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Role of epigenetic deregulation in hematogenous dissemination of malignant uveal melanoma

Minireview

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It has become increasingly clear that epigenetic deregulation plays a fundamental role in cancer. Although the understanding of molecular, genetic and transcriptional alterations involved in the initiation and progression of uveal melanoma (UM) has grown significantly in recent years, little attention has been paid to the role of epigenetic changes. In cancer, epithelial-to-mesenchymal transition (EMT) enables trans-differentiation of epithelial tumor cells, endowing them with migratory and invasive properties. EMT-inducing transcription factors have been shown to interact with multiple epigenetic modifiers, thus reflecting the reversible nature of EMT. Therefore, the epigenetic therapy targeting these interactions may provide a promising therapeutic option, especially since no improvement in survival of patients with metastatic UM has been achieved using traditional approaches.

This review summarizes current knowledge of epigenetic regulation of EMT in UM and emphasizes the need for deeper understanding of these highly dynamic and reversible processes. The potential for targeting individual members of the epigenetic machinery is also addressed.

Key words: uveal melanoma, DNA methylation, histone modifications, miRNA, epithelial-to-mesenchymal transition, tumor cell dormancy

Uveal melanoma (UM) is the most frequent intraocular tumor in adults, representing approximately 83% of ocular and 3% of all melanomas [1]. The average annual incidence varies widely according to age, ethnicity and latitude and the highest incidence is in white Caucasians (5.5–6.0 per million) [2]. Risk factors for the development of UM include white race, fair skin and light iris color, dysplastic nevus syndrome, ocular melanocytosis and germline BRCA1-associated protein 1 (*BAP1*) mutations [3]. The UM tumors arise from melanocytes located in the uveal layer of the eye, with the choroid the most frequent site (82%), followed by the ciliary body (15%) and iris (3%) [4]. Both cutaneous melanomas (CMs) and UMs originate from neural crest-derived melanocytes but they have a distinct spectrum of chromosome aberrations and gene mutations and different metastatic routes and tropism. [5]. While UM tumors lack *BRAF* or *NRAS* mutations in the mitogen-activated protein kinase (MAPK) pathway typical for CM [6], the constitutive activation of the MAPK pathway in UM is mediated by *GNAQ* and *GNA11* mutations in the G-protein pathway [7, 8]. Patient management has changed in the recent past to eye-conserving approaches: the most common are radiotherapy, laser therapy and surgical resection [3, 9]. Large tumor size, involvement of the optic disc and irrecoverable total vision loss are indications for the enucleation, required in 20–40% of UM cases [10].

Despite highly effective treatment of the primary disease, development of metastases, often observed more than 5 years later, occurs in up to 50 % of patients [11, 12]. Tumor dormancy has been considered the leading reason for the

delayed appearance of metastasis [13]. Various clinical, pathological, molecular and cytogenetic markers predict metastatic risk and survival (Table 1).

The main clinical characteristics associated with the poor prognosis are large tumor diameter and thickness, ciliary body involvement and extra-ocular spread [14]. The unfavorable histopathological prognostic factors are epithelioid melanoma cytomorphology, extra-vascular matrix pattern, high mitotic rate and inflammatory infiltration [15]. Chromosome 3 loss, often co-occurring with *BAP1* inactivating mutations, is one of the most significant-cytogenetic alterations that correlates with development of metastases [16, 17]. Gene expression profiling that allows prediction of metastatic risk with higher accuracy than clinical stage or chromosome 3 status, categorizes UM tumors as Class 1 (low metastatic risk) and Class 2 (high metastatic risk) [18, 19]. Increased gene expression of preferentially expressed antigen in melanoma (*PRAME*) positively associated with *SF3B1* mutations, predicts metastatic risk in patients with Class 1 or disomy 3 tumors [20]. Metastatic UM has a clear predilection for the liver which is afflicted in almost all Class 2 patients, while other metastatic sites, mostly in Class 1 tumors, include lung, bone and stomach [20]. Metastatic disease is associated with poor prognosis and median overall survival ranging from 4 to 15 months [21].

Epigenetic mechanisms, such as DNA methylation, histone modification and the action of non-coding RNAs are essential for normal development and maintenance of tissue-specific gene expression patterns in mammals. Their disruption can lead to altered gene function, malignant cellular transformation and metastatic progression.

Although numerous studies have addressed the genetic events in the development of UM (reviewed in [7, 22]), only a few have focused on epigenetic changes (reviewed in [23, 24]). However, a recently published study applying an enormously comprehensive array of biomedical techniques including analysis of methylomes and non-coding RNAs has provided complex insight into UM pathogenesis [8]. The authors demonstrated that monosomy 3 is associated with a distinct global DNA methylation pattern, suggesting that *BAP1* aberrancy results in a metastasis-prone methylation state. Moreover, monosomy 3 UM is divided into two subsets by copy number alterations, RNA/non-coding, RNA expression and cellular pathway activity profiles [8]. Expression levels of a number of histone-modifying genes and polycomb family members are significantly lower in monosomy 3/Class 2 UMs, thus supporting the role of general deregulation of epigenetic modifiers in UM with a poor prognosis [25]. Deregulation of the UM microRNA (miRNA) network has been shown to promote cell-cycle progression, resistance to apoptosis, invasion and metastasis [24].

