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Review Article

Current perspectives on the pathogenesis, molecular pathways, and therapeutic targets in diabetic retinopathy

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ABSTRACT

Diabetic retinopathy (DR) is a serious sight-threatening complication that occurs due to constant hyperglycemia. It is the most common and leading cause of vision impairment worldwide. The development and progression of DR involve a complex network of genetic and environmental factors. Vascular inflammatory pathways, oxidative stress and epigenetic modifications have been linked to the development of diabetic mediated retinopathy. Candidate gene studies have implicated variants in genes involved in glucose metabolism such as (ALR2), vascular regulation (VEGF) are closely associated with DR susceptibility. Hyperglycemia triggers several factors such as polyol pathway, advanced glycation end-products (AGEs) formation, activation of protein kinase C (PKC), dysregulation of the renin-angiotensin system (RAS). These pathways collectively induce oxidative stress, inflammation, vascular dysfunction and pathological angiogenesis that further intensify microvascular lesions resulting in DR pathogenesis. Emerging therapeutic strategies present anti-VEGF agents, PKC inhibitors, and drugs modulating RAS system. In addition, targeted medicine based on genetic risk profiling and novel gene therapy approaches hold great promise in DR treatment. Further research integrating multi-omics data, gene-environment interactions, and precise translational studies are required for improving DR management and associated risk factor.

Keywords: Gene editing, Hyperglycemia, ROS, PKC inhibitors, VEGF, Vascular leakage

INTRODUCTION

Diabetic retinopathy (DR) is a microvascular complication of diabetes which affects the peripheral retina and macula greatly. It is the leading cause of vision impairment worldwide. Approximately one-third of individuals suffering with diabetes develop DR, with an overall prevalence of 34.6% globally.[1] The DR pathogenesis involves retinal microvascular changes such as capillary basement membrane thickening, endothelial cell dysfunction and aberrant neovascularization of retina. Chronic hyperglycemia triggers multiple molecular cascades that collectively contribute to the onset and progression of DR.[2] The polyol pathway, driven by the enzyme aldose reductase (AR) plays a significant role in the development of DR. In this pathway, excess glucose in the diabetic state is converted to sorbitol, and its accumulation within retinal cells leads to osmotic stress, oxidative damage, and other detrimental effects that contribute to retinal damage (Figure 1). A study demonstrated that diabetic rats exhibited elevated retinal AR activity, leading to increased oxidative stress,

upregulation of inflammatory cytokines (TNF-α, ICAM-1), and enhanced retinal leukostasis. These pathogenic changes were significantly attenuated by AR inhibition using sorbinil, confirming the direct contribution of the polyol pathway to retinal oxidative stress, inflammation, and vascular dysfunction in DR.[3] Another pathway involves the activation of protein kinase C (PKC) isoforms, particularly PKC-β, which alters retinal blood flow, increases vascular permeability, and promotes neovascularization through modulation of endothelial nitric oxide synthase and vascular endothelial growth factor (VEGF) expression. Study mentions that PKC activation contributes to retinal vascular dysfunction by disrupting the activity of key enzymes. In endothelial cells, it affects nitric oxide (NO), endothelin-1 (ET-1), and VEGF. In pericytes, it alters the function of platelet-derived growth factor (PDGF), increases reactive oxygen species (ROS), and activates signaling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK).[4] In diabetic nephropathy, vascular contractile responses become more sensitive. Studies in diabetic mice have shown a marked increase in phenylephrine-triggered contraction of the interlobar artery (ILA), leading to impaired ILA function. This dysfunction compromises glomerular blood flow, thereby accelerating the development of diabetic nephropathy. Administration of rottlerin, an inhibitor of calcium-independent protein kinase C delta (PKC-δ), effectively reduced the excessive baseline contraction.[5] In parallel, hyperglycemia induces epigenetic modifications such as DNA methylation and histone alterations, which suppress the expression of antioxidant defense genes like Sod2 and enhance the transcription of matrix-degrading enzymes such as MMP-9, leading to oxidative stress and extracellular matrix remodeling in the retina.[6] It has been observed that elevated glucose levels increase DNA methyltransferases (DNMTs) activity, resulting in hypermethylation of the regulatory region of POLG gene. This disrupts POLG's ability to bind to the D-loop region of mitochondrial DNA (mtDNA), thereby hindering mtDNA biogenesis. Additionally, hyperglycemia alters the methylation pattern of the MMP-9 promoter, leading to its overexpression and accumulation within mitochondria.[7] This mitochondrial buildup compromises membrane integrity and triggers apoptosis, which ultimately contribute to the progression of DR.[8] Hyperglycemia-mediated epigenetic modifications of DNA methylation in MLH1 promoter decreases its transcription and mitochondrial accumulation, which lead to increased mtDNA mismatches in DR. Research indicate that microRNA-320a, part of the microRNA-320 family, is significantly reduced in the retinas of diabetic animal models. However, its upregulation has been found to reduce both retinal inflammation and vascular leakage. Study has also demonstrated that microRNA-320a directly targets VEGF, a key molecule responsible for angiogenesis and a major contributor to the progression of DR. By downregulating VEGF, microRNA-320a may help inhibit abnormal blood vessel formation and neovascularization, which are critical drivers of vision impairment in DR.[9] In addition, high blood glucose levels can influence histone acetylation patterns in the promoter region of the miR-320 gene. Genetic predisposition also plays a significant role, with candidate genes like ALR2 and VEGF, and epigenetic mechanisms such as histone modifications, and non-coding RNAs contributing to disease susceptibility and the phenomenon of "metabolic memory," which explains DR progression even after glycemic normalization. Upregulation of VEGF due to hypoxia-induced epigenetic changes, along with polymorphisms in the ALR2 gene encoding AR, contributes to the acceleration of retinal damage in DR.[10]

