Received: 25 October 2018 | Accepted: 15 November 2018

DOI: 10.1002/jcp.27844

WILEY Journal of Cellular Physiology

MINI-REVIEW

Role of histone modification and DNA methylation in signaling pathways involved in diabetic retinopathy

Rana Shafabakhsh[1] | Esmat Aghadavod[1] | Majid Ghayour-Mobarhan[2] | Gordon Ferns[3] | Zatollah Asemi[1]

[1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

[2]Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[3]Division of Medical Education, Brighton & Sussex Medical School, Brighton, UK

Correspondence
Esmat Aghadavod and Zatollah Asemi, Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan 88715973474, Iran.
Email: aghadavod_m@yahoo.com (E. A.)
asemi_r@yahoo.com (Z. A.)

Abstract

Retinopathy, characterized by an alteration of the retinal microvasculature, is a common complication of diabetes mellitus. These changes can cause increased permeability and alter endothelial cell proliferation, edema, and abnormal neovascularization and eventually result in blindness. The pathogenesis of diabetic retinopathy (DR) is complicated, involving many factors/mediators such as genetic susceptibility, microRNAs, and cytokines. One of the factors involved in DR pathogenesis is epigenetic changes that can have a key role in the regulation of gene expression; these include microRNAs, histone modifications, and methylation of DNA. The main epigenetic modifications are DNA methylation and posttranslational modifications of the histones. Generally, the studies on epigenetics can provide new opportunities to investigate the molecular basis of diseases with complicated pathogenesis, including DR, and provide essential insights into the potential design of strategies for its treatment. The aim of this study is an investigation of DR pathogenesis and epigenetic modifications that involve in DR development.

KEYWORDS
diabetic retinopathy, epigenetic, modification, pathogenesis

1 | DIABETIC RETINOPATHY (DR)

DR is a common complication of diabetes mellitus, affecting 50% of Type 1 diabetic patients and 80% of Type 2 diabetic patients who become insulin-requiring have DR in many developed nations (Heng et al., 2013). As stated by World Health Organization (WHO), the prevalence of DR is predicted to increase, although glycemic control, lipid-lowering therapy, and control of blood pressure can reduce its incidence and progression (Ola, Nawaz, Siddiquei, Al-Amro, & Abu El-Asrar, 2012; Patel et al., 2008). The retinal microvascular circulation is affected by diabetic mellitus and results in a range of retinal structural changes. These changes eventually cause increased permeability and alter the proliferation of endothelial cells, edema, and abnormal neovascularization and finally leading to vision loss (Shin, Sorenson, & Sheibani, 2014). DR is usually asymptomatic until the time that worsening vision is discovered; the clinical features of DR are the formation of microaneurysms, diabetic macular edema, neovascular glaucoma, and retinal detachment. Microaneurysms are found in virtually all patients with Type 1 diabetes after 20 years' duration of diabetes, and in 80% of patients with Type 2 diabetes (Das, Stroud, Mehta, & Rangasamy, 2015). Nowadays, DR is classified into two clinical forms: proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR). PDR involves the formation of retinal neovascularization, and then the formation of new fragile vessels from the venous side of the retinal circulation and may enter the inner limiting membrane into the vitreous humor. In addition, NPDR can be classified into four levels: mild, moderate, severe, and very severe (Das et al., 2015). Mild NPDR may be asymptomatic, whereas the second stage distinguished by the existence of a few microaneurysms, the third stage has more microaneurysms than the previous stage although less than severe NPDR. Severe NPDR is distinguished by presences of more than 20

intraretinal hemorrhages in every quadrant and prominent intraretinal microvascular irregularities in one quadrant (Mastropasqua et al., 2014). The serious effects of DR are damage to the macula and central visual acuity. This excessive, vasopermeability, and edematous damage to the retina is termed as diabetic macula edema, which is a common cause of blindness in diabetes (Joussen, Smyth, & Niessen, 2007).

