• Review Article •

New perspectives on DNA methylation modifications in ocular diseases

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Abstract

• The methylation of DNA is a prevalent epigenetic modification that plays a crucial role in the pathological progression of ocular diseases. DNA methylation can regulate gene expression, thereby affecting cell function and signal transduction. Ophthalmic diseases are a kind of complex diseases, and their pathogenesis involves many factors such as genetic, environmental and individual differences. In addition, inflammation, oxidative stress and lipid metabolism, which abnormal DNA methylation is closely related to, are also considered to be major factors in eye diseases. The current understanding of DNA methylation in eye diseases is becoming more complex and comprehensive. In addition to the simple suppression of gene expression by hypermethylation, factors such as hypomethylation or demethylation, DNA methylation in non-promoter regions, interactions with other epigenetic modifications, and dynamic changes in DNA methylation must also be considered. Interestingly, although some genes are at abnormal methylation levels, their expression is not significantly changed, which indirectly reflects the complexity of gene regulation. This review aims to summarize and compare some relevant studies, and provide with new ideas and methods for the prevention and treatment of different eye diseases, such as glaucoma, retinoblastoma, and diabetic retinopathy.

• **KEYWORDS:** DNA methylation modification; epigenetic; glaucoma; retinoblastoma; diabetic retinopathy; methylase inhibitors

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INTRODUCTION

Various epigenetic phenomena have been identified, such as RNA methylation[1], histone modification[2], genetic imprinting[3], X-chromosome inactivation[4], and transposon recruitment[5]. However, DNA methylation is the most predominant form of storing epigenetic information and is considered to be the core of epigenetic inheritance[6]. Endogenous factors like DNA methyltransferase[7] and some exogenous factors can introduce methyl groups into DNA molecules[8-12]. In mammals and humans, DNA methylation has been closely linked to many biological phenomena, including aging[13-15], tumorigenesis[16-19], and death[20-22]. Cytosine-phosphate-guanine (CpG) dinucleotide cytosine methylation is the most common form of DNA methylation in the human body. It can alter genetic expression without modifying the DNA sequence and is one of the most important mechanisms of epigenetic regulation[23]. Recent studies in ophthalmology have demonstrated that abnormal DNA methylation can lead to aberrant expression of key genes[24-25], contributing to the onset and development of various ophthalmic diseases such as corneal and conjunctival diseases, glaucoma, cataract, retinal diseases, and ocular tumors. For example, abnormal DNA methylation disrupts the balance between proliferation and differentiation of corneal epithelial cells in corneal and conjunctival diseases, affecting corneal transparency and homeostasis[26-27]. Similarly, abnormal DNA methylation in glaucoma patients impacts the expression of genes involved

in intraocular pressure (IOP) regulation[28], thereby affecting aqueous humor flow and IOP control. Furthermore, aberrant DNA methylation state of lens epithelial cell is associated with cataract development which impairs lens transparency and function[29-30]. Abnormal DNA methylation also interferes with retinal cell function and signal transduction pathways leading to visual dysfunction in retinal diseases by affecting light perception and transmission within the retina[31-32]. Additionally, abnormal levels of DNA methylation are closely related to the occurrence and progression of ocular tumors as they influence tumor suppressor gene expression as well as oncogenes impacting tumor cell proliferation apoptosis, and metastasis[33]. Overall, the role played by aberrant DNA methylation cannot be overlooked when considering ophthalmic diseases. The objective of this review is to elucidate the mechanisms underlying DNA methylation in various ophthalmic diseases, thereby providing novel insights for the development of relevant therapeutic strategies and offering more precise and effective treatment targets.

REVIEW OF DNA METHYLATION

DNA Methylation DNA methylation is a form of chemical modification in which methyl groups are selectively added to a DNA molecule through covalent bonding in the presence of DNA methyltransferase[34].

Structure DNA methylation modifications can occur at sites such as the C5 position of cytosine (5mC), the N6 position of adenine (6mA), and the N4 position of basal cytosine (4mC)[35-37]. The term "DNA methylation" in general studies mainly refers to the process of methylation that occurs at the 5th carbon atom on cytosine in CpG dinucleotides, resulting in a product called 5-methylcytosine (5mC)[38-39]. Different DNA methylation enzymes catalyze various methylations[40-41].

