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Review

Role of Epigenetics in Uveal Melanoma

Yongyun Li, Renbing Jia✉, Shengfang Ge✉

Department of Ophthalmology, Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, People's Republic of China

✉ Corresponding authors: Shengfang Ge or Renbing Jia. geshengfang@sjtu.edu.cn or jrb19760517@hotmail.com

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Abstract

Uveal melanoma (UM) is a severe human malignancy with a high mortality rate that demands continued research into new and alternative forms of prevention and treatment. The emerging field of epigenetics is beginning to unfold an era of contemporary approaches to reducing the risk and improving the clinical treatment of UM. Epigenetic changes have a high prevalence rate in cancer, are reversible in nature, and can lead to cancer characteristics even in mutation-free cells. The information contained in this review highlights and expands on the main mechanisms of epigenetic dysregulation in UM tumorigenesis, progression and metastasis, including microRNA expression, hypermethylation of genes and histone modification. Epigenetic drugs have been shown to enhance tumor suppressor gene expression and drug sensitivity in many other cancer cell lines and animal models. An increased understanding of epigenetic mechanisms in UM will be invaluable in the design of more potent epigenetic drugs, which when used in combination with traditional therapies, may permit improved therapeutic outcomes.

Key words: Epigenetics; Gene Therapy; MicroRNA; DNA Methylation; Uveal Melanoma.

Introduction

Cancer is defined as uncontrolled cell growth and the acquisition of metastatic capacities. There are various mechanisms by which these cellular changes occur. The typical mechanisms are mutation, chromosomal deletion or translocation, and dysregulated signaling pathways. These events may activate genes that promote uncontrolled cell cycling or inactivate apoptosis. Uveal melanoma (UM) is the second most common form of human melanoma and the most common primary intraocular malignant tumor in adults, with an annual incidence of 6–7 cases per million per year [1, 2]. According to the Collaborative Ocular Melanoma Study group (2001), about 50% of UM patients will develop liver metastasis within 10–15 years of enucleation [3]. Early metastasis leads to the high death rate associated with UM [4].

The characteristic processes associated with UM generation are well described in the existing literature, and numerous comprehensive reviews are available on each topic. For instance, monosomy of chromosome 3 and gain of 8q are often found in UMs. In addition, studies revealed that a mutation in the alpha subunit of the heterotrimeric G gene (*GNAQ*) was present in almost 50% of all UMs examined, and that UM metastatic spread was closely related to mutations in the BRCA associated protein 1 (*BAP1*) gene on chromosome 3 [5, 6]. However, more data is needed to elucidate the process of tumorigenesis of UM, which is currently still poorly characterized.

Compared with the genetic mechanisms involved in UMs, the role of epigenetics in carcinogenesis is less well defined. Recent studies propose that epigenetic alterations may be another hallmark of cancer due to their role in the initiation of carcinogenesis [7, 8]. Epigenetic changes can lead to cancer characteristics even in mutation-free cells. Epigenetic mechanisms include microRNA expression level variations, hypermethylation of tumor suppressor genes, hypomethylation of oncogenes, and histone modification patterns. In this review, we will discuss the role of epigenetics in UM tumorigenesis and the potential modes of therapy derived from this area of research.

Epigenetic mechanisms in UM

Noncoding RNAs

MicroRNAs

Recent research has shed light on the involvement of a class of noncoding RNAs, known as miRNAs, in UM. miRNAs are a class of short (17–22 nucleotides in length), endogenous, noncoding RNAs involved in the regulation of gene expression [9]. Many miRNAs manifest differential expression levels in UM tissues and cell lines. By base-pairing with the complementary sites on the 3′-untranslated region (3′UTR) of mRNAs, miRNAs regulate target genes by degrading mRNAs and repressing their translation [10]. Several studies have reported that dysregulation of miRNAs can promote cell-cycle progression, confer resistance to apoptosis, and enhance invasiveness and metastasis of cancer cells. In a recent study, six miRNAs (let-7b, miR-199a, miR-199a*, miR-143, miR-193b and miR-652) were found to differentiate class 1 and class 2 UM tumors [11]. Another study identified 19 miRNAs expressed in non-metastasizing melanoma were absent in metastasizing melanoma, and 11 miRNAs expressed in metastasizing melanoma were absent in non-metastasizing melanoma [12]. Lori *et al.* used a microarray to analyze miRNA expression levels in UM with metastasis and found that let-7b and miRNA-199a showed high sensitivity and specificity for differentiation [11].