This article summarizes the current evidence on the role of epigenetic deregulation in UM metastatic spread. Because of

Table 1. Clinical, histological and genetic markers for prediction of metastatic risk.

Prognostic predictors	Risk factor	Genes	Incidence/Prognosis	Reference
Clinical	High tumor diameter, thickness, ciliary body involvement, extra-ocular spread			[14]
Pathological	Epithelioid melanoma cytomorphology, extravascular matrix pattern, high mitotic rate			[15]
Cytogenetic	Monosomy 3	*CTNNB1, SOX2*	~50 % of UM	[16]
	Chromosomal abnormalities of chromosomes 1, 6 and 8	*GNAQ, GNA11, LZTS1, DDEF1, PTP4A3, TCEB1, BAP1*	17–63% depending on abnormality	[8, 22]
Molecular	Class 2 gene expression signature		40% of Class 2 patients metastasize	[18, 19]
	Aberrant gene expression	*PRAME*	15% of Class 1 patients metastasize	[20]
Genetic	Germline/ somatic mutations	*BAP1*	Germline mutations 1.6% -3%, somatic mutations <50%	[8, 17, 126]
	Oncogenic mutations in genes associated with the G-protein-α subunits	*GNAQ, GNA11*	≥80% of primary UM (44% each)	[8, 127]
	Other driver mutated genes	*EIF1AX*, *SF3B1*	*EIF1AX* (17%) associated with Class 1 tumors, good prognosis; *SF3B1* (24%) associated with younger age, good prognosis	[8, 127, 128]
Genetic/Epigenetic	Somatic copy number alterations/ RNA expression	*EIF1AX*-, *SRSF2*, *SF3B1*	Bad prognosis UMs differ by copy number variations and distinct mRNA/ lncRNA/ miRNA transcription profiles	[8]
Epigenetic	DNA methylation		Bad prognosis UMs have distinct methylation profile	[8]

the lack of data on UM dormancy we link UM related discoveries with the relevant findings in the other cancer types to emphasize the need for deeper understanding of these highly dynamic and reversible changes.

Metastatic dissemination and tumor cell dormancy in UM

Metastasis itself is a complex process, because the successful metastatic cell must traverse multiple steps in order to develop into a clinically relevant metastatic lesion. The major role in the initiation of metastases in UM is attributed to epithelial-to-mesenchymal transition (EMT); the trans-differentiation of epithelial tumor cells into motile mesenchymal cells. EMT plays a physiological role during development and wound healing, but contributes pathologically to fibrosis and cancer. Increasing evidence suggests that epigenetic mechanisms have important roles in EMT/mesenchymal-to-epithelial (MET) transitional changes [26, 27]. As UM disseminates almost exclusively via hematogenous spread, the study of epigenetic deregulation during EMT/MET is highly relevant. It has been demonstrated that hematogenous dissemination of UM cells correlates with patient outcome and that a change in the number of circulating tumor cells (CTCs) during treatment is predictive of therapy response [28–31].

EMT is the process in which epithelial cells from the primary tumor lose their cell polarity and cell-cell adhesion, gain migratory and invasive properties and become CTCs. Catenin beta 1 (*CTNNB1*) gene product β-catenin is part of a protein complex that is necessary for the creation and maintenance of epithelial cell layers and regulating cell growth and adhesion between cells [32]. The main binding partner of β-catenin is E-cadherin, encoded by the *CDH1* gene that is often down-regulated in tumor progression [33]. The loss of E-cadherin is considered a fundamental event in EMT which allows tumor cells to enter the bloodstream and become CTCs [34]. EMT is induced by interplay of soluble growth factors, extracellular matrix or hypoxic conditions that activate signaling pathways leading to the expression or post-transcriptional and post-translational modification of EMT transcription factors [35].

The Snail family transcription repressors (SNAI1 and SNAI2), zinc-finger E-box-binding (ZEB) and basic helix-loop-helix transcription factors (TWIST) are key transcription factors involved in EMT [36]. It was shown that down-regulation of *ZEB1*, *Twist1*, and *Snai1 in vitro* reduced the invasive properties of UM cells. Moreover, the elevated mRNA levels of *ZEB1* and *Twist1* were associated with a more aggressive clinical phenotype in primary UM samples [37]. Cells undergoing EMT can also acquire cancer stem cell (CSC) properties including the capacity for self-renewal, re-differentiation, dormancy, active DNA repair and drug resistance [38]. The re-programming of gene expression during EMT and reciprocal MET is facilitated through the rapid regulatory mechanism controlled by a variety of epigenetic regulations that are critical in integrating signals from multiple transcription factors [35, 39].

