Chapter

Uveal Melanoma: Factors Determining Metastatic Process, Epidemiology, Diagnosis, and Treatment

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Abstract

Uveal melanoma (UM) is an ocular tumor with a dismal prognosis. It is the most frequent primary intraocular tumor in adults. The primary goal of treatment for uveal melanomas is to prevent metastasis. Despite outstanding advances in the diagnosis and treatment of primary UM, nearly 50% of patients develop metastases via hematogenous dissemination. Estimation of prognosis for patients with UM can be achieved by detecting genetic alterations or epigenetic changes in the tumor tissues. However, these techniques are not always available. The clinicopathological characteristics with limited accuracy are widely used instead to predict metastatic potential. Identifying novel markers with prognostic potential can help refine the prognosis of UM patients. As we know, no existing therapy has a significantly better impact on preventing metastasis. Based on published theories, the key role is existing micrometastasis before therapy starts. Researchers are focusing on developing adjuvant systemic therapy for metastatic UM. Getting to know the cause of metastatic uveal melanoma is crucial in it.

Keywords: uveal melanoma, metastases, genetic changes in UM, epigenetic changes in UM, epidemiology of UM, diagnosis and treatment UM

1. Introduction

Uveal melanoma is a rare form of melanoma, but the most frequent intraocular tumor in adults [1]. Comprising approximately 83% of ocular and 3% of all melanomas. It arises from melanocytes along the uveal layer of the eye, including the iris, ciliary body, and most often the choroid [2].

Primary UM is treated with either surgery or radiation with a low local recurrence rate. However, almost half of UM patients develop metastases, which may be caused by a virtually undetectable neoplasm already present at the time of the primary tumor diagnosis [3]. Most UM patients survive less than 12 months after metastases

diagnosis due to the lack of effective therapies [4]. UM spreads through the blood. The liver is the preferred metastatic site, followed by the lungs and bones [5].

Various clinical, pathological, molecular, and cytogenetic markers assessed in tumors, such as specific chromosome copy number alterations [6], gene expression profiles [7], and the mutation status of known UM driver genes [8], can predict the risk of metastases and survival.

2. Genetic changes in uveal melanoma

2.1 Chromosomal rearrangements

The most frequent UM-specific aberrations include monosomy of chromosome 3 (M3), a gain in the short arm of chromosome 6 (6p), or a gain in the long arm of chromosome 8 (8q). Similar to the loss of the short arm of chromosome 8 (8p), the long arm of chromosome 6 (6q), and the short arm of chromosome 1 (1p) pose a high metastatic risk and present a poor prognosis, [9–11].

Conversely, the presence of 6p amplification represents a protective factor due to its association with a good prognosis and lowered metastatic risk [12]. Although their prognostic value has been proven, and their sensitivity and specificity are limited in clinical use [13]. The problem seems to be that results differ based on laboratory methods used for detecting the amount of chromosomal copies, and they are not accurate.

2.2 Change in gene expression

Another way to predict the risk of metastasis is via gene expression analysis. A commercially available expression panel of 15 genes developed by Castle Biosciences categorizes patients as Class 1 (low metastatic risk) or Class 2 transcriptional subtype (high metastatic risk) [7, 14]. Four molecular subsets were proposed recently, based on a more complex classification [15, 16].

2.3 Mutation of genes

UM occurs mostly sporadically, however, rarely it occurs in families with an inherited predisposition for this malignancy. Mutations in gene BAP 1 are segregated in an autosomal dominant manner in the hereditary tumor syndrome. It is characterized by the occurrence of tumor disease in a family member at a young age, by the presence of numerous primary tumors, often bilaterally when the steam organs are affected. BAP 1 mutation is associated with cutaneous melanoma, mesothelioma, meningioma, and many others. The clinical phenotype includes UM in patients with oculodermal melanocytosis, skin melanoma, neurofibromatosis type 1, and Li-Fraumeni syndrome. In the case of a familiar form, the combination of clinical signs and genetic information can be used for early diagnosis in patients [17–19].

3. Epigenetics in uveal melanoma

The term epigenetics includes changes in gene expression and chromatin structure that are not related to a change in primary genetic information, that is, changes not

encoded in the sequence of bases in the DNA chain [20]. In the broadest sense of the word, epigenetics can be understood as a bridge between the genotype and the phenotype of a cell [21].