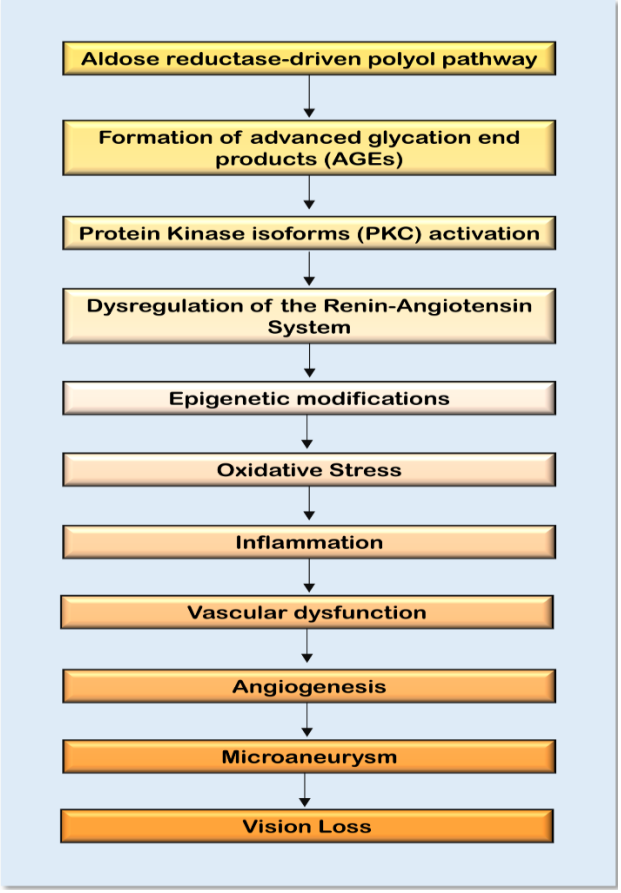

Figure 1: This schematic illustrates the progressive molecular events involved in the pathogenesis of diabetic retinopathy.

Early biomarkers such as retinal vessel tortuosity and reduced fractal dimension (FD) enable detection before significant vision loss occur. Tortuosity refers to the degree of winding or twisting of blood vessels. Increased tortuosity, particularly in retinal arterioles is associated with various retinal diseases. It can be an early sign of microvascular damage before other clinical signs of retinopathy is present.[11] FD is a mathematical measure that quantifies the complexity and branching patterns of the retinal vascular network. A lower FD indicates a less complex and potentially sparse vascular network.[12] Therapeutically, Anti-VEGF agents have significantly changed the treatment approach for diabetic macular

edema (DME) and proliferative diabetic retinopathy (PDR). Faricimab, a newer bispecific agent that targets both VEGF-A and angiopoietin-2, has shown promising results with non-inferior visual outcomes compared to other anti-VEGF treatments. Anti-VEGF agents are also valuable in managing PDR, particularly in cases where neovascularization persists despite PRP. They can reduce retinal neovascularization, improve visual acuity, and reduce the need for vitrectomy.[13] Emerging pharmacological strategies include PKC-β inhibitors, NOX/ROS-targeting antioxidants, RAS modulators, and epigenetic therapies (e.g., DNMT and histone modification inhibitors, miR-320 mimics) aimed at reducing oxidative and inflammatory stresses. Gene therapy efforts using siRNA and viral vectors to modulate pathogenic gene expression in the retina show preclinical promise. Gene therapy targets both inherited and acquired diseases, such as DR, DME, Age-Related Macular Degeneration (AMD), Leber congenital amaurosis (LCA), Achromatopsia, Retinitis Pigmentosa, and Leber Hereditary Optic Neuropathy (LHON).[14] The integration of genetic risk profiling, multi-omics biomarkers, AI-assisted retinal imaging, and personalized therapeutic regimens including diet and blood pressure control heralds a precision medicine era in DR diagnosis, which potentially transforms early detection and disease-modifying intervention.