After remission, a considerable number of UM patients relapse. Metastatic UM can re-occur several months or even years after complete tumor resection [40]. As CTCs were found in UM patients who had been enucleated several years earlier, it was suggested that CTCs can colonize distant organs, remain dormant for several years and sporadically seed new tumor cells into circulation [41]. Several groups reported the presence of occult, dormant, sub-clinical single cells or micro-metastatic foci in the bone marrow or livers of patients with a history of UM [42–46].

Experimental dormancy has been described as cancer cell quiescence, including altered cellular signaling (extrinsic and/or intrinsic), pre-angiogenic micro-metastases with balanced cell division, apoptosis and immune evasion [47]. EMT programming in cancer cells enables in the remodeling of extracellular matrix to break the dormancy of relapse-initiating CSCs [48]. The product of SRY-related HMG-box (SOX2) contributes to cell proliferation and de-differentiation through the regulation of a set of genes controlling G1/S transition and EMT phenotype. This gene is involved in CSC maintenance, with the capacity to impair cell growth and tumorigenicity [49–51]. Emerging evidence proposes that cancer dormancy is driven by the flexible nature of the epigenetic machinery [52–54]. The ability of the epigenetic drugs to reduce cancer relapses supports this hypothesis and the identification of epigenetic regulatory mechanisms during EMT/MET can provide novel therapeutic opportunities [55].

Although histone deacetylase (HDAC) inhibitors were proven successful in inducing prolonged dormancy of micrometastatic disease in UM, the roles of epigenetic regulation in UM dormancy have not been studied [56, 57].

While the established animal models serve as powerful tools for identifying relevant pathways and developing novel therapeutic strategies [58], they exhibit several limitations which may have led to the delay in development of novel, efficient drugs for metastatic UM. Reliable testing of novel therapeutic regimes and accurate evaluation of therapy response will be possible only by refinement of potent animal models which mimic UM development and progression. These should integrate unique UM characteristics, including genetic attributes, specific features of the ocular immune system, the hematogenous dissemination and colonization of the liver and also the dormancy and angiogenic switch of hepatic micro-metastases [58, 59].

Epigenetic changes in UM progression

The expression of proteins dynamically changes during EMT from epithelial (E-cadherin, desmoplakin, cytokeratins, occludins and mucins) to mesenchymal (N-cadherin, vimentin, vitronectin, fibronectin and α-smooth muscle

actin) [27]. This plasticity is enabled by underlying shifts in epigenetic regulation and by interaction between multiple layers of epigenetic control mechanisms.

DNA methylation

DNA methylation is a covalent modification with addition of a methyl group (-CH3) to the cytosine residue in the CpG dinucleotide sequence, and methylation/demethylation is an important mechanism in maintaining cell- or tissue-specific gene expression. The global DNA hypomethylation and inactivation of tumor suppressor genes by their promoter hypermethylation are common epigenetic events in the development of a variety of tumors [60]. When UMs were clustered according to the global DNA methylomes, they were divided into the same classes as when clustered according to their gene expression profiles; thus suggesting an epigenetic contribution to the underlying molecular pathology that produces this transcriptome [8, 25].

Aberrant hypomethylation of *PRAME*, resulting in its transcriptional activation, is associated with increased metastatic risk mainly in Class 1 UMs [61]. Most of the hypermethylated genes in UM (*p16*, *TIMP3*, *RASSF1A, TIMP3, RASEF, hTERT and EFS*) [62–68] are involved in cell cycle regulation (Table 2). Few of these, namely *RASSF1A* and *p16*, were also aberrantly methylated in CM, while the others (*PTEN*, *TNFSF10D*, *COL1A2*, *MAGE* or *CLDN11*) have not been reported in UM [69].

The reduced levels of E-cadherin identified in 56.2% of UM samples inversely correlated with promoter methylation [70]. The reactivation of E-cadherin through promoter demethylation may therefore present a promising therapeutic strategy. It has been proven that treatment of UM cell lines with methylation and deacetylation inhibitors results in up-regulation of E-cadherin expression accompanied by phenotypic change from a spindle to more epithelial cell type [6].

Post-translational modifications of histones

Post-translational covalent modifications of histones by histone-modifying enzymes lead to changes in the state of chromatin compaction which facilitates DNA-based processes such as transcription, replication, recombination and repair. The combination of local chromatin marks, such as methylation, acetylation, phosphorylation, ubiquitination and sumoylation, all with different degrees of modification (mono-, di-, tri-), affect chromatin mobility and stability and regulate DNA packing into transcriptionally silent heterochromatin or active euchromatin.

Histone acetylation is associated with active gene transcription, and while trimethylation of lysine residue K27 on histone 3 (H3K27met3) catalyzed by the polycomb group proteins represses gene activity [71], trithorax group proteins activate gene expression via histone 3 lysine 4 trimethylation (H3K4met3) [72]. Snai1 promotes EMT by suppressing

Table 2. DNA methylation in UM.

