

REVIEW ARTICLE

Epigenetic landscape of ocular cancer: A roadmap to understanding gene and protein dysregulation

Shalini Sanyal^{1*}, Sayantan Ghosh¹, and Abhijit Ghosh²¹Prof. Brien Holden Eye Research Centre, L. V. Prasad Eye Institute, Hyderabad, Telangana, India²Molecular Parasitology Laboratory, National Institute of Animal Biotechnology, Hyderabad, Telangana, India

Abstract

Ocular malignancies exhibit profound epigenetic dysregulation that orchestrates oncogenic activation, tumor suppressor silencing, and transcriptional reprogramming. This review delineates the epigenetic mechanisms implicated in ocular cancers, encompassing DNA methylation aberrations, histone post-translational modifications, non-coding RNAs (ncRNAs), and chromatin-remodeling complexes that cooperatively modulate gene expression dynamics, cellular plasticity, and tumor–microenvironment interactions. Perturbations in the DNA methylome, such as CpG island hypermethylation of *RB1* and *CDKN2A*, and global hypomethylation of transposable elements, potentiate genomic instability, facilitate immune evasion, and reinforce tumorigenic transcriptional circuits. Similarly, dysregulated histone acetylation and methylation landscapes alter chromatin accessibility, disrupting pathways governing cell cycle progression, apoptosis resistance, and metastatic competence. ncRNAs, such as oncogenic microRNA-17–92 clusters and lncRNA HOTAIR, further amplify oncogenic cascades by post-transcriptional repression of tumor suppressors and modulation of chromatin-associated effector proteins. This review provides an overview of current advances in the understanding of epigenetic modifications, including DNA methylation dynamics, histone modification networks, and ncRNA-mediated regulation, in retinoblastoma, uveal melanoma, and other ocular malignancies. By integrating recent findings from multi-omics analyses, the review highlights how epigenetic reprogramming intersects with genomic instability to drive tumor heterogeneity and therapeutic resistance. Furthermore, it underscores the translational potential of epigenetic biomarkers for risk stratification, prognostication, and therapeutic response prediction, and discusses emerging strategies targeting DNA methyltransferases and histone deacetylases to reverse aberrant epigenetic states. Collectively, this review aims to contextualize the evolving epigenomic landscape of ocular cancers and outline avenues for precision epigenetic therapy in ocular oncology.

Keywords: Ocular neoplasms; Retinoblastoma; Uveal melanoma; Epigenetics; Therapeutics; DNA methylation; Histone modifications

***Corresponding author:**
Shalini Sanyal
(sanyal.shalini@gmail.com)

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1. Introduction

Malignant neoplasms of the eye exhibit distinct genetic and epigenetic landscapes, contributing to their complexity and heterogeneity, while posing significant challenges due to their aggressive nature, potential for metastasis, and, in some cases, resistance to conventional therapies. For example, retinoblastoma (RB), the most common intraocular malignancy in children, arises primarily from biallelic inactivation of the *RB1* gene,¹ whereas uveal melanoma (UM), the predominant intraocular cancer in adults, is driven by mutations in *GNAQ*, *GNA11*, *BAP1*, and other tumor-related genes.² Despite these well-characterized genetic drivers, accumulating evidence suggests that epigenetic dysregulation plays a crucial role in tumor progression, heterogeneity, and therapeutic resistance in these malignancies.³

Epigenetics encompasses heritable yet reversible modifications that influence gene expression without altering the DNA sequence.^{4,5} These modifications, including DNA methylation, histone modifications, non-coding RNA (ncRNA)-mediated regulation, and chromatin remodeling, orchestrate complex transcriptional programs that govern cellular identity and transformation. In ocular cancers, aberrant DNA methylation silences tumor suppressors, dysregulated histone modifications reshape chromatin architecture, and altered ncRNAs modulate oncogenic signaling pathways, collectively driving malignancy.³⁻⁶ Understanding these epigenetic alterations offers novel insights into tumor biology and potential avenues for therapeutic intervention.

The emergence of epigenetic-targeted therapies, including DNA methyltransferase (DNMT) inhibitors (DNMTis), histone deacetylase (HDAC) inhibitors (HDACis), and RNA-based therapeutics, highlights the translational relevance of this field.⁷ Given the growing recognition of epigenetics in ocular oncology, this review aims to provide a comprehensive overview of the epigenetic landscape in RB, UM, and other ocular malignancies, discussing key regulatory mechanisms, recent advances, and potential clinical implications.

2. Epigenetic mechanisms overview in relation to cancer

Epigenetics refers to specific modifications distinct from DNA sequences that affect gene expression and, subsequently, phenotype.⁴ These modifications are essential for cellular functions, such as differentiation, proliferation, and apoptosis, and play an important role in health and disease.⁸ In cancer, the dysregulation of epigenetic processes plays a critical role in tumorigenesis by silencing tumor suppressor genes, activating oncogenes,

and disrupting normal cellular homeostasis. Unlike genetic mutations, which are often irreversible, epigenetic modifications are dynamic and reversible, making them attractive targets for therapeutic intervention.^{9,10}

In ocular cancers, such as RB, UM, and conjunctival melanoma, epigenetic alterations have been increasingly recognized as key contributors to tumor initiation, progression, and resistance to therapy.^{8,11-15} For example, in RB, epigenetic silencing of the *RB1* gene, often through promoter hypermethylation, can mimic the effects of a genetic mutation, leading to unchecked cellular proliferation.¹⁶ Similarly, UM, which is driven by mutations in *GNAQ/GNA11*,¹⁷ also exhibits epigenetic dysregulation, including aberrant DNA methylation and histone modifications, which contribute to its aggressive behavior and resistance to conventional therapies.¹⁸ Moreover, metastatic progression of UM has been shown to be strongly associated with mutations in the *BAP1* gene on chromosome 3.¹⁹

The identification of epigenetic biomarkers offers new opportunities for early diagnosis and prognosis, while the development of epigenetic-targeted therapies—such as DNMTis and HDACis^{20,21}—holds promise for more effective treatment strategies.

The primary epigenetic mechanisms implicated in ocular cancers include DNA methylation,²² histone modifications,²³ ncRNAs,²⁴ and chromatin remodeling complexes,²⁵ each of which plays a distinct role in shaping the tumor epigenome²⁶ (Figure 1).

2.1. DNA methylation

DNA methylation is one of the most well-characterized epigenetic modifications, playing a crucial role in gene expression regulation. It involves the covalent addition of a methyl group ($-CH_3$) to the cytosine residue of CpG dinucleotides, a process primarily mediated by DNMTs, such as DNMT1, DNMT3a, and DNMT3b.²⁷ Under normal physiological conditions, DNA methylation maintains genomic stability and regulates gene expression by silencing repetitive elements, imprinting genes, and ensuring appropriate cell differentiation.²⁷⁻²⁹ However, aberrant DNA methylation plays a central role in ocular cancer pathogenesis, influencing tumor suppressor gene silencing, oncogene activation, and genomic stability (Figure 2).

2.1.1. Hypermethylation of tumor suppressor genes

Tumor suppressor gene silencing via promoter hypermethylation is a well-documented mechanism in several cancers, including ocular malignancies such as RB and UM (Table 1).

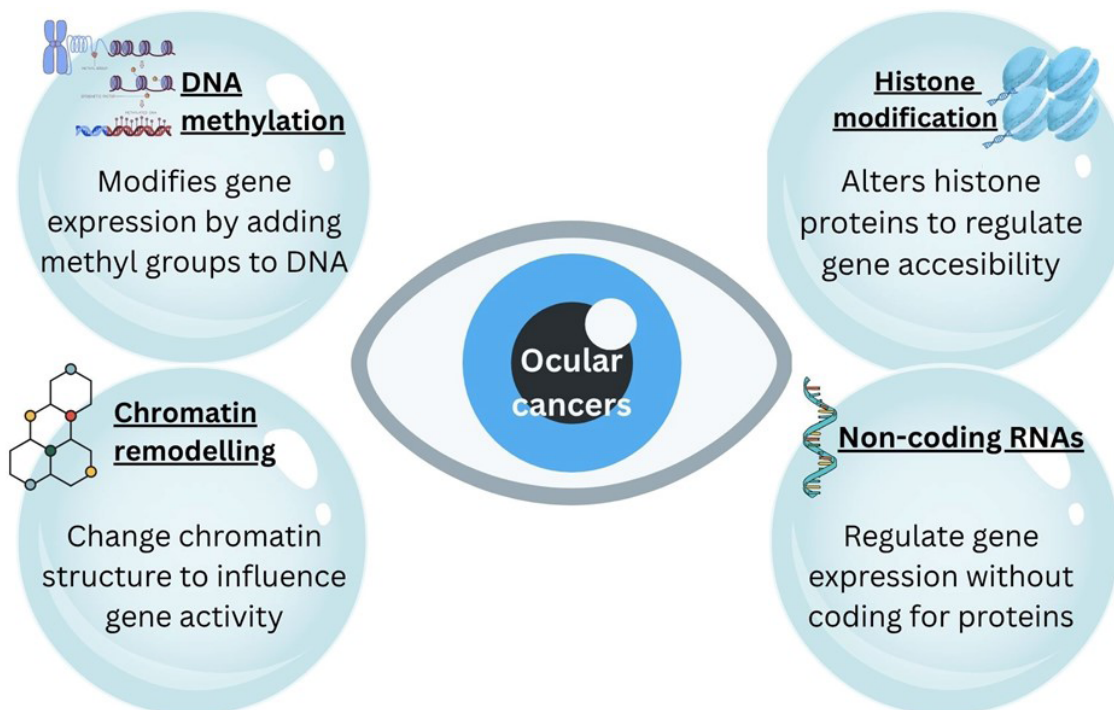


Figure 1. Role of different epigenetic mechanisms in cancer progression. Created with Canva