miR-34a: miR-34a inhibits the proliferation and migration of UM cells. Bioinformatic prediction suggested that the oncogene, c-Met, is a target of miR-34a in UM cells. Furthermore, miR-34a can down-regulate phosphorylated Akt (protein kinase B) and many cell cycle-related proteins [13].

miR-137: Chen *et al.* demonstrated that miR-137 expression was lower in UM cell lines than in benign uveal melanocytes [14]. Functional analysis of miR-137 indicated that over-expression of miR-137 increased G1 cell cycle arrest, leading to a significant reduction in cell growth in UM. Ectopic transfection of miR-137 into UM cells down-regulated MITF, a transcription factor with oncogenic activity. In addition, over-expression of miR-137 down-regulated the oncogenic tyrosine kinase protein receptor c-Met and cell cycle-related proteins, including CDK6.

miR-149*: The miR-149* expression level has a statistically significant association with liver metastasis in UMs.[15] Glycogen synthase kinase-3α (*GSK-3α*), a known gene target of miR-149*, encodes an important melanoma growth regulator [16].

miR-134: miR-134 is associated with invasiveness and metastasis in many other tumors with putative gene targets including the *VEGFA*, *FOXM1*, *MYCN*, *CD9* and *WWOX1* genes [17]. Venkatesan *et al.* discovered a higher percentage of miR-134 (94.11%) in UM with liver metastasis than those without metastasis, irrespective of chromosome 3 aberrations, which suggests that miR-134 could be a potential biomarker for class 2 tumors [15].

Let 7b: Let 7b, a known tumor suppressor miRNA, is down-regulated in various cancers such as acute lymphoblastic leukemia and retinoblastoma [18, 19]. Restoration of let-7b is regarded as a potential therapeutic option in many cancers. Let-7 has also been demonstrated as a strong discriminator in primary UM, and has been reported at low levels in OCM1 cells [11, 20]. Research indicates that let-7b over-expression down-regulates cyclin D1 expression, which plays a critical role in cell cycle arrest, and enhances the radio-sensitivity of UM through cell cycle arrest [21].

miR-34b/c: Feng *et al.* discovered that miR-34b/c expression was dramatically decreased in 5 specimens in contrast to normal uveal tissues. The transfection of miR-34b/c into UM cells leads to a significant decrease in cell growth and metastasis. miR-34b/c caused cell cycle G1 arrest rather than the induction of apoptosis. Met proto-oncogene (*c-Met*) is considered a target of miR-34b/c in UM cells. Furthermore, miR-34b/c was confirmed to down-regulate the expression of p-Akt, and many cell cycle-related proteins [22].

Table 1. Main functions of the dysregulated miRNAs in UM.

Name	Expression	Target gene	Role	Reference
miR-34a	Decreased	c-Met, Akt	Suppressor	[13]
miR-137	Decreased	MITF, c-Met, CDK6	Suppressor	[14]
miR-149*	Over expressed	GSK-3α	Oncogene	[15,16]
miR-134	Over expressed	VEGFA,FOXM1,MYCN,CD9, WWOX1	Oncogene	[15,17]
miR-214	Decreased	PTEN, AP2, TP53	Suppressor	[24, 25]
miR-146b	Over expressed	NF-kB, SMAD4	Oncogene	[26]
Let 7b	Decreased	cyclin D1	Suppressor	[11,18-21]
miR-34b/c	Decreased	c-Met, Akt	Suppressor	[22]
miR-182	Decreased	MITF, BCL2, cyclin D2, Akt and ERK1/2	Suppressor	[23]

miR-182: miR-182 expression is dependent on p53 induction in UM cells. Interestingly, Yan *et al.* found that compared with normal uveal tissues, the expression of miR-182 was significantly decreased in tumor specimens. Transient transfection of miR-182 into cultured UM cells induced a significant decrease in cell growth, migration and invasiveness. Cells transfected with miR-182 manifested increased cell cycle G1 arrest and apoptotic activity. *MITF*, *BCL2* and *cyclin D2* are three potential target genes of miR-182. In addition, the expression of oncogene *c-Met* and its downstream Akt and ERK1/2 pathways are also down-regulated by miR-182 [23].