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

Hyperglycemia and its effects on the retina

Hyperglycemia leads to an increased flux through the polyol pathway, where glucose is reduced to sorbitol by the enzyme AR, and sorbitol is subsequently converted to fructose by sorbitol dehydrogenase. The accumulation of sorbitol and fructose in retinal cells, particularly pericytes and endothelial cells, causes osmotic stress and oxidative damage. This occurs due to increased intracellular osmotic pressure, leading to cellular swelling and eventual cell death, depletion of nicotinamide adenine dinucleotide phosphate (NADPH), and increased production of reactive oxygen species (ROS) through the autoxidation of fructose.[15] Hyperglycemia promotes the non-enzymatic glycation of proteins, lipids, and nucleic acids, leading to the formation of advanced glycation end-products (AGEs). AGEs can modify and cross-link proteins, altering their structure and function. Furthermore, AGEs interact with specific receptors (RAGE) on retinal cells, triggering downstream signaling cascades that amplify oxidative stress and inflammatory responses. The binding of AGEs to RAGE activates nuclear factor-kappa B (NF-κB), which upregulates the expression of inflammatory cytokines, adhesion molecules, and growth factors, including VEGF.[16] Additionally, AGE-RAGE interaction induces the activation of mitogen-activated protein kinases (MAPKs) and the production of ROS, contributing to cellular dysfunction and apoptosis.[17] Hyperglycemia also leads to an increased de novo synthesis of diacylglycerol (DAG), an activator of the protein kinase C (PKC) enzyme family. Activation of PKC isoforms, particularly PKC-β, has been implicated in various pathological processes in DR, including increased vascular permeability and disruption of the blood-retinal barrier., upregulation of VEGF expression, promoting angiogenesis and neovascularization.[4] Induction of inflammatory mediators, such as cytokines and adhesion molecules, and inhibition of Na+/K+ ATPase activity, leading to cellular edema and dysfunction. Studies suggest that orally administered LY333531, a β-isoform specific PKC inhibitor, may be effective in ameliorating retinopathy progression, proliferation, and retinal vascular leakage.[18]

Oxidative stress and inflammation

Oxidative stress and inflammation are closely intertwined processes that play a central role in the pathogenesis of DR. The molecular mechanisms underlying these processes involve complex interactions between various signaling pathways and cellular responses. Hyperglycemia, along with the accumulation of AGEs and increased polyol pathway activity, leads to an upsurge in ROS generation.17 The primary sources of ROS in the diabetic retina include mitochondrial dysfunction, where hyperglycemia induces mitochondrial dysfunction, leading to increased electron leakage from the electron transport chain and subsequent superoxide production, NADPH oxidase activation, where AGEs and inflammatory cytokines activate NADPH oxidase, an enzyme complex that generates superoxide radicals, and uncoupling of nitric oxide synthase (NOS), where hyperglycemia causes NOS uncoupling, leading to the production of superoxide instead of nitric oxide.[19] Moreover, ROS can activate stress-responsive signaling pathways, such as nuclear factor erythroid 2-related factor 2 (Nrf2) and NF-κB, which regulate the expression of antioxidant and inflammatory genes, respectively. Inflammation is closely linked to oxidative stress in DR. The molecular mechanisms involved in the inflammatory response include NF-κB activation, where ROS and AGEs can activate NF-κB, a master regulator of inflammation, leading to the transcription of pro-inflammatory genes, including cytokines (e.g., interleukin-1β, tumor necrosis factor-α), chemokines, and adhesion molecules. The leukocyte recruitment, where upregulation of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) facilitates the recruitment and adhesion of leukocytes to the retinal vasculature, which further amplifies inflammatory response.[20] Furthermore, cytokine signaling where pro-inflammatory cytokines such as IL-1β and TNF-α, can induce the production of additional cytokines, chemokines, and growth factors that perpetuate inflammatory cascade and contributing to vascular dysfunction and neovascularization. Oxidative stress and inflammation are closely intertwined, with each process potentiating the other. ROS can activate inflammatory

signaling pathways, while inflammatory mediators such as cytokines and chemokines can further stimulate ROS production, creating a self-perpetuating cycle. This vicious cycle of oxidative stress and inflammation contributes to retinal vascular leakage, cellular dysfunction, and neovascularization that further exacerbate the progression of DR.[18]

Vascular changes and neovascularization

The microvascular complications of DR are characterized by progressive capillary basement membrane thickening, endothelial cell dysfunction, pericyte dropout, and the formation of acellular capillaries. These vascular abnormalities arise from a complex interplay of various molecular mechanisms triggered by hyperglycemia, oxidative stress, and inflammation. Chronic hyperglycemia leads to the accumulation of advanced glycation end-products (AGEs) in the retinal vasculature. As highlighted in a study by Kang et al., hyperglycemia-induced AGEs accumulate in retinal tissues and interact with the receptor for AGEs (RAGE), triggering oxidative stress and inflammation, which further damages the retinal microvasculature and accelerates the progression of DR. AGEs can cross-link with basement membrane proteins, such as collagen and laminin, resulting in basement membrane thickening and impaired flexibility.[21] Moreover, AGEs can indeed induce apoptosis (programmed cell death) in pericytes, which are vital for maintaining capillary integrity and regulating endothelial cell proliferation. This pericyte apoptosis can contribute to the development of various diseases, including DR. Pro-inflammatory cytokines such as TNF-α and IL-1β, disrupt tight junctions between endothelial cells, and also stimulate VEGF production through the activation of signaling pathways, including NF-κB and MAPKs.[22]The loss of pericytes and endothelial cell dysfunction result in the formation of acellular capillaries, which are non-perfused and devoid of cellular components. These acellular capillaries contribute to retinal ischemia and hypoxia, triggering compensatory mechanisms aimed at restoring oxygen supply. In response to ischemia and hypoxia, the retina upregulates the production of VEGF, a potent angiogenic factor that stimulates the formation of new blood vessels. While VEGF initially aims to restore oxygen supply, the newly formed blood vessels are often abnormal, fragile, and leaky, leading to vitreous hemorrhage and retinal detachment.[23] These abnormal vessels lack proper pericyte coverage and have impaired basement membrane integrity, further exacerbating vascular leakage and retinal edema. The molecular pathways involved in VEGF upregulation include, Hypoxia-inducible factor-1 (HIF-1) activation. Hypoxic conditions stabilize HIF-1α, a transcription factor that binds to the VEGF promoter and induces its expression. Studies identified VEGF as an important factor associated with angiogenesis in DR. Patients with PDR exhibit significantly elevated levels of VEGF in the vitreous humor compared to individuals with normal physiological levels. Research supports the effectiveness of anti-VEGF therapies in suppressing abnormal neovascularization associated with PDR. Among the regulators of VEGF, HIF-1α has emerged as a critical mediator. It has been observed that HIF-1α directly activates the transcription of the VEGF gene. Since, HIF-1α regulates various genes involved in retinal neovascularization, it is believed to contribute substantially to DR progression.[24] Furthermore, studies have shown a strong correlation between the expression levels of HIF-1α and VEGF and the severity of DR-related lesions, suggesting that modulation of VEGF expression is a potential pathway through which HIF-1α influences the advancement of the disease. The vascular changes and aberrant neovascularization in DR are driven by a complex interplay of molecular mechanisms involving hyperglycemia, AGE accumulation, oxidative stress, inflammation, and dysregulated angiogenic signaling.