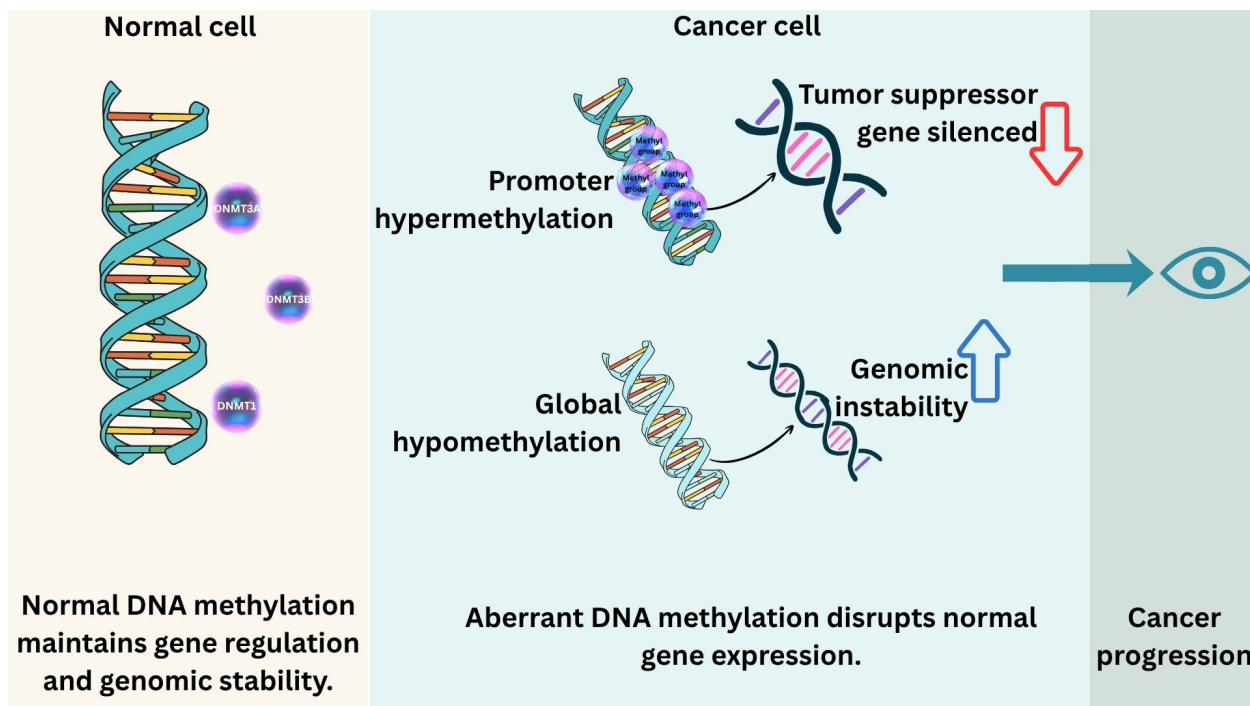


Figure 2. Role of DNA methylation in cancer progression. Created with Canva.

Table 1. Studies documenting hypermethylation of tumor suppressor genes in ocular cancers

Gene	% of patients with hypermethylation	Disease	Function	References
<i>RB1</i>	100% (All five patients)	Retinoblastoma	Tumor suppressor	Sakai <i>et al.</i> ²⁹
<i>RB1</i>	100% (All nine patients)	Retinoblastoma	Tumor suppressor	Ohtani-Fujita <i>et al.</i> ³⁰
<i>RASSF1A</i>	82–89%	Retinoblastoma/ Uveal melanoma	RAS-associated domain family	Cohen <i>et al.</i> , ³¹ Harada <i>et al.</i> , ³² Maat <i>et al.</i> , ³³ Maat <i>et al.</i> , ³⁴ Merhavi <i>et al.</i> , ³⁵ Voelter <i>et al.</i> ³⁶
<i>MGMT</i>	15–58%	Retinoblastoma/ Uveal melanoma	MGMT (DNA repair)	Choy <i>et al.</i> , ³⁷ Choy <i>et al.</i> , ³⁸ Maat <i>et al.</i> , ³² Maat <i>et al.</i> , ³³ Merhavi <i>et</i> <i>al.</i> , ³⁵ Voelter <i>et al.</i> ³⁶
<i>NEUROG1</i>	52%	Retinoblastoma	Neurogenin	Cohen <i>et al.</i> , ³¹ Livide <i>et al.</i> ³⁹
<i>MSH6</i>	50%	Retinoblastoma	DNA mismatch repair MutS family	Cohen <i>et al.</i> , ³¹ Livide <i>et al.</i> ³⁹
<i>CD44</i>	42%	Retinoblastoma	Cell-surface glycoprotein	Cohen <i>et al.</i> , ³¹ Livide <i>et al.</i> ³⁹
<i>PAX5</i>	42%	Retinoblastoma	Transcription factor	Cohen <i>et al.</i> , ³¹ Livide <i>et al.</i> ³⁹
<i>GATA5</i>	25%	Retinoblastoma	Transcription factor	Cohen <i>et al.</i> , ³¹ Livide <i>et al.</i> ³⁹
<i>TFF3</i>	All eight retinoblastoma cell lines	Retinoblastoma	Trefoil factor	Philippeit <i>et al.</i> ⁴⁰
<i>CASP8</i>	Two retinoblastoma cell lines	Retinoblastoma	Apoptotic effector	Corson & Gallie, ⁴¹ Poulaki <i>et al.</i> ⁴²
<i>MLH1</i>	67%	Retinoblastoma	DNA repair gene	Choy <i>et al.</i> ⁴³
<i>APC2</i>	70%	Retinoblastoma	APC	Beta <i>et al.</i> ⁴⁴
<i>RB2/p130</i>	40%	Retinoblastoma	Retinoblastoma-related protein	Tosi <i>et al.</i> , ⁴⁵ De Falco & Giordano ⁴⁶
<i>TERT</i>	52%	Uveal melanoma	Ribonucleoprotein polymerase	Moulin <i>et al.</i> , ⁴⁷ Venza <i>et al.</i> ⁴⁸
<i>DCR1</i> and <i>DCR2</i>	91–97%	Uveal melanoma	Receptors for TRAIL	Moulin <i>et al.</i> , ⁴⁷ Venza <i>et al.</i> ⁴⁸
<i>CXCR4</i> and <i>CCR7</i>	-	Uveal melanoma	Hypermethylation inhibits metastasis	Li <i>et al.</i> , ⁴⁹ Li <i>et al.</i> , ⁵⁰ Li <i>et al.</i> ⁵¹
<i>p16/INK4A</i>	Partial in <i>Chlamydia psittaci</i> - negative cases	Marginal zone lymphoma of the ocular adnexa	Stabilizer of tumor suppressor protein	Carugi <i>et al.</i> ⁵²
<i>CDKN2A</i>	46%	Periocular sebaceous carcinoma	Stabilizer of tumor suppressor protein	Liau <i>et al.</i> ⁵³
<i>CDH1</i>	72%	Eyelid sebaceous gland carcinoma	Component of the cell–cell adhesion complex	Jayaraj <i>et al.</i> ⁵⁴
<i>DNMT3L</i>	Loss of methylation	Ocular surface squamous neoplasia	DNA (cytosine-5)- methyltransferase 3-like	Manderwad <i>et al.</i> ⁵⁵

Abbreviations: APC: Adenomatous polyposis coli; MGMT: O⁶-methylguanine-DNA methyltransferase; MutS: Mutator S; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

In RB, epigenetic silencing of the *RB1* gene via promoter hypermethylation can mimic the functional loss caused by genetic mutations, leading to uncontrolled retinal progenitor cell proliferation. Studies have shown that *DNMT* overexpression correlates with *RB1* hypermethylation, suggesting an active role for DNMTs in RB progression.^{12,30,56}

Aberrant CpG island methylation, as a secondary mechanism of gene silencing, reinforces the notion that epigenetic alterations cooperate with genetic mutations to drive tumorigenesis.¹² This finding aligns with broader evidence indicating that hypermethylation-mediated gene repression affects key regulatory pathways in ocular cancers, potentially serving as both a diagnostic biomarker and a therapeutic target.

Similarly, in UM, the hypermethylation of *CDKN2A* (encoding p16-INK4a and p14-ARF) leads to deregulated cell cycle control, allowing melanocytes to proliferate unchecked. Additionally, hypermethylation of *SOCS1* (suppressor of cytokine signaling 1) has been linked to immune evasion, allowing tumor cells to escape immune surveillance.^{57,58}

The tumor-suppressive function of RAS association domain family member 1A (*RASSF1A*) is frequently lost in melanoma, primarily due to abnormal promoter hypermethylation.⁵⁹ In conjunctival melanoma, aberrant promoter methylation of *RASSF1A* has been observed, disrupting apoptosis and promoting tumor progression.²⁶ While specific studies on *RASSF1A* promoter methylation in conjunctival melanoma are limited, similar epigenetic inactivation of *RASSF1A* has been observed in UM, indicating that *RASSF1A* promoter methylation is a common event in melanoma development.^{60,61}

Hypermethylation-mediated gene silencing can simultaneously inactivate multiple tumor suppressor genes in ocular cancers such as RB and UM, thereby compounding genetic lesions and promoting aggressive tumor behavior⁶² (Figure 3). For example, in RB, hypermethylation of the *RASSF1A* promoter has been detected in 82% to 89% of cases, leading to its inactivation. Additionally, hypermethylation of genes such as *MGMT*, *NEUROG1*, *MSH6*, *CD44*, *PAX5*, and *GATA5* has been observed, contributing to tumor progression.²⁵ Additionally, *MGMT* promoter methylation, which silences the gene and reduces the protein, prevents tumor cells from repairing the damage caused by alkylating agents, making them more susceptible to cell death. This makes *MGMT* promoter methylation a biomarker for predicting a positive response to therapies.³³ Similarly, in UM, increased promoter methylation of tumor suppressor genes such as *MEGF10*, *GSTP1*, and *KLF10* has been associated with metastasis.⁶³

While it has yet to be explored in the context of ocular cancers, hypermethylation of *IGF2*, *NEUROG1*, *SFRP1*, and *SFRP2* has been reported in adenomas, where it occurs prior to somatic mutation or inactivation of the predisposing oncogene.⁶⁴ Hypermethylation of the *MSH6* promoter, leading to gene silencing, has been associated with the DNA mismatch repair pathway in some cancers, such as endometrial cancer,⁶⁵ while similar hypermethylation of the *PAX5* promoter has been reported in non-small cell lung cancer.⁶⁶ Hypermethylation of *CD44* has been associated with lymphomas,⁶⁷ and poor clinical prognosis in renal cell carcinoma has been linked to hypermethylation of the *GATA5* CpG island (CGI).⁶⁸

2.1.2. Global hypomethylation

In contrast to hypermethylation of specific gene promoters, global DNA hypomethylation refers to the loss of methylation across the genome, particularly in repetitive elements, oncogenes, and transposable elements⁶⁹ (Figure 4). This process leads to:

- Chromosomal instability: Hypomethylation can activate endogenous retrotransposons (such as *LINE1* and Alu elements), increasing the likelihood of chromosomal rearrangements and aneuploidy—both of which are common in aggressive ocular tumors.⁷⁰
- Oncogene activation: In some ocular cancers, hypomethylation has been linked to the overexpression of oncogenes that drive tumor progression.⁷¹ For example, hypomethylation of *MYC* and *MDM2* has been observed in UM, contributing to uncontrolled cell division and resistance to apoptosis.⁷²
- Increased mutation rates: Loss of gene expression via methylation in DNA repair genes (such as *MLH1* and *MGMT*) reduces the cell's ability to repair DNA damage, increasing the likelihood of tumor accumulation of mutations and drug resistance. For example, in colorectal cancers, promoter methylation accounts for 80–90% of *MLH1* inactivation, leading to mismatch repair deficiencies and microsatellite instability.⁷³

2.1.3. Clinical implications and therapeutic potential

The reversibility of DNA methylation offers a compelling therapeutic avenue for ocular cancers. DNMTis, such as 5-azacytidine and decitabine, have been investigated for their potential to reactivate silenced tumor suppressor genes in malignancies such as RB and UM.