The detailed mechanisms of action of miRNAs in tumor development and progression are complex and numerous [27]. However, most of them converge on common signaling pathways that govern cell proliferation, apoptosis and invasion [28]. The significance of specific miRNAs in UM progression should be interpreted in appropriate biological backgrounds as miRNA interacts widely with other signaling cascades and often behaves diversely in different histological subtypes of UM. Population-based differences in miRNA dysregulation, and the diagnostic or prognostic use of miRNAs in different racial groups are also key considerations [29]. Recent advances in the development of internal RNA delivery systems may open up new opportunities for the use of miRNAs as new cancer therapeutics [30]. It is anticipated that, with a more comprehensive understanding of miRNAs and the associated abnormalities in cellular signaling in UM, novel therapeutics will emerge before long.

Long non-coding RNAs

Long non-coding RNAs (long ncRNAs, lncRNA) are non-protein coding transcripts longer than 200 nucleotides, which were initially considered to be the 'dark matter' of the genome. In recent years, the importance of the role played by lncRNAs on the regulation of gene expression has been increasingly recognized. Unlike miRNAs, lncRNAs display complex secondary and tertiary structures allowing them to bind vital proteins, RNA and DNA to carry out their regulatory functions [31]. Accumulating evidence suggests that lncRNAs play important roles in a range of processes including transcriptional regulation, tumorigenesis and the metastatic cascade [32, 33]. For instance, the lncRNA Kcnq1ot1 forms chromatin loops to control genomic imprinting [34]. Recent studies have also revealed that the CASC15 lncRNA was upregulated during melanoma progression and correlated with cell proliferation and invasion phenotypes of melanoma [35]. In addition, our laboratory found that knockdown of lncRNA P2RX7-V3 expression in UM cells resulted in a cell growth defect, decreased invasion and a decreased rate of colony formation of melanoma cells. We further discovered that the PI3K-AKT signaling pathway served as a major target of P2RX7-V3. These data indicated that P2RX7-V3 plays a regulatory role in tumor progression and may serve as a new oncoRNA (manuscript in press).

Besides, lncRNAs can also work together with other epigenetic mechanisms, such as histone methylation and microRNAs, to modulate the cancer behaviors. Fan used epigenetic approaches to demonstrate that the lncRNA ROR acts as a necessary decoy oncogenic RNA (oncoRNA) that plays an important regulatory role in tumorigenesis of UM cells and colorectal cancer cells and represents a novel style of histone modification [36]. Ding *et al.* discovered that lncRNA PAUPAR acted as a necessary UM suppressor and could silence HES1 expression, which significantly reduced metastasis. Mechanistically, PAUPAR inhibits histone H3K4 methylation to modulate HES1 expression [37]. Lei demonstrated that lncRNA MALAT1 was upregulated in the uveal melanoma tissues and cell lines. The knockdown of MALAT1 suppressed the uveal melanoma cell proliferation, colony information, invasion and migration partly through modulating miR-140 expression [38].

Actually, lncRNAs sometimes play as a downstream target of cancer suppressors. LncRNA-numb was found to restore the function of HIC1 in UM cells, which is an important protein to modulate uveal melanoma progression. Overexpression of HIC1 led to the normal level of lncRNA-numb [39].

Researches in other noncoding RNAs like circRNA and ceRNA are getting more prevalent in many diseases such as Alzheimer's disease (AD), Hirschsprung's disease and cancers [40-42]. In the field of uveal melanoma, however, studies related with circRNAs could not be found so far and deep researches are necessary in the future.

DNA methylation

Epigenetic modification of gene expression is an important mechanism in tumorigenesis, and may be reversed by specific treatment.

DNA hypermethylation

Abnormal promoter hyper-methylation of CpG islands is thought to play an important role in the inactivation of tumor suppressor genes (TSGs) in cancer [43].

$p16^{INK4a}$(cyclin-dependent kinase inhibitor 2A):