Role of genetics in development of DR

The development and progression of DR have significant genetic components which include heritability studies, familial clustering, and genetic association analyses. Heritability studies have demonstrated a substantial hereditary contribution to the risk of developing DR. Twin studies provide a powerful approach to estimate heritability that have consistently shown a higher concordance rate of DR in monozygotic twins compared to dizygotic twins, suggesting significant genetic influence.[25] A strong correlation in the severity of DR has been observed among twins affected by both type 1 and type 2 diabetes. Studies have shown that, depending on the specific DR phenotype and the ethnic group studied, siblings and other close relatives of diabetic individuals with DR face a 2- to 3-fold increased risk of developing DR compared to relatives of diabetic individuals without the condition. This familial clustering is more pronounced in the more advanced stages of retinopathy. Estimates suggest that the heritability of DR can reach up to 27%, while for PDR, it may be as high as 52%. Additionally, familial clustering of DR has been observed, with individuals having a first-degree relative with the condition being at higher risk of developing the disease. Also, candidate gene studies have been extensively employed to identify genetic variants associated with DR susceptibility.[26] These studies have focused on genes involved in various pathways implicated in the pathogenesis of the disease, including glucose metabolism, vascular regulation, and inflammatory processes. One of the most widely studied candidate genes is the vascular endothelial growth factor (VEGF) gene. Polymorphisms in the VEGF gene, particularly the -634C>G and +936C>T variants, have been associated with an increased risk of developing DR.[27] Another candidate gene of interest is the aldose reductase (ALR2) gene, which encodes the rate-limiting enzyme in the polyol pathway. Polymorphisms in the ALR2 gene, such as the (CA)n dinucleotide repeat microsatellite and C-106T variant, have been linked to an increased susceptibility to DR. These variants are believed to

influence enzyme activity and contribute to the accumulation of intracellular sorbitol, leading to osmotic stress and oxidative damage.[26] In addition to candidate gene studies, genome-wide association studies (GWAS) have been employed to identify novel susceptibility loci for DR. GWAS are powerful tools for detecting common genetic variants associated with complex diseases without prior assumptions about the underlying biological mechanisms. One of the earliest GWAS for DR identified several susceptibility loci, including the CDK5RAP1 gene, which is involved in regulating cell cycle progression and neuronal migration. Also, GWAS have identified additional loci such as the PLXDC2 gene, which encodes a protein involved in angiogenesis and vascular development.[28] Ongoing research efforts aim to integrate genetic data with functional genomic studies including gene expression analysis and epigenetic profiling to elucidate the molecular mechanisms by which these genetic variants contribute to disease pathogenesis.

MOLECULAR PATHWAYS LINKED TO DR PROGRESSION

Polyol pathway in diabetic retinopathy

Under hyperglycemic conditions, excess glucose is diverted into the polyol pathway, where AR converts glucose into sorbitol using NADPH, which is then oxidized to fructose by sorbitol dehydrogenase. This process consumes NADPH, disrupting cellular redox homeostasis and increasing oxidative stress, particularly in retinal pericytes and endothelial cells.[19] Sorbitol accumulation causes osmotic stress, leading to cellular swelling and membrane damage, which impairs retinal vascular integrity (Figure 2). The polyol pathway depletes myo-inositol, disrupting phosphoinositide signaling and contributing to retinal neuronal dysfunction. This occurs because the polyol pathway, specifically the enzyme AR, converts glucose to sorbitol, and this process consumes NADPH, a crucial cofactor for myo-inositol synthesis. Furthermore, high glucose can inhibit myo-inositol uptake into cells. The resulting myo-inositol depletion disrupts the production of phosphoinositides, which are essential for cellular signaling, including those involved in neuronal function.[15] A study demonstrated that polyol pathway activation in human retinal pigment epithelial cells under hyperglycemia triggers mitochondrial dysfunction, elevating ROS and accelerating retinal degeneration. Under normal conditions, the mitochondrial electron transport chain (ETC) facilitates the transfer of electrons from NADH and $FADH_2$ to molecular oxygen which generates water through oxidative phosphorylation. However, during hyperglycemia, an excess supply of metabolic substrates leads to increased production of NADH and $FADH_2$. This overload raises the mitochondrial membrane potential and causes electron leakage primarily at complexes I and III, triggering the generation of superoxide ($O_2^{\bullet-}$). This mechanism plays a critical role in initiating oxidative stress associated with DR.[29] Furthermore, it was reported that polyol pathway hyperactivity correlates with reduced retinal blood flow and increased acellular capillaries in diabetic models, linking it to microvascular damage in DR. For instance, a study by Dagher et al. found that administering the aldose reductase inhibitor (ARI) sorbinil to diabetic rats prevented early complement activation in retinal vessels, reduced apoptosis of pericytes and endothelial cells, and abolished development of acellular capillaries, thus preventing DR progression.[30] in another long-term study of diabetic rats treated with sorbinil for nine months, ARI therapy not only preserved retinal blood vessel integrity but also prevented the formation of acellular capillaries.[31] Investigations in diabetic rat arterioles showed that high glucose induced reductions in flow-dependent dilation were largely mediated by polyol pathway activity. Using ARIs like zopolrestat restored this impaired vasodilatory response, indicating polyol flux compromises microvascular blood flow functionality.

