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Metastatic Uveal Melanoma: Biology and Emerging Treatments

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Abstract

Uveal melanoma is the most common primary intraocular cancer in adults. Nearly half of primary uveal melanoma tumors metastasize, but there are currently no effective therapies for metastatic uveal melanoma. The recent discovery of mutations that underlie uveal melanoma metastasis, growth and survival provide a key to the molecular understanding of this disease. Much work is now underway to leverage this knowledge to develop effective therapies. This review summarizes recently discovered molecular features of uveal melanoma and therapies being explored to capitalize on this knowledge.

Keywords

uveal melanoma; *GNAQ*; *GNA11*; *BAP1*

Uveal melanoma is the most common primary intraocular cancer of the eye in adults.¹ Melanocytes within the uveal tract (iris, ciliary body, and choroid) of the eye can give rise to uveal melanoma. Tumors that develop in the iris are deemed anterior uveal melanomas versus tumors that develop in the ciliary body and/or choroid are termed posterior uveal melanomas. Multiple anatomical, histological and molecular poor prognostic features within primary tumors have been identified: 1) ciliary body (poorer) > choroid >> iris (rarely metastasize), 2) greater tumor size, 3) extrascleral invasion, 4) epithelioid > spindle cell histology, 5) greater mitotic number, 6) presence of monosomy 3, 7) presence of chr 8q gain, and 8) a class 2 gene expression profile.²⁻⁵ However, the strongest indicators of whether a primary uveal melanoma tumor will metastasize are copy number profile (e.g. monosomy 3, chr 8q gain) and/or a class 2 gene expression profile.^{6,7}

Approximately half of patients diagnosed with primary posterior uveal melanoma will develop metastatic uveal melanoma. Although there are effective therapies (radio-plaque, proton-beam, and enucleation) to eradicate and prevent local recurrence of primary uveal melanomas within the eye, there are, to-date, no effective therapies for metastatic uveal melanoma.⁸ The highest propensity areas to which uveal melanoma metastasizes are liver (95%), lungs (24%), bone (16%) and skin (11%), but uveal melanoma infrequently metastasize to lymph nodes or brain.⁹ The clinical course of patients with uveal melanoma is highly dependent on disease progression in the liver. The median survival after diagnosis of patients with liver metastases is approximately 4-6 months with a 1 year survival of about

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10-15%.¹⁰ Patients with metastases not involving the liver have a median survival of approximately 19-28 months with a 1 year survival of about 76%. Thus hepatic versus extrahepatic only groups may represent distinct molecular pathogenesises.¹¹⁻¹³

This review will focus on the newly identified molecular targets in uveal melanoma and potential systemic therapies to address these targets. This review will not address focal liver therapies such as surgical resection, radiofrequency ablation, hyperthermic isolated hepatic perfusion, hepatic chemoembolization, and hepatic arterial chemoinfusion, for which a very good review has been previously written.¹

Development of Uveal Tract Melanocytes

The melanocytes that reside in the uveal tract appear to have a distinct developmental lineage compared to their epidermal skin melanocyte counterparts. All melanocytes are derived from pluripotent neural crest cells that migrate out of the neural crest and populate different anatomical locations (e.g., epidermis, dermis, and uveal tract). Mouse models exhibiting differential KIT activity show that melanocytes in the dermis and uveal tract are less dependent on KIT signaling compared with those in the epidermis.¹⁴ Dermal and uveal tract melanocytes are highly dependent on endothelin-3 (ET3) and hepatocyte growth factor (HGF) signaling. ET3 signals through the endothelin B receptor (EDNRB), which mediates its signaling through the alpha g-proteins GNAQ and GNA11. A large-scale chemical mutagenesis screen to elucidate genes involved in the hyperpigmentation of mice showed mutations in the alpha subunits of the heterotrimeric g-proteins *GNAQ* and *GNA11* to be involved.¹⁵ Mutations in these genes resulted in *dermal* melanocytosis (uveal tract melanocytes were not investigated in this study). These findings were consistent with the notion that the ET3/EDNRB/GNAQ or GNA11 pathway is an important developmental pathway for dermal (and likely uveal) melanocytes, distinct from the developmental pathways which result in epidermal melanocytes. Uveal melanoma tumors appear to have aberrations in these same pathways that are crucial to uveal melanocyte development.

