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Translational pathology, genomics and the development of systemic therapies for acral melanoma

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Abstract

Acral melanomas arise on the non-hair bearing skin of the palms, soles and in the nail beds. These rare tumors comprise 2–3 % of all melanomas, are not linked to UV-exposure, and represent the most frequent subtype of melanomas in patients of Asian, African and Hispanic origin. Although recent work has revealed candidate molecular events that underlie acral melanoma development, this knowledge is not yet been translated into efficacious local, regional, or systemic therapies. In the current review, we describe the clinical characteristics of acral melanoma and outline the genetic basis of acral melanoma development. Further discussion is given to the current status of systemic therapy for acral melanoma with a focus on ongoing developments in both immunotherapy and targeted therapy for the treatment of advanced disease.

Keywords

Acral melanoma; Translational genomics; Systemic therapies

1. Introduction

The past 8 years have seen remarkable breakthroughs in the development of novel therapies for cutaneous melanoma. The observation that 50 % of all cutaneous melanomas harbor activating mutations in the serine-threonine kinase *BRAF* led to the clinical development of BRAF inhibitors and then the BRAF-MEK inhibitor combinations. The BRAF-MEK inhibitor combination can deliver durable responses in patients whose melanomas harbor BRAF mutations and is associated with a 5-year survival rate of ~33 % [1]. At the same time, immunotherapy approaches such as the immune checkpoint inhibitors (including anti-

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Declaration of Competing Interest

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CTLA-4 and anti-PD-1) have also proven effective in the clinic and are associated with durable responses in ~30 % of patients [2].

However, considerably less progress has been made in the management of the rare subtypes of melanoma. Acral melanoma is a little-studied subtype of melanoma that arises on the non-hair-bearing skin of the palms, soles and in the nail beds (subungual). Acral melanomas comprise 2–3 % of all melanoma cases, are not linked to UV-exposure and tend to be the most frequent subtype of melanomas in patients of Asian, African and Hispanic origin. Acral melanoma has a worse prognosis than cutaneous melanoma and is associated with lower rates of overall survival. Melanomas that develop on acral skin sites are distinct from cutaneous melanomas in having lower mutational burdens and different oncogenic drivers, including lower frequencies of *BRAF* mutations (10–23 %), variable *KIT* mutation rates (3–29 %), amplification of *CCND1* and *CDK4* and deletion/mutations in *CDK2NA*, *PTEN*, *NF1* and hTERT (Table 1). Laboratory models of acral melanoma are lacking, which hinders the development of new treatments. At this time, no therapies are FDA-approved specifically for acral melanoma, and the drugs that have recently been approved to treat advanced cutaneous melanoma work less well, or not at all, for most patients with acral melanoma. Additional research is urgently needed in this area to develop novel therapies for patients with advanced acral melanoma. Here, we discuss the latest basic and clinical research findings on acral melanoma. We begin by focusing upon the clinical presentation of acral melanoma and the genetic events that underlie the development of acral melanoma. We then describe the signaling pathways and immune landscape of the disease. The most recent data on acral melanoma clinical trials are then discussed and the future directions for the field are outlined.

2. Clinical presentation and etiology of acral melanoma

In 1969, Wallace Clark published his seminal work on the classification of melanoma, based on clinical features and histologic growth patterns of the tumor in the epidermis and underlying dermis [3]. These subtypes of melanoma remain the basis of the current World Health Organization (WHO) classification of melanoma, and while no longer considered prognostically significant, they have more recently been found to be fairly distinct genomically [4]. The original classification recognized three subtypes: superficial spreading, nodular, and lentigo maligna melanoma. In 1977, Arrington and colleagues described a fourth “plantar lentiginous” subtype of melanoma involving acral skin, characterized by a lentiginous epidermal component, common occurrence in black patients, and poor prognosis (Fig. 1A, B) [5]. This nomenclature was later revised to acral lentiginous melanoma; others propose the term acral melanoma in view of the fact that not all lesions actually show the characteristic lentiginous growth pattern [6]. Acral melanoma is defined as melanoma arising on the non-hair-bearing (glabrous) skin of the palms, soles, or subungual regions. In Western populations, it accounts for 2–3 % of all melanomas [7] but is the most common melanoma subtype in Asian, Hispanic, and African populations [7,8]. In East Asian countries such as Taiwan, China, Japan, Korea, Hong Kong, and Singapore, acral melanoma accounts for 50–58 % of all melanomas [9]. Acral melanoma presents at a more advanced stage than other melanoma subtypes: in the largest study using the Surveillance, Epidemiology and End Reports (SEER) database, 62 % were diagnosed at stage II or above,

