Review

Clinical and therapeutic implications of melanoma genomics

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Abstract

Melanoma represents just 1% of skin cancer but is responsible for the vast majority of skin cancer deaths. Given its implications for therapeutic advancement, the field of melanoma genomics has dramatically expanded in recent years. At one time classified mainly by anatomical location - non-acral cutaneous melanoma (NACM), acral cutaneous melanoma (ACM), mucosal melanoma (MuM), or uveal melanoma (UM) are now further sub-classified based on the mutated genes that drive their initiation, progression, and survival. *BRAF* gene mutations in NACM are the most frequently occurring and the best-studied, giving rise to the successful use of BRAF inhibitors in clinical practice for the last decade. This development has opened the door for many promising clinical trials and countless investigations into melanoma's genetic underpinnings. In this review, we offer an overview of melanoma genomics and discuss the most relevant somatic mutations such as *BRAF*, *NRAS*, and *NF1* in NACM, *KIT* in ACM and MuM, and *GNAQ*, *GNA11*, and *BAP1* in UM. Particular emphasis is placed on the biochemical pathways driven by each mutation, their associated clinical manifestations, and their role as current and future therapeutic targets.

Keywords: Melanoma, cutaneous melanoma, genetics, genomics, BRAF, NRAS, NF1, skin cancer

INTRODUCTION

In 2018, there will be an estimated 91,270 new cases of melanoma and 9320 deaths attributable to melanoma[1]. Compared to the estimates from ten years prior in 2008 of 62,480 cases and 8420 deaths, it is clear that the incidence continues to dramatically rise while the number of deaths has stabilized[2]. This apparent improvement in survival is due, in part, to the discovery of novel therapeutic agents targeting specific melanoma genetic drivers, such as vemurafenib, dabrafenib, and trametinib in *BRAF*-mutant tumors[3,4].

Given our growing understanding of the mutations driving melanoma progression, we now have multiple options for recurrent and metastatic tumors that were once considered untreatable. We are also better able to identify those patients who would benefit from earlier and more thorough cancer screening due to the discovery of hereditary forms of cancer and their associations with cancers of other organs[5]. Despite our expanding knowledge of melanoma's genetic landscape with over 40 culprit mutated genes identified to date, a relatively small number of clinically-relevant drugs have been developed[6]. This disparity is due to the remarkably intricate nature of cancer genetics, involving the complex interplay between driver and passenger mutations and variability in gene expression and gene-gene interactions. Considering the modest progress towards improving the prognosis of uveal melanoma, or in developing a universal melanoma chemotherapeutic agent, it is clear that much remains to be discovered.

We will focus largely on somatic driver mutations in melanoma. An extensive discussion of germline variants and their associated familial cancer syndromes is beyond the scope of this review.

NON-ACRAL CUTANEOUS MELANOMA

Non-acral cutaneous melanoma (NACM), comprised of the superficial spreading, nodular, lentigo maligna, and desmoplastic subtypes, is the most common type of melanoma, and thus the most well-studied and well-understood in terms of its genetic foundation. NACM predominantly affects sun-exposed surfaces of white individuals with fair skin, and its risk is highly associated with UV radiation exposure[7]. Superficial spreading melanoma is the most common form, representing 70% of all cases of melanoma, and is more likely to be associated with a prior nevus and a history of sporadic and intense UV exposure[8]. Nodular melanoma often presents as a darkly-pigmented or amelanotic nodule that is thicker than other subtypes at the time of diagnosis. Lentigo maligna melanoma primarily arises in chronically sun-damaged skin of older individuals. Finally, the desmoplastic subtype is marked by an amelanotic scar-like formation that is characterized histologically by spindled melanocytes and abundant stroma[9]. From a genomic standpoint, NACM is generally characterized as being made up of four major subclasses: *BRAF*, NRAS, NF1, and triple-wild type [Table 1].

BRAF

Mutations in *BRAF* are the most frequently occurring driver mutations in melanoma (60% of all tumors)[36]. *BRAF* encodes a serine/threonine protein kinase that regulates the mitogen-activated protein kinase (MAPK) pathway, which is involved in cell proliferation, differentiation, and survival. *BRAF* mutations have been implicated in several other malignancies, such as colorectal carcinoma, ovarian carcinoma, and various sarcomas[36]. The V600E missense mutation, which results in a valine to glutamic acid substitution, is present in 80% of *BRAF*-mutated melanomas. This mutation significantly upregulates BRAF kinase activity thereby activating downstream MAPK signaling and driving cancer progression[36].