Advanced AGEs in diabetic retinopathy

In chronic hyperglycemic conditions, as seen in diabetes, elevated intracellular glucose levels drive the non-enzymatic glycation of proteins, lipids, and nucleic acids, leading to the formation and accumulation of AGEs. These stable and heterogeneous compounds are primarily generated through the Maillard reaction and are accelerated under oxidative stress and high-glucose environments. Although initially associated with the polyol pathway, AGE formation can occur independently through multiple pathways, including the auto-oxidation of glucose, lipid peroxidation, and the degradation of Amadori products. AGEs exert deleterious effects in DR largely through their interaction with the receptor for advanced glycation end products (RAGE), which is expressed in various retinal cells including endothelial cells, Müller cells, microglia, and pericytes. Upon ligand binding, the AGEs–RAGE interaction initiates a cascade of intracellular signaling events involving the activation of NADPH oxidase (NOX), PKC, MAPKs, and the transcription factor NF-Kb. Importantly, AGEs/RAGE signaling upregulates pro-inflammatory cytokines (e.g., TNF-α and IL-6), adhesion molecules (such as ICAM-1 and VCAM-1), and pro-angiogenic factors including VEGF and angiopoietin-2 (Ang-2), which promote leukostasis, vascular leakage, and neovascularization in the retina.[32] NF-κB activation has been specifically linked to the loss of retinal pericytes and breakdown of the blood-retinal barrier (BRB). For Instance, a study documented that systemic administration of IMD-0354 significantly inhibited NF-κB activation in both diabetic rat retina and high glucose treated glial cells, ameliorated oxidative injury, inflammatory responses, VEGF production, and glial cell activation.[33] It has been studied that administration of AGEs to normal rats led to increased expression of RAGE and ICAM-1, resulting in retinal hyperpermeability and leukocyte adhesion. However, this pathological process was effectively inhibited by co-treatment with pigment epithelium-derived factor (PEDF), which is known to suppress AGE-

induced ROS generation, NF-κB activation, and VEGF expression.[32] Moreover, recent studies indicate that AGEs contribute to endoplasmic reticulum (ER) stress in retinal pericytes, triggering hyperactivation of the unfolded protein response (UPR) and maladaptive autophagy pathways, ultimately leading to pericyte apoptosis.[34] This mechanism is critical, as pericyte loss is strongly associated with microaneurysm formation and capillary dropout in DR.[35] AGE–RAGE axis plays a key role in the pathogenesis of DR by promoting oxidative stress, inflammation, vascular dysfunction, and nerve cell damage in the retina.[32] Therefore, targeting this pathway, either by inhibiting AGE formation or blocking RAGE signaling, remains a promising therapeutic approach to slow down or prevent the progression of DR.

PKC activation

Hyperglycemia leads to an increased de novo synthesis of diacylglycerol (DAG), an activator of the protein kinase C (PKC) enzyme family. Activation of PKC isoforms, particularly PKC-β, has been implicated in various pathological processes in DR. Activated PKC can contribute to increased vascular permeability and disruption of the blood-retinal barrier by altering the expression and localization of tight junction proteins in endothelial cells. For instance, PKC activation, particularly by isoforms like PKCδ can lead to the phosphorylation and subsequent disruption of tight junction proteins like ZO-1, occludin, and claudin-5, which are crucial for maintaining the integrity of the BRB. PKC activation has also been shown to upregulate the expression of VEGF which further exacerbate angiogenesis and neovascularization progressing DR from nonproliferative (NPDR) to PDR stages. However, if NPDR is left untreated, VEGF protein levels upregulate due to ischemia/hypoxia escorted through hypoxia-inducible factor 1 (HIF-1) activation. Moreover, PKC activation mediates the progression of reduced retinal blood flow in DM. In experimental diabetic rat models, a marked prolongation of mean circulation time (MCT) has been documented. However, administration of the selective PKC-β inhibitor LY333531 via intravitreal injection significantly improved retinal perfusion, reducing MCT to nearly half of that observed in untreated diabetic rats.[36] In addition, PKC activation also contribute to the upregulation of endothelin-1 (ET-1), a potent vasoconstrictor that may further aid for the reduction in retinal blood flow under diabetic conditions. In bovine retinal endothelial cells (BRECs) exposed to high-glucose environments, both PKC activation and ET-1 expression were found to increase approximately twofold. For instance, treatment with general PKC inhibitor GF109203X suppressed the overexpression of ET-1. Further observation revealed marked translocation and overexpression of PKC-β and PKC-δ in the membrane fractions, indicating that these specific PKC isoforms are key mediators of ET-1 induction in response to hyperglycemia.[37] It has been observed that nitric oxide (NO) insufficiency also contributes in the alteration of retinal blood flow. The synthesis of NO from retinal microvascular endothelial cells (RMECs) was downregulated under hyperglycemic conditions, whereas a PKC inhibitor increased NO accumulation and restored the blood flow in the retina.[38] Studies documented that VEGF is mainly studied in terms of retinal vascular permeability. The expression of PKC-β and VEGF were both significantly increased under high-glucose conditions, and the inhibition of PKC-β and PKC-β mutant mice showed attenuated vascular barrier function and less albumin leakage.[39] PKC-β activation induced occludin Ser490 phosphorylation, which led to the ubiquitination required for VEGF-induced permeability and exacerbated retinal barrier dysfunction.[4]