The basic epigenetic mechanisms of gene expression regulation include DNA methylation, histone modification with subsequent chromatin remodeling, and noncoding RNA [22]. These mechanisms are essential for the normal development and homeostasis of the organism, and their disruption can lead to changes in gene function and malignant transformation, and can have an impact on individual signaling pathways involved in metastasis [23].

Epigenetic inactivation plays a role in genes located on chromosomes 1, 3, 6, or 8, that is, in chromosomes with proven abnormalities in UM. Monosomy 3 is present in approximately half of patients with UM. Genes that play a key role in hematogenous dissemination are located on this chromosome, for example, BAP1, RASSF1A, FHIT, CTNNB1, and SRY.

3.1 Methylation

It is the binding of a methyl group (-CH3) to the fifth carbon of cytosine by a covalent bond. Compared to normal cells, tumor cells have a disturbed DNA methylation pattern either by decreasing (hypomethylation) or increasing (hypermethylation) the number of methyl groups. During the onset of oncological diseases, these are significant processes that lead to an increase in chromosome instability. Primarily hypermethylation of promoters of tumor suppressor genes, hypomethylation of proto-oncogenes, and global hypomethylation [24].

In UM patients, DNA methylation was identified as the cause of inactivation of several genes. Aberrant hypomethylation of the PRAME gene, leading to its transcriptional inactivation, was associated with an increased metastatic risk [25]. The majority of hypermethylated genes in UM are p16, TIMP3, RASSF1A, RASEF, hTERT, and ES genes. They participate in the regulation of the cell cycle. Only the RASSF1A and p16 genes are also methylated in skin melanoma. In comparison, genes methylated in cutaneous melanoma, such as pTEN, TNFSF10D, COL1A2, MAGE, or CLDN11, were not methylated in UM [26].

Decreased levels of E-cadherin, a key protein that is inhibited in the epithelial-mesenchymal transition process, were identified in 56.2% of UM. They were indirectly correlated with the methylation of the CDH1 promoter gene, which encodes it [27, 28].

The researchers induced an increase in the expression of E-cadherin, which affected the phenotypic change in UM cells from spindle cell to epithelial type. Reactivation of the expression of aberrantly methylated genes by DNMTs inhibitors may represent a promising therapeutic strategy [23].

3.2 modifikácie histónov

Histones are basic proteins abundant in lysine and arginine residues that are found in nuclei of eukaryotic cells. They create structural units called nucleosomes. We know five families of histones H1/H5 (linker histones), H2, H3, and H4 (core histones). The nucleosome core is formed of two H2A–H2B dimers and a H3–H4 tetramer. Nucleosomes are wrapped into fibers of tightly packed chromatin. That means DNA winds around them. Histones prevent DNA from becoming tangled and protect it from DNA damage. They play important roles in DNA replication and gene regulation [29].

Post-translational covalent changes occur at the N-terminal ends of histones in mammalian cells through the action of histone-modifying enzymes. The most common modifications of histones, which play a key role in the regulation of gene expression are methylation, acetylation, phosphorylation, and ubiquitination. They affect the mobility and stability of chromatin and regulate its transcription [23].

Most UM Class 2 transcriptional subtype (high metastatic risk) contains inactivating mutations of the tumor suppressor gene BAP1. It encodes bap 1, which has a role in the progression of UM. It modifies histones by catalyzing the removal of ubiquitin from histone H2A. Its depletion leads to hyperubiquitination of H2A in melanocytes and melanoma cells and subsequent loss of differentiation and acquisition of tumor stem cell properties [30].

Histone deacetylase inhibitors (HDAC), therefore enable the restoration of the expression of epigenetically inactivated genes, necessary, for example, to control the cell cycle. In UM cell lines, primocultures created from patient tumor cells, and HDAC inhibitors, such as valproic acid, trichostatin A, panobinostat LBH-589, and suberoylanilide hydroxamic acid-induced proliferation inhibition, cell cycle arrest, increased tumor cell apoptosis, morphological and transcriptional changes consistent with melanocyte differentiation. HDAC inhibitors are in preclinical studies for the treatment of UM with the aim of prolonging the dormancy of micrometastatic disease [31, 32].

