries. A common feature of a number of these therapies is that they inhibit production of inflammatory mediators. The concept that localized inflammatory processes play a role in the development of diabetic retinopathy is relatively new, but evidence that supports the hypothesis is accumulating rapidly. The focus of this chapter is on the inflammatory nature of many of the molecular and cellular processes leading to this vascular damage, as well as on the pathologic neovascularization that often accompanies it. Finally, clinical findings validating the role of inflammation in DR are described.

2. An inflammation in the early performance of diabetic retinopathy

Diabetic retinopathy classically has been regarded as a disease of the retinal microvasculature, and the natural history of the disease has been divided into an early, nonproliferative (or background) stage, and a later, proliferative stage. It is becoming appreciated also that cells of the neuroretina also are affected in diabetes. A number of metabolic or molecular abnormalities that are characteristic of inflammation have been detected in retinas of diabetic animals or patients, or in retinal cells exposed to elevated concentrations of glucose. Histologically, vascular lesions in the early stages of diabetic retinopathy in man and animals are characterized by the presence of saccular capillary microaneurysms, pericyte deficient capillaries, and obliterated and degenerate capillaries. These degenerate capillaries are not perfused, and so increases in their frequency represent reductions in retinal perfusion.

Capillary occlusion and degeneration initially occurs in single, isolated capillaries, and has no clinical importance when only few capillaries have become nonperfused. As more and more capillaries become occluded, however, retinal perfusion likely decreases, at least locally. Mechanisms believed to contribute to the degeneration of retinal capillaries in diabetes include occlusion of the vascular lumen by white blood cells or platelets, death of capillary cells secondary to biochemical abnormalities within the vascular cells themselves, or capillary cell death secondary to products generated by other nearby cells (such as neurons or glia). All species studied today have been found to show degeneration of retinal capillaries as well as death of pericytes and endothelial cells, but microaneurysms are not commonly found in rodent models of diabetic retinopathy. Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Inflammation typically has beneficial effects on an acute basis, but can have undesirable effects if persisting chronically. The increased expression of many inflammatory proteins is regulated at the level of gene transcription through the activation of proinflammatory transcription factors, including NF-κB. These proinflammatory transcription factors are activated and play a critical role in amplifying and perpetuating the inflammatory process. Transcription factors associated with production of proinflammatory mediators include NF-κB, activator protein 1 (AP-1), specificity protein 1 (Sp1), peroxisome proliferator-activated receptors (PPARs) and other members of the nuclear receptor superfamily. Proinflammatory proteins (including COX-2, interleukin-1, tumor necrosis factor alpha) can contribute to cell damage and death in tissues including brain and retina, at least in part via activation of NF-κB (Fig.1.).

2.1 NF-κB

NF-κB is a widely expressed inducible transcription factor that is an important regulator of many genes involved in mammalian inflammatory and immune responses, proliferation and apoptosis. Evidence in support of an important role of NF-κB in the pathogenesis of early stages of diabetic retinopathy is twofold. First, inhibition of proteins whose expression is regulated by NF-κB (such as iNOS and ICAM) inhibit diabetes-induced degeneration of retinal capillaries. Second, compounds known to inhibit NF-κB likewise inhibit the development of the retinopathy. For example, several different antioxidants which inhibit the development of capillary degeneration and pericyte loss in retinas of diabetic rats also inhibit the diabetes-induced activation of retinal NF-κB. Likewise, low-intermediate doses of salicylates (aspirin, sodium salicylate, and sulfasalazine) which inhibited NF-κB activation in retinas of diabetic rats, also inhibited expression of inflammatory mediators like iNOS and ICAM-1, and capillary degeneration and pericyte loss in those animals. Aspirin is known to inhibit also production of prostaglandins, but salicylate and sulfasalazine have much less of this activity, suggesting that the common action of these 3 salicylates to inhibit retinopathy in diabetes was not primarily mediated by inhibition of prostaglandins.

Our experiments showed that Ubiqutin-proteasome system can influence the occurrence and development of DR by regulating NF-κB and IκB expression. Application of MG 132, ubiqutin-proteasome inhibitor, can inhibit the ubiquitination of IκB degradation, and block the activation of NF-κB, which may play an early intervention role in DR.