BRAF-mutated melanomas are more often found in younger patients and in areas exposed to intermittent sunlight[10], but the same V600E mutation is also present in 80% of benign nevi, suggesting that tumorigenesis requires additional co-mutations[11].

BRAF-mutated melanomas were first successfully treated with the BRAF inhibitor vemurafenib in 2010, and now are treated with the gold standard combination of dabrafenib (BRAF inhibitor, BRAFi) and trametinib (MEK inhibitor, MEKi)[3,12,37]. Trametinib targets downstream MEK1 and MEK2. The combination of BRAFi+MEKi suppresses MAPK signaling at two points which enhances efficacy[38]. Several resistance mechanisms have developed in response to BRAF inhibitors including novel splice variants in *BRAF*, *BRAF* gene amplification, activation of receptor tyrosine kinases and other kinases, or through an immune-mediated mechanism[23]. Clinical trials are currently investigating treatments for these resistance patterns. One promising option may be a combination of the current standard of dabrafenib/trametinib with immunomodula-

Table 1. Summary of the major melanoma driver mutations

Melanoma Subtype	Mutated gene (% of subtype)	Clinical manifestations	Relative prognostic implications	Treatment options
Non-acral cutaneous	BRAF (60)[6]	Younger patients, intermittent sunlight, presence in benign nevi[10,11]	neutral	Gold standard: combination dabrafenib and trametinib or immune checkpoint inhibitors. Clinical trials: dabrafenib and trametinib with PD-1 inhibitors. Several others[12,13]
	NRAS (28)[6]	Older patients, non-sun-damaged skin, presence in benign nevi[10,14,15]	Unfavorable[16]	Clinical trials: MEK1/2 inhibitors, CDK4/6 inhibitors[17,18]
	NF1 (14)[6]	Older/male patients, sun-exposed skin[19]	Unfavorable[20]	No ongoing trials specifically targeting this gene mutation
	Triple wild-type (15)[6]	Male patients[20]	Unfavorable	No ongoing trials or targeted therapy options
Mucosal/ Acral cutaneous	KIT (39 MuM/36 ACM)[21]	Chronically sun-damaged skin[21]	Unfavorable[22]	Limited results with kinase inhibitors (imatinib, dasatinib, sorafenib, and nilotinib). Additional trials: kinase inhibitors with immunotherapy[23]
	PDGFRA (4 MuM/7 ACM)[24]	Non-sun-damaged skin[24]	Neutral	Preliminary results with imatinib and crenolanib[25]
	Cyclin D1 (45 ACM)[26]	Sun-damaged skin, resistance to BRAFi[26]	Neutral[27,28]	Clinical trials: CDK inhibitor P276-00[29]
Uveal	GNAQ/GNA11 (99)[30]	Presence in benign nevi[31]	Neutral[30,32]	Clinical trials: solumetinib, protein kinase C inhibitors[33]
	BAP1 (45)[30]	BAP1 cancer syndrome, associated with other malignancies[34]	Unfavorable[34]	Clinical trials: Niraparib (PARP inhibitor)[35]
	EIF1AX (14)[30]	None reported	Favorable[34]	No ongoing trials
	SF3B1 (22)[30]	Younger patients, associated with late metastasis[34]	Unfavorable[34]	

MuM: mucosal melanoma; ACM: acral cutaneous melanoma; CDK: cyclin-dependent kinase

tory agents such as ipilimumab and nivolumab[13].

NRAS

NRAS mutations, present in 1/3 of NACMs, are the second most common driver mutation in melanoma[6]. The RAS family is a group of G-regulatory proteins that regulate cell growth and malignant transformation by activating both the MAPK pathway (as in *BRAF*-mutant melanomas) as well as the phosphoinositide 3-kinase (PI3K) pathway, an essential cell signaling pathway that promotes growth and survival independent of MAPK[39] [Figure 1]. *NRAS*, in particular, is mutated in 28% of *RAS*-mutant tumors, compared to *HRAS* in 1% and *KRAS* in 1%[6]. NRAS Q61 is an activating missense mutation that renders the NRAS protein constitutively guanosine triphosphate (GTP)-bound and active, thus affecting a large number of downstream signaling molecules involved in cell cycle dysregulation, survival, and proliferation, such as the aforementioned PI3K and RAF kinases[40].