Cytogenetic Alterations in Uveal Melanoma

Uveal melanomas have a distinct cytogenetic profile compared to cutaneous melanoma. Uveal melanoma tumors often contain alterations in chromosome 1, 3, 6 and 8. By far the most salient chromosomal aberration associated with metastatic uveal melanoma is loss of chromosome 3. The finding of monosomy 3 in a primary tumor strongly correlates with risk of metastatic disease. Other chromosomal alterations appear to correlate and augment the loss of chromosome 3. For example, a few groups have shown that loss of 1p in addition to monosomy 3 is an independent prognostic factor for reduced disease free survival.^{16,17} Likewise, chromosome 8q copy gains, which often occur in the same tumors that have chromosome 3 loss, appear to portend a worse prognosis.¹⁸ In contrast, chromosome 6p gains are nearly mutually exclusive with chromosome 3 loss and are prognostic of a non-metastatic phenotype.¹⁹ With the exception of chromosome 3, the identification of specific genes that correlate functionally with these chromosomal aberrations has been elusive.

Gene Alterations in Uveal Melanoma

Given the observation that activating mutations in *GNAQ* or *GNA11* result in dermal melanocytosis in mice, van Raamsdonk and Bastian investigated the *GNAQ* and *GNA11* mutation status of tissues from intradermal melanocytic proliferative conditions, such as blue nevi. In addition, given the known correlation of particular blue nevi with the development of uveal melanoma, the latter were also interrogated. They discovered mutually exclusive recurrent mutations in exon 4 (R183) or exon 5 (Q209) in both *GNAQ* and *GNA11* in both blue nevi and uveal melanoma²⁰(Table 1). The distribution of these mutations was

distinct. *GNAQ* (Q209) mutations were more frequent in blue nevi and primary uveal melanomas, compared to *GNA11* (Q209), *GNAQ* (R183) or *GNA11* (R183) mutations. Although there was a suggestion that *GNA11* (Q209) mutant tumor may have a higher propensity to metastasize, the number of tissues on which these percentages were based was too small to make any general conclusions. *GNAQ* or *GNA11* (R183) mutations were far less frequent than *GNAQ* or *GNA11* (Q209) mutations in all tissue types (nevi, primary, or metastatic). No statistically significant correlation have been observed between *GNAQ* or *GNA11* mutations in the primary uveal melanoma tumors when compared to sex, age, overall survival, metastasis-free survival, tumor thickness, diameter, pigmentation, extracellular matrix patterns, cytogenetics (e.g., chromosome 3 status, 8q gain, 6p gain, 8p loss), or molecular (β -catenin, e-cadherin, cytokeratin-18) variables.²⁰⁻²² *GNA11* mutations were, however, observed to be more prevalent in ciliochoroid tumors (i.e., tumors that involve both the ciliary body and choroid).²⁰

Non-truncating (missense, in-frame deletions and termination read-through) and truncating (nonsense, splice, and insertion/deletion) mutations in the nuclear ubiquitin carboxy-terminal hydrolase *BAP1* have also recently been identified in primary uveal melanoma tumors.²³ These genetic alterations appear to result in the loss of BAP1 protein expression. Given the localization of *BAP1* on chr 3p21.1, the identification of *BAP1* mutations primarily in tumors with monosomy 3 provides strong evidence that loss of heterozygosity of *BAP1* may be a very important mediator of metastatic disease. Within tumors that showed monosomy 3, and for which *BAP1* mutant status could be determined, *BAP1* mutations were present in 81% (21/26) of cases. *BAP1* mutations were highly correlated with class 2 tumor status (a gene expression profiling test for high metastatic risk), chromosome 3 loss in primary tumors, and the ultimate emergence of metastatic disease in the patients (Table 2).

Previous studies have shown BAP1 to have tumor suppressor activity.²⁴ BAP1 has been shown to regulate cell proliferation by de-ubiquitinating hcf-1, a cell cycle regulator.²⁵ A recent study shows *BAP1* to be the previously uncharacterized drosophila gene calypso which is part of the polycomb group repressive de-ubiquitinase complex involved in removal of monoubiquitin from histone H2A, and ultimately stem cell pluripotency and organismal development.²⁶ The exact mechanism(s) by which loss of BAP1 mediates primary uveal melanoma metastasis is currently being investigated. However, a recent study indicates that loss of BAP1 results in the accumulation of mono-ubiquitinated histone H2A and a more de-differentiated cellular phenotype.²⁷