Gene	Location	Nb	Function	Presence of methylation	Method	Reference
APC	5q22.2	23 PTs	antagonist of the Wnt signaling pathway, *	0%	MS-SSCA and MS-DBA	[67]
BAP1	3p21.1	66 PTs and blood DNA	deubiquitinating enzyme, *	0%	Bisulfite sequencing	[129]
RASSF1A	3p21.3	39PT/23 PTs Moulin	*	50% / 70% / 13%	Melting temperature analysis / RT-QMSP / MS-SSCA and MS-DBA	[65, 66] [67]
RARB	3p24.2	40 / 20 / 23 PTs	Nuclear transcriptional regulators	7.5% / 0% / 13%	Bisulphite genomic sequencing and MSP/ RT-QMSP / MSMS-SSCA and MS-DBA	[64, 66, 67]
RAB31	18p11.22	63 PTs/ 12 control tissues	RAS oncogene superfamily member	47,8% hypermethylated (better prognosis)	Methylation-specific PCR	[130]
LZTS1	8p21.3	6 PTs	*	association with class 2B expression signature	Methylation-sensitive restriction endonuclease *Eag*I digestion	[131]
ALCAM	3q13.11	40 PTs	Cell adhesion molecule	0%	Bisulphite genomic sequencing and MSP	[64]
CDH1	16q22.1	40 PTs	Calcium-dependent cell adhesion protein	0%	Bisulphite genomic sequencing and MSP	[64]
RB1	13q14.2	40 PTs	*	0%	Bisulphite genomic sequencing and MSP	[64]
VHL	3p25.3	40 PTs	Ubiquitination and subsequent proteasomal degradation	0%	Bisulphite genomic sequencing and MSP	[64]

Table 2. ***Continued***

Gene	Location	Nb	Function	Presence of methylation	Method	Reference
CDKN2A pINK4a p16	9p21.3	22/ 23 / 40 PTs	*	32% / 7.5% / 4%	MS-SSCA and MS-DBA	[62, 64, 67]
RASEF	9q21.32	35 PTs	GTPase	31%	Melting temperature analysis	[68]
MGMT	10q26.3		DNA repair protein	Mean 5%	RT-QMSP	[66, 132]
hTERT	5p15.33	23 PTs Moulin	Ribonucleoprotein polymerase	52%	MS-SSCA and MS-DBA	[67]
FHIT	3p14.2	40 PTs / 23 PTs	Hydrolase involved in purine metabolism	0% / 0%	MS-SSCA and MS-DBA	[64, 67]
TRAIL decoy receptors *DcR1* and *DcR2*	3q26.31		Cytokine that belongs to the TNF ligand family			[133]
CXCR4	2q22.1		Chemokine receptor specific for stromal cell-derived factor-1			[134–136]
CCR7	17q21.2		G protein-coupled receptor			[134–136]
TIMP3	22q12.3	23 PTs; 1 TIMP3 negative PT	Inhibitor of the matrix metalloproteinases	n.a. / 9%	MSP, MS-SSCA and MS-DBA	[63, 67]
DAPK	9q21.33		Calcium/calmodulin-dependent serine/threonine kinase	Mean 5%	RT-QMSP	[66]
RUNX3	1p36.11		Transcription factor	Mean 25%	RT-QMSP	[66]
CACNA1G	17q21.33		Voltage-sensitive calcium channel	Mean 5%	RT-QMSP	[66]
CTNNB1	3p22.1		Downstream component of the canonical Wnt signaling pathway	0%	Bisulphite genomic sequencing and MSP	[64]
SOCS1	16p13.13		Suppressor of cytokine signaling	Mean 0%	RT-QMSP	[66]
IGF2	11p15.5		Growth factor	Mean 0%	RT-QMSP	[66]
NEUROG1	5q31.1		Transcriptional regulator	Mean 5%	RT-QMSP	[66]
KDM4B	19p13.3	19 PTs	Histone demethylase	0%	Bisulfite Sequencing	[25]
KDM6B	17p13.1	19 PTs	Histone demethylase	0%	Bisulfite Sequencing	[25]
KAT2B	3p24.3	19 PTs	Histone acetyltransferase	0%	Bisulfite Sequencing	[25]
PRAME	22q11.22	80 PTs	Hypomethylation, transcriptional repressor		Infinium HumanMethylation 450K BeadChip	[61]
EFS	14q11.2	16 PTs	Docking protein	Full 50%, partial 15%, no 35%	Bisulfite sequencing	[137]

Abbreviations: MSP: methylation-specific PCR; RT-QMSP: Real-Time Quantitative Methylation-Specific PCR; methylation-sensitive single-strand conformation analysis (MS-SSCA) and methylation-sensitive dot-blot assay (MS-DBA), PT: primary tumor; *tumor suppressor

E-cadherin expression both directly, through its direct interaction with its promoter, and indirectly by inducing the synthesis of other repressors, including Zeb1. The binding of Snai1 to the E2-boxes of its target gene promoters elicits transcriptional-repressing epigenetic modifications, including H3K9 deacetylation, H3K4 demethylation and H3K9 and H3K27 methylation [73, 74].