2 | PATHOGENESIS OF DR

Generally, alterations of the blood–retinal barrier (BRB) are the characteristic of the pathogenesis of DR. The collapse of the BRB can lead to intraretinal hemorrhages in macular edema that is increased during progression from mild to moderate to serve grades of NPDR. Selective loss of perivascular cells is one of the early histopathologic causes of lesions seen in DR and can lead to the formation of microaneurysms (Das et al., 2015; Frank, 2004). The number of interconnected biochemical mechanisms associated with hyperglycemia may be involved in the pathogenesis of DR. Neuronal death resulting from apoptosis, may take place in the ganglion cell layer before the vascular lesions. This silent death of neurons before the appearance of the vascular lesions may be evident as a failure of dark adaptation and decreased the sensitivity of contrast seen in diabetic patients before the development of retinopathy (Das et al., 2015). The biochemical mechanisms involved may comprise oxidative stress, polyol pathway, and hexosamine activity, activation of protein kinase C and advanced glycation end-products formation (Li & Puro, 2002). Other pathways related to DR include the inflammatory response, the upregulation of the renin-angiotensin system, and finally genomic structural modifications (epigenetic changes; Porta, Maldari, & Mazzaglia, 2011). Over production of mitochondrial superoxide dismutase (SOD) and antioxidants to inhibit superoxide can reduce capillary degeneration during DR (Kowluru, Engerman, Case, & Kern, 2001; Kowluru, Kowluru, Xiong, & Ho, 2006).

Recent studies show that chronic inflammation has a vital role in the development of diabetes and its late complications thus several mediators such as proinflammatory cytokines and chemokines may be involved in the development of DR (Wan, Li, Sun, Li, & Su, 2015). Proinflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), and IL-6 may be found at remarkably high concentrations in the vitreous humor of PDR patients (Adamiec-Mroczek, Oficjalska-Mlynczak, & Misiuk-Hojlo, 2010; Noma, Funatsu, Mimura, Harino, & Hori, 2009). Increased level of IL-6, TNF-α, and IL-1β in retinal cells of diabetic patients are associated with BRB breakdown, retinal leukostasis, and apoptosis-related to DR (Adamis & Berman, 2008). Chemokines such as monocyte chemoattractant protein 1 (MCP-1), interferon-γ-inducible protein, IL-8, and stromal-derived factor-1 have a significant role in the pathogenesis of DR (Ola et al., 2012). MCP-1, a potential activator of macrophages and monocytes, involves in the pathogenesis of DR, which may be mediated via pathways, including vascular endothelial growth factor (Hong, Ryu, & Han, 2005). Other key inflammatory factors involving nitric oxide synthase, cyclooxygenase-2 (COX-2), and matrix metalloproteinase-9 (MMP-9; gelatinase B) may lead to retinal cell damage leading to DR (Ola et al., 2012).

3 | EPIGENETIC CHANGES

Epigenetics is the study of heritable phenotype changes or gene expression (active in apposition inactive genes) that affect genomic structural modifications without altering in the underlying DNA sequence (Liu, Chan, & Tuo, 2013). Therefore, epigenetic modifications act through switches that affect gene activity and allow changes in functions of the genome without changing the gene sequences (Kowluru & Mishra, 2015). Epigenetic changes are a normal phenomenon and are affected by several factors that include: age, environment, lifestyle, and disease condition (Gemenetzi & Lotery, 2014). Consequently, epigenetic changes can play a major role in many chronic diseases such as metabolic syndrome disease, diabetes, and cancer where small modifications in the epigenome eventually are considered to lead to disease manifestation (Portela & Esteller, 2010).

The mechanisms of epigenetic regulation of gene expression regulation include DNA methylation, histone modifications, and microRNAs (Liu et al., 2013). The main epigenetic modifications are the methylation of DNA and posttranslational modifications in the histones (Kowluru, Kowluru, Mishra, & Kumar, 2015). The open chromatin structure is discriminated by a widely spaced nucleosome that can facilitate binding of transcription factors to DNA and, consequently allows DNA transcription to happen. These processes are mediated through DNA methyltransferases (DNMTs) and histone acetyltransferase (HAT) activity (Kwa & Thrimawithana, 2014). Studies on epigenetics may clarify our understanding of the biological phenomena related with the development, inflammation, and angiogenesis pathways in DR (He, Li, Chan, & Hinton, 2013). Also, epigenetics can provide new opportunities to investigate the molecular basis of diseases with complex pathogenesis, such as DR that would provide essential insights into the design of strategies for treatment of DR (Kwa & Thrimawithana, 2014; Figure 1).