Molecular Alterations in Uveal Melanoma

The MEK/MAPK signaling pathway is clearly activated in uveal melanoma cells.^{28,29} The majority of uveal melanoma cell lines demonstrate growth arrest to small molecule MEK inhibitors.³⁰ However, unlike their cutaneous counterparts, uveal melanoma tissues lack the typical oncogenic upstream mediators of this pathway (e.g., mutant *BRAF*, *NRAS*, *KIT*). In uveal melanoma, mutant *GNAQ* and *GNA11* appear to be major upstream mediators of the MEK/MAPK pathway. Exogenous expression of mutant *GNAQ* increased MAPK phosphorylation, whereas knockdown of *GNAQ* in uveal melanoma cell lines with mutant *GNAQ* diminished MAPK phosphorylation and increases the number of cells in the sub-G0/G1 fraction.^{20,31}

The PI3K/AKT signaling pathway also appears to be highly active in uveal melanoma.^{32,33} There is some evidence to suggest that activation of AKT is associated with a higher risk of metastatic disease, however, these observations were seen in enucleated-only (versus radiotherapy and enucleated eyes),³² and in another study only associated with phospho-AKT (Thr308), not phospho-AKT (Ser473).³³ The effect of activated *GNAQ* or *GNA11* on

PI3K/AKT pathway signaling appears to be cell-type specific,^{34,35} and has not been established in uveal melanoma. We have determined that typical activating mutations in *AKT* (1,2,3) or *PI3K* found in other cancers are not present in uveal melanoma cell lines and loss of *GNAQ* had little effect on the activation of AKT, although inhibition of MEK results in a compensatory upregulation of phospho-AKT in these cell lines (submitted for publication). Activation of the PI3K/AKT pathway in some uveal melanoma tumors may be mediated through the loss of the tumor suppressor phosphatase and tensin homolog (*PTEN*). One report has shown that approximately three-fourths of primary uveal melanoma tumors show a loss of *PTEN* heterozygosity and about roughly one-tenth of these exhibit mutations in *PTEN*.³⁶ Loss of cytoplasmic *PTEN* in primary uveal melanoma tumors was associated with shortened disease-free survival in this study.

Given the impressive tropism of metastatic uveal melanoma cells for the liver, effort has been expended to determine whether a particular symbiosis exists between uveal melanoma cells and the hepatic microenvironment. A major focus of this effort has been in the examination of the secreted hepatocyte growth factor (HGF) which is produced in the liver and its corresponding tyrosine kinase receptor c-Met (MET). Activated MET is a well characterized mediator of proliferation, survival, and cell migration, and is known to be upregulated in multiple other cancer types. A number of researchers have examined MET expression levels in primary uveal melanoma tissues by immunohistochemistry, and despite various methods of quantification being used, MET appears to be highly expressed in primary uveal melanoma cells.³⁷⁻⁴⁰ Of interest, one study showed that primary tumors that metastasized had higher expression of MET compared to tumors that did not metastasize, and correlated with uveal melanoma-specific mortality.³⁹ A detailed analysis of MET expression in metastatic uveal melanoma has not been performed.

Another hormone highly secreted by the liver is insulin-like growth factor 1 (IGF-1). IGF-1 mediates its effect through the IGF-1 receptor (IGF-1R) resulting in cell proliferation, survival and migration. IGF-1R has been shown to be expressed in primary uveal melanoma tissues^{38,40,41}, and multivariate analysis correlates elevated IGF-1R expression by immunohistochemistry with uveal melanoma-specific mortality.⁴¹ Like MET, the expression and role of the IGF-1/IGF-1R axis in metastatic uveal melanoma has not been determined, although the use of cyclolignan picropodophyllin (PPP), a purported IGF-1R inhibitor blocks activity of the receptor *in vitro* and significantly reduced tumor volume in mouse xenograft experiments.⁴²