3.3 Non-coding mRNA

MicroRNA (miRNA) is mainly considered non-coding mRNA. These are short nucleotide single-stranded RNA molecules that participate in the post-transcriptional regulation of the expression of mediator RNAs (mRNA). It has been proven that miRNA functions as an oncogene or tumor suppressor gene in carcinogenesis. It binds to complementary mRNA and thereby inhibits mRNA translation and inactivates target genes [33].

Changes in the expression of many miRNAs have been described in cell lines of tumor structures and peripheral blood from patients with UM [34]. They play an important role in the deregulation of oncogenic pathways in UM and may promote metastatic spread. In addition to the fact that miRNAs can be interesting diagnostic and prognostic biomarkers, they offer us new therapeutic targets [35].

Epigenetic changes play an important role in the pathogenesis of oncological diseases. They are reversible; therefore, they are a good therapeutic target. In many preclinical studies, it has been proven that epigenetic drugs enable the restoration of aberrantly inactivated tumor-suppressor genes, and increase the sensitivity of resistant tumor cells to treatment.

The prerequisite for the discovery of effective drugs for the adjuvant therapy of UM and the treatment of metastatic UM is to necessarily accept the importance of epigenetic changes and understand their role in the pathogenesis of this disease.

4. Epidemiology

The most common primary intraocular malignancy in adults is uveal melanoma. It arises from melanocytes in the choroid, ciliary body, or iris. The incidence is 5.1 per million and has remained stable since at least 1970s. UM is the most common in Caucasians during the fifth to sixth decade of life [1]. Approximately 85% of UM is

localized in the choroid [36], about 4–7% in the ciliary body, and 2–4% in iris, which is associated with early diagnosis and the best prognosis [37]. Associated with the worst prognosis is UM in the ciliary body.

5. Clinical diagnosis

Physical examination and health history are used to help diagnose intraocular melanoma, as well as eye exam with the dilated pupil (by ophthalmoscopy or slit-lamp biomicroscopy). Diagnosing uveal melanoma often requires serial fundus photography. Fluorescein angiography or indocyanine green angiography is used in the screening and follow-up of suspicious lesions. Other critical tools in the diagnosis of uveal melanoma are A and B scan ultrasonography and optical coherence tomography.

6. Management

The primary goal of treatment for uveal melanomas is to prevent metastasis. However, treatment of small lesions (less than 3 mm in thickness) is controversial, and it is not proven whether it prevents metastasis. Observation is generally recommended whenever it is possible.

Biopsy of the lesion is the only way to definitively identify uveal melanoma. It can be done after enucleation or by fine needle aspiration biopsy. The collected material is used for histological examination and cytopathological analysis.

Historically, enucleation (eyeball removal) was the standard treatment for primary UM, and it is still used when large tumors are present. However, it has been largely replaced by radiation therapy (i.e., brachytherapy or proton beam therapy) to spare the affected eye.

The results of the Collaborative Ocular Melanoma Study (COMS) in 2001, a large multicenter randomized control trial with 1317 patients confirmed that there was no significant difference in mortality after brachytherapy in comparison to enucleation for malignant UM [38]. Later other publications reported similar positive findings [39]. The decision to use brachytherapy vs. proton beam therapy is now largely made in regard to the size and location of the tumor and patient preference [40–42].

For small tumors, the less commonly available treatment options can be used. These include transpupillary thermotherapy, photocoagulation, photodynamic therapy, and local resection.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

UM	Uveal melanoma
BAP 1	BRCA1 associated protein 1
RASSF1	Ras association domain family member 1

FHIT 2	Fragile Histidine Triad Diadenosine Triphosphatase 2
CTNNB 1	Catenin Cadherin-Associated Protein Beta 1
SRY, SOX2	Sex determining region Y-box 2
PRAME	Nuclear Receptor Transcriptional Regulator
p16, CDKN2A	Cyclin-dependent kinase inhibitor 2A
TIMP3	TIMP metallopeptidase inhibitor 3
RASSF1	Ras association domain family member 1
RASEF	RAS And EF-Hand Domain Containing
hTERT	Telomerase reverse transcriptase in humans
PTEN	Phosphatase and tensin homolog
TNFSF10D	Tumor necrosis factor receptor super family member 10D
COL1A2	Collagen Type I Alpha 2 Chain
MAGE	The Melanoma Antigen Gene
CLDN11	Claudin 11
DNMTs	DNA methyltransferases
CDH1	Cadherin 1
HDAC	Histone deacetylase inhibitors

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