2.2 iNOS

iNOS expression is regulated at least in part by NF-κB. Interestingly, experimental sympathectomy itself increases gene and protein expression of iNOS in retinas of nondiabetic rats, suggesting that loss of sympathetic activity, such as which occurs in diabetes, might contribute to the upregulation of this inflammatory protein in the retina. In retinas of diabetic animals, increased levels of nitric oxide products (nitrotyrosine, nitrite, nitrate) have been reported. Upregulation of iNOS has been found in retinas of experimental diabetic rodents and patients in most studies. Diabetes-induced alterations inexpression of other isoforms of nitric oxide synthase also have been reported. A possible role of iNOS in the pathogenesis of diabetic retinopathy is suggested by the studies of aminoguanidine. Aminoguanidine is a relatively selective inhibitor of iNOS, and has been found to inhibit the diabetes-induced increase nitric oxide production and iNOS expression in retina. Aminoguanidine also has been found to inhibit the development of the microvascular lesions of diabetic retinopathy in diabetic dogs, rats, and mice. Nevertheless, aminoguanidine also has other effects, so this therapy does not absolutely prove a role of iNOS in the pathogenesis of the retinopathy. The role of iNOS in the development of the early stages of diabetic retinopathy recently has been investigated directly using mice genetically deficient in iNOS. In that study, wildtype diabetic mice developed the expected degeneration of retinal capillaries, as well as increase in leukostasis and superoxide generation. In contrast, diabetic mice deficient in iNOS did not develop these structural or functional abnormalities. eNOS expression also has been reported to be elevated in the retinas in the diabetic rats, and it has been suggested that eNOS might play a role in the development of diabetes-induced leukostasis and/or retinopathy. This posibility has not been experimentally addressed due, in part, to the hypertension that results in the absence of eNOS, as well as a lack of specific inhibitors of the enzyme.

2.3 Cyclooxygenases

COX-2 expression is regulated at least in part by NF-κB. In retinas of diabetic animals, induction of COX-2 as well as increased production of prostaglandins has been reported. Researchers have shown that PGE_2 production by retinas from diabetic rats was significantly inhibited by celecoxib (a selective COX-2 inhibitor), but not by a COX-1 inhibitor, suggesting that COX-2 is primarily responsible for the diabetes-induced increase in retinal production of PGE_2 in diabetic rats. Inhibition of COX-2 has been reported to inhibit the diabetes-induced upregulation of retinal prostaglandins and VEGF, the increase in retinal vessel permeability and leukostasis, and the death of retinal endothelial cells cultured in diabetic-like concentrations of glucose. The COX-2 inhibitor, Meloxicam, also reduced eNOS levels, inhibited NF-κB activation in the diabetic retina, and modestly, but significantly, reduced TNFα levels in the retina. Its effect on histologic lesions of diabetic retinopathy was not studied. Less selective COX inhibitors have inhibited the development of the retinopathy in diabetic dogs and rodents, as well as the increase in vascular permeability in diabetic rodents. Nepafenac is an inhibitor of cyclooxygenases that can be applied in eye drops. It was found to inhibit diabetes-induced prostaglandin production and leukocyte adhesion in retinal vessels of diabetic rats, and the diabetes-induced increase in the number of TUNEL-positive capillary cells, acellular capillaries, and pericyte ghosts in the retina.

Micro RNAs (miRNAs) are a class of highly conserved, small non-coding RNAs that powerfully regulate gene expression at the posttranscriptional level. A growing number of

reports have established a link between miRNAs and DR in recent years. Kovacs B et al. proposed upregulation of NF-κB-, VEFG-, and p53- responsive miRNAs constituted key miRNA signatures, reflecting ongoing pathologic changes of early DR. But the exact roles of miRNAs in DR are still unknown. Our teams are still devoting the study of differentially expressed miRNA of human retinal capillary endothelial cells in high glucose environment by miRNA gene chip.(Table 1,2)