4 | EPIGENETIC CHANGES DURING RETINAL AGING AND DISEASES

In humans, a gradual deterioration is experienced in multiple psychophysical variables of the visual function with advanced age; these include contrast sensitivity and dark adaptation, with rod-mediated scotopic vision being the most influenced (Owsley et al., 2014). Structural and cellular changes in the aging retina are correlated with dysfunction or loss of neuronal and nonneuronal cells, even in the absence of any ocular pathology (Cavallotti, Artico, Pescosolido, Leali, & Feher, 2004). Rods are more influenced than cones, especially in the central retina where cones are stable whereas the number of rods reduces (Bonnel, Mohand-Said, & Sahel, 2003). Neural retina and retinal pigment epithelium (RPE) are widely

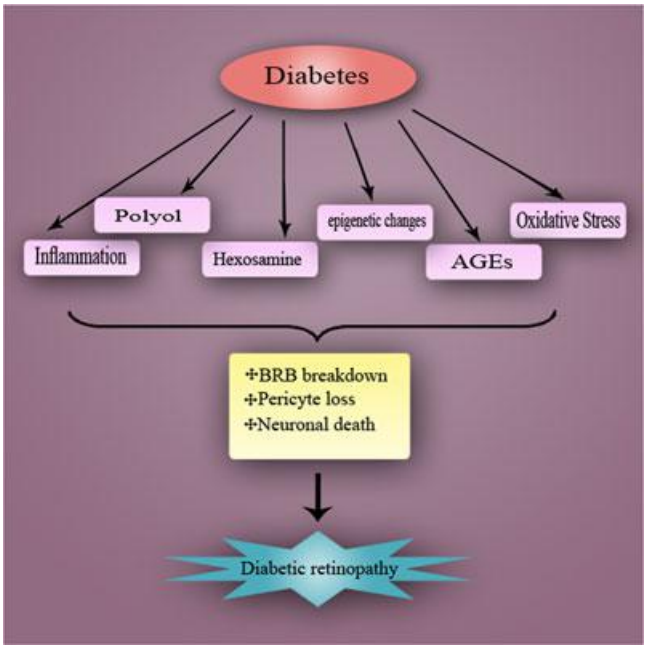

FIGURE 1 Schematic representation of epigenetic changes of diabetic retinopathy. BRB: blood–retinal barrier [Color figure can be viewed at wileyonlinelibrary.com]

exposed to light and oxidative damage, leading to cellular and molecular alterations such as mitochondrial DNA damage, impaired lysosomal and mitochondrial functions, accumulation of lipofuscin in RPE (Bonnel et al., 2003), local chronic inflammation, and drusen accumulation in the Bruch's membrane (Booij, Baas, Beisekeeva, Gorgels, & Bergen, 2010).

5 | ROLE OF EPIGENETIC CHANGES IN THE METABOLIC MEMORY OF DR

DR is a common complication of diabetes with multiple clinical features such as macular edema, angiogenesis, microvascular damage, and proliferative retinopathy (Wong, Cheung, Larsen, Sharma, & Simo, 2016). Hyperglycemia is the driver of diabetes, and the notion of "metabolic memory" or "hyperglycemic memory" has been claimed since the disease develops after long, and even interrupted, exposure to a persistent hyperglycemic state, demonstrating an epigenetic imprint (Kowluru, 2017). The epigenetic imbalance of the diabetic retina was first reported by studies indicating global though contradictory changes in histone acetylation levels and altered expression/activity of histone deacetylases and histone acetyltransferases (HATs) that persisted after the termination of hyperglycemia in diabetic rats (Kadiyala et al., 2012).

6 | DNA METHYLATION

DNA methylation is an important type of epigenetic modification (Voisin, Eynon, Yan, & Bishop, 2015) and refers to the covalent addition of a methyl (–CH3) group from the s-adenosylmethionine (SAM) to the fifth carbon of the cytosine base by DNMTs enzymes (Marzese & Hoon, 2015). DNA methylation often occurs in the context of CpG dinucleotides, CpG islands, that have more than 200 bp of nucleotides with a G + C content of 50%, and is also involve in the regulation of chromatin structure and gene expression (Hamidi, Singh, & Chen, 2015; Saxonov, Berg, & Brutlag, 2006). Genetic studies show that the DNA methylation machinery is necessary for cell development and also has an essential role in numerous biological processes, including genomic imprinting and transposon silencing (Smith & Meissner, 2013). Therefore, aberrant DNA methylation machinery may induce abnormal expression, related to several human diseases, including cancer, metabolic disorders, and neurological disorders (Hamidi et al., 2015). DNA methylation patterns can be made by laboratory techniques, such as sodium bisulfite sequencing, methyl-sensitive polymerase chain reaction (PCR) and DNA methylation array microchips (Shen & Waterland, 2007; Figure 2).