NRAS-mutant tumors typically occur in non-sun-damaged skin in older patients but are also known to affect acral and mucosal sites. They have increased thickness, higher mitotic rates, and lower incidence of ulceration than their counterparts[10,14]. They also exhibit increased aggressiveness and poor survival[16]. Like *BRAF* variants, *NRAS* mutations are commonly found in congenital nevi, again suggesting that *NRAS* variants alone are insufficient for tumorigenesis[15]. Despite activating the same MAPK pathway as *BRAF* mutations, *NRAS* variants are very rarely found within *BRAF*-mutated tumors, which has obvious implications for treatment development[41].
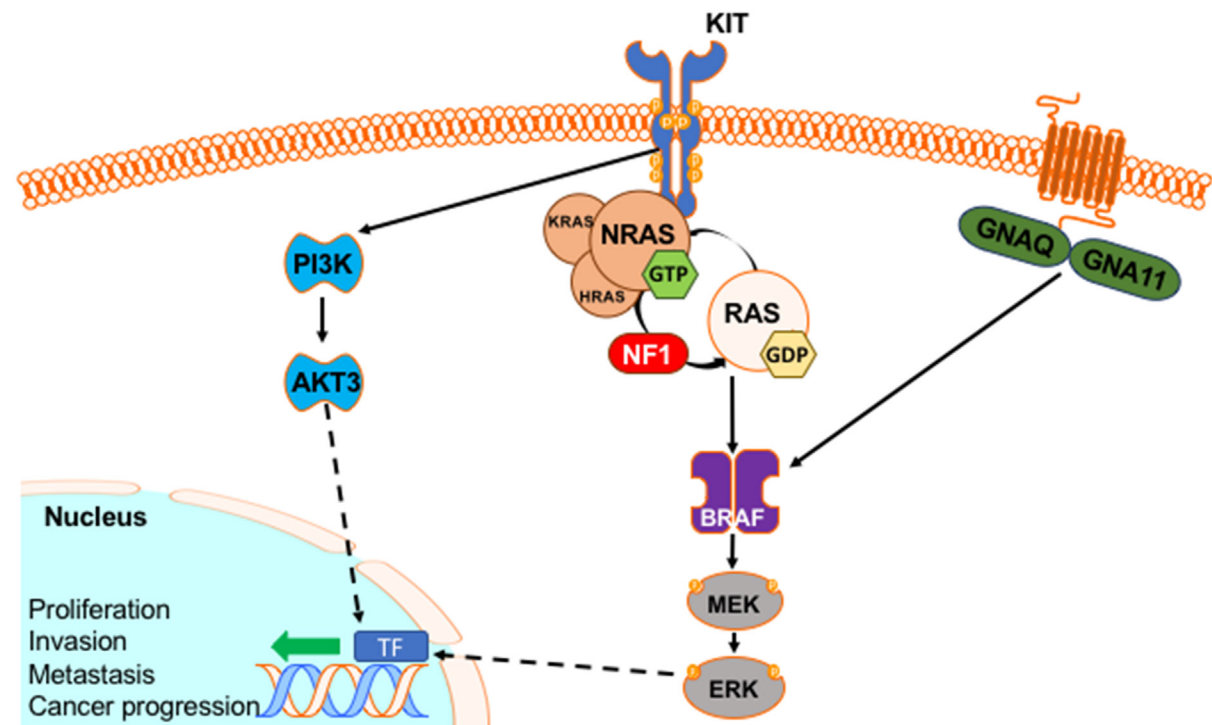
Figure 1. The interactions between the RAS/RAF/MEK/ERK, PI3K/AKT3/mTOR, KIT, and GNAQ/GNA11 pathways

There is a lack of targeted treatment options for *NRAS*-variant tumors, with only a few clinical trials and no approved drugs to date. Binimetinib, a MEK1/2 inhibitor that works downstream of the MAPK pathway, has demonstrated improvement over the traditional chemotherapeutic agent dacarbazine in a recent clinical trial[17]. Several other options are currently being explored, most notably the combined use of MEK and cyclin-dependent kinase 4 (CDK4/6) inhibitors[18].