miRNAs	倍数	miRNAs	倍数
hsa-miR-886-5p	4.73	hsa-miR-93	2.18
hsa-miR-147b	4.52	hsa-miR-148b	2.17
hsa-miR-886-3p	3.62	hsa-miR-455-3p	2.17
hsa-miR-18a	2.92	hsa-miR-130b	2.16
hsa-miRPlus-F1147	2.74	hsa-miR-1265	2.14
hsa-miR-200a	2.69	hsa-let-7f	2.14
hsa-miR-185	2.63	hsa-miR-195	2.11
hsa-miR-155	2.58	hsa-miR-19b	2.09
hsa-miR-106b	2.42	hsa-miR-320b	2.09
hsa-miR-320c	2.28	hsa-miR-505*	2.05
hsa-miR-320d	2.28	hsa-miR-151-3p	2.05
hsa-miR-10a	2.28	hsa-miR-20a	2.04
hsa-miR-1913	2.25	hsa-miR-98	2.03
hsa-miR-374b	2.24	hsa-miR-500	2.02
hsa-miR-29a*	2.23	hsa-let-7d	2.02
		hsa-miR-101	2.02

Table 1. The up-regulated miRNA（Fold change>2) A: Normal control group B: High glucose group

miRNAs	倍数
hsa-miR-483-3p	0.16
hsa-miRPlus-E1238	0.23
hsa-miR-365*	0.23
hsa-miR-943	0.26
hsa-miR-1908	0.29
hsa-miR-3202	0.33
hsa-miR-1246	0.36
hsa-miRPlus-E1077	0.36
hsa-miRPlus-E1285	0.38
hsa-miRPlus-F1099	0.44
hsa-miR-491-3p	0.44
hsa-miR-765	0.45
hsa-miRPlus-F1155	0.46
hsa-miRPlus-E1153	0.48
hsa-miRPlus-F1026	0.48
hsa-miR-513a-5p	0.49
hsa-miR-1264	0.49
hsa-miRPlus-E1133	0.49

Table 2. The down-regulated miRNAs(Fold change<0.5) A: Normal control group B: High glucose group

3. Leukocyte activation and endothelial cell injury

Attraction and adhesion of leukocytes to the vascular wall are important components of inflammatory processes. This leukostasis has been found to be significantly increased in retinas of diabetic animals, and might contribute to the capillary nonperfusion in diabetic retinopathy. Leukocyte stiffness has been reported to be increased in diabetes (decreased filterability) and to contribute to the development of capillary nonperfusion in retinal vessels. A second line of evidence shows that abnormal leukocyte adherence to retinal vessels in diabetes occurs via adhesion molecules.