Depletion of BAP1 protein leads to hyperubiquitination of H2A in melanoma cells and melanocytes leading to loss of differentiation and gain of stem-like properties [56, 75]. The H2A hyperubiquitination was reversed by treatment with HDAC inhibitors *in vivo* in a xenograft model that may have therapeutic potential for inducing differentiation and prolonged dormancy of micrometastatic UM disease [56]. The HDAC inhibitors were suggested as adjuvant treatment in high-risk patients because of their ability to initiate a shift from de-differentiated Class 2 UM cells to more differentiated, less aggressive cells [56, 76]. However, it is likely that more than one mechanism by which HDAC inhibitors alter UM cell function will be revealed [77].

The current findings for aberrant histone modification pattern in UM are summarized in Table 3. Hyperactivation of the histone-lysine N-methyltransferase enzyme EZH2 that also mediates transcriptional inactivation of E-cadherin and higher expression of histone-lysine N-methyltransferase *SETDB1* has been reported in the CM. [69]. The dormancy and recurrence periods have been shown to be regulated by epigenetic regulations in various cancer types [52]. In ovarian

Table 3. Histone modifications in UM.

Gene	Histone modification	Function	Method	Reference
histone methyltransferase EZH2, *MHC2TA*	H3K27me3	EZH2 contributes to silencing of *MHC2TA* in *UM* via histone modification	RT-PCR, Bisulphite sequencing, Chromatin immunoprecipitation	[71, 138]
LncRNA PAUPAR	H3K4 demethylation	*PAUPAR* acts as UM suppressor	RT-PCR, Chromatin immunoprecipitation	[139]

cancer the tissue inhibitor of metalloproteinase 3 (*TIMP3*) and *CDH1* were epigenetically activated in dormant cells and subsequently repressed in re-growing neoplasms [78]. Elevated *CDH1* expression during dormancy was associated with an increase in both H3K4me3 and H3K9Ac. *TIMP3* and *CDH1* expression is also inversely related to DNA methylation of their promoters in cell cultures and xenografts. Notably, DNA methyltransferase (DNMT) and HDAC inhibitors counteract *CDH1* and *TIMP3* silencing, thereby hampering re-activation of dormant cells [78].

miRNA-based epigenetic mechanisms

Micro RNAs (miRNA) are short, phylogenetically conserved single-stranded RNA molecules involved in the silencing of messenger RNAs (mRNA). The interaction between miRNAs and their target mRNA is responsible for the inhibition of translation initiation, elongation and mRNA decay. The miRNAs have been proven to function as either suppressors or oncogenes and are involved in EMT in various cancer types [79–81]. Although a number of miRNAs were identified to be up- or down-regulated in UM (Table 4), only a few have been studied in relation to hematogenous dissemination (reviewed in [24]).

As shown recently, the miRNA expression landscape is concordant with transcriptional UM subsets and it reveals the four main miRNA clusters clearly associated with monosomy 3 and DNA methylation state [8]. The following paragraphs investigate miRNAs' importance in UM and other cancers.

Class 2 UM has been accurately distinguished from Class 1 by the two most significant discriminators, let-7b and miR-199a [82]. Consistent with these findings, miR-199a-3p/5p, miR-199b-3p and let-7b-5p were up-regulated in monosomy 3 UM [8]. It has also recently been demonstrated *in vitro* that miR-199a contributes to E-cadherin regulation in hepatocellular and other carcinomas [83–85]. The expression of several miRNAs, including oncomiR miR-21-5p, is influenced by DNA methylation in UM [8]. miR-21 is one of the first microRNAs to be associated with tumor progression and metastasis in several cancers [86].

Successful reversal of EMT and CSC phenotype by hsa-miR-21 antagomir in breast cancer cells could be a novel therapeutic approach in other malignancies [86]. It was shown that miR-9, which suppresses UM cell migration and invasion partly through down-regulation of NF-κB1 signaling, is significantly reduced in highly invasive UM cell lines [87]. In contrast, this miRNA has been related to EMT, stem cell phenotype and tumor progression in breast cancer samples, where a high level of miR-9 was found an independent prognostic factor of disease-free survival [88]. miR-9 directly targets *CDH1* and increases breast cancer cells motility and invasiveness *in vitro* [89]. Further, miR-9 interacts with the 3'-untranslated region of E-cadherin and down-regulates its expression in esophageal squamous cell carcinoma. This then induced β-catenin nuclear translocation and subsequent up-regulation of c-myc and CD44 expression [90].

It has been shown that miR-34a inhibits UM cell proliferation and migration through down-regulating c-Met [91]. The decreased expression of miR-34a and also miR-34b/c was associated with proliferation and migration in UM cells and primary tumor samples [92]. Their up-regulation was induced by doxorubicin and epigenetic drugs [92]; similar to miR-137 whose expression was increased through treatment with DNA hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) and the trichostatin A HDAC inhibitor [93]. Both miR-34a and miR-137 act as Snail suppressors, negatively regulating EMT and the invasive and sphere-forming properties of ovarian cancer cells [94]. miR-137 was also dramatically down-regulated in clinical specimens of gastrointestinal stromal tumors, and *in vitro* experiments have demonstrated that it increased expression of E-cadherin and inhibited cell migration via Twist1 down-regulation [95]. Similar results were found in tongue squamous cell carcinoma, thus indicating that miR-137 suppresses EMT [96].