NF1

NF1 is a tumor suppressor gene that encodes the protein neurofibromin 1, and is the third most common NACM driver, found in about 14% of tumors[16,42]. The GTPase-activating protein-related domain of NF1 negatively regulates RAS through conversion of activated RAS-GTP to inactive RAS-guanosine diphosphate. This results in constitutive activation of both the MAPK and PI3K pathways, driving tumorigenesis through the same signaling pathway as in *BRAF* and *NRAS*-variant tumors [Figure 1]. Despite this shared pathway, tumors with putative loss-of-function mutations in the *NF1* gene generally lack the BRAF (V600E) mutation, and in fact, *NF1* mutations have been proposed as a source of resistance to BRAF inhibitors[43].

NF1-mutated tumors are clinically aggressive and have poor survival with very limited treatment options[20]. They tend to occur in sun-exposed skin in older male patients[19], and are also associated with desmoplastic tumors, occurring more often in desmoplastic melanoma than any other NACM subtype[44,45].

Triple-wild type

Triple-wild type NACM lacks any of the aforementioned mutations in *BRAF*, *NRAS*, or *NF1* [Figure 2]. It is a rare, heterogeneous group of cancers, with a predisposition for males between the ages of 60-70[20]. Interestingly, it often harbors mutations in what are normally considered uveal melanoma drivers (discussed below), such as *GNA11*, *GNAQ*, *SF3B1*, and *KIT* mutations[6,20,46]. Given the lack of a consistently present driver mutation, triple-wild type NACM currently offers little promise for possible chemotherapy targets.
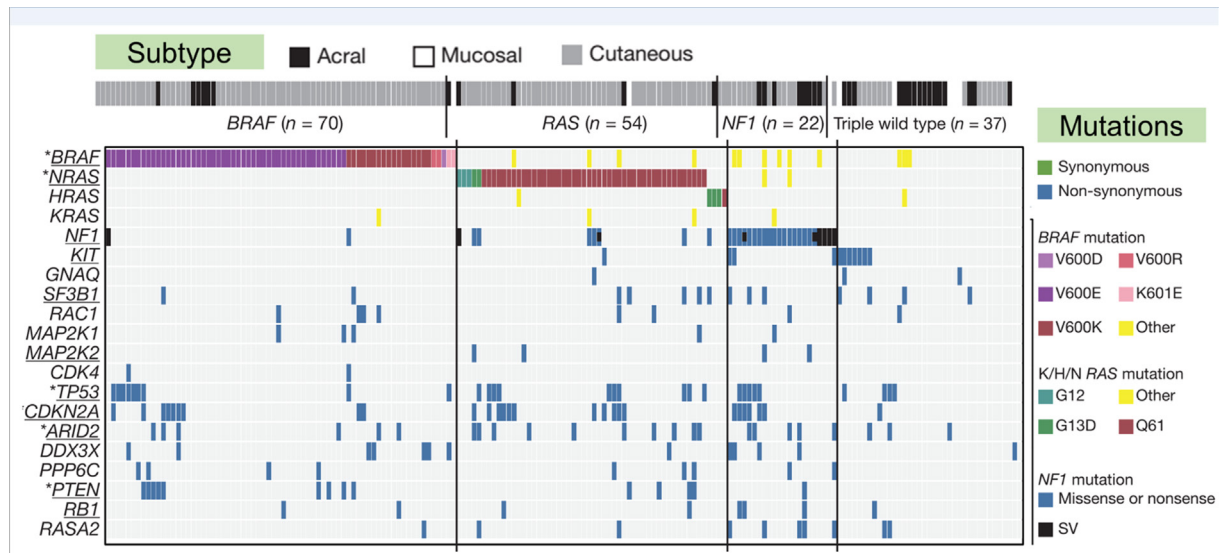
Figure 2. Selected driver mutations in melanoma broken down by non-acral cutaneous melanoma genomic subclass (BRAF, RAS, NF1, and triple-wild type) and melanoma subtype (acral, mucosal, cutaneous). Adapted with permission from Hayward *et al*.[46]