Location in the Genome DNA methylation is a crucial epigenetic modification that typically occurs at CpG sites within the genome, which are base pairs formed by cytosine (C) and guanine (G) in the DNA strand[42]. These CpG sites are widely distributed throughout the genome but tend to cluster together in CpG islands, regions with a high density of aggregated CpG sites located near the promoter region of a gene. The presence of CpG islands significantly impacts gene regulation and expression because DNA methylation within the gene's promoter region can impede transcription factor binding, thereby interfering with the formation of the transcription initiation complex and leading to gene silencing[43-44]. In addition to densely clustered regions in CpG islands, there are also scattered distributions of CpG sites across the genome. These scattered CpG sites may play a role in regulating individual genes' expression or specific gene regions' methylation status. Furthermore, apart from CpG sites, DNA methylation may occasionally occur at non-CpG sites; however, this non-canonical form of methylation is relatively rare in mammals[45-46]. This non-CpG methylated form might have essential functions in certain cell types and specific physiological states[47]; nevertheless, its precise functions and regulatory mechanisms remain incompletely understood.

Mechanisms of DNA Methylation The methylation pattern of DNA is achieved through the action of DNA methyltransferases.

DNA methylation enzymes: two classes The first type is maintenance DNA methyltransferase (DNMT1)[48-50], while the second type includes ab initio methylases such as DNMT3A[51-52], DNMT3B[53-54], and DNMT3L[55-56]. During DNA methylation, cytosine protrudes from the DNA double helix into a cleft that can bind to the enzyme. Cytosine methyltransferase catalyzes the transfer of an active methyl group from S-monoadenosylmethionine to the cytosine 5-position, resulting in the formation of 5-methylcytosine.

DNA methylation reactions: two types *Ab initio* methylation refers to the methylation modification of non-methylated DNA, which mainly occurs in the early stage of embryonic development and is used to establish the methylation status of cells in the early embryo[57-58]. Retention of methylation occurs after each replication of methylated DNA. The nascent DNA strand is initially in a non-methylated state due to semi-conserved replication. At this point, specific DNA methyltransferases utilize the semimethylated DNA as a template for methylation modification of the non-methylated DNA strand, ensuring that the replicated DNA double strand maintains the methylated state inherited from parental DNA[59-60]. Without methyltransferase activity, passive demethylation occurs after multiple rounds of replication[61]. Figure 1 provides a brief summary of DNA methylation content.

DNA DEMETHYLATION

Normally, the CpG island region near the promoter is not methylated, and methylation in the gene promoter region can lead to transcriptional silence. The methylation process is reversible, and demethylation usually means reactivation of gene expression[62-63]. DNA demethylation is mainly divided into active demethylation[64-65] and passive demethylation[66-67]. Active demethylation refers to the direct removal of methyl groups from DNA through the action of enzymes. Passive demethylation, on the other hand, refers to the loss of DNMT activity, which results in incorrect copying and delivery of methyl groups to the newly synthesized DNA strand. Known DNMT inhibitors can be classified into two categories: nucleoside analogs and non-nucleoside analogs[68]. Nucleoside analogs have different modifications on the cytosine ring that block methylation by binding to newly synthesized DNA; they are essentially cytosine analogs. Interestingly, DNMT inhibitors may cause proteasomal degradation of the target