in contrast to 32 % of cutaneous melanomas. Men are more likely to be diagnosed with tumors > 2.0 mm in depth, and Asian/Pacific Islanders were most likely to present with nodal or distant disease [8].

The etiology of acral melanoma has yet to be fully elucidated, but the anatomic location makes it clear that most cases are not related to sun exposure. Acral melanoma shows a higher number of structural chromosomal changes and a lower number of point mutations than non-acral melanoma, furthering this hypothesis [10]. However, one study showed that a small number of subungual acral melanomas (8.6 %) had significant numbers of UV-associated mutations, suggesting at least a partial relationship to sun exposure [11]. Genomically, a significant proportion of acral melanoma falls into the triple wild type category, with only 38–55 % of tumors having mutations in *BRAF, NRAS*, or *NF1* [12,13]. The genetics underlying the development of acral melanoma will be discussed in more depth in the following sections.

There has long been a suspicion that acral melanoma development, particularly on the foot, is linked to mechanical injury. Earlier studies reported that weight bearing areas of the soles, had higher incidence of acral melanoma than other areas of the soles [14,15]. Anatomical mapping of plantar acral melanoma demonstrates a higher incidence on the weight-bearing portions such as the sole and inner forefoot, with the long axis parallel to the creases of skin, raising the possibility that mechanical or physical stress may play a possible etiologic role [16]. The findings of more acral melanomas are found in the weight-bearing areas than the none-weight bearing areas are also supported by a retrospective study conducted in Taiwan with 153 acral melanomas [17], but disputed by a study conducted at Mayo Clinics [18]. Although there are different findings on whether more acral melanomas are found in the weight-bearing areas between studies, a shared observation across multiple studies, including the Mayo study [18], is that more acral melanomas are observed in the heel than other areas of the plantar surface of the foot [16–19].

The majority (~78 %) of acral melanoma arises in the lower extremities, with the remainder on the upper limb. Of these, the subungual region is the site of origin in 20–37 % of cases [20], with the great toe most frequently involved, followed by the thumb [21]. There is a similar incidence and distribution of lesions in males and females [8]. Patients with acral melanoma present at an older age than other subtypes, with a mean age of 63 years [8]. This subtype of melanoma presents as a darkly pigmented plaque or nodule, and tumors are frequently ulcerated at the time of diagnosis [5]. There is typically a long radial growth phase, characterized by a black patch that expands for months to years before the development of a nodular component indicating invasive tumor [22]. However, some lesions present as non-pigmented nodules; these are frequently misdiagnosed as benign conditions such as callus, tinea pedis, ingrown toenail or verruca [23]. Subungual melanoma often presents as longitudinal melanonychia, with multiple brown to black pigmented nail lines of irregular thickness. Extension of the pigment beyond the proximal nail fold or hyponychium, which is described as Hutchinson’s sign, is a helpful clinical clue [24]. Dermoscopy is helpful in identifying the parallel ridge pattern of bands of brown/black pigment on the ridges of the skin, as opposed to pigmentation occurring within the furrows, as it does with benign acral nevi [25].