Previous studies have found that the loss of $p16^{INK4A}$ expression in patients with progressing melanoma is associated with increased tumor cell proliferation and decreased patient survival [44, 45]. Progression of tumor cells through the G1 phase of the cell cycle is stimulated by the association of cyclin D with cyclin-dependent kinases (CDKs) that phosphorylate Rb [46]. Upon Rb phosphorylation, E2F is activated and enhances S-phase-specific gene expression. $p16^{INK4a}$ has been identified as an inhibitor of the cyclin D/CDK complex,[47] as it can restrict the cyclin D-CDK4 and cyclin D-CDK6 kinases and result in cell cycle control at the G1-S restriction point. Although $p16^{INK4a}$ is commonly inactivated in a wide range of malignancies [48], germ-line mutations of $p16^{INK4a}$ are uniquely associated with familial cutaneous melanoma instead of UM [49, 50]. An alternative mechanism for tumor suppressor gene inactivation is *de novo* methylation of CpG islands, which generally reduces transcription. *De novo* methylation of the $p16^{INK4a}$ promoter region occurs in a wide range of malignancies [51] and releases the cell from a potent cell cycle inhibitor. A recent study found that in both primary UM and UM cell lines, $p16^{INK4a}$ is frequently inactivated by hypermethylation, which is accompanied by down-regulated expression of $p16^{INK4a}$ [52]. This study also reported that loss of $p16^{INK4a}$ expression, attributable to CpG methylation, could be reversed when treated with the demethylating drug 5-aza-2-deoxycytidine. Interestingly, metastasis tends to be more common in UM patients who possess a tumor with a methylated $p16^{INK4a}$ promoter, so aberrant methylation can be modulated and, hence, provides an effective target for the treatment of UM. Another study showed that epigenetic alterations in the $p14^{ARF}$ and $p16^{INK4A}$ genes were frequently associated with cutaneous as well as UMs,[8] and they used ChIP experiments to clearly demonstrate that DNMT1 and DNMT3b played a dominant role in $p16^{INK4A}$ repression.

RASSF1A (RAS association domain family 1 isoform A): The *RASSF1A* promoter gene is known to be extremely common in cancers of the breast, head and neck, lung and cutaneous melanoma [53]. It has been discovered that RASSF1A plays an important role in cell-cycle regulation, apoptosis and microtubule stability [54, 55]. The *RASSF1A* gene is located on chromosome 3p21.3, and its absence or inactivation has been shown to be a contributing factor in UM tumor formation and progression [56]. One study showed that RASSF1A expression suppresses UM tumorigenesis and is frequently silenced in the UM-15 cell line and that re-expression of RASSF1A in UM-15 cells reverses the tumoral behavior, as demonstrated by a slower proliferation rate and restoration of sensitivity to cisplatin treatment [57]. The *RASSF1A* gene contains two CpG islands, spanning the promoter and the first exon gene regions, which are susceptible to *de novo* methylation. Methylation of these sites blocks cell-cycle progression from G1 to S phase by controlling entry at the retinoblastoma check point and inhibiting cyclin D1 protein accumulation at the post-transcriptional level [58].

Hypermethylation-induced loss of RASSF1A expression leads to a reduction in G1/S-phase cell-cycle control. In human mammary epithelial cells, RASSF1A dominates the oncogenic RAS effects, which means that loss of RASSF1A may be a determining step for oncogenic transformation in the absence of RAS-activating mutations. In addition, overexpression of RASSF1A enhances the formation of stable microtubules and blocks RAS-activated genomic instability, suggesting that the RASSF1A protein plays a potential role in the maintenance of spindle function and genomic stability [59]. Loss of one copy of chromosome 3 (monosomy 3) has been reported in approximately half of all UMs and is related to the metastatic capacity of the tumor. Given the location of RASSF1A on the p21.3 region of chromosome 3, it might serve as a tumor suppressor gene whose silencing by methylation acts as a 'second hit' after monosomy occurs [56]. Although the methylation of *RASSF1A* may not be considered wholly responsible for UM development, it could be a contributing factor in tumor formation and progression. This assumption is supported by a study showing that down-regulated expression of *RASSF1A* frequently occurs in primary UM [60]. One study of reported a positive trend between DNA methylation and UM patients' survival [56]. The same study also suggested that the methylation of RASSF1A protein is a potential tumor marker in UM.

RASEF (Ras and EF-hand domain-containing protein): Recently, segregate studies in families with uveal and cutaneous melanoma identified 9q21 as a potential locus harboring a tumor suppressor gene. One of the genes in this region, *RASEF*, was analyzed as a candidate tumor suppressor gene. The *RASEF* gene, also known as *RAB45* or *FLJ31614*, is located on chromosome 9, region q21 [61]. It encodes a protein with a calcium-binding EF-hand and Ras GTPase (Rab family) motif, which is potentially involved in the RAS pathway prominent in the development of melanoma [62]. In a study by Maat *et al.*, 11 UM cell lines and 35 primary UM samples were screened for mutations in the *RASEF* gene region by high-resolution melting-curve and digestion analysis. They found that all cell lines and samples that did not express *RASEF* contained a methylated promoter,

whereas those with *RASEF* expression lacked this methylation. Furthermore, they demonstrated methylation not only coincided with low expression but also with a homozygous genotype, suggesting that a combination of methylation and loss of heterozygosity may be the mechanism for loss of expression [63]. Additional effects of the loss of heterozygosity seem to be related to the aggressive behavior of the tumor, because homozygous tumors with a methylated *RASEF* promoter region tend to display decreased survival compared with heterozygous tumors without methylation (P=0.019).