The successful restoration of miR-124a expression by treatment with decitabine and trichostatin A in UM cell lines suggests its epigenetic regulation [97]. This miRNA is thought to be involved in the EMT of retinal pigment epithelium in the pathogenesis of proliferative vitreo-retinopathy [98]. *SNAI2* and *ZEB2* were identified as direct functional target genes of miR-124 in breast and prostate cancer cells, respectively [99, 100].

It has been shown that miR-145 is one of the miRNAs significantly down-regulated in UM compared to healthy tissues [101, 102], and its up-regulation can inhibit EMT, invasion and metastasis by regulating the expression of Snai1 in osteosarcoma cell lines [103]. In the lung adenocarcinoma-initiating cells, miR-145 down-regulated the CSC properties and EMT process by targeting the Oct4 [104]. Furthermore, miR-145 inhibits gastric cancer cell invasive-

Table 4. List of miRNAs and lncRNAs up- or down-regulated in UM.

miR	Specimen	Expression in UM	Target genes/clinical relevance	Method	Reference
miR-9	MUM-2B, C918, MUM-2C and OCM-1A UM cell lines	↓* in invasive cell lines	*NFKB1* signaling and its downstream genes *MMP2*, *MMP9* and *VEGFA*	qRT-PCR	[87]
miR-20a	10 PTs and 10 control tissues, MUM-2B, MUM-2C UM and D78 cells	↑+ in UM cells and tissues		qRT-PCR	[140]
miR-34b/c	SP6.5 UM cell line, 5 PT	↓ in UM cells and clinical samples	*MET*, *p-Akt*, and some cell cycle proteins	qRT-PCR	[92]
miR-124a	M17, M21, M23, SP6.5, um95# and HEK-293 cells, 6 primary UMs	↓* in UM cells and clinical samples	*CDK4*, *CDK6*, *CCND2* and *EZH2*	qRT-PCR	[97, 141]
miR-137	M17, M23, SP6.5, um95# and HEK-293 cells	↓ in UM cell lines than in uveal melanocytes	*MITF* and *CDK6*	qRT-PCR	[93]
miR-144	5 PTs and control melanocytes, MUM-2B, C918, MUM-2C, OCM-1A UM and D78 cells	↓ in UM cells and tissues	*MET*	qRT-PCR	[142]
miR-146a	14 serum and tissue samples from UM patients and serum from 14 healthy controls	↑ in UM tissues and serum		TaqMan Low Density arrays/ qRT-PCR	[143]
miR-155	25 PTs and adjacent normal tissues, OCM-1A, MUM-2C, C918, MUM-2B and D78	↑ in UM cells and tissues	*NDFIP1*	qRT-PCR	[144]
miR-181	3 UMs and 3 healthy tissues, SP6.5, VUP, OCM1, 92-1 and RPE cells	↑ in UM tissues and most UM cells	*CTDSPL*	qRT-PCR	[145]
miR-182	M23 and SP6.5 UM cell lines; HEK-293 cells	↓* in UM cell lines	*MITF*, *BCL2*, *CCND2*, *MET*	qRT-PCR	[106]
miR-367	28 PTs and adjacent healthy tissues; M17, M23, MUM-2B, C918 and um95# cells	↑ in UM cells and tissues	*PTEN*	qRT-PCR	[146]
miR-454	25 PT and adjacent control tissues; OCM-1A, MUM-2C, C918, MUM-2B UM and D78 cells	↑+ in UM cells and tissues	*PTEN*	qRT-PCR	[147]
miR-20a, miR-125b, miR-**146a**, miR-155, miR-181a, and **miR-223&**	Plasma samples and fine needle aspiration biopsies from 6 UMs and 26 healthy donors	↑ in patients	Plasma level increased and miR-181a decreased when metastasis manifested	qRT-PCR	[114]
miR-92b, miR-199-5p, **miR-223&**	55 PTs	↑ in monosomy 3 UM		Illumina miRNA profiling chip/ qRT-PCR	[115]
let-7b, **miR-199a**, miR-143, **miR-193b&**, and miR-652	24 PTs	↑ in class 2 tumors	Association with class 2 gene expression signature	Agilent microarray/qRT-PCR	[82]
miR-549, miR-497, miR-885-5p, miR-585, miR-640, miR-512-5p, miR-556-5p, miR-135b, miR-325, miR-99a, miR-33a, miR-196a,	1 invasive tumor with liver metastasis, 1 noninvasive PTs	↑ in metastatic tumor	Tumor suppressor and metastasis suppressor genes	Agilent microarray	[111]
miR-586, miR-493, miR-377, miR-376c, miR-369-3p, **34c-5p**, miR-26a-2, **miR-218&**, miR-19b-1, miR-181a, miR-154, miR-133a, miR-129, miR-10a, miR-1, **Let-7e,** miR-495, miR-18a	1 invasive tumor with liver metastasis, 1 noninvasive PTs	↓ in metastatic tumor	Tumor suppressor and metastasis suppressor genes	Agilent microarray	[111]
miR-20a, miR-106a, miR-17, **miR-21**, **miR-34a**	4 PTs and 4 normal uveal tissues	↑ in tumors		Microarray/RT-PCR	[101]