The key pathologic feature of acral melanoma is a broad, intraepidermal growth of single melanocytes that only focally coalesce into nests, which is characteristic of the lentiginous growth pattern. Lesional melanocytes are often dendritic in shape, with perinuclear halos, and may show pagetoid involvement of the acral epidermis (Fig. 1C) [26]. There is often prominent extension of melanoma *in situ* within eccrine epithelium. Invasive acral melanoma may be of epithelioid or spindle morphology (Fig. 1D). A subset of acral melanomas displays a superficial spreading pattern of growth, characterized by mostly nested growth of the junctional component and prominent pagetoid spread. The invasive component of acral melanoma is notorious for exhibiting divergent ("heterologous") differentiation, particularly osteocartilaginous; this may lead to diagnostic challenges, especially in metastatic lesions from an acral primary that only demonstrate the heterologous component [27,28]. It is interesting that the phenomenon of divergent differentiation is most common in the two melanoma subtypes that arise from non-sun-exposed skin: acral and mucosal melanoma. When tumors present with dermal invasion, diagnosis of acral melanoma is not a particular diagnostic challenge. However, early lesions may be subtle and difficult to distinguish from acral nevi [26]. Immunohistochemical staining is frequently employed to confirm the diagnosis in early lesions. Acral melanoma shows staining for the most commonly employed melanoma markers, including S-100 (95 %), SOX10 (100 %), Melan-A (70 %), and HMB-45 (80 %) [29,30]. However, S-100 negative acral melanomas have been reported, and this marker alone should not be relied on to establish the diagnosis [31].

3. Genetics and signaling in acral melanoma: the MAPK pathway

One defining characteristic of the vast majority of melanomas is constitutive activation of the mitogen activated protein kinase (MAPK) signaling pathway [32], which most frequently results from mutations in components of the signaling pathway. The most frequent of these are activating mutations in the serine-threonine kinase, BRAF, which occurs in up to 50 % of cases of cutaneous melanoma [33]. Acquisition of *BRAF* mutations, which are most common at position 600 (V600E, V600 K, V600D and V600R) leads to the stabilization of the kinase in the active state, and stimulation of the MAPK pathway [34,35]. Another major oncogene in cutaneous melanoma is *NRAS*, which is mutated in 15–20 % of cases [36]. These mutations which in melanoma most frequently occur in the GTP binding site at Glutamine 61, result in inactivation of the intrinsic GTPase activity without turning itself off so that the RAS protein remains in the "On" position. Other mutations associated with constitutive MAPK activation in melanoma include inactivating mutations in the tumor suppressor *NF1*, leading to a similar loss of control over RAS/MAPK signaling, and activating mutations in *Rac1* which activates the MAPK pathway through transactivation of PAK1 [37–39]. Once hyperactivated, the MAPK pathway contributes to many aspects of the oncogenic behavior of melanoma cells including uncontrolled proliferation by enhanced Cyclin D1 (CCND1) expression and suppression of p27, cell survival by suppression of pro-apoptotic BIM and upregulation of MCL-1 expression, as well as invasion via regulation of integrins and the actin cytoskeleton [40–42]. MAPK pathway hyperactivation also contributes to immune escape by decreasing the expression of major histocompatibility complex (MHC)-I and increasing the expression levels of immune checkpoint ligands [43].

One of the earliest genetic surveys of acral melanoma compared a cohort of melanomas from sun-exposed sites and those from skin with chronic sun exposure, to those from sun-protected sites (including acral and mucosal melanomas) [30]. These studies showed that while the commonly mutated cutaneous melanoma driver genes, *BRAF* and *NRAS*, were also sometimes mutated in acral melanoma, mutation rates were much lower [44,45]. Mutated positions were similar to those observed in cutaneous: *BRAF* V600 and *NRAS* G12, G13, and Q61. *BRAF* and *NRAS* mutations were generally found to be mutually exclusive. Subsequent studies using targeted or whole exome sequencing showed similar patterns: *BRAF* and *NRAS* were mutated at previously observed positions, but at lower frequencies [13,37,46,47]. A recent genetic/transcriptomic study of 34 acral melanomas identified *NRAS* mutations in 12 % of the patients, compared to 15–20 % typically seen in cutaneous melanoma [13]. Three of these patients had a hotspot Q61 K mutation. The frequency of *BRAF* mutations in the same cohort was 18 % with 4 of these being V600E mutations, one G466E mutation and one V600 K mutation. Homozygous loss of NF1, was also identified in 9 % of acral melanoma samples [13]. Other rare mutations in genes that could also potentially activate the MAPK pathway were identified, including those in *EGFR, KRAS, PREX2* and *ERBB3*.