Epigenetic modifications

Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) have emerged as important regulators of gene expression in DR. Altered DNA methylation patterns have been observed in the retinas of individuals with DR, where hyperglycemia and oxidative stress can induce changes in DNA methylation (Figure. 2), affecting the expression of genes involved in various pathways implicated in the disease, such as inflammation, angiogenesis, and metabolic pathways.[40] Histone modifications, including acetylation, methylation, and phosphorylation can also influence gene expression by altering chromatin structure and accessibility to transcriptional machinery, and dysregulation of histone-modifying enzymes such as histone deacetylases (HDACs) has been implicated in the development of DR. Experimental study using both in vitro and in vivo models of DR have demonstrated a significant increase in HDAC activity alongside a reduction in histone acetyltransferase (HAT) activity within the retina and its microvascular cells under diabetic conditions.[41] This imbalance contributes to a global decrease in histone acetylation, indicating epigenetic dysregulation in the diabetic retinal environment.

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play crucial roles in post-transcriptional gene regulation, with numerous miRNAs and lncRNAs found to be dysregulated in DR. Studies have investigated the roles of miRNAs in DR, using HRECs and RPE cells as in vitro and in vivo models of streptozotocin (STZ)-induced diabetic retinas.[42] For Example, one study investigating the retinal effects of diabetes identified a distinct set of microRNAs (miRNAs) with altered expression in the retinas and retinal endothelial cells (RECs) of streptozotocin (STZ)-induced diabetic rats, three months post-diabetes induction. This research offered the first substantial evidence of miRNA involvement in the pathogenesis of DR. Through miRNA array profiling, it was revealed that 80 miRNAs were significantly upregulated and 6 miRNAs was downregulated in the retinas of diabetic rats compared to non-diabetic controls. In RECs, 16 miRNAs showed significant upregulation ($p<0.01$), while 104 miRNAs were found to be downregulated ($p<0.01$). Additionally, several of the differentially expressed miRNAs were

found to be responsive to key regulatory pathways, including those mediated by NF-κB, VEGF, and p53. Remarkably, the elevated expression of miR-146, miR-155, miR-132, and miR-21 in diabetic RECs was associated with NF-κB activation, indicating a potential miRNA signature linked to inflammatory signaling in the diabetic retina.[43] The competing endogenous RNA (ceRNA) hypothesis has recently emerged, proposing that mRNAs and long non-coding RNAs (lncRNAs) can interact and regulate one another by competing for shared microRNAs (miRNAs). In this context, lncRNAs can function as molecular sponges, sequestering specific miRNAs and thereby influencing their availability for binding to target mRNAs. In a study, Yan et al. introduced a regulatory model involving lncRNA-MIAT, miR-150-5p, and VEGF mRNA. Their findings demonstrated that hyperglycemic conditions in diabetic rats lead to a marked upregulation of MIAT expression. Furthermore, knockdown of miR-150-5p resulted in a further increase in MIAT levels, suggesting a reciprocal regulatory mechanism. Co-localization studies also confirmed that both MIAT and miR-150-5p are co-expressed within the nuclei of RF/6A cells, supporting their potential interaction within the ceRNA network.[44] miRNAs have recently emerged as a potent class of gene expression regulators implicated in the pathogenesis of numerous human diseases, including DR. Microarray-based expression profiling has provided compelling evidence of miRNA dysregulation in DR, and the functional roles of several aberrantly expressed miRNAs have been progressively elucidated. Notably, a single miRNA can modulate multiple target genes simultaneously, thereby impacting various interconnected signaling pathways. Among the miRNAs extensively studied in the context of DR are miR-200b, miR-146a, and miR-126, which are closely associated with key pathological processes such as angiogenesis, inflammation, and oxidative stress.[9]

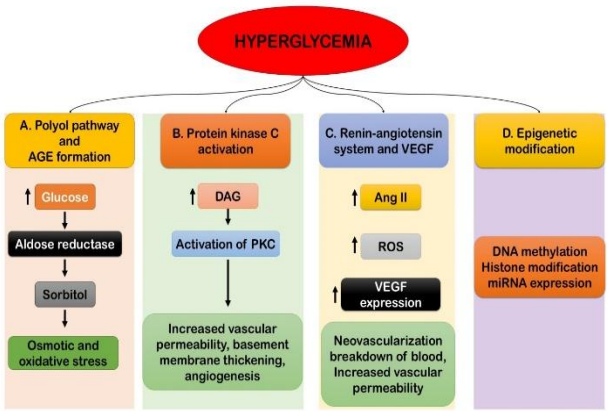

Figure 2: This schematic illustrates how hyperglycemia activates multiple molecular pathways including the polyol pathway, PKC activation, RAS/VEGF signaling, and epigenetic modifications that contribute to oxidative stress, inflammation, vascular permeability, and retinal damage in diabetic retinopathy.