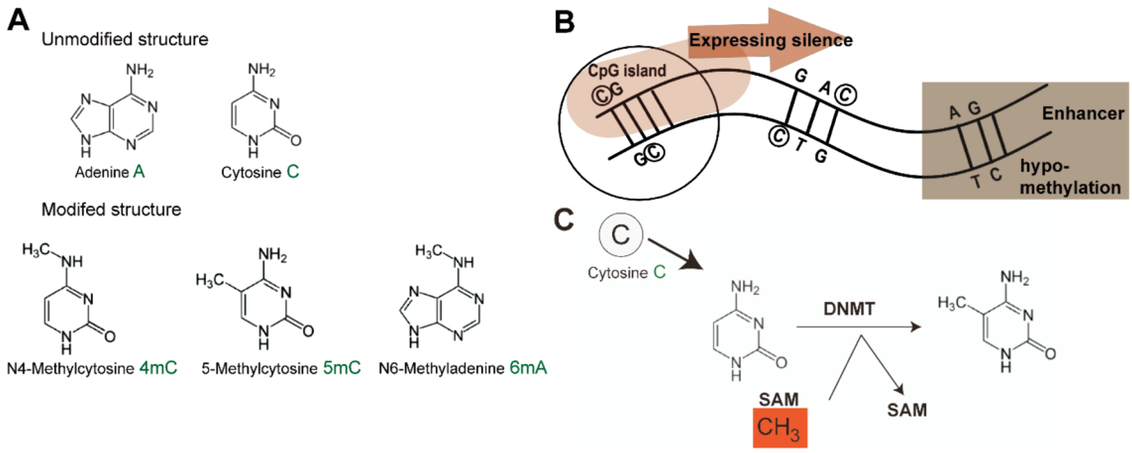

Figure 1 DNA methylation modifications and mechanisms A: Three methylation modifications, namely the N4 position of basal cytosine (4mC), C5 position of cytosine (5mC) , and the N6 position of adenine (6mA); B: Overall process of DNA methylation; C: Selective addition of methyl groups to a DNA molecule by DNA methyltransferases.

Table 1 Inhibitors of DNMTs and their mechanisms

Drug	Mechanism of action	Clinical application
Azacitidine[69]	Replaces cytidine during DNA replication, forms a covalent bond with DNMT, and inhibits DNA cytosine methylation	Myelodysplastic syndromes, chronic myeloid leukemia, other cancers
Decitabine[70]	Binds directly to DNA, inhibits DNMT, reduces DNA methylation, induces cell differentiation or apoptosis	
Guadecitabine[71]	Cytidine analog, inhibits DNA methylation, chemically stable, lower cytotoxicity, orally available	No approved clinical application yet
Arsenic Trioxide[80]	It is cytotoxic to leukemia cells, promotes apoptosis and cell differentiation, and partially inhibits DNMT3A/B	Acute promyelocytic leukemia
Procaine[77]	Inhibiting DNMT1 activity, it acts on CpG island regions	Potential application in breast and liver cancer therapy
MG98[79]	Reduces the expression of DNMT1 protein in tumor cells and exhibits synergy with other drugs	No approved clinical application yet

The table summarizes three nucleoside inhibitors, namely azacitidine, decitabine, and foldobarbital; two non-nucleoside inhibitors, arsenic trioxide and procaine; as well as the antisense nucleotide analog MG98. DNMT: DNA methyltransferase. DNMT1, DNMT3A, and DNMT3B are three major members of the DNA methyltransferase family.

enzyme (at least in the case of DNMT1). Nucleoside analog inhibitors include azacitidine[69], decitabine[70], foldobarbital[71], and fazarabine[72].

The risk of using nucleoside analogs as DNMT inhibitors is associated with their binding to DNA, which may result in toxicity and undesired side effects due to the potential formation of mutagenic damage[73]. Additionally, several compounds have been proposed as DNMT inhibitors, including SGI-110[74], RG108[75], hydralazine[76], procaine[77], among others. Another strategy involves the development of antisense oligonucleotides that can inhibit DNMT at the translational level[78]. MG98[79] represents this class of inhibitors, and its ability to suppress DNA methylation of tumor suppressor genes has been investigated in preclinical studies and clinical phase I/II trials. Table 1[69-71,77,79-80] provides a summary of relevant DNA demethylation drugs.

Abnormal DNA Methylation Modifications and Ocular Membrane-Related Diseases (Table 2)

DNA methylation modifications and Fuchs endothelial corneal dystrophy Fuchs endothelial corneal dystrophy (FECD) is a common chronic progressive corneal disease[81-82]. The disease primarily affects the corneal endothelial cells[83], which are located in the inner layers of the cornea[84] and play an important role in maintaining corneal clarity and preventing edema[85-86]. In patients with FECD, the progressive loss and dysfunction of corneal endothelial cells lead to severe impairment of vision[87]. The characteristic pathological change in FECD is the accumulation of abnormal extracellular matrix (ECM)[88-89]. However, the molecular pathological mechanisms behind this disease are not fully understood.