Other mutations in NACM

Several additional mutations are crucial in NACM development, progression, and survival. microphthalmia-associated transcription factor (MITF) is a transcription factor that is required for early melanocyte develop-ment. While there are no activating mutations in MITF as in BRAF, about 10% of tumors exhibit amplifi-cation of the MITF locus[47,48]. It is associated with a decreased 5-year survival and a specific MITF variant (p.E318K) is also rarely seen as the product of a germline mutation predisposing patients to both melanoma and renal cell carcinoma[5,32]. Mutations in phosphatase and tensin homolog (PTEN), a tumor suppressor and key regulator of the PI3K pathway, are found in about 14% of melanomas[49,50]. Germline PTEN muta-tions are associated with Cowden syndrome in adults and Bannayan-Riley-Ruvalcaba syndrome in children and impart an increased risk for breast, thyroid, endometrial, kidney, and colorectal cancer in addition to melanoma[5]. Telomerase reverse transcriptase (TERT) encodes the catalytic subunit of the holoenzyme telomerase that is essential for sustaining telomere length and chromosomal stability, enabling cells to over-come replication-induced senescence, while allowing for additional mutations to accrue[51]. Amplification of the TERT locus along with TERT promoter mutations are quite common in melanoma[6]. TERT promoter variants recruit the GABP transcription factor and are present in 90% of aggressive malignancies[52]. Cyclin-dependent kinase inhibitor 2A (CDKN2A) deletions and mutations along with cyclin-dependent kinase 4 (CDK4) amplifications and activating mutations disrupt G1-S transition in the cell cycle and lead to melano-ma tumorigenesis[6,46]. Mutations in both genes have been implicated in hereditary melanoma, an autosomal dominant group of disorders characterized by patients with hundreds of dysplastic nevi and an increased risk for melanoma and other malignancies[5].

MUCOSAL MELANOMA AND ACRAL CUTANEOUS MELANOMA

Perhaps as they both arise in sun-protected skin areas, acral cutaneous melanoma (ACM) and mucosal mel-anoma (MuM) are more genetically similar to each other than to any of the other subtypes. Both account for higher percentages of melanoma among Black, Asian, and Hispanic populations, which reflects the lower rates of UV-related NACMs among these populations[6,53]. ACM represents 2% of primary melanomas[54]. It is an aggressive tumor that is associated with delayed diagnosis and poor prognosis[55]. MuM represents 1.3% of primary melanomas and is similarly associated with an advanced stage at diagnosis and a poor prognosis[56]. ACMs less commonly contain mutations in *BRAF*, *NRAS*, *PTEN*, *TP53*, and *MAP2K2*[46,57], while MuMs often harbor *GNAQ* and *SF3B1* gene mutations that are typically considered more characteristic of uveal

melanoma[58,59]. A few of their most frequently recognized mutations are in the *KIT*, *PDGFRA*, and *Cyclin D1* genes [Table 1].

KIT (MuM and ACM)

KIT mutations are present in just 3% of all melanomas but are found in as many as 39% of MuM and 36% of ACM, making them the most common variant in both of these subtypes[21]. Additionally, it is the most commonly identified mutation in chronically sun-damaged skin at 28%[21]. *KIT* encodes a type III transmembrane receptor tyrosine kinase that is vital for normal melanocyte development, as it is the receptor for stem cell factor (SCF). Upon binding SCF, KIT dimerizes and subsequently activates signaling pathways, including the MAPK/ERK and the PI3K/AKT/mTOR survival pathways [Figure 1]. Activating KIT mutations simulate this very same SCF ligand binding, thus activating pathways that influence cancer cell growth, proliferation, invasion, metastasis, and apoptosis evasion[60]. In melanoma, *KIT* mutations correlate with increased disease invasion and metastasis, highlighting its tumor suppressive function[22]. They are mutually exclusive with mutations in *BRAF* and *NRAS*, but still induce the same MAPK and PI3K pathways that are crucial to the tumorigenesis of several other melanoma subtypes.

Clinical trials have focused on the use of various kinase inhibitors, such as imatinib, dasatinib, sorafenib, and nilotinib, all with limited results in the attempted treatment of *KIT*-mutated tumors[23].