7 | DNA METHYLATION MACHINERY

DNA methylation is catalyzed by the DNA methyltransferase enzyme family (Bird, 2002), of which there are four-independent methyltransferases kinds as well as DNMT1, DNMT3a, DNMT3b, and DNMT3L, which involve in DNA methylation related to inhibition of gene transcription (Turek-Plewa & Jagodzinski, 2005). DNA methyltransferase families mediate this reaction by help SAM as the methyl

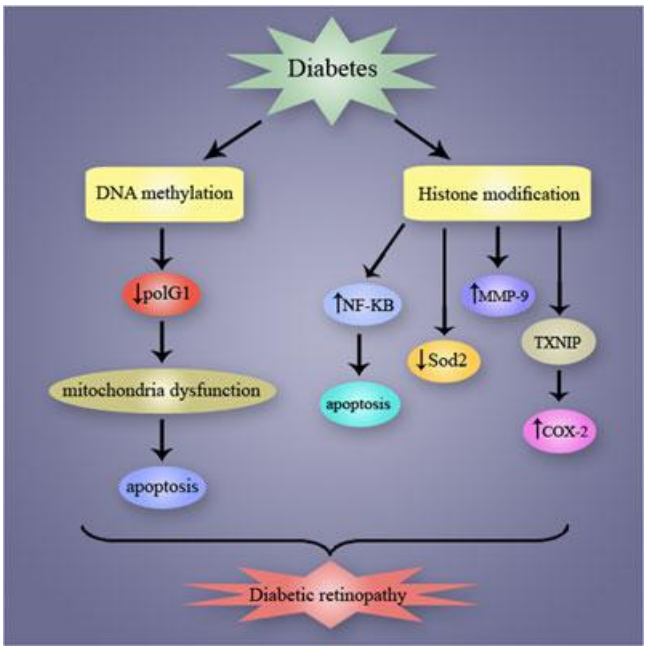

FIGURE 2 Schematic representation of DNA methylation and histone modifications in diabetic retinopathy. COX-2: cyclooxygenase-2; MMP-9: matrix metalloproteinase-9; NF-κB: nuclear factor κB; polG1: polymerase γ; Sod2: superoxide dismutase-2; TXNIP: thioredoxin-interacting protein [Color figure can be viewed at wileyonlinelibrary.com]

donor (Heyward & Sweatt, 2015). DNMT1 is an essential enzyme responsible for the preservation of existing methylation throughout the DNA replication process. DNMT3a and DNMT3b are involved in de novo methylation, but also participate in the maintenance of methylation activity. DNMT3L can modulate the DNA methylation activity of DNMT3a and DNMT3b (Yuan, Li, Xu, Jiang, & Zhou, 2014). In contrast, methylated cytosines are distinguished by the methyl binding domain (MBD) protein family that can mediate the recruitment of enzymes which involved in chromatin remodeling including histone deacetylases thus leading to local changes in chromatin structure (Delpu, Cordelier, Cho, & Torrisani, 2013). Alternatively, DNA demethylating enzymes include not only 5-methylcytosine glycosylase, which can remove the methylated cytosine from DNA, leaving the deoxyribose intact but also MBD2b, which is an isoform that results from initiation of translation at the second methionine codon of the gene encoding MBD2 proteins. In contrast, MBD2b do not have any glycosylase or nuclease activity thus it may cause demethylation by hydrolyzing 5-methylcytosine to cytosine and methanol (Akhavan-Niaki & Samadani, 2013). However, the absence of DNMT enzymes can result in multiple regulatory mechanisms impairment, including misregulation of genes, loss of imprinting, and reactivation of transposable and other repeat elements (Baubec & Schubeler, 2014; Figure 2).