Table 4. ***Continued***

miR	Specimen	Expression in UM	Target genes/clinical relevance	Method	Reference
miR-145, **miR-204**	4 PTs and 4 normal uveal tissues	↓ in tumors		Microarray/RT-PCR	[101]
miR-214, miR146b, miR-143, miR-199a and miR-134	3 M3 PTs and 3 D3 PTs/ 11 metastatic and 40 non-metastatic M3 PTs, 6 metastatic and 29 non-metastatic D3 PTs	Differentially expressed	*SMAD4*, *WISP1*, *HIPK1*, *HDAC8* and *KIT*	Agilent microarray/qRT-PCR	[148]
miR378d and miR378g	12 normal controls, 11 PTs; MUM-2B and OCM-1 cell lines	↑ in tumors		Agilent microarray/qRT-PCR	[102]
miR204-5p, miR143-3p, and **miR145-5p**	12 normal controls, 11 PTs; MUM-2B and OCM-1 cell lines	↓ in tumors	*IRS-1*	Agilent microarray/qRT-PCR	[102]
miR-199a-3p/5p, miR-199b-3p, let-7b-5p/ miR-142, miR-150, **miR-21**, miR-29b, miR-146b and miR-155	80 UMs	↑ in M3 cluster3 / ↑ in M3 cluster4	miRNA expression landscape concordant with transcriptional UM subsets	miRNA-Seq	[8]
LncRNA PAUPAR	12 PTs, and 5 normal tissues, MUM2B, OCM1, OM431 and 293T UM cell lines, ARPE-19 cells	↓ in UM cell lines and PTs	*HES1* via H3K4 demethylation	qRT-PCR	[139]
LncRNA ROR	MUM2B, OM431	↑ in tumor cells	*TESC*	qRT-PCR	[149]
LncRNA HOXA11-AS	5 PTs; OCM-1A, MUM-2C, C918, MUM-2B and D78 cells	↑ in UM tissues and cells	p21 and miR-124 via *EZH2*		[150]
LncRNA FTH1P3	25 PTs, OCM-1A, MUM-2C, C918, MUM-2B and D78 cells	↑ in UM tissues and cells	LncRNA FTH1P3 target gene of miR-224-5p	qRT-PCR	[151]
LncRNA PVT1	80 UMs	↑ associated with malignant behavior		Data mining	[152]
LncRNA CYTOR, BANCR and PVT1/NEAT1 and MALAT1	80 UMs	↑ or differentially expressed in clusters 3 and 4		RNA-seq	[8]

mi-RNAs involved in EMT in various cancers are highlighted by bold; [&]miRNAs involved in tumor dormancy; Abbreviations: PT primary tumor; M3 monosomy 3; D3 disomy 3; [#] primary human melanocytes; ↓ down-regulated/decreased; ↑ up-regulated/over-expressed; [˙]putative tumor suppressor miRNA; [+]putative oncogenic miRNA

ness through targeting N-cadherin and ZEB2 [105], and the double-negative feedback loop between ZEB2 and miR-145 regulates EMT and stem cell properties in prostate cancer cells [100].

The expression of miR-182 was decreased in UM tissue samples while its over-expression suppressed the *in vivo* growth of UM cells, thus suggesting its tumor suppressor role in UM [106]. This miRNA has been proven to be involved in EMT regulation in prostate and colorectal cancer cells via different targets (*VIM*, *ZEB1*, and *SNAI2*) [107, 108]. Finally, TGF-β receptor 2 and SNAI2 were confirmed to be direct targets of miR-204, and reduced miR-204 expression in fetal human retinal pigment epithelium cells led to reduced expression of claudins; the most important components of cell tight junctions [109].

Although not yet studied in UM dormancy models, non-coding RNAs appear deeply involved in regulation of dormancy-proliferation cycles in other cancer types. A consensus-set of 19 miRNAs governed the phenotypic switch from dormant to fast-growing tumors in breast carcinoma, glioblastoma, liposarcoma and osteosarcoma *in vivo* experimental dormancy models [110]. Two of these, miR-193b and miR-218, were significantly up- and down-regulated in UM, respectively [82, 111]. miR-34a was one of three miRNAs identified as regulators of dormancy in a mouse model of human osterosarcoma [112]. In the breast cancer metastasis models, four miRNAs secreted by tumor-associated stroma cells induced cancer cell dormancy, thereby providing a mechanistic substrate for CTC survival [113]. miR-223 was one of these four miRNAs, and its expression is up-regulated in monosomy 3 and metastatic UM tumors [114, 115]. miRNA expression profiling has identified several miRNAs, some of which are also associated with UM, which have a crucial role in cell proliferation, migration, and invasion.