THERAPEUTIC IMPLICATIONS

Targeting specific molecular pathways

Advancements in understanding the molecular mechanisms underlying DR have laid the foundation for the development of targeted therapeutic approaches. Several clinical trials have investigated the potential of pharmacological agents targeting specific pathways implicated in the disease pathogenesis. One of the most extensively studied targets is the VEGF pathway. Anti-VEGF agents, such as ranibizumab, aflibercept, and bevacizumab, have shown significant efficacy in the treatment of DME and PDR. These agents inhibit VEGF activity, thereby reducing vascular permeability, retinal edema, and neovascularization.[45] Another therapeutic approach involves targeting the renin-angiotensin system (RAS). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been investigated for their potential in slowing the progression of DR. These agents modulate the RAS and have been shown to reduce VEGF expression, oxidative stress, and inflammation in the retina.[46] Anti-VEGF therapy are not always effective as it may impair neuronal and vascular survival function, thus it requires repeated treatment. PKC inhibitors have also been explored as potential therapeutic agents for DR. Ruboxistaurin, a selective PKC-β inhibitor, has been evaluated in clinical trials and shown promise in reducing the risk of sustained moderate visual loss in patients with DR.[47] Besides Ruboxistaurin, other PKC inhibitors being investigated for DR include Rottlerin and Midostaurin. Rottlerin is a natural compound that has shown promise in preclinical studies for DR. It can inhibit PKC-δ, which is implicated in vascular permeability and breakdown of the BRB. While not as widely studied as Ruboxistaurin or Rottlerin, Midostaurin is also a PKC inhibitor and has been explored for its potential in various diseases, including DR.[48] Furthermore, agents targeting inflammation and AGEs are also potential therapeutic options. anti-inflammatory drugs such as Etanercept and Infliximab which work by blocking TNF-α-induced inflammation have been demonstrated their efficiency in preventing retinal inflammation, retina cell injury and vessel leakage. Moreover, intravitreal delivery of steroids has shown great potential in both pre-clinical and clinical studies. In a rat model of DR, intravitreal injection of dexamethasone suppressed up-regulation of ICAM-1, leukostasis, and prevented retinal vascular leakage.[49]

Personalized medicine based on genetic risk

The identification of genetic risk factors associated with DR has opened up the possibility of personalized medicine approaches. By assessing an individual's genetic profile, healthcare professionals can potentially stratify patients based on their risk of developing or progressing to more severe forms of DR.[50] Genetic risk scores, derived from the cumulative effects of multiple genetic variants can be used to identify high-risk individuals who

may benefit from more intensive monitoring and early intervention strategies.[51] Conversely, individuals with a lower genetic risk profile may require less frequent screening and follow-up. Furthermore, understanding the genetic foundations of DR may guide the selection of targeted therapies based on an individual's genetic makeup. For example, patients with specific genetic variants that influence VEGF expression or the renin-angiotensin system may respond better to therapies targeting these pathways. The VEGFA gene with polymorphisms such as rs699947, rs833061, and rs2010963 significantly affecting the extent of retinal neovascularization which is a primary driver of PDR.[52] In same way IL-6 gene polymorphisms like rs1800795 affect DR progress by regulating systemic and local inflammatory responses. As mentioned previously that High IL-6 levels not only escalate retinal vascular permeability but also encourage inflammatory cell infiltration and cytokine release, which further damage retinal cells.[53] Additionally, genetic polymorphisms in the AKR1B1 gene, which encodes aldose reductase have been significantly linked to an increased risk of developing DR.[54] These genetic variations may influence the susceptibility of retinal cells to oxidative stress, thereby contributing to the progression and severity of retinopathy.

