

Review Article

A review of prognostic biomarkers in uveal melanomas

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ABSTRACT

Prognostication of uveal melanomas (UM) has evolved from basic histopathological factors like tumour size, location and cell morphology to more sophisticated methods like counting chromosomal gains and losses which can be detected using FISH analysis and karyotyping. A number of driver mutations have been discovered which allow testing of response to targeted therapies. GNAQ and GNA11 mutations are early events while BAP1, SF3B1 and EIF1AX mutations occur later. Gene expression profiling is a highly accurate and informative standard for molecular prognostication. In addition, since UM spreads hematogenously, therefore, blood biomarkers may be helpful for monitoring the disease progression. Thus, understanding the prognostic significance of these mutations and blood biomarkers could facilitate their use in precision medicine.

Keywords: Biomarkers, Melanomas, Prognostication, Uveal

INTRODUCTION

Uveal melanoma, the most common primary intraocular melanoma, arises from melanocytes within the uveal tract, with more than 90% of cases involving the choroid and the remainder affecting the iris and ciliary body.¹ It has an annual incidence of 0.7/100,000 in the western population with 50% of patients ultimately dying of metastatic disease as metastatic uveal melanoma is notoriously resistant to conventional chemotherapy.² No effective treatment exists after a diagnosis of metastatic disease is made. UV Melanoma spreads haematogenously with the most common site of metastases being the liver.¹

In this article, we shall discuss about the genomic profiles of uveal melanomas along with clinically relevant genetic and hematological prognostic marker.

GENOMIC LANDSCAPING OF UVEAL MELANOMAS

BRAF mutant, NRAS mutant, NF-1 loss and triple wild type (TWT) are the four main genomic types of

melanomas based on the occurrence of the driver mutations.³ Although it is not possible to distinguish each of these genomic subtypes histopathologically or based on their site of origin, these genomic subtypes do follow some patterns. For instance, almost 50% of cutaneous melanomas are BRAF mutant.⁴

Almost all uveal melanomas fall into the triple wild type category which is defined as a heterogeneous subgroup characterized by a lack of hot-spot BRAF, N/H/K-RAS, or NF1 mutations.⁵ Among the various melanomas, lowest mutational densities have been observed in uveal melanomas. Some of the recurring somatic mutations observed in 80-90% uveal melanomas include activating mutations in guanine nucleotide proteins GNAQ and GNA11 which are present in benign nevi also; therefore they are thought to be initiating events in uveal melanomas and do not have much prognostic significance.⁶ Both protein kinase C (PKC) and mitogen activated protein kinase (MAPK) pathways are activated by GNAQ and GNA11 mutations. GNAQ mutations or loss of PTEN activity may also activate PI3K/AKT pathway.⁷

The cysteinyl leukotriene receptor 2 (CYSLTR2) gene encodes the CysLT2R GPCR and is constitutively activated via a Leu129Gln mutation in 4% of primary uveal melanomas.⁸ A second subgroup shows mutations in BAP1, EIF1AX and SF3B1. A study by Decatur et al revealed that mutations in GNAQ and GNA11 were mutually exclusive. Mutations in BAP1 and SF3B1 and mutations in BAP1 and EIF1AX were all mutually exclusive. Mutations in SF3B1 and EIF1AX were also predominantly mutually exclusive, with only one tumor having a mutation in both.⁹

Late onset secondary alterations modulate the effect of the above-mentioned driver oncogenes. For instance, chromosome 3 monosomy and BAP1 loss, which are associated with a poor prognosis, enhance the activation of GNAQ mediated PKC MAP Kinase pathway.^{10,12} Also, poor prognostic UM (lacking BAP1 and chromosome 3) can be further divided into two subsets with distinct profiles- Hypoxia, MYC transcription signaling and active DNA damage response are features of the first profile while the second profile is associated with FOXA1 and FOXM1 transcription factors and elevated MAPK and AKT activity.¹⁰

Similarly, the expression of melanocytic differentiation specific genes (MITF, TYR, DCT and TRPM1) is promoted by CysLT2R activation.⁸