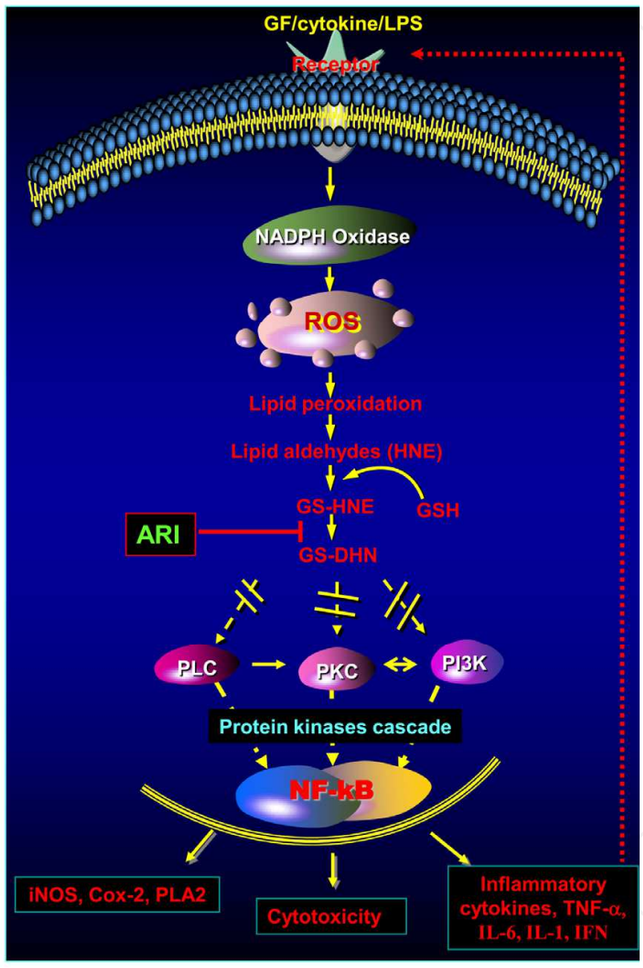

Fig. 1.Role of aldose reductase in mediation of inflammatory signals. Cytokines, growth factors (GF), and lipopolysaccharide (LPS) cause oxidative stress via generation of ROS which forms toxic lipid aldehydes such as HNE by lipid peroxidation. HNE being highly electrophilic conjugates with cellular glutathione (GSH) spontaneously or catalyzed by GST to form GS-HNE. The reduced products of GS-aldehydes, GS-DHN, transduce inflammatory signaling via cascade of protein kinases leading to activation of NF-κB. Activation of NF-κB transcribes genes responsible for various inflammatory pathologies.（Reproduced from Int J Biochem Cell Biol. 2010 January ; 42(1): 17–20. doi:10.1016/j.biocel.2009.09.009.）

Diabetes increases expression of ICAM-1 in retinas of animals and humans and interaction of this adhesion molecule on retinal endothelia with the CD18 adhesion molecule on monocytes and neutrophils contributes to the diabetes-induced increase in leukostasis within retinal vessels. Leukostasis has been postulated to be a factor in death of retinal endothelial cells in diabetes. Using in situ perfusion methods, evidence consistent with capillary occlusion secondary to leukostasis has been observed in occasional retinal vessels, but it is unclear whether this occurred in vivo or was an artifact caused by the perfusion in vitro. Retinas from diabetic mice lacking ICAM-1 and CD18 are protected from the development of diabetes-induced increase in leukostasis, vascular permeability, and degeneration of retinal capillaries, showing these proteins to be important in the development of early stages of diabetic retinopathy. Whether their role in the development of the retinal disease results from capillary occlusion or some other mechanism, however, has not been explored.

In experimental studies employing rodent models of diabetes, diabetic retinal vascular leakage, capillary nonperfusion, and endothelial cell damage are temporally and spatially correlated with a low-level leukocyte influx and persistent retinal leukostasis. This leukostasis is mediated by retinal upregulation of ICAM-1, together with an increased expression of its cognate integrin ligands on neutrophils. Subsequently, endothelial cell injury and death result from Fas/FasL-mediated apoptosis.

In response to this injury, the endothelium maintains a sustained high rate of cell division, which is believed to result in exhaustion of its regenerative capacity. This stress is further exacerbated by a diabetes-induced defect in the ability of endothelial precursor cells to repair the damaged vasculature. While the vascular damage is primarily a function of infiltrating leukocytes, DR is also associated with ischemic neovascularization, a process that is amplified by the influx of macrophages.

4. Causes of inflammation

4.1 Vascular Endothelial Growth Factor (VEGF)

VEGF is a proinflammatory molecule that plays a well-recognized role in neovascularization and in increased permeability. VEGF expression is regulated largely by hypoxia, but it also accumulates in the retina early in diabetes, before any retinal hypoxia is yet apparent. It is produced by multiple cell types in the retina in diabetes, including ganglion cells, Müller cells, and pericytes. Repeated injections of high concentrations of VEGF in the eyes of non-diabetic monkeys result in retinal changes which in some ways resemble those in the early stages of diabetic retinopathy, including vascular tortuosity and microaneurysms.

4.2 Tumor Necrosis Factor-α (TNF-α)

The levels of several proinflammatory cytokines including IL-1β, TNF-α, IL-6, and IL-8 are increased in the vitreous of patients with proliferative diabetic retinopathy and in retinas from diabetic rodents. Inflammation is one of the processes implicated in the apoptosis of retinal cells , and TNF-α is considered as an important mediator of apoptosis of retinal endothelial cells in diabetes.

Evidence supporting a role for TNF-α in DR comes from studies demonstrating elevations of TNF-α in ocular fibrovascular membranes, platelets, and plasma or serum of patients

with DR. Vitreous elevations in TNF-α in patients with proliferative DR were reported in one study, although another study found no difference in the vitreous levels of TNF-α between those with proliferative DR and those with noninflammatory retinopathies. The susceptibility to diabetic retinopathy has been associated with TNF-α gene polymorphism and expression of HLA-DR3 and HLA-DR4 phenotypes. In addition, TNF-α is found in the extracellular matrix, endothelium, and vessel walls of fibrovascular tissue of eyes with proliferative diabetic retinopathy.