Potential gene therapy approaches

Gene therapy represents a promising approach for the treatment of DR, particularly in advanced stages where conventional therapies may be less effective. Several gene therapy strategies have been explored in preclinical studies and early-phase clinical trials. One approach involves the delivery of therapeutic genes that can counteract the pathogenic mechanisms responsible for DR progression.[14] For example, gene therapy using adeno-associated viral (AAV) vectors encoding antioxidant enzymes such as superoxide dismutase or catalase has been shown to reduce oxidative stress and protect retinal cells in animal models of DR. In their study, Lee et al. demonstrated that AAV2 and AAV9 had significantly higher transduction efficiency in 2-month-old diabetic mouse retinas compared to younger diabetic and non-diabetic controls. AAV2 transduced multiple retinal cell types, while AAV9 was mainly limited to RGCs and horizontal cells. AAV5 and AAV8 showed no significant improvement. The enhanced efficiency correlated with increased receptor expression in diabetic retinas, suggesting AAV2 and AAV9 as promising vectors for gene therapy in DR.[55] Another strategy involves the use of RNA interference (RNAi) technologies to silence the expression of disease-associated genes. Small interfering RNAs (siRNAs) or microRNA (miRNA) mimics targeting VEGF, PKC isoforms, or inflammatory mediators have demonstrated therapeutic potential in preclinical studies.[42] Anti-angiogenic gene therapy focuses on inhibiting key mediators such as VEGF, which plays a central role in the progression of proliferative DR. By directly interfering with neovascularization, this approach holds potential to effectively arrest disease advancement. In parallel, anti-inflammatory gene therapy aims to regulate chronic retinal inflammation by targeting specific cytokines and chemokines, thereby addressing one of the fundamental drivers of DR pathology.[49] Additionally, gene therapy directed at oxidative stress mechanisms involves the upregulation of antioxidant enzymes, including superoxide dismutase and catalase, to reduce oxidative damage in the retina.[56] This antioxidant-based strategy is particularly critical during the early stages of DR, as it seeks to preserve retinal integrity by mitigating oxidative stress-induced injury. Additionally, gene editing techniques such as CRISPR/Cas9, have emerged as potential tools for modulating gene expression or correcting disease-causing mutations in DR. As some forms of DR are linked to specific gene mutations, CRISPR/Cas9 can be used to correct these mutations. For instance, it can be used to knock down the expression of genes like VEGF-A, which promotes blood vessel growth, or to enhance the expression of genes that protect against damage. In recent years, CRISPR/Cas9 gene editing has shown its great promise.[57] However, significant challenges remain, including the development of safe and efficient delivery systems and addressing potential off-target effects. While gene therapy approaches hold promise for DR treatment. Further research should focus on the challenges related to delivery, specificity, and long-term safety.

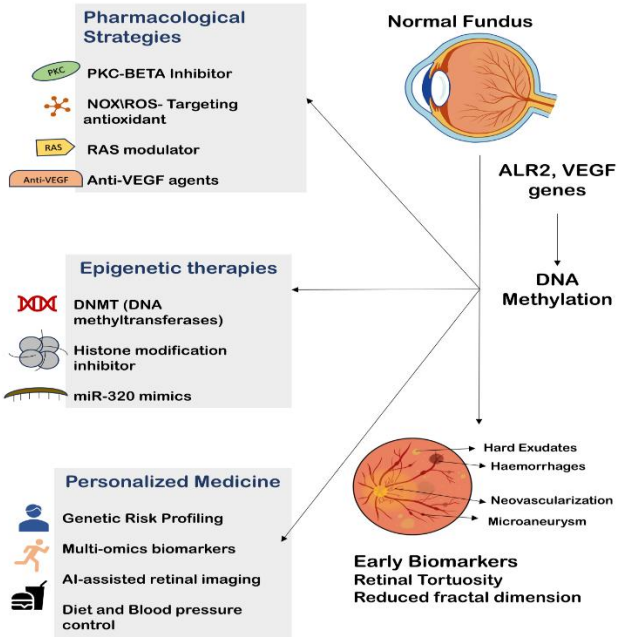

Figure 3. Emerging therapeutic and diagnostic approaches in diabetic retinopathy.

DISCUSSION

This review has highlighted the complex genetic and molecular cascades that contribute to the development and progression of DR. The substantial heritability and

familial clustering observed in DR underscore the significant role of genetic factors in disease susceptibility. Insights from candidate gene studies and genome-wide association studies have identified specific genetic variants associated with increased risk, providing valuable clues about the involved biological pathways. At the molecular level, hyperglycemia triggers a cascade of deleterious events, including increased flux through the polyol pathway, formation of AGEs, activation of PKC, dysregulation of RAS and VEGF signaling, as well as epigenetic modifications. The convergence of these pathways leads to oxidative stress, inflammation, vascular dysfunction, and pathological angiogenesis, ultimately culminating in the characteristic microvascular lesions of DR. Understanding the genetic and molecular mechanisms is crucial as it paves the way for the development of targeted therapeutic interventions. Several promising approaches, such as anti-VEGF agents, PKC inhibitors, and drugs modulating the RAS, have shown efficacy in clinical trials by targeting specific pathways implicated in the disease pathogenesis. Moreover, the identification of genetic risk factors opens up avenues for personalized medicine, enabling risk stratification and tailored treatment strategies. While significant progress has been made, continued research efforts are imperative to further elucidate the complex interplay between genetic and environmental factors, unravel the intricate molecular networks, and translate these findings into improved clinical management and prevention strategies for DR. Integrating potential domain such as genetics, molecular biology, and clinical research will accelerate progress in DR.

CONCLUSION

Diabetic retinopathy is a multifactorial microvascular complication driven by sustained hyperglycemia and the convergence of metabolic, inflammatory, oxidative, genetic and epigenetic mechanisms. There are some key pathogenic pathways such as polyol flux, AGE–RAGE signaling, PKC activation, VEGF-driven angiogenesis and epigenetic dysregulation which collectively disrupt retinal vascular integrity and promote disease progression. Advances in molecular genetics and epigenomics have enhanced understanding of disease susceptibility and metabolic memory, while targeted therapies such as anti-VEGF agents, PKC inhibitors, RAS modulators and emerging gene- and RNA-based interventions offer promising disease-modifying potential. Future integration of advanced strategies such as multi-omics, AI-assisted retinal imaging and personalized medicine could transform early diagnosis, risk stratification and precision management of DR.

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