Rb and p53 pathways, although not directly related to initiating oncogenic drivers, are also critical in UM progression. Cyclin D1, an essential regulator for cell cycle progression from G1 to S phase, has been recognized as an independent prognostic factor. Over expression of CyclinD1 leads to hyperphosphorylation and consequent inactivation of Rb protein while overexpression of murine double minute 2 (MDM2) leads to inactivation of p53 pathway. Thus, both Cyclin D1 overexpression and MDM2 overexpression are associated with poor prognosis.¹¹

RECEPTOR TYROSINE KINASES

Receptor tyrosine kinases (RTK) like c-kit, c-Met, insulin like growth factor are overexpressed in metastatic uveal melanomas. C-kit is over expressed in 60-70% of uveal melanomas while c-met is over expressed in almost 98% of uveal melanomas.¹⁰ Epidermal growth factor receptor expression has also been reported in UM in about 20% cases. This immunoreactivity may be due to EGFR positive macrophages, hence may be overestimated.¹² Although the mechanism of RTK is not well understood, autocrine receptor stimulation is the mechanism involved in uveal melanomas rather than gene mutations or amplifications.¹³

PI3K/AKT PATHWAY

Upregulation of receptor tyrosine kinases and loss of the phosphatase and tensin homolog protein activate the

PI3K/AKT cascade which is generally not stimulated by GNAQ/GNA11 activity.¹⁴ PTEN immunoreactivity is downregulated in UM by overexpression of the microRNAs miR-367 and miR-454.¹⁵ Importantly, loss of cytoplasmic PTEN expression is associated with shortened disease-free survival in UM.¹⁶

CHROMOSOMAL ASSAYS

Chromosomal copy number alterations in the form of chromosomal copy number gains and losses can be seen commonly in uveal melanoma. There are two main chromosomal subsets based on aberrations in Chromosome 3- Those with Disomy3 (D3) and the other group with monosomy 3 (M3).¹⁷

M3 subset is associated with poor prognosis and disseminated disease while D3 subset is associated with a better prognosis. M3 has greater value as a prognostic indicator than the clinicopathologic factors.¹⁸

There are two subsets within the D3 cluster of uveal melanomas also. One subset is associated with gain in short arm of chromosome 6 while second subset is associated with gains of long arm of chromosome 6p and 8q as well as mutations in SF3B1. Gain of the long arm of chromosome 8q is also associated with poor prognosis.¹⁹

Gene expression profiling

Gene expression profile (GEP) classification can be used to cluster uveal melanomas into 2 prognostically significant molecular classes. Class 1 UMs have a low metastatic risk and have a more differentiated histopathology picture whereas class 2 UMs have a high metastatic risk and exhibit a dedifferentiated stem cell-like morphology. As mentioned earlier BAP1 located on chromosome 3 is commonly lost in uveal melanoma. In majority of metastasizing class 2 tumors, consistent with the “two hit” model for mutation of tumour suppressor gene, one copy of BAP1 is mutated while the other is absent through loss of the entire chromosome. There is a strong relationship between monosomy 3 and the class 2 GEP.^{20,21}

In a study by Onken et al the prognostic performance of a 15 gene expression profiling (GEP) assay that stratifies primary posterior uveal melanomas to prognostic subgroups: class 1 (low metastatic risk) and class 2 (high metastatic risk), was evaluated.²² A total of 446/459 (97.2%). 61.9% cases belonged to class 1 while 38.1 % cases belonged to class 2. On median follow-up of 17.4 months, a higher percentage of class 2 tumours showed metastasis (25.9%) compared to class1 tumours (only 1.1%).