Abnormal DNA methylation of miRNA genes has been found in corneal endothelial cells of FECD patients, which may result in altered expression levels of miRNAs. Specifically, altered methylation of the promoter region of the miR-199B gene leads to reduced expression levels of miR-199b-5p. Furthermore, it was discovered that miR-199b-5p negatively regulates two transcription factors, Snai1 and ZEB1, thereby increasing ECM deposition in FECD[90]. Hypermethylation of the promoter DNA region of the *SLC4A11* gene in late-onset FECD can silence the *SLC4A11* gene and subsequently affect ion transport function, leading to corneal endothelial dysgenesis[91]. Additionally, sporadic changes in DNA

Table 2 Studies on DNA methylation in ophthalmic diseases

Disease	Genes with DNA methylation modifications and their effects	Insights
Fuchs endothelial corneal dystrophy	Abnormal methylation at 3488 CpG sites in the *TCF4* gene, but no changes in the gene[94]	DNA methylation alone may have limited impact on gene regulation
Uveitis	DNA methylation inhibitor Zebularine targeted CD4 T cells, suppressed IFN-γ and IL-17[96]	Modulating DNA methylation levels in immune cells may be a novel therapeutic strategy for uveitis
Diabetic retinopathy	Base mismatches and high methylation of cytosine in mitochondrial DNA lead to damage[115]	Interventions targeting mitochondrial DNA and cytosine demethylation may be new strategies for treating diabetic retinopathy
AMD	Hypomethylation of the *IL17RC* gene may be associated with AMD pathogenesis[128]	More replication studies are needed before considering clinical applications of epigenetic association studies for AMD pathogenesis
Choroidal melanoma	Demethylation targeting tumor suppressor genes may inhibit tumor progression[131]	Combining targeted therapy and DNA methylation inhibitors may be a potential treatment for choroidal melanoma
RB	High methylation of the *RB1* gene promoter DNA detected in aqueous humor[139]	Aqueous humor *RB1* gene promoter DNA methylation levels provide potential for early diagnosis and gene therapy for clinical RB
Glaucoma	DNA methylation modulates genes related to intraocular pressure[141-142]	The connection between DNA methylation and gene mutations should be considered
Cataract	Increased methylation levels of the αA-crystallin gene observed in cataract patients[153]	DNA methylation inhibitors may be a new strategy for treating eye diseases post-surgery

AMD: Age-related macular degeneration; RB: Retinoblastoma. This table summarizes selected studies on DNA methylation-related ophthalmic diseases that are mentioned in the full text and provides corresponding insights.

methylation accumulate in fundamental biological processes within corneal endothelial cells, resulting in alterations to the expression and function of related genes. These genes are involved in important functions of corneal endothelial cells, such as cytoskeletal organization, ion transport, hematopoietic cell differentiation, and cellular metabolism. An amplification of cytosine-thymine-guanine repeats at the CTG18.1 locus in the *TCF4* gene has been found in some diseases, leading to abnormalities in the *TCF4* gene that may be one of the key factors in FECD pathogenesis[92-93].

Previous studies have focused on the role of hypermethylation in FECD, but aberrant DNA methylation is not directly linked to FECD. A recent study identified aberrant methylation at 3488 CpG sites of the *TCF4* gene in the corneal endothelium of patients with delayed-onset FECD. However, significant alterations in *TCF4* gene expression were not found, and the study ruled out hypermethylation as a pathogenic disease mechanism[94].

DNA methylation modifications and uveitis Methylation modifications regulate the production of cytokines and the modulation of the immune response in immune cells[95]. In uveitis, it was found that methylation changes occurred in specific genes Tbx21 and Rorc's CpG sites, which were associated with cytokines produced by immune cells such as interferon (IFN)-γ and interleukin (IL)-17[96]. The overexpression of TET2 may lead to the downregulation of Notch1 methylation, activating the Notch1 signaling pathway and inducing differentiation of primitive CD4 T cells into the Th17 subpopulation. This disturbance in balance between Th17/Treg ratio can be observed in uveitis patients[97]. Th17 cells primarily produce pro-inflammatory cytokines such as IL-17, which are involved in regulating immune responses and inflammatory reactions. On the other hand, Treg cells have immunosuppressive and immunomodulatory functions by producing inhibitory cytokines like IL-10 and tumor necrosis factor (TGF-β)[98]. Intraocular inflammation occurs when this balance is disrupted. These studies suggest that methylation plays a crucial role in regulating immune responses and the development of uveitis.