The relatively high abundance of MAPK pathway activating mutations in acral melanoma was supported by immunohistochemical (IHC) studies that examined specific pathway mediators. In a recent acral melanoma sequencing study from Britain, *BRAF* and *NRAS* mutations were identified in 11 % and 12 % of the tested tumors respectively, and 25 % of tested acral melanoma samples were positive for phosphorylated ERK (pERK) [48]. Interestingly, these two mutations were mutually exclusive, and 67 % of samples with high expression levels of pERK had either *BRAF* or *NRAS* mutation [48]. A recent small-scale analysis of 17 primary acral melanomas from a Spanish cohort identified *NRAS* mutations in 17 % of samples [48], and no *BRAF* mutations [49]. This work additionally identified copy number gains in other RAS-associated genes including *CCND1, TERT*, and *NRAS*, indicating that RAS pathway activation occurred in 87.5 % of samples [49]. Another cohort of Swedish patients (n = 88) with primary acral melanoma reported the mutational rates of *KIT, BRAF* and *NRAS* to be 15 %, 17 % and 15 %, respectively [50]. Similar findings were also reported in a series of 13 primary and 15 metastatic acral melanoma samples from Japan. In this particular cohort, *BRAF/NRAS* mutations were less common, with one patient harboring an *NRAS* Q61R mutation and 3 samples harboring *BRAF* V600E mutations [51]. Despite the low occurrence rate of these mutations, the MAPK pathway was found to be active (by pERK staining) in 79 % of the samples. *CCND1* was amplified by FISH analysis in 24 % of the tumors. Interestingly, in 2 of the three tumors with negative pERK expression (according to Western Blot) CCND1 amplification was observed, suggesting that increasing the *CCND1* gene dosage may have effects similar to pERK in cell growth [51]. In a Taiwanese study, 7 % of samples harbored mutations in the *MEK1* gene, in addition to the presence of *BRAF* and *NRAS* mutations [52]. A study of 88 acral melanoma cases from Korea reported *BRAF* mutation rates to be 34 %, *NRAS* mutation rates to be 22 %, GNAQ to be 17 %, *NF1* to be 17 % and *KIT* to be 11 % [47]. A study from Brazil reported on the staining of 16 primary acral melanomas and identified high expression levels of multiple components of the MAPK pathway including MEK2 and ERK1/2 [53].

Finally, whole genome sequencing studies have also investigated acral melanomas and provided similar findings to those described above [12,54]. Across different studies, *BRAF* has been found to be mutated in ~20 % of acral tumors and *NRAS* in ~10 %. Although not observed in all studies, other mutated genes included *NF1*, MEK1 and MEK2. In addition, *TERT* promoter mutations were observed in 5–10 %, which is much lower than in cutaneous melanoma. Overall mutation rates are lower in acral melanomas than in sun-exposed cutaneous melanomas. Sequencing studies analyzing the whole exome or whole genome were able to demonstrate decreased rates of specific ultraviolet radiation (UV)-associated signatures and identified other mutation signatures not usually present in cutaneous melanoma [12,13,54]. These findings confirm clinical and pathological observations that the etiology of acral melanoma is distinct from that of cutaneous melanoma. However, as common genes are mutated in both malignancies, it is possible that similarities exist in the molecular events that underlie both acral melanoma and cutaneous melanoma development.