8 | HISTONE MODIFICATIONS

Histones play an important role in the maintenance of chromatin structure and the dynamic and long-term regulation of genes (Stoll, Wang, & Qiu, 2018). In the eukaryotic nucleus, the DNA strand has a highly compacted structure attained through wrapping around histone proteins, so forming a chromatin macromolecular complex (Fan, Krautkramer, Feldman, & Denu, 2015). The nucleosome is the fundamental unit of chromatin, consists of approximately 146 bp of DNA that is wound approximately twice around a histone octamer (Krude, 1999). In contrast, the histone tails only involve multiple posttranslational modifications (PTMs) that include phosphorylation, acetylation, methylation, biotinylation, carbonylation, ubiquitylation, glycosylation, ADP-ribosylation, citrullination, sumoylation, *N*-formylation, butyrylation, propionylation, crotonylation, proline, and aspartic acid isomerization (Sadakierska-Chudy & Filip, 2015). Some studies show complicated PTMs affects their biological functions and action mechanisms (Strahl & Allis, 2000), which have effects on the recognition of processes related to DNA and treatments of diseases such as cancer or DR (Chi, Allis, & Wang, 2010). Therefore, histone modifications affect gene transcription by multiple mechanisms that can be divided into two crucial categories including altering chromatin compaction (a direct effect) and by affecting the employment of effectors complexes (indirect effects). Modifications of histones can also influence chromatin compaction by changing the electrostatic charge association between histone proteins and DNA (Yerra & Advani, 2018). Therefore, histone modification pathways can activate gene or inhibit in the dependent process (Lo et al., 2000). Additionally, histone modifications are associated with epigenetic and important pathways that can co-operate to silence some antitumor genes (Yang, Gu, & Zhen, 2014; Figure 2). Human and mouse retina express most of the genes encoding the histone-modifying enzymes that have been explained so far. Importantly, some of them, including methyltransferase Set7/9 and positive regulatory domain 16 indicated high expression in the adult mouse retina (Reik, Dean, & Walter, 2001). Temporal and spatial expression of enzymes during development allows implementation of regulatory programs essential for cell-type specification and maturation. Interestingly, genes encoding histone methyltransferases such as Ezh1, Ezh2, Mecom, and Prdm8 have dynamic expression patterns through development, indicating their importance in retinogenesis (Cui, Fu, & Dempsey, 2019).

Several studies have explored the association between the transcription of specific genes during retinal development and corresponding deposition of H3K4me2/3 (associated with activation) and H3K27me3 (associated with repression). For example, transcriptional activation of the Ath5 gene, encoding a key TF of the bHLH family, during retinal development has been associated with H3K4me2 deposition at its promoter (Skowronska-Krawczyk, Ballivet, Dynlacht, & Matter, 2004). Similarly, the expression levels of Sox4 and Sox11 are positively associated with H3 acetylation and H3K4me3 and negatively associated with H3K27me3 (Usui et al., 2013).

9 | HISTONES ACETYLATION

Histone acetylation occurs through the action of a HAT and histone deacetylase (HDACs) that maintain the balance between acetylation and deacetylation (Yang et al., 2014). HATs catalyze the transfer of acetyl groups to the ε-amino group of the lysine side chain of histone thus neutralizes the positive charge of histones resulting in not only reduces histones and DNA interaction but also decreases the electrostatic affinity between histone to DNA, and in that way can promote a chromatin structure that is more tolerant to gene transcription (Yerra & Advani, 2018).

10 | HISTONES METHYLATION

HMT enzymes catalyze histone methylation on either arginine or lysine residues. A methyl group from SAM is transferred to ε-amino groups on lysine residues of histone tails by histone-lysine methyltransferases whereas methyl groups from SAM to ω-guanidino nitrogen atoms on arginine residues are transferred by protein arginine methyltransferases (RMTs) (Wolf, 2009). The methylation of histone proteins can affect chromatin folding by an electrostatic mechanism (Volkel & Angrand, 2007) thus histone methylation can result in activation or inhibition of

gene expression that depends on its localization in the histone tail (Sadakierska-Chudy & Filip, 2015).

11 | HISTONES PHOSPHORYLATION

Histone phosphorylation is catalyzed by kinase enzymes that can phosphorylate hydroxyl groups of serine, threonine, and tyrosine residues in histone proteins thus phosphorylation of histones, give a negative charge, correlated with open chromatin followed by facilitation of gene transcription (Awad et al., 2015). The more negatively charged phosphate group could induce alterations in the structure of chromatin and chromatin function. These changes can control multiple processes including the DNA damage response, apoptosis, and gene expression (Awad et al., 2015; Metzger et al., 2008; Singh & Gunjan, 2011).

12 | EPIGENETIC CHANGES AND DR

Hyperglycemia can induce epigenetic modifications in diabetes mellitus (Zhang, Zhao, Hambly, Bao, & Wang, 2017). However, the identification of the common genetic variants and the relationship between genetic factors and DR is not yet completely elucidated (Torres, Cox, & Philipson, 2013).