Additionally, the use of Zebularine, a DNA methylation inhibitor, made it possible to target CD4 T cells and inhibit the expression of IFN-γ and IL-17. This led to alleviation of intraocular inflammation and retinal tissue damage, demonstrating the potential of drugs that modulate methylation levels in uveitis treatment[99]. In summary, methylation plays an important role in immune cell development and uveitis. Modulating DNA methylation levels in immune cells may be a new strategy for treating uveitis.

DNA methylation modification and diabetic retinopathy In diabetic patients, hyperglycemia damages the microvasculature of the retina[100] and leads to pathological changes in the microvasculature, such as increased vascular permeability[101], leakage[102], and neovascularization[103]. These abnormal vascular changes result in insufficient blood supply and hypoxia in the retina[104], which subsequently triggers damage, oxidative stress, and inflammatory responses in retinal tissues[105]. Simultaneously, the activity of DNA methylation enzymes (*e.g.*, DNMT1) increases in hyperglycemic states, leading to elevated levels of DNA methylation[106]. This causes a series of changes including increased methylation of certain key genes that suppress their expression, such as DAAO[107], PPARα[108], MEG3[109], and Sirtuin1. Hyperglycemia accelerates Rac1 transcription through dynamic DNA methylation-hydroxymethylation of the Rac1 promoter, resulting in activation of the Rac1-Nox2 signaling pathway and mitochondrial damage.

In addition, SPT, an enzyme that inhibits the *de novo* biosynthesis of sphingosine phospholipids, regulates

the activation of methylation and hydroxymethylation mechanisms. This regulation prevents the increase in Rac1 transcription, attenuates the activation of the Rac1-Nox2 signaling pathway, and protects mitochondria from cytoplasmic reactive oxygen species (ROS) damage. Consequently, it prevents the loss of retinal capillary cells[110]. Findings suggest that in diabetic patients, hyperhomocysteinemia promotes the development of diabetic retinopathy by altering DNA methylation and hydroxymethylation. It also reduces TIMP1-MMP-9 interaction while activating MMP-9 to promote apoptosis in capillary cells[111].

Furthermore, folic acid was found to affect the regulation of DNA methylation modification in diabetic retinopathy (DR) retinal microvascular cells in a hyperglycemic rat model[112]. Numerous studies have indeed confirmed the close relationship between mitochondrial damage and DNA methylation[113-114]. In addition to changes induced by methylation in certain genes leading to oxidative damage in mitochondria, mitochondrial damage in the retina during the development of DR may be attributed to base mismatches in mitochondrial DNA and hypermethylated cytosine. The regulation of DNA methylation or its deamination could potentially slow down the progression of diabetic retinopathy by preventing the formation of mitochondrial dysfunction[115], which provides an important rationale for developing new therapeutic strategies and drugs.

By interfering with DNA methylation and cytosine deaminase, we expect to improve the retinal condition of diabetic patients and reduce the risk and severity of diabetic retinopathy. This study also highlights the importance of the metabolic memory phenomenon[116] in DR, where interactions between DNA methylation and base mismatch persist even after termination of hyperglycemia, resulting in long-lasting effects on the further development of retinal damage. Therefore, by intervening in DNA methylation and cytosine deaminase processes, we anticipate enhancing the retinal condition of individuals with diabetes while decreasing their susceptibility to and severity of DR.

DNA methylation modifications and retinitis pigmentosa Retinitis pigmentosa (RP) is a group of neurodegenerative retinopathies that result in blindness due to progressive and irreversible death of photoreceptor cells[117]. Abnormalities in DNA methylation have been implicated in the pathogenesis of RP, as aberrant methylation states interfere with the development and function of photoreceptor cells, leading to RP[118-119].