DNA hypomethylation

Compared with DNA hypermethylation of tumor suppressor genes in tumorigenesis, DNA hypomethylation is less common. For instance, Preferentially Expressed Antigen in Melanoma (*PRAME*) is an accurate biomarker of metastasis in uveal melanoma [64]. Field *et al.* found that specific CpG sites around the *PRAME* promoter are differentially hypomethylated. As a result, the gene is activated in Class 1 and Class 2 uveal melanomas and is associated with increased metastatic risk in both classes [65]. Besides, a recent study discovered that 41/64 uveal melanomas (64.1%) showed higher expression of Deleted in Split hand/Split foot 1 (*DSS1*) gene than normal tissues. There was a significant association between high *DSS1* expression levels and some clinicopathological features. An inverse correlation between DSS1 expression activity and methylation status of its promoter was verified, while DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine could significantly increase *DSS1* expression *in vitro* [66].

Histone modification

Histone modification refers to the process of histone methylation, acetylation, phosphorylation, polyadenylation, ubiquitination and ADP ribosylation, carried out with assistance from the related enzyme.

Histone methylation: Post-translational methylation of histone lysine or arginine residues is real common and plays important roles in gene regulation. Aberrant histone methylation due to gene mutation, translocation, or overexpression can often lead to initiation of a cancer. For example, monomethylation of H4K20 and H2BK5; trimethylation of H3K4, H3K36 and H3K79 promote gene expression, whereas dimethylation of H3K9 and trimethylation of H3K9 and H3K27 inhibit gene expression [70, 71]. In UM cells, Holling *et al.* reported an association between impaired CIITA transcript levels and a high rate of trimethylated histone H3-lysine 27 (H3K27me3) in CIITA-PIV chromatin, rather than DNA methylation of MHC2TA promoter IV (CIITA-PIV). They demonstrated the presence of the histone methyltransferase EZH2 in CIITA-PIV chromatin, which is known to be a component of the polycomb repressive complex 2 and able to triple methylate histone H3-lysine 27 [72]. In addition, transcription factor HES1 is overexpressed in UM cell lines and is associated with its metastatic capacity. And one of the reasons of upregulated expression of HES1 in UM cells is H3K4 trimethylation of the HES1 promoter [37].

Histone phosphorylation: Histone phosphorylation plays an important role in transcriptional activation and chromatin compaction during cell mitosis and meiosis [73]. Especially, histone phosphorylation of H1, H2B, H3 has extensive functions in DNA repair and gene regulation [74]. For example, Ser10 and Ser28 of H3 specifically at the promoter locus of FOS and JUN genes are often be phosphorylated by mitogen and stress-activated kinase 1 and 2 (MSK1/2) in tumors. This phenomenon is common in breast, prostate and colorectal cancers [75, 76]. Histone H3, phosphorylated at Ser28, is regarded as an M-phase protein marker. Zhang *et al.* found that in uveal melanoma, irradiated tumor cells showed G2 phase arrest as well as the high expression of histone H3 phosphorylated at Ser28, which could be reversed by knockdown of p21 [77].

Table 2. Functional characterization of the methylated promoters in UM.

Gene	The Percentage of patients with hypermethylation	Function	Reference
RASSF1A	91%	RAS-associated domain family	[53-60]
MGMT	10%-30%	O^6-methylguanine-DNA methyltransferase	[67]
DcR1, DcR2	91%-97%	Receptors for TRAIL	[68]
p16/INK4a	/	Stabilizer of the tumor suppressor protein	[8, 44-52]
CXCR4, CCR7	/	Hypermethylation of this gene can inhibit metastasis	[69]
RASEF	46%-54%	RAS pathway	[61-63]

Histone acetylation: The balance between acetylation and deacetylation of a gene is determined by the relative activities of histone acetyltransferases and histone deacetylases (HDACs). Increased acetylation promotes greater chromatin accessibility for gene expression. For example, acetylation of H3K9 and H3K14 enhances gene expression [78]. Studies suggest that down regulated expression of *BAP1* led to impaired differentiation in UM cells. And this important function can be partially reversed by HDAC inhibitors, which can increase histone H3 acetylation [79].