In RB, studies have shown that epigenetic silencing of the *RB1* gene through promoter hypermethylation can be reversed using DNMTis, thereby restoring gene function and inhibiting tumor growth.⁷⁴ Similarly, in

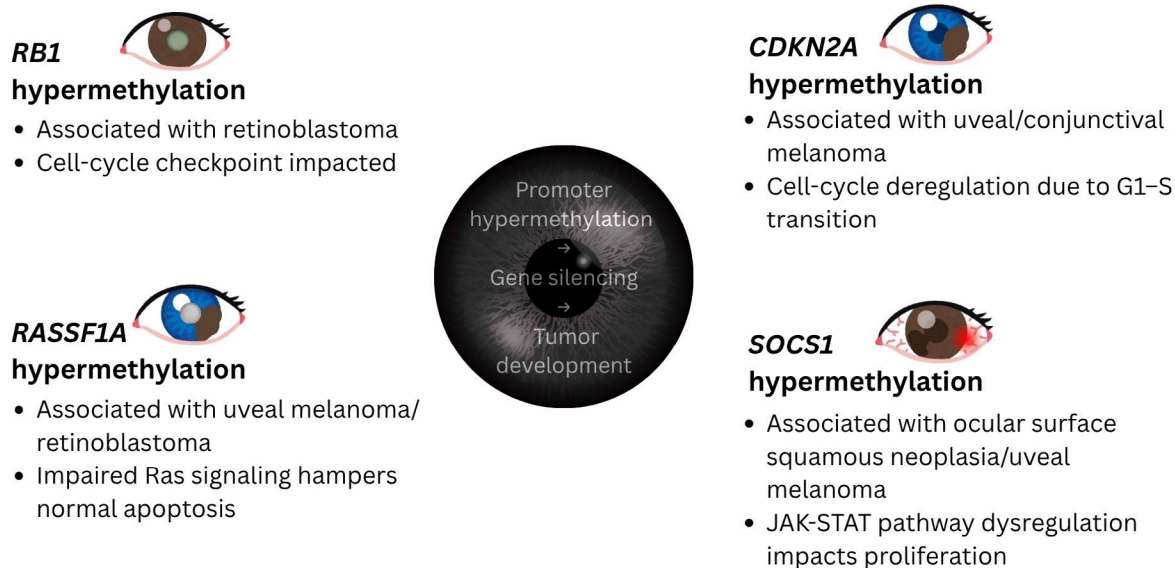


Figure 3. Importance of hypermethylation in cancer: Hypermethylation of tumor suppressor gene promoters reduces their expression, disrupting cell cycle regulation and apoptotic control—key early events in ocular cancer pathogenesis. Created with Canva. Abbreviations: JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

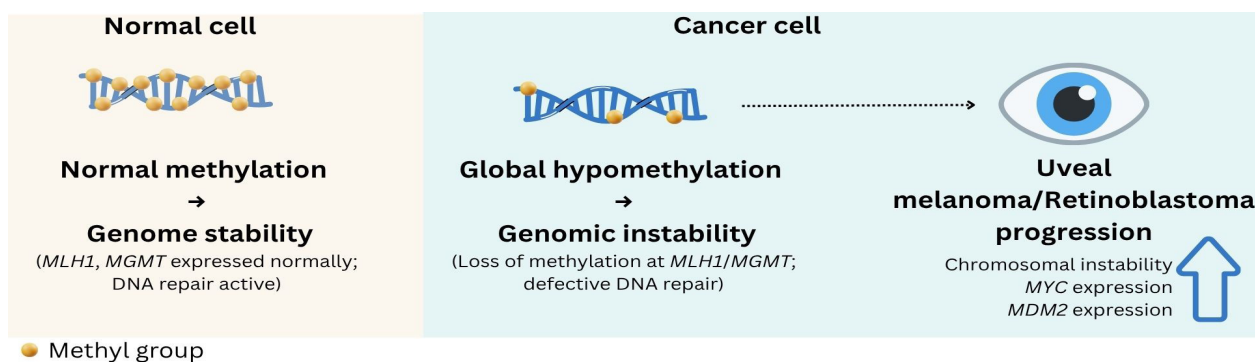


Figure 4. Global DNA hypomethylation: Loss of DNA methylation undermines genome integrity by activating oncogenes and disabling repair pathways, thereby accelerating ocular tumorigenesis, as seen in UM or RB. Created with Canva.

UM, hypermethylation of tumor suppressor genes such as *RASSF1A* and *p16INK4a* has been observed.⁵⁸ The application of DNMTis aims to demethylate these promoters, potentially reactivating gene expression and impeding tumor progression.

However, the clinical application of DNMTis in ocular cancers faces challenges, including off-target effects and drug resistance. These issues underscore the need for further research to refine epigenetic therapies, optimize treatment regimens, and identify biomarkers that predict patient response. Integrating DNMTis with other therapeutic modalities may enhance efficacy and reduce adverse effects, offering a more comprehensive approach

to managing ocular malignancies.

2.2. Histone modifications

Histone modifications play a crucial role in chromatin remodeling and gene expression regulation (Table 2). These modifications, including acetylation, methylation, phosphorylation, and ubiquitination, are mediated by enzymes, including histone acetyltransferases (HATs), HDACs, histone methyltransferases (HMTs), and histone demethylases (Figure 5). Depending on the modification and its location, histone modifications can either promote an open chromatin state, facilitating transcription, or induce a closed chromatin structure, leading to gene silencing.

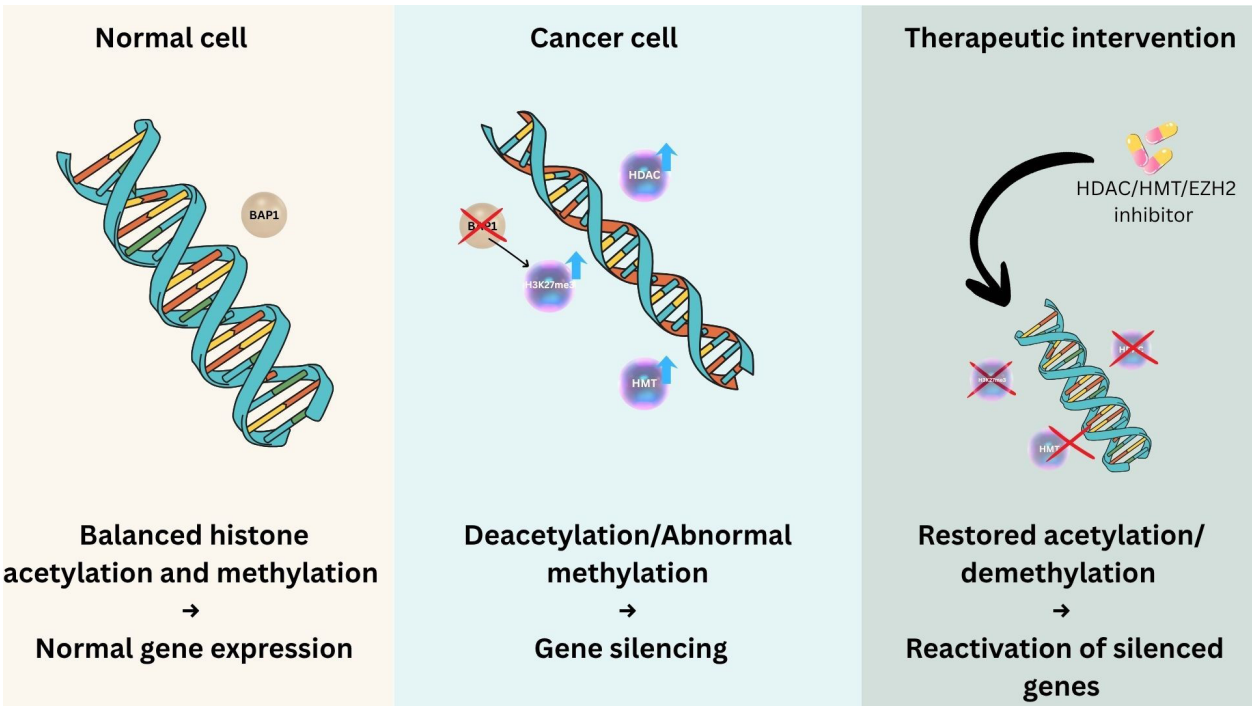


Figure 5. Reversal of aberrant histone modifications restores tumor suppressor activity in ocular cancers: *BAP1* loss and aberrant H3K27/HDAC/HMT methylation silence tumor suppressors; epigenetic therapy can restore gene activity. Created with Canva. Abbreviations: EZH2: Enhancer of zeste homolog 2; HDAC: Histone deacetylase; HMT: Histone methyltransferase.

Table 2. Studies linking histone modifications to ocular cancers

Gene	Modification	Disease	References
<i>Psq</i> and <i>Lola</i>	H3K9 deacetylation and H3K27 methylation	Tumorigenesis in the <i>Drosophila</i> eye	Ferres-Marco <i>et al.</i> ⁷⁵
<i>MHC2TA</i>	H3K27me3 trimethylation	Uveal melanoma	Radosevich <i>et al.</i> , ⁷⁶ Holling <i>et al.</i> ⁷⁷

2.2.1. Histone acetylation and deacetylation

Histone acetylation, typically associated with active gene transcription, is regulated by HATs, which add acetyl groups to lysine residues on histone tails, reducing chromatin compaction. In contrast, HDACs remove these acetyl groups, leading to chromatin condensation and transcriptional repression.

In ocular cancers, HDACs are overexpressed. In UM, increased HDAC expression has been reported, contributing to tumor progression by repressing tumor suppressor genes.^{78,79} HDACis, such as vorinostat and trichostatin A, have shown potential in preclinical studies by reactivating tumor suppressor pathways and inducing

apoptosis. Studies have demonstrated increased expression of HDACs, including HDAC1, HDAC3, HDAC4, and HDAC8, in high-risk UM tumors. This overexpression correlates with heightened human leukocyte antigen Class I expression, which may influence tumor immune evasion mechanisms.