Accumulation of ROS in retinal pigment epithelium, caused by damaged photoreceptor's daily recycling, induces the oxidative DNA damage, a key regulator of microglial activation and photoreceptor degeneration, as well as mutations in endogenous antioxidant pathways involved in DNA repair, oxidative stress protection and activation of antioxidant enzymes (*MUTYH*, *CERKL* and *GLO1* genes, respectively) [120]. The upregulation of the P2X7 receptor, causing pro-inflammatory cytokines and ROS release by macrophages and microglia, contributing to neuroinflammatory and neurodegenerative progression[121]. It has been found that the alkylating agent methyl methanesulfonate (MMS) can induce DNA base damage by adding alkyl groups to DNA, which affects epigenetic modifications. Decitabine ameliorates retinal photoreceptor cell damage induced by MMS by targeting and inhibiting DNMT3A and DNMT3B[122].

DNA methylation modification and age-related macular degeneration Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population worldwide[123]. Patients with AMD have reduced levels of DNA methylation in *IL17RC*, and promoter hypomethylation leads to increased expression of IL17RC proteins and mRNAs, suggesting that it may play a role in the pathogenesis of AMD[124]. The researchers used methods such as illumina human methylation450 bead arrays to detect DNA methylation of the IL17RC promoter. However, contrary to previous findings, some studies did not find evidence of differential methylation between AMD patients and age-matched controls[125]. Therefore, the study concluded that hypomethylation of the *IL17RC* gene promoter in peripheral blood is not suitable as a clinical biomarker for AMD. This emphasizes the need for more replication studies for epigenetic association research, as well as consideration of factors such as dynamic changes in DNA methylation before proceeding to clinical applications. Meanwhile, there are some more well-defined genes closely associated with AMD, such as ELOVL fatty acid elongase 2 (*ELOVL2*)[126-127]. The expression levels of the *ELOVL2* gene in the retina of patients with AMD are significantly reduced. Impaired function of ELOVL2 interferes with lipid synthesis, leading to increased endoplasmic reticulum stress and mitochondrial dysfunction. This, in turn, results in a critical senescence phenotype at both cellular and physiological levels[128].

DNA Methylation Modifications and Ocular Tumors

DNA methylation modification and uveal melanoma Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with an annual incidence ranging from 0.002‰ to 0.008‰. In terms of tumor treatment, demethylation, which regulates related genes, appears to be a potential way to inhibit tumor progression. Reactivation of E-cadherin protein expression through promoter demethylation may represent a potential therapeutic strategy for treating melanoma[129]. Inactivation of the *p16INK4A* gene is also caused by hypermethylation of its promoter region, which in turn affects the progression of UM[130]. However, it is crucial to focus on changes in certain oncogenes in the early stages of

cancer treatment for UM. While there may be a large number of genetic alterations throughout the entire cancer landscape and a strong link between hypermethylation levels and these genes, not all abnormalities in gene function resulting from dysregulated methylation will significantly affect tumors. Attention should be directed towards important mutated genes. Genes such as *RASSF1A*[131] and *p16*[132] are frequently hypermethylated in human cancers, serving as tumor suppressor genes. Hypermethylation of the *RASSF1A* promoter is also reflected in UM. Candidate genes and pathways correlated with metastasis development. For instance, BAP1 methylation has been recognized as an important prognostic marker of UM metastasis[133], and several studies have highlighted that DNA methylation can be used to trace the tissue of origin of various tumors[134-135]. Jurmeister *et al*[136] highlighted that only UMs are characterized by a different global DNA methylation profile, with distinct epigenetic signatures. Thus DNA methylation analysis differentiate UMs from melanomas of other primary sites. Methylation patterns of primary tumors and metastases are different. Comparing the methylation status of metastatic primary UM and their corresponding metastases founded that in the latter case methylation events are likely random events or eventually patient specific[137].

DNA methylation modification and retinoblastoma CCCTC-binding factor (CTCF) plays an important role in maintaining the proper chromatin structure of tumor suppressor gene promoters. Its absence may lead to altered chromatin structure, dysregulation of transcription factor interactions, and an increase in DNA methylation. These changes subsequently affect the expression and normal regulation of the tumor suppressor gene *Rb*[138]. DNA methylation modifications are not only present in DNA within tumor tissues; RB1 promoter DNA hypermethylation was also detected in free cellular DNA in ocular atrial fluid, similar to that found in tumor tissues with retinoblastoma (RB)[139].