PDGFRA (MuM and ACM)

A cell surface type III receptor tyrosine kinase, PDGFRA normally binds to platelet-derived growth factors and leads to the activation of cell signaling pathways essential for growth and differentiation. Mutations have also been implicated in the dysregulation of survival and tumor progression. Mutant *PDGFRA* is present in around 7% of ACM and 4% of MuM. *PDGFRA* mutations are mutually exclusive with *KIT* mutations and occur almost entirely in skin without chronic sun-damage[24].

CCND1 (ACM)

CCND1 encodes the major cell cycle control protein cyclin D1. Cyclin D1 effectively controls cell proliferation through binding and stimulating CDK4/6, resulting in the phosphorylation of the retinoblastoma protein and subsequent cell cycle entry[61]. Amplification of the *CCND1* gene is present in approximately 45% of ACMs[26], and it is considered an ACM driver. However, the gene is also amplified in 6% of NACMs, particularly in chronically sun-damaged skin[26]. CCND1 variants have even been found to incur resistance to BRAF inhibitors in NACM[61].

UVEAL MELANOMA

Uveal melanoma (UM) arises from melanocytes of the uveal tract of the eye, and it is both the most common primary intraocular malignancy and the most common of the non-cutaneous melanomas (comprising 80% of these tumors)[34,62]. UM has a poor prognosis, with nearly half of affected patients developing metastatic disease with an expected survival ranging from months to a year. The rarity of the disease limits patient availability for clinical trials and currently no effective systemic therapy exists[63]. Like cutaneous forms of melanoma, UM occurs primarily in white patients, particularly in those with light skin and light eyes, highlighting the possible significance of UV radiation in its development or the inherent susceptibility of melanocytes from these vulnerable populations[63,64]. The genetic landscape of UM is distinct from other melanomas, as evidenced by observations that UM rarely exhibits *BRAF* or *NRAS* mutations, which are characteristically present at all other melanoma sites, but rather is defined by *GNAQ*, *GNA11*, *BAP1*, *EIF1AX*, and *SF3B1* mutations [Table 1].

GNAQ and *GNA11*

Up to 99% of UM harbor *GNAQ* or *GNA11* gene mutations[30]. *GNAQ* mutations alone have been found in

33% of uveal and 1.4% of cutaneous melanoma, and variants in *GNA11* have been identified in 39% of uveal and 1.3% of cutaneous[31]. They are the most common UM driver mutations, and they were among the first to be described. The proteins these two genes encode are close relatives of the large GTPases in the G alpha subunit (Gα_q) family, which are subunits of heterotrimeric G proteins operating downstream of G protein-coupled receptors (GPCRs)[65]. GNAQ and GNA11 encode the Gα_q and alpha subunit 11 (Gα11) respectively[66]. Both proteins mediate signaling between GPCRs and downstream effectors. Recurrent activating GNAQ (p.Q209) and GNA11 (p.Q209) mutations converge on the MAPK/ERK pathway and serve to constitutively upregulate the MAP kinase pathway, similarly to *BRAF* and *NRAS* activation in cutaneous melanoma[59,67] [Figure 1]. *GNAQ* and *GNA11* gene mutations display mutual exclusivity and are very rarely found to co-occur in the same tumor. Mutations in these genes are also present in benign uveal nevi and dermal melanocytic tumors and are considered an early event in uveal melanoma development and progression.

Despite *GNA11* mutations displaying a stronger association with metastasis than those of *GNAQ*, neither mutation reveals any correlation with prognosis[30,32]. There have been very few promising trials to date. However, some moderate effects have been demonstrated with the MEK inhibitor, selumetinib, and recent studies are currently investigating protein kinase C as a potential target[33].

BAP1
BRCA1-associated protein 1, or *BAP1*, is a tumor suppressor gene that is lost due to the occurrence of monosomy 3 in 45% of UM[30]. The protein product of *BAP1* is a deubiquitinating hydrolase. *BAP1* loss results in severe dysregulation of cell cycle regulation, DNA repair, and gene expression in multiple genomic regions[5,68].