Additionally, studies have indicated that HDACis can restore the expression of epigenetically silenced genes in RB cells, offering a promising therapeutic strategy.^{80,81}

2.2.2. Histone methylation and demethylation

Histone methylation, mediated by HMTs and histone demethylases, can either activate or repress gene expression, depending on the specific residues modified:

- *BAP1* mutations and histone modification: Inactivating mutations in the *BAP1* gene, which encodes a deubiquitinase involved in chromatin modulation, are strongly associated with metastasis in UM. Loss of *BAP1* function leads to distinct histone modification patterns, contributing to aggressive tumor behavior.⁸²⁻⁸⁴
- H3K27 methylation alterations: Differences in histone marks, particularly H3K27 methylation, have been observed between uveal and skin melanocytes.²⁴ These variations may underlie the distinct clinical behaviors and therapeutic responses of melanomas arising in different tissues.

2.2.3. Therapeutic implications

Targeting aberrant histone modifications presents a promising therapeutic strategy in ocular cancers. HDACis are being explored for their potential to reverse epigenetic alterations and suppress tumor progression. However, challenges such as off-target effects and drug resistance

necessitate further research to optimize these therapies and identify predictive biomarkers for patient stratification.

2.3. Non-coding RNAs in ocular cancer

Non-coding RNAs have emerged as critical regulators of gene expression in ocular malignancies, orchestrating tumor-promoting and tumor-suppressive processes through diverse molecular mechanisms (Table 3). These RNAs, which do not encode proteins, exert their regulatory effects via chromatin remodeling, transcriptional interference, RNA degradation, and translational repression. Among them, microRNAs (miRNAs/miR) and long non-coding RNAs (lncRNAs) have been extensively studied, with accumulating evidence highlighting their roles in cell cycle regulation, apoptosis, invasion, and immune evasion in ocular tumors.⁸⁵ Additionally, recent studies have uncovered the involvement of circular RNAs (circRNAs) and p-element-induced wimpy testis (PIWI)-interacting RNAs (piRNAs) in modulating oncogenic and epigenetic landscapes in these malignancies.

Table 3. Studies on non-coding RNA modifications and their function in ocular cancers

Non-coding RNA	Expression in the tumor	Function	Disease	References
let-7	Decreased	Repress oncogenes	Retinoblastoma	Johnson <i>et al.</i> , ⁸⁶ Mayr <i>et al.</i> , ⁸⁷ Sampson <i>et al.</i> , ⁸⁸ Mu <i>et al.</i> ⁸⁹
miR-34a	Decreased	Suppress tumor	Retinoblastoma	Dalgard <i>et al.</i> , ⁹⁰ Martin <i>et al.</i> ⁹¹
miR-24, 125b, 191, 181a, 423	Decreased	Suppress tumor	Retinoblastoma	Huang <i>et al.</i> ⁹²
miR-124a	Decreased	Suppress tumor	Uveal melanoma	Jazirehi <i>et al.</i> , ⁹³ Chen <i>et al.</i> ⁹⁴
miR-137	Decreased	Downregulate MITF	Uveal melanoma	Chen <i>et al.</i> ⁹⁵
miR-34b/c	Decreased	Downregulate c-MET, p-AKT, and cell cycle proteins	Uveal melanoma	Dong & Lou ⁹⁶
miR-17-92 cluster	Overexpressed	Oncogenic miRNA	Retinoblastoma	Conkrite <i>et al.</i> , ⁹⁷ Nittner <i>et al.</i> ⁹⁸
miR-181b	-	-	Retinoblastoma	Xu <i>et al.</i> , ⁹⁹ Xu <i>et al.</i> ¹⁰⁰
miR-20a, 125b, 146a, 155, 181a, 223	Overexpressed	Oncogenic miRNAs	Uveal melanoma	Achberger <i>et al.</i> ¹⁰¹
miR-18a, 199a, 495, 549, let-7b	Overexpressed	Oncogenic miRNAs	Uveal melanoma	Worley <i>et al.</i> , ¹⁰² Radhakrishnan <i>et al.</i> ¹⁰³
lncRNA BANCR	Overexpressed	Promotes retinoblastoma cell proliferation, migration, and invasion	Retinoblastoma	Su <i>et al.</i> ¹⁰⁴
lncRNA ROR	Overexpressed	Promotes TESC expression	Uveal melanoma	Fan <i>et al.</i> ¹⁰⁵

Abbreviations: c-MET: Cytosolic mesenchymal transition factor; lncRNA: Long non-coding RNA; miR/miRNA: MicroRNA; MITF: Microphthalmia-associated transcription factor; TESC: Tescalcin.

2.3.1. MicroRNAs: Key regulators of post-transcriptional gene silencing

MicroRNAs, typically 18–24 nucleotides in length, function as post-transcriptional regulators by binding to complementary sequences within the 3'-untranslated regions (3'-UTRs) of target messenger RNAs (mRNAs), leading to translational inhibition or mRNA degradation.^{19,106} In ocular cancers, specifically UM, dysregulated miRNA expression profoundly alters tumor progression by influencing cell proliferation, differentiation, apoptosis, and metastatic potential.⁶⁸

Several miRNAs exhibit aberrant expression patterns across different ocular malignancies. The miR-17–miR-92 cluster, a well-characterized oncogenic miRNA group, is overexpressed in RB, where it promotes unchecked cell proliferation by directly targeting *E2F1* and *MYCN*, two key regulators of cell cycle progression.¹⁰⁷ Conversely, miR-34a, a critical tumor suppressor miRNA, is frequently downregulated in both RB and UM, impairing tumor protein p53 (TP53)-dependent apoptotic pathways and thereby fostering tumor cell survival.¹⁰⁸ Other miRNAs, such as miR-204 and miR-211, have been implicated in UM, where their suppression facilitates tumor progression via *MITF* and *BCL2* regulation.^{97,109} Similarly, miR-9 has been shown to enhance epithelial-to-mesenchymal transition in UM, thereby promoting invasion and metastasis through e-cadherin suppression.¹¹⁰

2.3.2. Long non-coding RNAs: Chromatin regulators and competing endogenous RNA networks

Long non-coding RNAs, which exceed 200 nucleotides in length, modulate gene expression at multiple levels, including chromatin remodeling, transcriptional interference, and post-transcriptional regulation via competing endogenous RNA mechanisms. Several lncRNAs have been identified as key players in ocular tumorigenesis, influencing chromatin accessibility and oncogenic signaling pathways.¹⁹

One of the most extensively studied lncRNAs in ocular malignancies is HOTAIR (HOX transcript antisense RNA), which is significantly upregulated in UM.^{111,112} HOTAIR recruits polycomb repressive complex 2 (PRC2) to silence tumor suppressor genes, thereby facilitating tumor invasiveness and metastatic progression.¹¹³ Similarly, MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) has been found to drive RB progression by modulating Wnt/ β -catenin signaling, promoting sustained tumor cell survival and proliferation.^{114,115}

Additional lncRNAs, such as NEAT1 (nuclear-enriched abundant transcript 1) and TUG1 (taurine-upregulated gene 1), also exhibit dysregulated expression patterns in

ocular cancers. NEAT1 has been shown to contribute to chemoresistance in RB by modulating BCL2 and autophagy pathways.^{116,117}

2.3.3. Circular RNAs and PIWI-interacting RNAs in ocular tumorigenesis

Recent studies have expanded the landscape of ncRNA involvement in ocular cancer, with circRNAs and piRNAs gaining increasing attention for their roles in post-transcriptional regulation and chromatin remodeling. CircRNAs, which arise from back-splicing events, act as molecular sponges for miRNAs, sequestering them and preventing their interaction with target mRNAs. In UM, circRNA_0001093 has been identified as a regulator of the circRNA–miRNA–mRNA axis, functioning as a sponge for tumor-suppressive miRNAs and thereby enhancing oncogenic signaling cascades.¹¹⁸

Additionally, piRNAs, a class of small regulatory RNAs primarily involved in transposon silencing and chromatin modification, have been implicated in choroidal neovascularization.¹¹⁹ For example, piR-823 has been shown to alter histone methylation patterns, facilitating the establishment of a permissive chromatin state that sustains tumorigenic transcriptional programs in ocular tumors.

2.3.4. Therapeutic potential of non-coding RNAs in ocular oncology

Given their role in tumor initiation and progression, ncRNAs represent promising therapeutic targets in ocular cancer. Strategies aimed at targeting oncogenic ncRNAs or restoring tumor-suppressive ncRNAs are being actively explored. The development of miRNA mimics, anti-miR therapies, and lncRNA inhibitors has shown potential in preclinical models, offering a framework for RNA-based therapeutic interventions. Furthermore, advances in RNA delivery platforms, including lipid nanoparticles and aptamer-based systems, may enhance the clinical applicability of ncRNA-targeted therapies.¹²⁰

As research into ncRNA-mediated gene regulation in ocular malignancies continues to evolve, comprehensive transcriptomic and epigenomic profiling approaches will be critical for identifying novel therapeutic vulnerabilities. The integration of multi-omics data and functional validation studies will pave the way for precision medicine strategies aimed at targeting ncRNA-driven oncogenic networks in ocular oncology.¹²¹

2.4. Chromatin remodeling in ocular malignancies

Chromatin remodeling plays an important role in the epigenetic regulation of gene expression in ocular malignancies, dynamically altering chromatin accessibility

to transcriptional machinery.¹²² Chromatin remodelers are multi-protein complexes that utilize ATP hydrolysis to reposition, eject, or restructure nucleosomes, thereby modulating transcriptional states. Dysregulation of these complexes contributes to oncogenesis by perturbing the balance between euchromatin and heterochromatin, influencing oncogenes and tumor suppressors¹²³ (Figure 6).

2.4.1. Switch/sucrose non-fermentable complexes and transcriptional reprogramming

Among the major chromatin remodeling families, the switch/sucrose non-fermentable (SWI/SNF) complexes have been implicated in ocular cancer pathogenesis, such as RB.¹²⁴ Mutations or functional alterations in *ARID1A*, a key SWI/SNF subunit, have been associated with aggressive UM phenotypes, leading to widespread transcriptional reprogramming and aberrant activation of oncogenic pathways.¹²⁵ Similarly, *BAP1* (BRCA1-associated protein 1) loss in UM is a defining molecular event that disrupts chromatin dynamics, promoting metastatic dissemination through global transcriptional deregulation.¹²⁶

2.4.2. Polycomb repressive complexes in ocular tumorigenesis

Beyond classical chromatin remodelers, emerging epigenetic regulators, such as PRC1 and PRC2, have

garnered attention in ocular tumorigenesis.¹²⁷ In RB, aberrant *EZH2*-mediated H3K27 trimethylation silences tumor suppressor networks, fostering uncontrolled proliferation.^{128,129} The oncogenic activity of polycomb group proteins in UM has also been linked to immune evasion and metastatic progression, suggesting their potential as therapeutic targets.