Eternacept is a soluble TNF-α receptor that acts as competitive inhibitor to block effects of TNF-α binding to cells. Eternacept reduced leukocyte adherence in retinal blood vessels of diabetic rats for 1 week compared to control. Eternacept did not reduce retinal VEGF levels, but it inhibited blood-retinal barrier breakdown and NF-κB activation in the diabetic retina.

4.3 Inter-cellular Adhesion Molecule 1 (ICAM-1)

White blood cells bind to ICAM-1 on the surface of endothelial cells as a component of a multistep process leading to adherence of the white blood cell to the endothelial wall. ICAM-1 is a peptide known to mediate leukocyte adhesion and transmigration. ICAM-1 may be operative in the stasis observed in diabetic retinopathy, because ICAM-1 immunoreactivity is increased in the diabetic retinal vasculature of humans.

ICAM-1 is upregulated by several stimuli, including VEGF, PARP activation, oxidative stress, and dylipidemia, at least in part by NF-κB.

4.4 Endothelin-1(ET-1)

ET-1 is one of the strongest vasoconstrictive factors. The DAG/PKC pathway determines blood flow dysregulation by decreasing endothelial NOS activity and/or increasing the synthesis of ET-1. Observations indicate that the participation of endothelin in coagulation disorders is also essential for the development of proliferative diabetic retinopathy (PDR). Some studies point out the fact that thrombosis in the rat microcirculation and a DIC-like process in the rabbit circulation develop under the influence of ET-1. An important element in the development of this disturbance is the documented mitogen-activated protein (MAPK kinase)-dependent ET-1 production. Another study has found that the molecular function of ET-1 and PKC is predicted. According to this study, different pathways can be derived from ET-1 and PKC; however, ET-1–PKC produces the same pathway as PKC. This could mean that the interaction between ET-1 and PKC results in increased activity of the PKC pathway but does not generate any new pathway.

4.5 IL-6

Clinical reports show that IL-6 in the vitreous fluid increases not only in uveitis but also in diabetic retinopathy, retinal vein occlusion, and retinal detachment. Research with experimental animals has shown that diffusible factors, IL-6 and other proteins in the IL-6 family, such as leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF), are expressed in the retina. Both IL-6 and LIF are found in Müller glial cells, and CNTF is found in the retinal ganglion cells and astrocytes around the vessels. These endogenous IL-6 family proteins are upregulated during inflammation and function to promote pathogenesis of the vascular system.

IL-6 family proteins use cytokine-specific receptors to activate a transmembrane receptor, gp130, which then recruits Janus kinase (JAK) to activate transcription factor signal transducer and activator of transcription 3 (STAT3). STAT3 then regulates various molecules at the transcriptional level, including suppressor of cytokine signaling 3 (SOCS3). SOCS3 acts as a negative feedback modulator of STAT3 by inhibiting JAK and subsequent STAT3 activation. In the retina, SOCS3 is expressed in the photoreceptor cells, Müller glial cells, and retinal ganglion cells, and it inhibits STAT3 activation in these cells. Since STAT3 activation induces further STAT3-activating factors, such as the IL-6 family ligands, the balance between STAT3 activation and SOCS3 level is one of the key determinants of an inflammatory reaction.

5. Anti-inflammatory and effects of anti-inflammatory drug treatment

5.1 Glucocorticoid

Glucocorticoids are well-established anti-inflammatory compounds that may be effective in reversing or preventing the progression of macular edema, and are currently under investigation as a therapy for diabetic retinopathy. Glucocorticoids are effective at reversing VEGF-induced permeability in animal models. In addition to the anti-inflammatory effect of glucocorticoids, our laboratory has demonstrated that these steroids also induce the synthesis and assembly of tight junctions and the dephosphorylation of occluding commensurate with a reduction in endothelial permeability. Recent work revealed the presence of a novel enhancer element unlike the canonical glucocorticoid response element, in the occludin promoter that controls glucocorticoid responsiveness of this gene (manuscript submitted). Future studies may reveal more specific means to control expression of the tight junction proteins and barrier properties.