13 | HISTONE MODIFICATIONS AND DR

In vitro and in vivo studies of DR have shown that the activity of HDACs is increased whereas the activity of HAT is decreased in the retina of diabetic patients, and acetylation of histone proteins is decreased (Zhong & Kowluru, 2010). Mass spectrometry studies show that hyperglycemia induces retinal histones acetylation, which is correlated with increases in proinflammatory responses in the development of DR (Kadiyala et al., 2012). The methyltransferase enzyme causes methylation H3K9 histone that leads to the onset of DR. In contrast, a cohort study on 3,000 diabetic Type 2 patients showed that a polymorphism in the methyltransferase gene was related to microvascular complications (Joglekar, Januszewski, Jenkins, & Hardikar, 2016). The lysine-specific demethylase 1 (LSD1) reduces the level of histone H3 dimethyl lysine 9 (H3K9me2) in the promoter region of MMP-9 and increasing factor of the levels of acetyl H3K9 (Ac-H3K9; Miao et al., 2008). Recent studies show that LSD1 can downregulate SOD2 through demethylation of H3K4 (Kowluru, Santos, & Mishra, 2013). In hyperglycemic condition, histone methyltransferase may increase at the promoter of nuclear factor κB (NF-κB) that associated with its increased transcription (El-Osta et al., 2008), and activated NF-κB pathway can increase apoptosis of retinal capillary cells in diabetes (Romeo, Liu, Asnaghi, Kern, & Lorenzi, 2002). In addition, histone modifications of thioredoxin-interacting protein that is an endogenous inhibitor of antioxidant thioredoxin can help sustain COX-2 expression in the retinal cells of diabetic patients (Perrone, Devi, Hosoya, Terasaki, & Singh, 2009). In streptozotocin-treated rats, microarray studies on the retinal endothelial cells showed that the expression of histone deacetylase enzymes was significantly increased, whereas the activity of a histone acetyltransferase was reduced (Zhong & Kowluru, 2010). In contrast, HAT involved in endothelial fibronectin expression related to DR (Kaur et al., 2006).

14 | DNA METHYLATION AND DR

Some studies suggest a positive relationship between DNA methylation and progression and development of DR. Alternatively, diabetes may be associated with an activation of the enzymes responsible for DNA methylation position in the retinal cells (Kowluru, Mishra, Kowluru, & Kumar, 2016; Mishra & Kowluru, 2014; Zhong & Kowluru, 2013). One study demonstrated that the content of 5-methylcytosine in leukocytes of DR patients was higher than for patients without DR, suggesting that the higher DNA methylation level can be a potential risk factor for the early stages of DR development (Maghbooli, Hossein-nezhad, Larijani, Amini, & Keshtkar, 2015). In contrast, the analyses of blood DNA showed that methylation at CpG sites within some of the genes, including TNF, GIRP, and GPX1 in patients with PDR. Particularly, the genes contributing to the natural killer pathway showed a significantly higher level of DNA methylation, thus methylation in peripheral blood cells can be applied as a predictor for Type 1 diabetes-complicated PDR (Agardh et al., 2015). Hypermethylation of the regulatory region of DNA polymerase γ (POLG1) at the CpG sites may induce progression of DR. POLG1 is involved in DNA transcription that the epigenetic modification results in disorder of the mitochondrial DNA replication system leading to apoptosis of retinal capillary cells (Tewari, Santos, & Kowluru, 2012).

15 | CONCLUSIONS

DR may affect the macula and central visual acuity, therefore, edematous damage is the commonest cause of blindness in diabetes. Studies show epigenetic modifications have an important role in development and progression of DR. Epigenetic modifications can act through switches helping to manage gene activity such as inflammatory response, NF-κB pathway and SOD. In contrast, hyperglycemia is one of the essential factors that can induce epigenetic modifications in diabetic mellitus. However, the identification of common genetic variants and the relationship between genetic factors and DR is not yet to be completely elucidated.

ORCID

Majid Ghayour-Mobarhan http://orcid.org/0000-0001-5947-8904
Zatollah Asemi http://orcid.org/0000-0001-5265-4792

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How to cite this article: Shafabakhsh R, Aghadavod E, Ghayour-Mobarhan M, Ferns G, Asemi Z. Role of histone modification and DNA methylation in signaling pathways involved in diabetic retinopathy. *J Cell Physiol*. 2018;1–8. https://doi.org/10.1002/jcp.27844