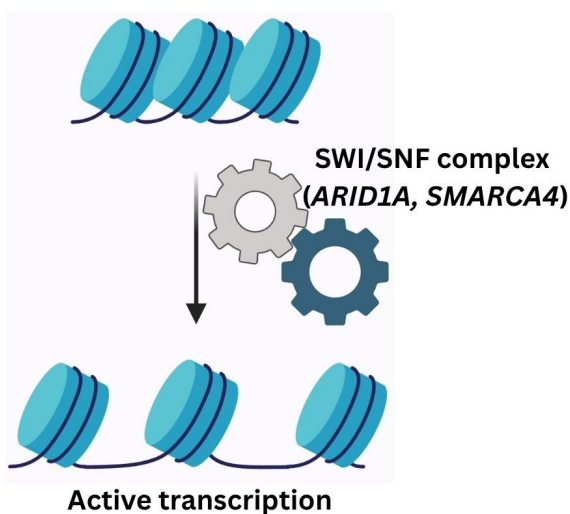
2.4.3. Chromodomain helicases and epigenetic regulation

Deregulation of the chromodomain helicase DNA-binding (CHD) proteins, including CHD4, has been linked to disrupted DNA repair and transcriptional repression, both of which are associated with general tumor dependency.¹³⁰ CHD proteins function as part of nucleosome remodeling and deacetylase complexes, integrating chromatin remodeling with transcriptional repression and genome stability mechanisms. While they have not been directly linked with ocular malignancies, their dysregulation may contribute to aberrant gene silencing and chemoresistance in ocular tumors.¹³¹

2.4.4. ATP-dependent nucleosome remodelers and histone chaperones

Further complexity is introduced by ATP-dependent nucleosome remodelers, such as imitation switch (ISWI) and inositol requiring 80 (INO80), which have been

Normal chromatin remodeling



Mutated chromatin remodeling

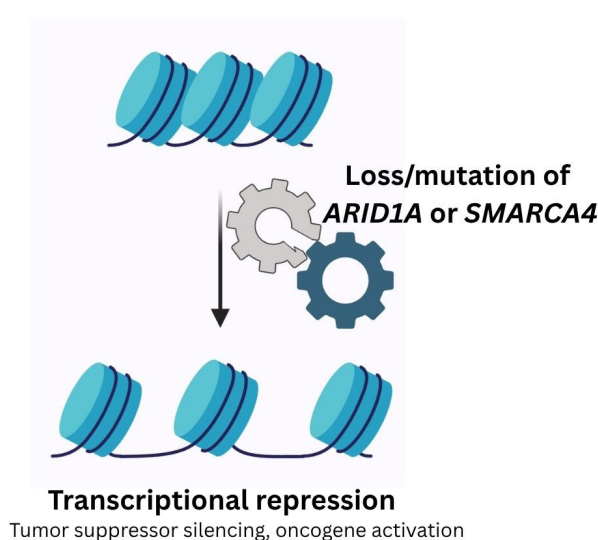


Figure 6. Mutations in chromatin remodeling complexes compact chromatin and drive tumor progression in ocular malignancies. The loss or mutation of subunits like *ARID1A* (a key switch/sucrose non-fermentable [SWI/SNF] subunit, which is known to be associated with aggressive uveal melanoma phenotypes) or *SMARCA4* (implicated in the pathogenesis of retinoblastoma) leads to transcriptional repression and the silencing of tumor suppressors, which are key drivers in the development of retinoblastoma and uveal melanoma. Created with Canva.

implicated in maintaining chromatin homeostasis and DNA damage response pathways such as non-homologous end joining (NHEJ), in various cancers,^{132,133} though their roles in ocular malignancies remain underexplored.

Histone chaperones, including HIRA and anti-silencing function 1 (ASF1), are emerging as crucial mediators of chromatin assembly and transcriptional fidelity.¹³⁴ However, their specific roles in ocular tumor progression remain to be fully elucidated, necessitating further investigation to establish potential mechanistic links.

2.4.5. Therapeutic potential of chromatin remodeling in ocular oncology

Targeting chromatin remodelers represents a promising therapeutic avenue for ocular malignancies, offering strategies to reverse epigenetic dysregulation. Small-molecule inhibitors of enhancer of zeste homolog 2 (EZH2), such as tazemetostat, have demonstrated efficacy in preclinical models by reactivating tumor suppressor pathways silenced by aberrant H3K27me3 deposition.¹²⁹ Similarly, bromodomain and extra-terminal motif (BET) inhibitors, which disrupt chromatin-reader proteins such as bromodomain-containing protein 4 (BRD4), hold potential for attenuating oncogenic transcriptional programs through the BRD4–nuclear factor-kappa B 2 (NFκB2)–secreted phosphoprotein 1 (SPP1) axis in UM.¹³⁵

Restoring SWI/SNF complex functionality is another emerging strategy,¹²⁵ with synthetic lethality approaches targeting *ARID1A*-deficient tumors showing promise in early investigations.¹³⁵ Additionally, HDACis, including vorinostat^{136–138} and romidepsin,^{139–141} are under evaluation for their ability to modulate chromatin accessibility and reprogram transcriptional landscapes in RB and UM.

Given the intricate interplay between chromatin remodeling and DNA repair mechanisms, combinatorial approaches integrating epigenetic inhibitors with immune checkpoint blockade or DNA-damaging agents may offer synergistic therapeutic benefits. However, further studies leveraging patient-derived models and advanced epigenomic profiling are warranted to refine these strategies and enhance their clinical applicability in ocular oncology (Figure 7).

The preceding section delineates the principal epigenetic mechanisms—DNA methylation, histone modifications, ncRNAs, and chromatin remodeling—that govern gene expression dynamics; however, while epigenetic dysfunction is fundamental across ocular cancers, the specific patterns of modification differ among malignancies. These are explored in Section 3.

3. Epigenetics in ocular cancer

3.1. Retinoblastoma

With an incidence rate of 1 in 18,000 live births¹⁴² and over 80% of cases reported from low- and middle-income countries in Africa, Asia, and Latin America,⁸¹ RB is the most common pediatric intraocular malignancy.

Its significant intra- and intertumoral heterogeneity makes prognosis and treatment stratification difficult. While biallelic *RB1* inactivation is the primary oncogenic driver,¹ accumulating evidence highlights the significant roles of genomic, transcriptomic, and epigenetic alterations that contribute to divergent histopathological and clinical trajectories,¹⁴³ thereby silencing tumor suppressor genes and activating oncogenic pathways in RB.

Dysregulation of histone modifications plays an important role in RB pathogenesis, significantly altering chromatin dynamics and transcriptional control. Overexpression of *EZH2*, a core catalytic subunit of PRC2, drives excessive H3K27 trimethylation, effectively silencing critical tumor suppressor networks and promoting tumor progression.¹⁴⁴ In parallel, dysregulated histone acetylation patterns, particularly mediated by HDAC1 and HDAC2, contribute to aberrant gene repression, facilitating RB cell survival and resistance to apoptosis.¹⁴⁵

Additionally, aberrant DNA methylation patterns further contribute to RB tumorigenesis. Previous studies reported that hypermethylation of the *MGMT* promoter is detected in approximately 15% of RB tumors, correlating with reduced *MGMT* expression and potentially implicating chemoresistance.^{146,147} Such epigenetic silencing of DNA repair genes may render tumors more susceptible to alkylating agents, underscoring the need for further investigations into epigenetic-targeted therapeutic strategies. Moreover, Sun *et al.*¹⁴⁸ identified a panel of differentially methylated genes that hold potential as epigenetic biomarkers for early RB detection, emphasizing the translational relevance of methylation profiling in clinical settings.

Targeting these epigenetic aberrations has emerged as a promising therapeutic strategy. Knudsen *et al.*¹⁴⁹ demonstrated that HDACis restore normal histone acetylation patterns, thereby reactivating tumor suppressor genes and sensitizing RB cells to chemotherapy. This study highlights the therapeutic potential of epigenetic modulators in overcoming resistance mechanisms and improving patient outcomes. Collectively, these findings underscore the necessity for further mechanistic studies and clinical validation of epigenetic-targeted approaches in RB management.

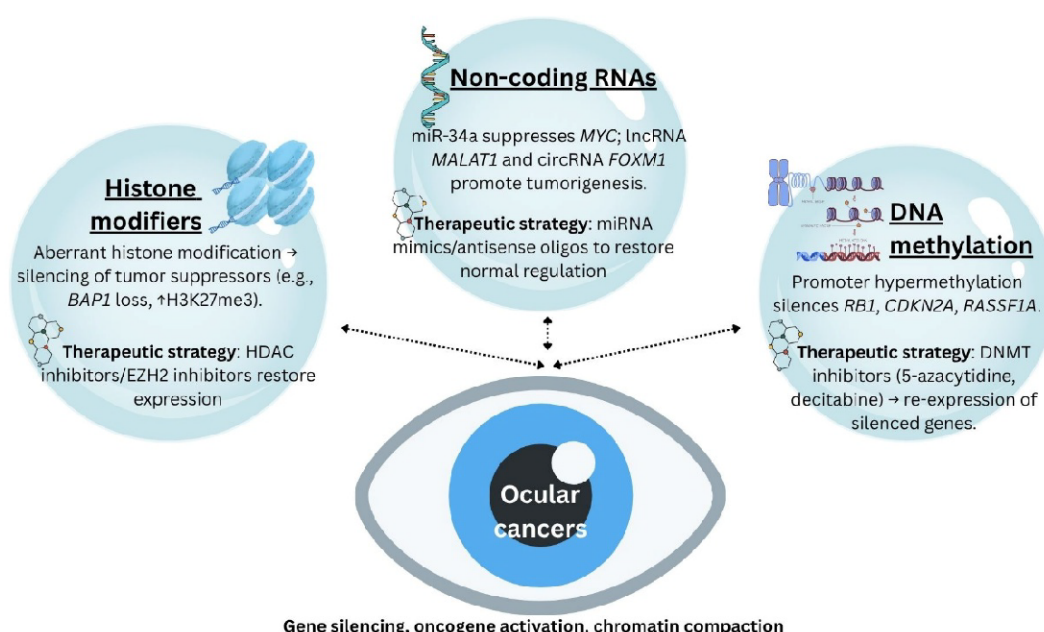


Figure 7. Epigenetic strategies and therapeutic targets in ocular cancer management: The figure depicts the tripartite relationship between major epigenetic mechanisms and their role in driving ocular malignancies, while highlighting specific avenues for clinical intervention. (i) Histone modifiers: Dysregulation in histone acetylation and methylation landscapes, such as the loss of *BAP1* or increased H3K27me3 mediated by EZH2, induces chromatin compaction and the silencing of gene networks essential for cell cycle control (e.g. in aggressive, metastatic uveal melanoma phenotypes); thus, small-molecule inhibitors, including HDAC inhibitors (e.g., vorinostat and romidepsin) and EZH2 inhibitors (e.g., tazemetostat), which aim to restore a permissive chromatin state and reactivate suppressed pathways, may be used therapeutically. (ii) Non-coding RNAs: Oncogenic lncRNAs (e.g., MALAT1) and circRNAs promote tumorigenesis by modulating signaling pathways such as Wnt/ β -catenin, while the downregulation of tumor-suppressive miRNAs (e.g., miR-34a) allows for the overexpression of oncogenes. The development of miRNA mimics to restore suppressor function or antisense oligonucleotides to inhibit oncogenic lncRNAs represents a frontier in precision medicine for ocular cancers. (iii) DNA methylation: Aberrant methylation leads to silencing of tumor suppressor genes, such as *RB1* in retinoblastoma and *CDKN2A* or *RASSF1A* in uveal melanoma. DNMTis, such as 5-azacytidine and decitabine, are used to reverse these methylation patterns and promote the re-expression of silenced tumor suppressors. Created with Canva. Abbreviations: circRNA: Circular RNA; DNMTi: DNA methyltransferase inhibitor; EZH2: Enhancer of zeste homolog 2; HDAC: Histone deacetylase; lncRNA: Long non-coding RNA; miRNA/miR: MicroRNA.