The GEP assay successfully classified 446/459 (97.2%) cases. A significant association was found between GEP class 2 and monosomy 3. However, 20.8% cases showed

discordant results for GEP and monosomy 3. Also, monosomy 3 did not provide any additional prognostic information, independent of GEP assay. Thus, GEP assay was the most accurate prognostic marker among all of the factors analyzed and provided better prognostic accuracy compared to clinicopathologic factors like tumour thickness, TNM staging and Chromosome 3 status.²² Decatur et al also conducted a similar study to evaluate the association between driver mutations and gene expression profile and concluded that BAP1 mutations were associated with adverse prognostic factors like GEP class 2 and high-risk of metastasis. In contrast, EIF1AX and SF3B1 mutations were associated with good prognostic factors (young age, GEP class 1).⁹

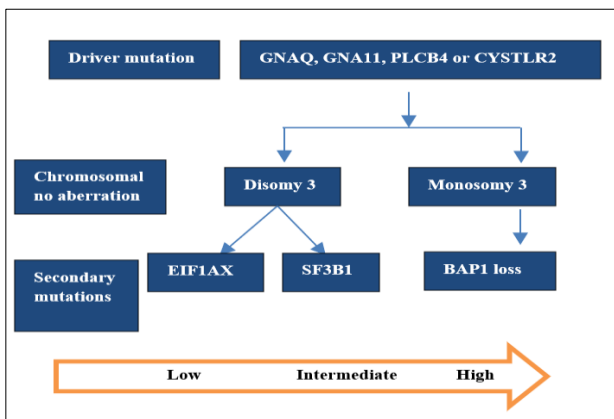


Figure 1: The common driver and secondary mutations along with their associated risk in uveal melanomas.

Clinical implications of gene expression profiling

The GEP assay is useful for stratification of patients into two prognostically significant groups as mentioned above before entry into clinical trials of adjuvant therapy. Onken et al recommended that including GEP class 2 patients in clinical trials at the time of initial diagnosis will reduce the length of time required to detect a difference in their outcome. Also, targeting BAP1 mutations offers scope for targeted therapy among GEP class 2 patients.²²

Current circulating biomarkers in uveal melanomas

There is a growing interest to develop new sensitive and specific serological markers capable of detecting disease progression and with sufficient clinical significance to modify decisions. As uveal melanoma most commonly metastasizes to liver, aim is to find new and suitable markers to detect it at the earliest as liver enzyme levels have low sensitivity and specificity in detecting the same.

S100 β was one of the first biomarkers tested in UM, due to its utility for monitoring cutaneous melanoma. In addition, high levels of S100 β are detected in vitreous and aqueous humor.²³ Missotten et al conducted a study wherein serum values of S100 beta of 64 patients of uveal

melanoma were compared with those of healthy control subjects. Thirty-seven (57.8%) of 64 patients with uveal melanoma showed detectable levels of serum S-100-beta. There was, however, no significant difference between serum levels of patients and control subjects. There was also no significant statistical correlation between S-100 beta concentration and clinicopathologic variables; thus, concluding that serum concentration of S100 β does not correlate with other prognostic factors in UM.²⁴

Melanoma inhibitory activity has been specifically expressed in cutaneous melanoma cells. MIA has been found to inhibit binding of melanoma cells to fibronectin and regulate detachment of tumour cells to extracellular matrix discovered, thus playing an important step in metastases. MIA has shown good correlation between stage of skin tumour and concentration of MIA protein in the blood.²⁵ Schaller and collaborators reported a statistically higher elevation of serum MIA levels in patients who develop metastases. However, progression of uveal melanoma cannot be excluded in patients with normal serum MIA levels, thus making it a poor predictive marker.²⁶

Osteopontin is another protein of interest which has been described in the context of various physiological functions including chemotaxis, cell adhesion, apoptosis and tumour metastasis. Increased levels of osteopontin have been seen in aggressive breast, lung, liver and prostate cancers. Soluble form of osteopontin is secreted into the blood which are known to have good correlation with advanced or metastatic cancers. Various studies have also shown that serum levels of osteopontin correlate with melanoma metastases in the liver with significant specificity and sensitivity.²⁷

CONCLUSION

Clinicopathologic prognostic factors, such as increased patient age, increased thickness and diameter of the primary tumor, ciliary body involvement and extraocular tumor extension, although associated with an increased risk of metastasis are of limited value when it comes to making clinical management decisions for patients. Understanding uveal melanomas pathogenesis is key to development of effective targeted therapy. Therefore, using gene expression profiling and chromosomal assays for molecular prognostication of patients along with subsequent enrolment of high-risk patients in clinical trials of targeted molecular therapy have now become the standard of care in the management of uveal melanoma.

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