4. Genetics and signaling in acral melanoma: the PI3K/AKT/PTEN signaling pathway

Another core signaling pathway in the development of cutaneous melanoma is the PI3K/AKT/PTEN pathway [55]. Activation of AKT signaling is thought to be important during early melanoma development, where PTEN loss or silencing may allow nascent melanoma cells to escape oncogene-induced senescence following the acquisition of a *BRAF* mutation [56]. As melanoma progresses, the PI3K/AKT pathway is known to be important for cell survival, resisting anoikis, and for the regulation of cellular metabolism [57]. There are multiple mechanisms through which PI3K/AKT pathway activation can occur, including increased receptor tyrosine kinase activation, loss of the PTEN tumor suppressor, and increased expression of AKT3 [57,58]. Activating mutations in AKT and PIK3CA occur infrequently in cutaneous melanoma. Immunohistochemical studies have identified alterations of the PI3K/AKT/PTEN pathway in acral melanoma. Some loss of PTEN expression, assessed by IHC staining, was observed in the majority of acral nevi, with levels of phosphorylated AKT (pAKT) increasing during progression from nevi through dysplastic nevi to advanced acral melanoma [59]. A mutational analysis of a cohort of Swedish patients with acral melanoma revealed a small subset of patients with mutations in PTEN [50]. In the aforementioned British study, almost 90 % of lesions showed expression of activated AKT, further supporting a role for the PI3K/AKT pathway in acral melanoma development [48].

Another pathway known to be frequently activated in melanoma is the JAK/STAT3 pathway with multiple studies implicating it in melanoma cell survival [60]. An IHC analysis of acral melanoma revealed increased S727 phosphorylation of STAT3 in more invasive acral melanoma samples compared to less advanced *in situ* acral melanoma samples [61]. The evidence to date suggests that although acral melanomas have fewer UV-signature mutations and different mutational profiles, they may rely upon similar signaling pathways as cutaneous melanomas. Integrated transcriptomic analysis showed that the major pathways associated with acral melanoma were the MAPK and PI3K/AKT pathways (in 66 % of

samples), TERT (37 % of cases), CDK4/CDKN2A (altered in 51 % of cases) and MDM2/TP53 (changes in 17 % of samples) [13].

5. Landscape of copy number alterations in acral melanoma

In addition to point mutations and small insertions, large chromosomal rearrangements and copy number variations also drive melanoma formation and progression. Early studies, using array comparative genomic hybridization, looked at the patterns of DNA copy number aberration across 102 primary melanomas (including those associated with chronic sun damage, as well as 28 acral melanomas). Among the melanomas without chronic sun damage, a narrow-amplified band at 4q12 was noted, with *KIT* being identified as one of the major genes [62]. Subsequent investigation revealed that oncogenic *KIT* mutations were found in 3 out of 7 samples with genomic amplification and that 36 % of acral melanoma samples had either mutations or copy number gains in *KIT*. In the majority of cases, *KIT* amplification was also associated with increased KIT protein expression [62]. A number of other common copy number alterations have been identified in acral melanomas. *CCND1* and *CDK4* are frequently amplified and *CDKN2A* is frequently lost [12,13,37,44,46]. Interestingly, these common copy number changes in cell cycle genes were seen more often in acral tumors lacking *BRAF* or *NRAS* mutations. Recurrent amplifications have been seen by some studies in *PAK1, RICTOR, CLTPM1L, KIT, BRAF, YAP1,* and *EP300. PAK1* was also observed to be part of gene fusion events [12], but the functional impact of its alteration is not yet clear. However, *RAC1*, which targets *PAK1*, is recurrently mutated in cutaneous melanoma at P29S [37], suggesting another potential common pathway. Although *TERT* may not be mutated as frequently as in cutaneous melanoma, it is often amplified in acral melanomas [12,13,46] suggesting it is an important contributor to acral melanoma development. Unlike cutaneous melanoma, *TP53* is not frequently mutated in acral melanoma, but copy number loss has been observed [12]. Interestingly, *MDM2* is located on the same chromosome arm as *CDK4* (~11 Mb downstream) and they are often amplified together. Disruption of the TP53 pathway as a whole was observed in 39.3 % of acral melanomas [46], suggesting alternate mechanisms for *TP53* inactivation. Overall, acral melanomas exhibit a higher frequency of copy number alterations covering a higher proportion of the genome compared to cutaneous melanomas. Whole genome studies have identified several breakage-fusion-bridge events and chromothripsis, a phenomenon that up to thousands of clusters of chromosomal rearrangement occur in a single event in confined genomics region [12,13]. This further highlighting chromosomal instability as a driving event in acral melanoma. One additional interesting feature of acral melanoma is the observation that the identified genomic aberrations are not confined to the tumor cells and may also be found in other surrounding cells, a.k.a. “the field effect”. As one example, it has been reported that the cell cycle driver, *CCND1*, is frequently amplified in the histologically normal cells that surround primary acral melanoma lesions. These *CCND1* aberration-carrying melanocytes can be detected as far as 3 mm from the identifiable margin of the original tumor, with these “field cells” being detected in 80 % of cases [63,64].