3.2. Uveal melanoma

Uveal melanoma exhibits distinct epigenetic landscapes that underpin tumor heterogeneity and prognostic stratification. Specific CpG island methylation signatures differentiate high-risk and low-risk UM subtypes, with aggressive variants frequently displaying hypermethylation-mediated silencing of tumor suppressor genes, such as *RASSF1A*, *TIMP3*, and *p16INK4a*, reinforcing their role in tumor suppression.¹⁵⁰ Notably, biallelic inactivation or loss-of-function mutations in *BAP1*, a key tumor suppressor, correlate with global DNA hypomethylation and chromatin dysregulation, underscoring its central role in transcriptional control and metastatic progression.¹⁵¹

Beyond DNA methylation, histone modifications play a crucial role in UM pathobiology.¹⁵² Loss of *BAP1* function impairs histone H2A deubiquitination, disrupting chromatin architecture and leading to aberrant transcriptional activation of metastasis-associated gene

networks.⁵⁸ Additionally, PRC2 overactivity, primarily mediated via EZH2, drives excessive H3K27 trimethylation, thereby repressing key tumor suppressor genes involved in cell cycle regulation, apoptosis, and differentiation.^{151,153} This epigenetic silencing contributes to a more aggressive phenotype, implicating EZH2 as a promising therapeutic target in UM.¹⁵⁴

Unlike cutaneous melanoma, which is characterized by global DNA hypomethylation, UM exhibits discrete hypermethylation events at specific tumor suppressor loci, suggesting a distinct epigenetic regulatory architecture.¹⁵ While HDACis have shown efficacy in cutaneous melanoma by reversing aberrant acetylation patterns, their potential therapeutic impact in UM remains an area of ongoing investigation.¹⁵⁵

3.3. Other ocular neoplasms

While epigenetic research in ocular oncology has largely focused on RB and UM, emerging evidence suggests

that epigenetic dysregulation also plays a crucial role in the pathogenesis of rare ocular malignancies, including conjunctival melanoma, sebaceous carcinoma, and ocular adnexal lymphomas.

A few investigations have examined the epigenetic landscape of primary conjunctival melanomas, with most existing research concentrating on DNA methylation, ncRNA profiles (including miRNAs and circRNAs), and RNA methylation.¹⁵ Conjunctival melanoma, in contrast to UM, exhibits global DNA hypomethylation patterns similar to cutaneous melanoma. Nevertheless, the initial locations of these tumors show distinct differences in promoter methylation and alterations in the copy number of genes linked to cancer;¹⁵ specifically, *BRAF* and *NRAS* mutations drive tumor progression through altered DNA methylation and chromatin remodeling.¹⁵⁶ This distinct epigenetic profile may contribute to its more aggressive behavior and necessitates further exploration of epigenetic biomarkers for prognostic stratification.

Sebaceous gland carcinoma, a rare but aggressive periocular malignancy, has its poor prognosis associated with aberrations in β -catenin,¹⁵⁷ miR-486-5p, miR-184,¹⁵⁸ lymphoid enhancer binding factor-1,^{159,160} Indian hedgehog (IHH) signaling, sonic hedgehog (SHH), cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), p53, and p21 pathways.¹⁶¹ Aberrant *p16INK4a* promoter hypermethylation and HDAC overexpression have been known to disrupt tumor suppressor pathways and promote unchecked proliferation.^{161,162} The potential for HDACis to reverse epigenetic silencing in this malignancy highlights a promising therapeutic avenue warranting further clinical evaluation.

Similarly, ocular adnexal lymphomas, particularly extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), exhibit abnormal DNA methylation of immune regulatory genes, which modulates tumor immune evasion mechanisms and fosters an immune-privileged microenvironment conducive to tumor persistence.¹⁶³ Alterations in epigenetic regulators have also been noted, including gain-of-function mutations in *EZH2* and loss-of-function mutations in *ARID1A*.^{164,165} Loss-of-function mutations and copy number alterations were identified in tumor suppressor genes such as *TP53* (in diffuse large B-cell and follicular lymphoma), *CDKN2A* (in diffuse large B-cell and marginal zone lymphoma), *PTEN*, *ATM*, and *NF1* (all in diffuse large B-cell lymphoma), along with gain-of-function mutations in the oncogenes *HRAS* (in follicular lymphoma) and *NRAS* (in diffuse large B-cell lymphoma).¹⁶⁶

In a study exploring recurrent chromosomal translocations in MALT lymphoma, methylation of

TNFAIP3 promoter—a gene also commonly mutated in ocular adnexal marginal zone B-cell lymphomas (OAMZL) of mucosa-associated lymphatic tissue—was detected in 19% of OAMZL cases.^{166–168} This methylation correlated with hemizygous deletion of *TNFAIP3* but occurred mutually exclusively with mutations in the same gene.^{169,170} These findings underscore the need for epigenetic profiling to refine diagnostic and therapeutic strategies for these understudied ocular malignancies.

However, while these findings underscore that epigenetic alterations rarely act in isolation but instead synergize with established genetic drivers to shape tumor behavior, it is essential to recognize the bidirectional interplay between genetic mutations and epigenetic alterations: genetic changes drive epigenetic dysregulation, and epigenetic alterations reinforce genetic instability. This warrants further mechanistic studies and clinical validation of these synergistic epigenetic–genetic interactions to understand how they specifically impact therapeutic resistance and prognosis.

4. Interplay between genetic and epigenetic alterations

The development of expression programs for different cell types relies on epigenetic regulation of gene expression, which involves chemical modifications of DNA and the chromatin that wraps it. This process leads to the development of transcriptionally active or repressive genes and domains. The primary mechanism by which DNA is modified in vertebrates is the addition of a methyl group to the 5' position of cytosines in CpG dinucleotides. Depending on the chromosomal context, this modification can be implicated in numerous interactions with transcriptional processes; however, it is typically associated with gene repression when it occurs in clusters of CpGs near transcription start sites.¹⁷¹

Post-translational histone modifications in chromatin represent the second category of epigenetic changes, including processes such as lysine acetylation and lysine and arginine methylation. The processes involve a large number of enzymatic groups, including HMTs, histone demethylases, HATs, and HDACs. Histone modification action on gene expression depends on both the modified amino acid residue and the chromosomal context.¹⁷¹ In most cases, multiple mechanisms are used to target genomic sites with epigenetic marks. Direct protein–protein interactions between epigenetic enzymes (DNMTs, HATs, HDACs, HMTs, histone demethylases, etc.) and sequence-specific transcription factors are necessary for accurate modifications. In some cases, such as phosphorylation or ligand binding, specific transcription factors can displace

enzymes that catalyze opposing reactions, such as HATs and HDACs.¹⁴⁹⁻¹⁵¹

Additionally, the physical restriction generated by the binding of epigenetic enzymes to transcription factors and other nuclear proteins can lead to epigenetic modifications.⁸¹ Also, some epigenetic modifications can push multiprotein complexes across domains that specifically recognize modified amino acid residues. Such complexes include other epigenetic enzymes that have the capacity to catalyze additional chromatin modifications.¹²⁹

4.1. Synergistic effects of genetic mutations and epigenetic changes in ocular cancer development

The interplay between genetic mutations and epigenetic modifications in ocular cancer is bidirectional: genetic mutations can drive epigenetic dysregulation, and, reciprocally, epigenetic alterations can reinforce genetic instability. Ocular cancers, including UM, RB, and ocular surface squamous neoplasia (OSSN), are influenced by both genetic mutations and epigenetic modifications.^{172,173} It is essential to comprehend the interaction between these two factors to elucidate the mechanisms underlying ocular cancer and to design targeted treatments. This understanding is crucial for advancing our knowledge of ocular cancer and improving therapeutic strategies.

Genetic mutations play a critical role in the development of ocular cancers, such as UM, RB, and OSSN. In UM, mutations in *GNAQ*, *GNA11*, and *BAP1* drive tumor growth and metastasis through the mitogen-activated protein kinase (MAPK) pathway.^{174,175} *BAP1* mutations disrupt histone deubiquitination, leading to widespread transcriptional reprogramming and increased metastatic potential.¹⁷⁶ In RB, *RB1*, and *TP53* mutations disrupt cell cycle regulation, promoting cancer progression. The loss of *RB1* affects both cell cycle progression and chromatin structure, causing polycomb-mediated repression of differentiation genes. Meanwhile, *TP53* mutations impair its ability to recruit HATs, resulting in widespread gene repression via chromatin compaction. OSSN is often associated with *TP53* and *HRAS* mutations, though its genetic landscape is less defined.

In addition to genetic mutations, epigenetic changes, such as in DNA methylation, histone modifications, and ncRNA expression, contribute to tumor development. For example, *CDKN2A* hypermethylation in UM leads to cell cycle dysregulation, while dysregulated histone modifications and altered miRNA expression further promote tumor growth and metastasis.¹⁷⁷ Together, genetic mutations and epigenetic modifications drive the uncontrolled growth of ocular tumors. This two-way communication between genetic mutations and epigenetic

changes creates a feedback loop in which each can influence the other, accelerating tumorigenesis. Understanding this interplay opens the door to new therapeutic strategies, including epigenetic therapies involving DNMTis and HDACis, offering a more comprehensive approach to treating ocular cancers by targeting both genetic and epigenetic alterations.