Tumors with *BAP1* alterations or loss are potentially more aggressive with a poor prognosis. They are often found in older patients and are associated with as many as 80% of metastatic UMs[34]. Germline *BAP1* mutations are found in BAP1 cancer syndrome, which predisposes patients to UM along with renal carcinoma, mesothelioma, and several other tumors. However, they are detected far more frequently as somatic variants[69]. Patients with BAP1 cancer syndrome are often recommended to pursue more frequent and thorough cancer screening along with genetic counseling. Unfortunately, few options remain for patients with *BAP1* mutations once their UM becomes metastatic. Unlike oncogenes that can be targeted with any number of small molecule inhibitors, the nature of *BAP1* as a loss-of-function tumor suppressor gene has posed a challenge for the development of a targeted therapy.

EIF1AX and SF3B1
EIF1AX and *SF3B1* mutations are less common among UM, found in 14% and 22% of samples, respectively[30]. The two proteins encoded by these genes are responsible for the nuclear processes of translation initiation and pre-mRNA splicing, respectively. Mutations in *EIF1AX* and *SF3B1* are nearly mutually exclusive with each other as well as with *BAP1* variants. *EIF1AX* mutations are associated with a favorable prognosis, while *SF3B1* mutations are found in younger patients and are associated with the development of late metastasis[34].

MELANOMA GENOMICS

Mutational Burden
Apart from differences in the underlying driver mutations, melanoma subtypes reveal variations in other key genomic attributes. For example, NACM has one of the highest tumor mutational burdens (TMB) among all human malignancies with around 10-50 mutations per megabase; in contrast, UM has one of the lowest and ACM/MuM only have around 2-3 mutations per megabase[20,70-72]. High TMB was initially established as a marker of clinical benefit in NACM after immunotherapy with CTLA-4 blockade by ipilimumab, and a high TMB in TCGA metastatic melanoma cohort was associated with improved survival[73,74]. One hypothesis is that increased TMB causes higher rates of neoantigen presentation and increased tumor im-

mune surveillance[75]. Even among cutaneous melanoma genomic subgroups, mutational load shows minor variations, with *NF1*-subtype tumors displaying a higher TMB compared to *BRAF*, *NRAS*, and triple wild-type tumors[20].

Mutational Signatures

Different environmental and molecular forces, such as exposure to carcinogens (smoking, UV light, *etc*.), result in distinct mutational processes leaving unique DNA "footprints," or combinations of mutation types termed "signatures." Over twenty mutational signatures have been described to date[76]. Cutaneous melanoma mutational spectra are most highly enriched in Signature 7, which is associated with ultraviolet radiation and a predominance of cytosine to thymine transitions. These C to T transitions are driven predominantly by photodimer creation through direct UV exposure or by indirect DNA damage from UV radiation[20,77]. The mutational signatures in NACM are entirely distinct from the non-ultraviolet radiation associated signatures found in acral and mucosal melanomas. Of the nine signatures characteristic of ACM and MuM, signature 1 (associated with increased patient age) and signature 5 (unknown etiology) are the most common, which is fitting given these tumors arise in infrequently sun-exposed areas. These observations reflect how differing levels of UV carcinogen exposure result in profound genomic delineation of these melanoma subtypes.

Structural variants

Structural variants include copy number variants (CNVs), amplifications, duplications, deletions, and fold-back inversions involving DNA regions of 1 kb or longer[78,79], and provides another dimension to tumor genetic diversity. Candidate CNV discovery and genotyping has already identified important genetic links to several complex disorders such as psoriasis and Crohn's disease[79].

The four genomic subtypes of NACM exhibit preferential gene amplifications. *BRAF* and *MITF* gene amplifications are more characteristic of the *BRAF*-mutant subtype, while the triple wild-type subtype frequently reveals *KIT* oncogene 4p12 focal amplification. The triple wild-type subtype also has significantly more copy-number segments overall than *BRAF*, *NRAS*, and *NF1* types. ACM and MuM both exhibit a higher frequency of chromosomal aberrations and CNVs compared to NACM[20,80]. ACM and MuM also are both more likely to show higher copy number alterations in *CDK4* and lower copy number alterations in *CDKN2A* and *PTEN*[80]. ACM reveal copy number gains in *TERT* in approximately one-fourth of cases[81]. KIT copy number gains or amplifications are also common in both ACM and MuM, observed in approximately one-fourth of cases of each tumor[82].