6. The immune landscape of acral melanoma

Melanoma is one of the most immunogenic tumors, and its micro-environment is often rich in infiltrating immune cells. During tumor development, immunoediting (e.g. eradicating melanoma cells that are recognized by the immune system) occurs, and selects for populations of tumor cells that can either evade or inactivate the innate immune response [65]. Over time, the immune system becomes unable to efficiently recognize the melanoma cells, a process linked to T cell exhaustion, decreased antigen presentation (following downregulation of MHC proteins on the tumor cells), and the accumulation of immune cells that negatively regulate the immune response. Multiple inhibitory immune populations including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and tissue-associated macrophages (TAMs) have been described, all of which serve to suppress cytotoxic T cell activity and melanoma cell killing [66].

Targeting these inhibitory processes, and restoring CD8 + T cell activity is the cornerstone of immunotherapy and one of the most exciting recent developments in systemic melanoma therapy [67]. These strategies, which use therapeutic antibodies to block inhibitory immune checkpoints, enable tumor-reactive T cells to overcome negative regulation, allowing them to mount effective anti-tumor responses [67]. The first immune checkpoint inhibitor to be FDA-approved was against CTLA-4, the major regulator of T cell function (which suppresses the function of T cell receptor (TCR)). In the single agent setting, the anti-CTLA-4 antibody, ipilimumab, led to durable responses in a minority of melanoma patients (~10 %) [68]. Another strategy has been the targeting of PD-1, a receptor that maintains peripheral immune tolerance by fine-tuning T cell responses through interaction with its ligands, PD-L1 and PD-L2 [67]. In the clinic, anti-PD-1 therapy has proven to be effective in >30 % of patients with advanced cutaneous melanoma, irrespective of tumor genotype [2]. In some cases, the anti-PD-1 and CTLA-4 antibodies have been used in combination, leading to improved response rates (60 %) often at the cost of increased toxicity (grade 3/4 toxicity in 59 % of patients) [69]. At this time, reliable predictive biomarkers of immune therapy response are lacking. There is however some suggestion that the likelihood of immunotherapy response is linked to tumor neoantigen load, and that increased mutational burden may be predictive of response [70]. With this biomarker in mind, it is likely that acral melanoma, with its lower mutational burden, may show a reduced rate of response to immunotherapy.

To date, there have been very few attempts to characterize the immune environment of acral melanoma. One recent study that did include acral melanoma samples reported on the expression of the PD-1 ligand, PD-L1, across multiple subtypes of melanoma (n = 200 total: with 16 acral melanomas). It was found that patients with acral melanoma had lower levels of PD-L1 expression than other melanoma subtypes: 33 % of acral melanomas were positive for PD-L1 expression as compared with 44 % of mucosal melanomas and 62 % of the sun-damaged melanomas [71]. Another study reported on the level of tumor-infiltrating lymphocytes (TIL) in a cohort of 148 surgical samples of acral melanomas [72]. It was found that a higher density of CD3 + TIL was associated with male gender, thinner Breslow thickness, negative lymph node, earlier disease stage, and p16 nuclear protein expression (> 10 % stained by IHC). It was further noted that an age younger than 66, female gender,