4.1.1. The two-hit hypothesis

Since the malignant transformation of ocular cells often depends on the complete inactivation of critical tumor suppressor genes, this convergence of genomic and epigenomic insults naturally leads to the question of how such biallelic loss occurs. The classical framework that explains this process is the two-hit hypothesis.

Tumor suppressor genes are prone to different types of mutations; however, most loss-of-function mutations have recessive features. Therefore, mutations in both alleles of the tumor suppressor gene must occur for a cell to become malignant. This process, referred to as the two-hit hypothesis, was described by geneticist Alfred Knudson in 1971.¹⁷⁸⁻¹⁸⁰ Currently, this hypothesis is a basic theory in cancer research, allowing for a better understanding of how mutations in these genes lead to oncogenesis.^{181,182}

The two-hit hypothesis represents a theoretical construct that explains the genetic basis of certain malignancies, particularly those involving tumor suppressor genes, as seen in ocular malignancies such as RB and UM. It involves two “hits”:

- (i) Initial hit: This phase typically refers to a genetic change or a loss of function in a tumor suppressor gene.
- (ii) Second hit: This phase entails the inactivation or modification of the second functional allele of the tumor suppressor gene. Inactivation may occur through various mechanisms, such as deletion, point mutation, or gene silencing. With both alleles compromised, the cell is no longer able to control growth, making it more prone to tumor formation.

In hereditary RB, the first hit (initial mutation) is inherited through genes, meaning a person inherits a defective copy of the *RB1* gene from an ancestor. In nonhereditary RB, however, the first hit arises somatically in an individual retinal cell.¹⁸³ Hypermethylation of the remaining *RB1* allele or other alterations that block its expression can cause epigenetic silencing (the second hit), leading to uncontrolled cell growth and loss of cell cycle regulation. In general, in RB, both initial and second hits result in inactivation of the *RB1* gene, leading to the uncontrolled growth of retinal cells.¹⁸⁴ Similarly, in UM, *GNAQ* and *GNA11* mutations can act as the second

event, allowing the neoplastic transformation of uveal melanocytes through the MAPK pathway.^{185,186}

The two-hit hypothesis is critical for understanding the mechanisms underlying the initiation and progression of ocular cancers. The hypothesis explains the increased susceptibility to cancer development in individuals with a genetic predisposition (the inherited first hit), as they need only a second hit for malignancy to occur, compared to those without such genetic predisposition, who need to undergo both hits to develop cancer.

4.1.2. Epigenetic silencing as a second hit in tumor suppressor genes

Epigenetic changes are heritable gene expression alterations that do not entail alterations in the underlying DNA sequence. Such changes can lead to silencing of tumor suppressor genes and thus supply the second hit in the two-hit model. The predominant mechanisms of epigenetic silencing include DNA methylation, histone modification, and ncRNA-mediated processes. Epigenetic silencing of key tumor suppressor genes, such as *CDKN2A*, which encodes p16INK4A, is often the second hit. A critical step towards UM metastasis is the deletion or silencing of the *BAP1* gene through both genetic mutations and epigenetic alterations (such as DNA methylation and histone modification). In OSSN, *TP53* mutations are frequent and can be accompanied by epigenetic silencing of other tumor suppressors that regulate cell cycle checkpoints and apoptosis, thereby facilitating tumor growth.¹⁸³⁻¹⁸⁵

4.2. Pathways and networks

4.2.1. Mitogen-activated protein kinase pathway

The MAPK signaling pathway is implicated in ocular cancers, such as UM, as it regulates cellular processes including growth, survival, differentiation, and apoptosis. Mutations in *GNAQ* and *GNAI1* in UM result in sustained activation of the MAPK pathway,¹⁸⁷ thereby affecting tumor growth. Additionally, the pathway triggers dramatic epigenetic changes that promote oncogenesis. MAPK signaling is implicated in chromatin remodeling, which affects histone acetylation, deacetylation, and methylation, thereby regulating gene expression.¹⁸⁸ For example, the extracellular signal-regulated kinase (ERK) protein may affect histone-modifying enzymes, leading to the silencing of genes that promote tumor growth. This pathway may also trigger DNA methylation of tumor suppressor genes, such as *CDKN2A*, thereby promoting uncontrolled cell growth. In addition, the MAPK pathway also regulates ncRNAs, such as miRNAs and lncRNAs, further affecting tumor growth. These ncRNAs modulate the expression of cancer-related genes, thereby contributing to metastasis.¹⁸⁹

In ocular cancers, the MAPK pathway is responsible for epigenetic repression of tumor suppressor genes, such as *CDKN2A*, *RB1*, and *BAP1*, which regulate cell cycle, apoptosis, and DNA repair.¹⁹⁰ These repressions lead to uncontrolled cell growth, genomic instability, and metastasis. Inhibition of the MAPK pathway, in combination with epigenetic therapy, may become a key strategy in the treatment of ocular neoplasms.

4.2.2. Phosphoinositide 3-kinase/AKT pathway

In ocular cancer, the phosphoinositide 3-kinase (PI3K)/AKT pathway plays a crucial role in cancer development, angiogenesis, metastasis, and drug resistance, and its dysregulation is strongly influenced by epigenetic mechanisms. *PTEN* hypermethylation causes excessive PI3K/AKT activation, promoting UM, RB, and OSSN.¹⁹¹ Conversely, *PIK3CA* hypomethylation promotes aberrant cell proliferation. Histone methylation, such as H3K27me3 repression of *PTEN* and H3K4me3 in *PIK3CA*, maintains PI3K/AKT activity in UM¹⁹² and enhances PI3K expression, respectively, maintaining tumorigenesis.¹⁹³ miRNAs, including miR-21 and miR-221/222, also inhibit *PTEN*, facilitating tumor growth and resistance to therapy, while miR-126 inhibits PI3K signaling, acting as a tumor suppressor. lncRNAs, such as HOTAIR and MALAT1, also promote PI3K/AKT activation, leading to angiogenesis and metastasis in UM and RB.¹⁹⁴

4.2.3. Nuclear factor-kappa B pathway

The NF-κB signaling pathway has important roles in inflammation, immune response, apoptosis, and tumorigenesis. Epigenetic changes may dysregulate the pathway, as seen in ocular cancers, including UM, RB, and OSSN. Aberrant DNA methylation, notably hypermethylation of tumor suppressor genes, including *CYLD* and *TNFAIP3*,¹⁹⁵ results in sustained NF-κB activation, chronic inflammation, tumor development, and resistance to apoptosis. On the other hand, hypomethylation of NF-κB target genes, such as *IL6* and *BCLXL*, enhances inflammatory signaling and survival of ocular tumor cells. Histone modifications, such as H3K27me3-mediated repression of NF-κB inhibitors, maintain NF-κB activation,¹⁹⁵ whereas H3K9-acetylation on NF-κB target genes induces pro-tumorigenic cytokine expression. MiRNAs, such as miR-146a and miR-155, regulate NF-κB activity: miR-146a is a tumor suppressor that suppresses NF-κB signaling, whereas miR-155 induces ocular cancer tumorigenesis by maintaining NF-κB activation. Furthermore, lncRNAs, such as HOTAIR and MALAT1, augment NF-κB signaling, inducing angiogenesis, metastasis, and immune evasion in ocular cancers.¹⁹⁶ These epigenetic modifications are responsible

for ocular tumorigenesis and therapy resistance, and thus DNMTis, HDACis, and miRNA-based therapy are promising strategies to regulate NF- κ B signaling and enhance treatment outcomes in ocular malignancies.

The dynamic and reversible nature of epigenetic modifications makes them highly promising targets for therapeutic intervention in ocular malignancies, as traditional approaches face significant challenges, such as off-target effects, associated toxicity, and drug resistance.

5. Epigenetics as diagnostic and therapeutic targets

A deeper understanding of epigenetic dysregulation in ocular cancers holds significant promise for advancing diagnostics, prognostication, and therapeutic interventions. Ocular malignancies, such as RB, UM, and ocular adnexal lymphoma, exhibit intricate epigenetic alterations that drive tumor initiation, progression, and resistance to standard therapies. Given the reversible nature of these modifications, epigenetic regulation offers a compelling therapeutic target (Figure 7).

The development of DNA methylation-based biomarkers and liquid biopsy approaches could facilitate early detection and personalized treatment strategies. Concurrently, epigenetic therapies, including small-molecule inhibitors targeting histone-modifying enzymes, miRNA-based therapeutics, and chromatin remodeling modulators, hold potential for precision oncology in ocular malignancies. However, translating these insights into clinical applications necessitates rigorous validation through robust preclinical and clinical studies. Future research should focus on elucidating the intricate interplay between genetic and epigenetic alterations, refining epigenetic drug targeting, and integrating multi-omics approaches to unravel the complexity of ocular cancer epigenetics. By bridging the gap between fundamental research and translational applications, the field is poised to unlock novel therapeutic opportunities, ultimately improving patient outcomes in ocular oncology.^{27,197,198}

5.1. Current epigenetic therapies

Numerous epigenetic pharmacological agents have been developed and are presently undergoing clinical evaluation for a variety of malignancies. Specifically, in ocular cancers, the emphasis has been placed on DNMTis, HDACis, and ncRNA therapeutics.

5.1.1. DNA methyltransferase inhibitors

These agents impede the silencing of tumor suppressor genes by inhibiting DNA methylation.¹⁵⁴ DNMTs function by obstructing the addition of methyl groups to DNA,

thereby facilitating the reactivation of silenced tumor suppressor genes. This mechanism has the potential to impede the progression of cancer and promote apoptosis in malignant cells.^{199,200} Azacytidine and decitabine are extensively used DNMTis and have demonstrated efficacy in reactivating silenced genes across a spectrum of cancers, including those affecting the ocular region.²⁰¹ However, challenges remain in the clinical application of these inhibitors; their therapeutic efficacy is limited by off-target effects and associated toxicity.

5.1.2. Histone deacetylase inhibitors

Through the modulation of histone acetylation, HDACis can reactivate silenced genes and promote apoptosis in neoplastic cells.¹⁵⁸ They inhibit histone deacetylation, resulting in a more open chromatin state. This alteration enables the reactivation of suppressed genes, potentially inducing cell cycle arrest, differentiation, and apoptosis in malignant cells.²⁰² Vorinostat and romidepsin are Food and Drug Administration (FDA)-approved HDACis for specific cancer types and are currently under investigation for their efficacy against ocular cancers.^{203,204} Like other epigenetic regulator drugs, the administration of HDACis may provoke adverse effects, including fatigue, nausea, and hematological toxicity.²⁰⁵

5.1.3. Non-coding RNA therapeutics

MicroRNAs and lncRNAs are being investigated for their capacity to regulate oncogenes and tumor suppressor genes. ncRNAs, such as miRNAs and lncRNAs, also regulate gene expression at both transcriptional and post-transcriptional levels. Therapeutics aimed at these RNA molecules can influence the activity of oncogenes and tumor suppressor genes.²⁰⁴⁻²⁰⁶ Currently, efforts are underway to develop miRNA mimics and inhibitors to restore normal gene expression in cancerous cells. Although RNA-based therapeutics have shown considerable promise as an epigenetic therapy, effective delivery to target tissues remains a major challenge.²⁰⁷

5.2. Upcoming therapies

The trajectory of epigenetic therapy for ocular malignancies is anticipated to encompass combination therapies, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology, biomarker development, multi-targeting agents, and artificial intelligence (AI).