This suggests that introducing related genes into the atrial fluid to treat RB could be a possibility. By introducing the *RB1* gene or related oncogenes, we can attempt to restore the function of tumor suppressor genes and chromatin structure, thereby inhibiting the proliferation and development of RB. Additionally, the level of DNA methylation in the *RB1* promoter in atrial fluid provides potential for early clinical diagnosis of RB.

DNA Methylation Modifications and Glaucoma Glaucoma is one of the diseases with high rates of blindness worldwide, and recent studies have found that the incidence and inheritance pattern of the disease vary considerably across populations. Additionally, numerous genetic causative loci may exist[140]. Some genes closely related to glaucoma, such as *MYOC*[141-142] and *CYP1B1*[143-144], which may be affected by epigenetic regulation, have remained poorly studied. The current study identified some genes related to IOP that are affected by DNA methylation regulation. However, the available evidence suggests that there is not a direct link between glaucoma and IOP[145-146]. Instead, gene mutations have a more significant association with the pathogenesis of glaucoma. DNA methylation appears to play a more crucial role than expected in regulating gene mutations. On one hand, methylation causes gene silencing; on the other hand, gene mutations lead to changes in methylation. Methylation of DNA itself stabilizes its structure. This stabilization helps prevent mutations and damage to DNA sequences, maintaining the integrity of the genome.

DNA Methylation Modification and Cataracts Cataract is a disease in which clouding occurs due to the degeneration of lens proteins and is mainly caused by aging, but it may also be caused by other factors such as genetics, trauma, and diabetes[147-148]. Oxidative stress is closely related to the development of age-related cataracts, and the *OGG1* gene is an important DNA repair gene involved in repairing DNA damage caused by oxidative stress[149-150]. It was found that CpG islands in the first exon of *OGG1* were hypermethylated in the lens cortex of senile cataract patients[151]. In addition, the GSTP1 promoter CpG island, which is an antioxidant, also showed a hypermethylated state[152]. Interestingly, one study found elevated methylation levels of the *αA-crystallin* gene in cataract patients after vitrectomy[153]. This suggests that DNA methylation is influenced not only by DNA methylation enzymes but also by external factors. Therefore, we need to consider a combination of surgical and environmental changes along with some methylation enzyme inhibitors to inhibit the progression of the disease.

DNA Methylation Modifications and Myopia Myopia involves the influence of both genetic and environmental or behavioral factors, as well as their interactions[154]. It has been found that children with high myopia have significantly lower levels of DNA methylation in certain genes, including *PCDHA10* and some genes previously associated with ocular phenotypes[155]. In contrast, other studies have indicated that DNA methylation levels of genes associated with eye axis length, such as *COL1A1* and *COL2A1*[156-158], may be altered in myopic eyes. These alterations may impact the expression of these genes, leading to abnormal eye growth and myopia.

DISCUSSION

Although DNA methylation plays a crucial role in gene regulation, and abnormal methylation of certain genes has been associated with specific diseases, the mechanisms of gene regulation are highly complex. Abnormal methylation of some genes may impact their expression, but it is also possible that

they remain unaffected. In the study of ophthalmic diseases, it is not sufficient to solely identify genes with abnormal methylation as predictive indicators for diseases; extensive clinical research is still required to conduct large-scale studies on the methylation status of more genes in order to accurately assess disease risks and predict outcomes. Furthermore, investigating the methylation patterns of corresponding genes in different cells and tissues will contribute to a deeper understanding of their roles in ophthalmic diseases and drive the development of treatment strategies. Currently, treatment approaches targeting abnormal DNA methylation may involve utilizing methyltransferase inhibitors or demethylating agents to regulate gene expression. However, most related drugs are still under development and have not been widely implemented clinically. The causes behind aberrant levels of DNA methylation are multifactorial and not well understood; they may involve interactions between genetic factors, environment, lifestyle choices among others. Relying solely on these drugs for treatment may yield limited results. With advancements in technologies such as single-cell transcriptomics and epigenomics techniques, we can anticipate gaining a more comprehensive understanding of the mechanisms underlying methylation regulation in ophthalmic diseases. These research findings will establish a foundation for future developments towards more effective treatments and personalized medical approaches while providing vital support for improving patients' quality of life with ophthalmic diseases.

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