Potential therapeutics targeting epigenetic regulators

Therapies targeting well-defined markers, such as overexpressed Her-2 in breast cancer and fused Bcr-abl in chronic myeloid leukemia, are often initially successful but falter when subpopulations of resistant cancer cells become dominant. Hence, the new paradigm of drug development is the targeting of multiple hallmarks of cancer simultaneously. Recent research has proven that epigenetics plays a role in the development of many cancers and strongly suggests that epigenetic mechanisms play an important role in the early diagnosis, treatment and prognosis of these tumors. Combining therapeutics targeting epigenetic regulators of cancer with traditional therapeutic strategies may offer great advantages. Exposure to epigenetic and non-epigenetic drugs that re-express tumor suppressor genes should enhance the efficiency of classical therapeutics of UM and sensitize the cancer cells to lower doses of traditional cytotoxic drugs [80].

In recent years, the potential clinical application of therapeutic methods aimed at epigenetic regulators have rapidly emerged. For example, miR-375 interference or destruction is a promising therapeutic avenue in the context of paclitaxel-resistant cervical cancer [81]. Treatment with HDACi sensitizes breast and ovarian cancer cell lines to the calpeptin, TRAIL, and telomere homolog oligonucleotides [82]. The demethylating agent, 5-azacitidine, sensitizes ovarian cancer cells to classical platinum-based chemotherapeutics [83]. In addition, the prognosis of acute leukemia patients can be determined by measuring the hypermethylation level of CpG islands in the *P15* gene. Along with advances in genomics methodology, researchers are uncovering abnormal DNA methylation patterns. This information can be applied to expression microarrays in their use as forecasting tools to predict cancer progression and prognosis. Such studies have been carried out for a number of tumor types and could potentially be applied to the diagnosis and prognosis of UM.

To date, no epigenetic drugs have been applied in clinical use for UM; however, this may change in the near future due to the emergence of a large number of new potential targets. MicroRNA is an important epigenetic regulatory system that may be targeted as a cancer therapy. Targeting specific miRNAs could be particularly effective in cancers in which miRNAs have been found to confer chemotherapeutic resistance. Zhou *et al*. found that let-7b could potentially be used as a radio-sensitivity enhancer in UM radiotherapy [21]. miR-34b/c expression, which is dramatically reduced in UM cells and clinical samples, can be up-regulated by doxorubicin and epigenetic drugs. It is anticipated that novel therapeutics will emerge as miRNA dysregulation and the associated abnormalities in cellular signaling in UM become more comprehensively understood.

Another common epigenetic mechanism in UM generation is hypermethylation of some important gene promoters. A prerequisite for re-expression of epigenetically-silenced tumor suppressor genes is demethylation of the regulatory regions. DNA methyltransferase-1 (DNMT1) inhibitors, such as 5-azacitidine and its derivatives, are the most well-known demethylating agents [80]. Chen *et al.* reported that a DNA hypomethylating agent, 5-aza-2′-deoxycytidine, could increase the expression levels of miR-137, which may be epigenetically silenced during UM tumorigenesis [14]. In addition, miR-124a expression could be regulated via epigenetic mechanisms, such as those involving the DNA hypomethylating agent, 5-aza-2′-deoxycytidine, or the histone deacetylase inhibitor, trichostatin A [84].

Epigenetics offers new promise for cancer therapeutics. Combining traditional therapies with novel epigenetic strategies may prove effective for the treatment of UM.

Conclusion

This review summarizes the currently available literature on the function of epigenetic alterations, particularly focusing on UM. Many epigenetic changes, including miRNA expression level variations, hypomethylation of oncogenes, hypermethylation of tumor suppressor genes and histone modification patterns, are known to be associated with UM tumorigenesis and many other cancers. Further studies are expected to elucidate how these variations are generated and, in turn, how they regulate the development and metastasis of cancer cells. An increased understanding of epigenetic mechanisms will not only be important in unraveling how cancer cells engender, transform and acquire

resistance to chemotherapy and radiation, but will also be invaluable in the design of more potent epigenetic drugs. These treatments, in combination with traditional therapies, will permit accurate targeting of cancer cells and likely reduce the significant mortality associated with cancer relapse.

Competing Interests

The authors have declared that no competing interest exists.

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