Gene expression profiling

The broad analysis of mRNA levels across thousands of known genes has significantly contributed to our understanding of the cellular and molecular mechanisms underlying melanoma development[83]. An early gene expression profiling (GEP) analysis of metastatic melanoma revealed 4 molecular subclasses (high immune, pigmentation, proliferative and normal-like) with the proliferative subclass having the worst outcome[84]. This 4-class categorization and prognostic association have since been validated in primary melanomas[85]. In TCGA melanoma specimens, GEP revealed 3 molecular subclasses of melanoma (keratin, *MITF*-low, and immune gene expression classes)[6]. Some metastatic melanomas show keratin class expression patterns with increased expression of keratins, kallikreins, and other genes of the epidermis. The *MITF*-low subclass, in contrast, is characterized by low expression of epithelial expression and pigmentation genes, as well as genes responsible for immuno-modulation, adhesion, and migration. The immune class is characterized by a high expression of immune signaling molecules, checkpoint proteins, and cytokines. This subset of melanoma patients presents with tumors containing an inflammatory infiltrate of T-lymphocytes and cytokines. Patients who develop tumors with the molecular expression pattern of the immune class show improved survival compared to keratin and *MITF*-low subclasses[6,86]. Given the expanding armamentarium and widespread use of immunotherapy,

melanomas with immune and non-immune gene expression signatures may be expected to show different responses to such immunotherapeutic agents.

UMs separate into two distinct classes upon GEP[87]. Class 1 uveal melanomas exhibit low-grade behavior, a low metastatic risk, and overall good prognosis[88]. In contrast, class 2 tumors show high-grade behavior and worse prognosis overall, with a 72% 5-year metastatic risk. Class 2 tumors are associated with loss-of-function *BAP1* mutations, which impart additional loss of tumor suppressive function and increased aggressive tumor behavior. The advancements in our understanding of GEP of UM has resulted in the development of a commercially available 15-gene FDA-approved qPCR-based assay to risk stratify patients according to class 1 and class 2 uveal melanoma tumor status[89]. The role of prognostic GEP for NACM is currently being explored, and further validation may help establish new guidelines for clinical risk-stratification with GEP[90,91].

Pan-cancer analyses

Thanks to the collaborative efforts and remarkably impactful initial results of TCGA, dozens of further studies have been published using the entire dataset of 33 cancer types and 1,1000 tumor samples that TCGA initially investigated[92]. These pan-cancer analyses, which utilize data across cancer types, are unique in that they contextualize melanoma among a comprehensive cancer panel. They have confirmed previously known findings about melanoma and are unveiling novel connections between genomics, immunology, molecular biology, and clinical outcomes in all 33 cancer types[93-96]. In their recent analysis of TCGA data, Bailey *et al*.[93] confirmed that UM and NACM have diametrically-opposed genetic features, even when considered amongst the larger cohort of tumor samples. By demonstrating that NACM harbors one of the largest amounts of overall mutations and UV signature mutations in the cohort, and UM one of the lowest, these results have helped to characterize the magnitude of the genetic differences among melanocytic tumors. In our pursuit of targeted treatments for uveal melanoma, perhaps we should focus elsewhere than simply on what is already known about cutaneous melanoma's molecular machinery. Pan-cancer analyses that evaluate cancer genomics as a whole, identifying shared features amongst cancer types, may be able to bridge the gap between UM's genomic foundations and its relatively grim prognosis.

CONCLUSION

Our current collective knowledge of melanoma's genetic landscape has already yielded significant clinical impact, dramatically altering the prognostic course for countless melanoma patients, and this knowledge will continue to expand in the coming years. Despite this progress, very few actionable discoveries have been made of targeted therapeutic strategies for the roughly half of patients whose melanomas are driven by mutations other than *BRAF*. Each melanoma subtype offers a unique set of therapeutic targets, only some of which have proven fruitful. New genes will continue to be identified, and in turn, chosen as possible therapeutic targets. Regardless, we will, unfortunately, continue to face a lack of universally-applicable treatments for metastatic melanoma. Melanoma genomics and the use of immune-mediated treatments provide one possible solution, but there remains much to be discovered.

DECLARATIONS

Authors' contributions
Design: Shaughnessy M
Literature research: Shaughnessy M
Manuscript writing, editing, revision: Shaughnessy M, Klebanov N, Tsao H

Availability of data and materials
Not applicable.

Conflicts of interest
All authors declared that there were no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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