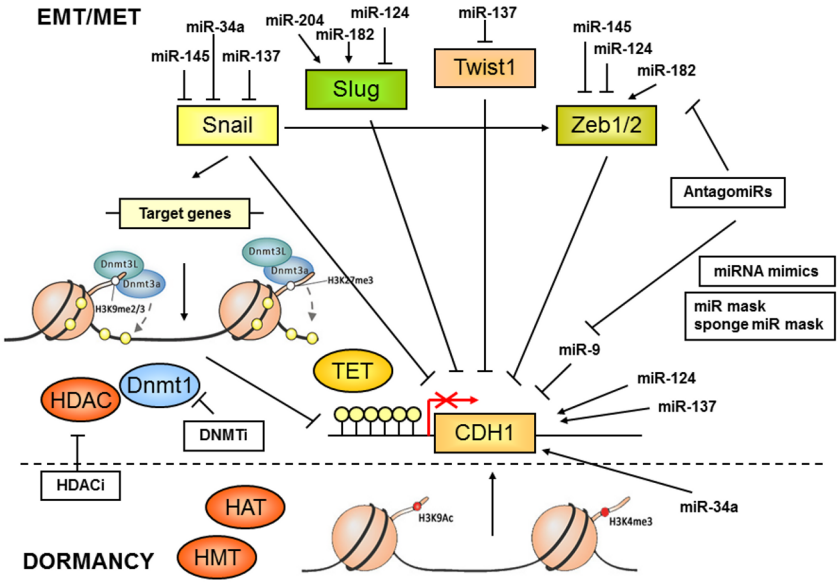

Figure 1. Schematic illustration of possible involvement of different epigenetic regulatory mechanisms in epithelial-to-mesenchymal transition in uveal melanoma. Abbreviations: HDAC, histone deacetylase; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HMT, histone methyltransferase; HDACi, histone deacetylase inhibitor; DNMTi, DNA methyltransferase inhibitor; TET, Ten-eleven translocation enzymes; yellow circles, methylated CpG dinucleotides; white circles, repressive histone modifications; red circles, histone marks associated with active transcription.

This profiling also identified miRNAs involved in the CM immune response and cellular apoptosis [116].

The significance of individual miRNAs in UM pathogenesis should be interpreted in appropriate biological contexts because miRNAs interact widely with other signaling cascades and they behave differently in particular histological subtypes. Since miRNAs can have a dual effect on EMT in different cancers, it is necessary to assess the functions of miRNA specifically for UM. However, increasing evidence of the association of miRNAs with EMT in various types of cancer strengthens the probability of their involvement in UM metastasis, and this calls for its comprehensive investigation.

Conclusions and future strategies

In contrast to genetic factors, the epigenetic inactivation of gene expression is a reversible mechanism and its understanding promises to be susceptible to treatment. Epigenetic therapies have been approved for hematological malignancies by regulatory bodies. Several agents have been studied for solid tumors and are currently used in clinical trials as mono- or combination therapy [117]. Despite favorable results in several cancers, such as non-small cell lung cancer, ovarian and breast cancer, other solid tumors including pancreatic ductal adenocarcinoma have proven less successful [118]. Two types of epigenetic therapies (DNMT and HDAC inhibitors) have been in the phase of clinical testing for UM [119, 120]. The rationale behind this is the DNMT and HDAC inhibitors' ability to reverse the epigenetic inactivation of tumor suppressors and other cancer-related genes [121].

Most experimental epigenetic therapies in UM focus on the role of BAP1 protein; trying to reverse the phenotypic effects of BAP1 loss [56]. Recently, HDAC inhibitor LBH-589 successfully converted UM cells from Class 2 to Class 1 and induced G0/G1 arrest and epigenetic reprogramming, which was consistent with melanocytic differentiation and dormancy in micrometastatic disease [56]. Similarly, low concentration of 5-aza-2'-deoxycytidine also known as decitabine, has suppressed proliferation and promoted CM cellular differentiation [122] and reduced growth, invasiveness, and clonogenicity of UM and CM cells *in vitro* [123]. Reactivation of epigenetically inactivated E-cadherin could be a promising therapeutic strategy for metastatic UM (Figure 1).

Beyond DNMT and HDAC inhibitors, new epigenetic players have emerged. They include the inhibitors of bromodomain and extra-terminal motif (BET) proteins, histone lysine methyltransferases EZH2 and DOT1L or lysine-specific demethylase 1A (LSD1). These have been used in clinical trials for different cancer indications [124]. In addition to the indirect modulation of miRNA profiles via DNMT or HDAC inhibition, the replacement of miRNAs can also be used as a therapeutic strategy. miRNAs can be targeted by

the antagomirs, novel class of chemically engineered oligonucleotides, which are able to silence endogenous miRNA expression. Emerging data suggests that epigenetic drugs can also improve the responses to cancer immunotherapy [125]. However, comprehensive understanding of the molecular mechanisms epigenetic drugs use to elicit their immunomodulatory effects is essential for the development of novel combination therapies for metastatic UM.

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