5.2 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medications worldwide. Aspirin and other chemically related compounds, used systemically for many decades for their analgesic, antipyretic, and anti-inflammatory properties, have more recently been prepared in topical ophthalmic formulations. As such, they have proven useful to enhance mydriasis, reduce postoperative inflammation, and prevent and treat cystoid macular edema (CME) associated with cataract surgery. In addition, they can be used to decrease pain and photophobia after refractive surgery and to alleviate itching associated with allergic conjunctivitis.The development of NSAIDs that preferentially inhibit COX-2 provides the potential for relieving pain and inflammation without the adverse effects of COX-1 blockade, but the advantages of this approach have been questioned. Although COX-2 inhibitors may reduce gastro-intestinal toxicity, they appear to have equivalent nephrotoxicity to conventional NSAIDs.

5.3 VEGF drugs for VEGF in the PDR

Both clinical and preclinical findings have implicated VEGF in the pathophysiology of diabetic retinopathy. The VEGF family, which includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor, plays an important role in angiogenesis and vascular permeability.

Three anti-VEGF pharmacologic agents are currently available commercially. Pegaptanib is a paginated aptamer that targets the VEGF165 isoform. It has been shown to inhibit VEGF's endothelial mitogen activity and its vascular permeability effects. The US Food and Drug Administration (FDA) has approved Macugen for the treatment of neovascular AMD. The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial established its safety and efficacy in neovascular AMD. Ranibizumab is a recombinant, humanized antibody fragment that binds all isoforms of VEGF, whereas bevacizumab (Avastin, Genentech, Inc.) is a recombinant, full-length, humanized antibody that also binds all VEGF isoforms. Lucentis is currently FDA-approved for neovascular AMD, while Avastin is used on an off-label basis for a variety of ophthalmic conditions. Large clinical trials of Avastin are currently underway for AMD, DME, and vein occlusions, but the safety and efficacy of Avastin for intraocular use remains to be demonstrated.

6. Conclusions

Acquired visual impairment of DR is the consequence of diabetic blood-retinal barrier breakdown. Peroxisome proliferator-activated receptor-gamma excitomotor (PPAR-γ), rosiglitazone, lessened much more of the pericytes, and decreased the number of proliferative endothelial cells with the lower permeability value of the blood-retinal barrier in our DM model rats research, induced by streptozotocin (STZ).

Diabetic retinopathy is a common microvascular complication in the eyes of diabetic individuals. Besides its serious threat to vision, the presence of retinopathy also signifies an excess risk of morbidity and mortality attributable to systemic micro and macrovascular disease. Numerous defects that develop in retinas as a result of diabetes are consistent with diabetes-induced inflammatory response in that tissue. These inflammatory changes apparently are important in the pathogenesis of diabetic retinopathy, since inhibition of this inflammatory cascade at any of multiple steps can inhibit the early stages of diabetic retinopathy in animals. Findings of diabetes induced inflammatory changes, generally, in the human eye also, are consistent with the postulate that inflammatory processes contribute to the development of diabetic retinopathy. The evidence in diabetic animals is sufficient to warrant further investigations of the role of inflammation in the development of diabetic retinopathy in patients.

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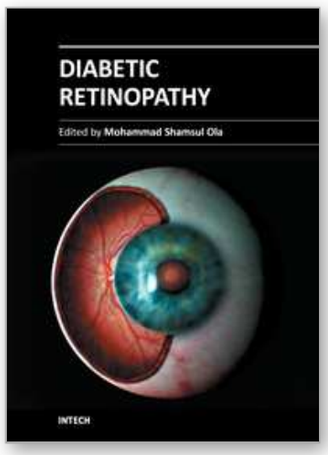

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The aim of this book is to provide a comprehensive overview of current concepts in pathogenesis, diagnosis and treatments of diabetic retinopathy. It provides a collection of topics written by excellent authors, covering discussions on advances in understanding of pathophysiology, immunological factors and emerging concepts, relating to clinical aspects and treatment strategies. The contents of the book will not only provide a resource for our knowledge but also improve diagnosis and treatment options for those patients who suffer vision loss due to diabetic retinopathy.

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