Emerging Treatments for Metastatic Uveal Melanoma

Despite many trials of chemotherapeutic and biological therapies, metastatic uveal melanoma remains recalcitrant to treatments utilized to-date. However, there is optimism that therapies based on the recently discovered molecular drivers in uveal melanoma will yield effective approaches. As direct targets, *GNAQ* and *GNA11* pose the difficulty that the mutations which activate these proteins cause the inactivation of the intrinsic GTPase within the molecule. This represents a traditionally difficult pharmacological space in which to design inhibitors. Thus, early approaches will likely attempt to inhibit key downstream effectors of mutant *GNAQ* or *GNA11*. The elucidation of these downstream effectors in uveal melanoma is an ongoing preclinical research effort. However, there is already clear data supporting the MEK/MAPK pathway as an important mediator of both activated *GNAQ* and *GNA11* in uveal melanoma.^{20,31,43}

Suggestive evidence for the use of MEK inhibitors in metastatic uveal melanoma comes from a review by Carvajal et al. of three distinct trials in which 20 metastatic uveal melanoma patients were treated either upfront with the MEK inhibitor AZD6244 or

following progression on temozolomide.⁴⁴ Taken together, there was an improvement in progression free survival in favor of MEK inhibitor treatment, although caution must be employed given the small number of patients and the retrospective analysis of three different trials. A phase I clinical trial in which seventy-two melanoma patients, including uveal melanoma patients, were treated with the GSK1120212 MEK inhibitor has recently been completed, and outcomes are awaiting publication.⁴⁵ Finally, a more definitive prospective phase II trial treating metastatic uveal melanoma patients with AZD6244 and assessing progression-free survival is currently accruing (NCT01143402). This trial will randomize temozolomide/dacarbazine naïve patients to either AZD6244 or temozolomide, with a *GNAQ* or *GNA11* mutant cohort versus a cohort accrued regardless of *GNAQ* or *GNA11* mutation status. A third cohort of temozolomide/dacarbazine exposed, *GNAQ* or *GNA11* mutant patients will also be assessed following AZD6244 treatment.

As IGF-1R activity has a putative role in uveal melanoma, a prospective, phase II, open-label clinical trial using IMC-A12 (recombinant human IgG1 monoclonal antibody that targets the IGF-1R) has been designed (NCT01413191). This study is currently accruing metastatic uveal melanoma patients. The primary objective of this trial is objective response rate with correlative studies to determine the expression level of IGF-1R in pre-treated tumors relative to tumor response rate. In addition, a phase II trial employing SOM230 (pasireotide) and RAD001 (everolimus) is also underway (NCT01252251). The rationale for this trial is that among its many potentially anti-cancer effects, pasireotide has been shown to diminish IGF-1 levels. Everolimus is an MTOR inhibitor, which may have efficacy by inhibiting the PI3K/AKT pathway in uveal melanoma. The combination of these agents has the benefit of blocking the feedback activation of AKT following the inhibition of MTOR, a negative regulator of IGF-1R. Given the aforementioned data on the potential linkage between HGF expression by liver cells and its receptor, MET, on uveal melanoma cells, a rational therapeutic approach may be to block the MET receptor in uveal melanoma. Although there are as of yet no MET inhibitor trials dedicated exclusively to uveal melanoma patients, there are multiple MET inhibitors in early phase clinical trials for solid tumors: GSK1363089, ARQ197, XL-184, EMD1204831, PF-02341066, and PRO143966.

Hsp90 inhibitors offer a different approach to oncogene targeting. For example, STA-9090 inhibits Hsp90 resulting in the degradation of multiple oncogenic Hsp90 client proteins. Many of these proteins are putative drivers of uveal melanoma, including AKT, IGF-1R, and MET. STA-9090 is currently in a phase II clinical trial in metastatic uveal melanoma (NCT01200238). The objective of this study is to determine progression free survival at four months of treatment and to determine the proportion of patients with greater than 50% decrease in MET after STA-9090 administration.

Loss of *BAP1* poses a difficult therapeutic challenge, as it appears to represent a classic loss of a tumor suppressor, and direct therapies would require the re-initiation of function. However, as with mutant *GNAQ* and *GNA11*, there is the potential to use agents that modulate the downstream effects of *BAP1* loss. A recent publication demonstrated that loss of *BAP1* results in an accumulation of mono-ubiquitin on histone H2A, thus altering the transcriptional profile within these cells.²⁷ *BAP1* was recently identified as a homologue of the drosophila *calypso* gene.²⁶ Calypso is part of a polycomb group (PcG) complex termed the polycomb repressive deubiquitinase (PR-DUB). The PR-DUB complex binds at PcG target genes, removes monoubiquitin from histone H2A. The deubiquitination of H2A mediated by *BAP1* as part of the PR-DUB complex is countered by the monoubiquitinating activity of the polycomb repressive complex 1 (PRC1). Histone deacetylase inhibitors (HDACis) have been shown to inhibit BMI1 within the PRC1 complex, thus potentially countering the accumulation of mono-ubiquitin on histone H2A in the setting of *BAP1* loss. A recent study showed that multiple HDACis have the capacity to reverse the accumulation