5.2.1. Combination therapies

The combination of epigenetic pharmacological agents with traditional therapeutic modalities, such as chemotherapy, radiotherapy, and immunotherapy, has the potential to

significantly enhance therapeutic efficacy. For example, DNMTi can enhance the sensitivity of neoplastic cells to chemotherapeutic agents by reactivating silenced tumor suppressor genes.²⁰⁸ Like any other therapy, this method may enhance therapeutic outcomes, diminish resistance to monotherapies, and improve survival rates. Even with augmented therapeutic capacity, determining optimal drug combinations and managing potential adverse effects poses a significant challenge.^{209,210}

5.2.2. CRISPR/Cas9 technology

The CRISPR/Cas9 technology represents a groundbreaking gene-editing technology capable of precisely targeting and modifying specific epigenetic alterations. In ocular malignancies, it shows promise in rectifying mutations or reversing dysregulated epigenetic modifications.²¹¹ Precision in targeting neoplastic cells, minimal off-target genetic effects, and enduring therapeutic benefits make this a prime therapeutic candidate. Though it is one of the best techniques for resolving disease conditions, addressing ethical dilemmas, and navigating the intricacies of delivery systems, the risk of unforeseen genetic modifications hinders its application.²¹²

5.2.3. Biomarker development

Identifying the right target *always* helps detect and ameliorate disease conditions with proper therapeutic interventions. Likewise, the identification of epigenetic biomarkers is instrumental in facilitating early diagnosis, prognostication, and individualized treatment strategies for ocular cancers.¹⁷⁰ For example, hypermethylation of particular genes may function as a diagnostic indicator. Early identification, personalized therapeutic approaches, and the capacity to monitor treatment efficacy will potentiate the benefits. In this journey, validating biomarkers and integrating them seamlessly into clinical practice pose a challenge.²¹³

5.2.4. Multi-targeting agents

The development of pharmacological agents that concurrently target various epigenetic pathways, including DNA methylation and histone modifications, can yield a holistic strategy for cancer treatment. Augmented therapeutic effectiveness and reduced risk of resistance make these regimens key contenders in the race to find the best suitable cure. Hindrances to this regimen include the complexity associated with drug design and the potential for heightened adverse effects.²¹³

5.2.5. Artificial intelligence in therapy design

Artificial intelligence possesses the capability to analyze extensive datasets to identify novel epigenetic targets

and predict the efficacy of therapeutic combinations. Furthermore, it can facilitate the design of personalized treatment regimens tailored to a patient's distinctive epigenetic profile. Accelerated drug discovery, enhanced precision in treatment modalities, and reduced reliance on trial-and-error methodologies in therapy selection will amplify its benefits. Ensuring the accuracy of data, addressing ethical implications, and integrating AI into established clinical workflows may hinder its seamless application.²¹⁴

Epigenetics research is rapidly transforming with AI, enabling systematic discovery of disease-relevant epigenetic targets and accelerating the design of epigenetic therapies. Current case studies have demonstrated how deep learning and machine learning are widely used for target discovery, biomarker identification, compound prioritization, and the design of epigenetic editing strategies.²¹⁴

A few recent studies have applied large-scale AI target-discovery platforms to accelerate hypothesis generation from heterogeneous datasets. The PandaOmics platform has been deployed in target identification case studies that integrate proteomics, transcriptomics, and literature-mined information to identify and validate novel targets for neurodegenerative diseases and cancer, providing a clear demonstration of how AI can triage epigenetically regulated pathways for downstream validation. This work highlights the practical integration of multi-omics evidence to prioritize mechanistically plausible targets for therapeutic follow-up.²¹⁵

To understand biomarker identification and functionality, deep learning methods were applied to DNA methylation datasets that have produced targets with profound clinical significance. A recent multi-cohort study used machine learning to identify epigenetic loci associated with relapse and recurrent forms of acute myeloid leukemia.²¹⁶ It identified multiple targets for therapeutic use, highlighting the immense power of AI to mine large-scale methylome data for prognostic markers and targetable chromatin regulators.

Another study showed that implementing DeepPGD, a specialized deep learning model, can identify and annotate DNA methylation sites from sequence and experimental attributes.²¹⁷ This model enhances the specificity and sensitivity of methylation site calling, enabling higher-quality inputs to pinpoint epigenetic drivers through a different predictive model. Improved site mapping supports target discovery workflows that rely on high-resolution epigenomic maps.

A recent study highlighted the implementation of AI in multi-omics integration, in silico lead prioritization, and

drug repositioning for epigenetic modulators for therapy design.²¹⁸ It also described AI-driven drug-repositioning pipelines that combine epigenomic perturbation signatures with chemogenomic databases to identify existing compounds, including dual-target epigenetic modulators, for rapid repurposing in female malignancies and related medical complications. Collectively, these studies illustrate a shortened timeline from computational modeling to preclinical studies for epigenetic therapies.

Understanding cell-type-specific epigenetic dysregulation has been enabled by combining single-cell and spatial epigenomics with interpretable deep learning. With the help of deep learning, single-cell epigenetic/transcriptomic datasets have revealed age- and disease-associated chromatin signatures and highlighted candidate epigenetic regulators whose modulation could restore healthy genetic and cellular conditions.²¹⁹ Given the known challenges of therapy resistance and off-target effects, moving beyond bulk tissue analysis to explore tumor heterogeneity at the cellular level is essential.

6. Single-cell transcriptomics and epigenomics

Single-cell sequencing technologies enhance our understanding of cellular dynamics by offering new biological insights into cellular compositional changes and cell-type-specific transcriptomic and epigenomic alterations.

Collin *et al.*²¹⁹ were the first to use single-cell RNA sequencing and assay for transposase-accessible chromatin using sequencing (ATAC) analyses on primary RB tissues to reveal that cone precursors at different stages of the cell cycle escape cell cycle arrest and/or apoptosis in RB tumors. This confirms RB tumor heterogeneity and that upstream regulators and signaling pathways play an important role in modulating the epigenetic landscape of RB.

Similarly, Liu *et al.*²²⁰ explored the single-cell transcriptomic landscape of intraocular and extraocular RB samples to identify the various sub-populations that affect its prognosis, while novel subclonal genomic complexity and transcriptional states have been identified in UM by Durante *et al.*²²¹ Meanwhile, Zhang *et al.*²²² explored the tumor microenvironment in ocular adnexal sebaceous carcinoma. However, while there is single-cell epigenomic work in non-tumor ocular/retinal tissue,^{223,224} no studies have yet established single-cell epigenomic profiles in ocular cancers.

Similarly, while patient-derived studies on ocular cancer epigenetics are yet to be explored, studies have

found differentially methylated CpG sites between diabetic retinopathy (DR) and non-DR control patients.²²⁵ Studies have also demonstrated that reversing certain epigenetic changes, such as DNA methylation, can restore vision in a mouse model of glaucoma and in aged mice (human studies are yet to be performed).²²⁶ While yet to be explored in ocular cancers, such studies lend credence to the hypothesis that epigenetic changes in ocular cancers can lead to the discovery of novel biomarkers and targets that allow the mitigation of the condition.

7. Limitations of the study

While this review provides a comprehensive synthesis of current advances in ocular cancer epigenetics, several limitations warrant acknowledgment. First, the field remains constrained by the limited availability of large-scale, multi-omics datasets for rare ocular malignancies, limiting the generalizability of certain findings. Second, much of the existing evidence is derived from small patient cohorts or in vitro models, underscoring the need for validation in clinically representative populations. Third, although key mechanisms involving DNA methylation, histone modifications, and ncRNA regulation have been highlighted, emerging dimensions of epigenetic control—such as 3D genome organization, enhancer dynamics, and RNA modifications—remain underexplored in ocular oncology. While these approaches remain preclinical in ocular cancers, this review highlights critical lacunae in the field and underscores the need for systematic exploration of emerging strategies, such as ncRNA-based and gene-editing approaches, which are still largely confined to experimental settings. Finally, as this review primarily draws from published literature, potential publication bias and underreporting of negative results may limit the scope of interpretation. Continued integration of high-resolution epigenomic profiling, spatial transcriptomics, and longitudinal clinical studies will be essential to address these gaps and refine mechanistic understanding.

8. Conclusion

Epigenetic mechanisms play a role in the pathogenesis and progression of ocular cancers, influencing gene expression through DNA methylation, histone modifications, ncRNA regulation, and chromatin remodeling. This review has highlighted how aberrant epigenetic modifications contribute to tumor initiation, progression, and therapeutic resistance in RB, UM, and other ocular malignancies. DNA methylation-based silencing of tumor suppressors, histone modifications that reprogram chromatin states, dysregulated ncRNAs, and disrupted chromatin remodeling complexes collectively drive

oncogenic pathways in these cancers. The identification of epigenetic signatures and their role in tumor heterogeneity underscores the necessity of integrating epigenetic insights into ocular oncology research.

A better knowledge of epigenetic dysregulation in ocular malignancies has great promise for improving diagnosis, prognosis, and therapeutic approaches. The development of DNA methylation-based biomarkers and liquid biopsy methods could lead to early identification and individualized treatment regimens. Furthermore, epigenetic treatments, such as small-molecule inhibitors of histone-modifying enzymes, miRNA-based medicines, and chromatin remodeling modulators, offer exciting opportunities for precision oncology in ocular malignancies. However, transferring these discoveries into therapeutic applications necessitates additional confirmation through rigorous preclinical and clinical trials. Future research should concentrate on understanding the relationship between genetic and epigenetic changes, improving epigenetic medication targeting, and integrating multi-omics techniques to unravel the complexities of ocular cancer epigenetics. By bridging the gap between fundamental epigenetic research and translational applications, the field is positioned to uncover potential therapeutic targets.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Shalini Sanyal, Sayantan Ghosh

Investigation: Shalini Sanyal, Sayantan Ghosh, Abhijit Ghosh

Visualization: Shalini Sanyal

Writing–original draft: Shalini Sanyal, Sayantan Ghosh, Abhijit Ghosh

Writing–review & editing: Shalini Sanyal, Sayantan Ghosh

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