of mono-ubiquitin on histone H2A in *BAP1* minus cells.²⁷ These observations require further functional studies, however, they offer potential insight into the use of HDACis (e.g., SAHA, valproic acid) in *BAP1* minus (i.e., the majority of metastatic) uveal melanoma.

Other approaches are also underway to treat metastatic uveal melanoma. One strategy has been to couple targeted therapies to chemotherapies with the intent to gain enhanced activity. For examples, although temozolamide has very little activity as a single agent in uveal melanoma,⁴⁶ there are two studies that couple temozolamide to agents that can inhibit angiogenesis. A phase II study using temozolamide and bevacizumab, a monoclonal anti-VEGF antibody (NCT01217398), and a Phase I/II study coupling temozolamide with sunitinib, a multi-tyrosine kinase inhibitor, one of whose targets is VEGFR (NCT00471471) are currently underway. Another strategy to enhance the activity of chemotherapeutic agents is to couple them with compounds that counter the anti-apoptotic process (e.g., Bcl2 expression) that can be induced with their use. A phase II open label study has been designed to do so using carboplatin/paclitaxel in combination with genasense (anti-sense dna to Bcl2) in metastatic uveal melanoma (NCT01200342). The aim of this study is to determine the objective tumor response, with correlative studies to assess *GNAQ* or *GNA11* mutation status and BCL2 levels.

Finally, immune-based therapies have a long history in the treatment of cutaneous melanoma. As cutaneous melanoma and uveal melanoma share many antigenic features, there is a rationale for also using immune-based therapies in uveal melanoma. A phase I dendritic cell (MART-1/gp100/Tyrosinase/NY-ESO-1 Peptide-Pulsed Dendritic Cells) vaccine therapy trial has recently been completed (NCT00313508). Ipilimumab (fully human monoclonal anti-CTLA4 antibody) has recently gained FDA-approval for the treatment of advanced cutaneous melanoma,⁴⁷ and an open label phase II trial using CP-675,206, also a fully human monoclonal anti-CTLA4 antibody, in unresectable or metastatic uveal melanoma patients is ongoing (NCT01034787).

Conclusion

Recent developments in the understanding of the molecular underpinnings of uveal melanoma have revealed potential ways in which to therapeutically intervene in this cancer. Although direct targeting of mutant *GNAQ* or *GNA11*, or *BAP1* loss is presently not possible, interventions that target downstream effectors of these genetic aberrations may be possible, in addition to targeting other important non-mutated molecular drivers. It is clear that mutations that activate *GNAQ* and *GNA11*, in part, signal through the MEK/MAPK pathway, and inhibition of this pathway with MEK inhibitors may affect cell growth. However, it is also likely that multiple other cellular processes are affected by mutated *GNAQ* and *GNA11*, *BAP1* loss, and other molecular aberrations in uveal melanoma tumors. Only with a more comprehensive understanding of the combined effect of the multiple molecular aberrations in uveal melanoma tumors will an ultimately effective treatment be designed. However, much will be gleaned from the multiple trials currently underway that target putative drivers of uveal melanoma metastasis, growth and survival.

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Table 1
***GNAQ* and *GNAI1* mutation frequency in blue nevi and uveal melanoma**

	<i>GNAQ</i>		<i>GNAI1</i>	
	Exon 4 (R183)	Exon 5 (Q209)	Exon 4 (R183)	Exon 5 (Q209)
Blue Nevus (all subtypes)	1%	54.5%	1%	6.5%
Primary	3%	45%	2%	32%
Metastasis	6%	22%	6%	56.5%

Adapted from ref. 18

Table 2
Relationship between *BAP1* mutations, chromosome 3 loss, metastasis and class status in uveal melanoma

	<i>BAP1</i> mutation	Chr 3 loss	Metastasis
Class 1 (n=26)	1	4 + (1 ND)	3
Class 2 (n=31)	26	22 + (6 ND)	15

ND = nondetermined

Adapted from ref. 21