Breslow thickness less than 6.0 mm, negative lymph nodes and stages I–II were associated with longer survival. Positive staining for nuclear p16, also known as cyclin-dependent kinase inhibitor 2A, (> 10 % stained by IHC) was strongly associated with longer survival. The composition of the immune infiltrate associated with the acral melanoma was further evaluated in a subset of 43 cases. The most frequent inflammatory cells observed were CD163+ histiocytes (median = 18.4 %), CD3 + T lymphocytes (median = 18 %), CD68+ histiocytes (median = 16.9 %), cytotoxic CD8 + T lymphocytes (median = 8.5 %), CD4+ cells (median = 7.6 %) and, CD20 + B lymphocytes (median = 2 %). CD163 and CD68 were used to identify macrophages [73]. The reported association between low p16 protein expression, low density of CD3+, CD8 + TIL and poor clinical outcomes suggest potential interaction between the tumor suppressor gene and the immune systems. A retrospective immunohistochemical Japanese study of 96 acral melanoma patients indicated that nuclear factor κB (NF-κB) was associated with melanoma invasion depth, and negatively associated with CD8 + T Cells [74]. It was further shown that PD-L1 negative patients (< 5 % staining) had higher invasion depth and that the presence of CD8 + T cells (cell number ≥ 25) was negatively associated with invasion depth. After adjusting for PD-L1 status and CD8 + T cells in a multivariable model, NF-κB was still found to be associated with invasion depth with statistical significance while other tested covariates were not. The results suggested that NF-κB, a transcription factor that stimulates expression of various inflammation and immune function genes, might play an important role in progression and metastases [74]. Inflammatory responses are crucial to cancer prognosis and patient response in general. Baseline peripheral blood samples from a study of 226 treatment-naïve acral melanoma patients were used to develop immune-related biomarkers to predict their clinical outcome after interferon alpha-2b (IFN-α−2b) therapy [75]. It found that acral melanoma patients with high lactate dehydrogenase (LDH), neutrophil-to-lymphocyte ratio (NLR ≥ 2.35), platelet-to-lymphocyte ratio (≥129), systemic immune-inflammation index (SII) (≥615 × 10^9/L), had poor relapse-free survival (RFS) and overall survival (OS) outcomes [75]. SII is calculated as (platelet count × neutrophil count)/lymphocyte count. In the multivariable analyses, SII was associated with RFS (HR = 1.67, 95 % CI: 1.07–2.59) and OS (HR = 2.07, 95 %CI: 1.20–3.56). Based on the idea of balancing activated T cells and opposing immune inflammatory responses, a novel prognostic index - the circulating T-cell immune index (CTII) – was developed. This value was defined as: cytotoxic T lymphocytes/(CD4 + regulatory T cells × CD8 + regulatory T cells). The CTII was associated with OS (HR = 1.73, 95 % CI: 1.01–2.94) in univariable analysis. A few earlier studies also showed that pretreatment neutrophil-lymphocyte ratio, neutrophil counts, and lymphocyte counts in melanoma patients are prognostic markers [76,77]. The observation that higher NLR ratio independently predicts worse OS and RFS outcomes is also reported by a recent comprehensive clinical characterization of a cohort of 152 Asian melanoma patients. In the cohort, more than a third of those were 58 acral melanoma patients [78]. Some of these measures are easily obtained during routine laboratory tests in clinics and could be a simple and low-cost biomarker for surveillance purposes.

7. Clinical management of acral melanoma

At this time, systemic therapy options for advanced or metastatic acral melanoma are similar to those for advanced cutaneous melanoma. Typically, anti-PD-1 immunotherapies are utilized for first-line treatment, as nivolumab and pembrolizumab are both FDA-approved for cutaneous melanoma, and the combination of nivolumab with the anti-CTLA4 antibody, ipilimumab, also remains an option [69]. Both the combination and ipilimumab monotherapy are also a possibility if patients have disease progression with anti-PD-1 monotherapy. The efficacy of anti-PD-1 therapy, specifically in acral melanoma, was analyzed in a retrospective analysis of US centers that included 25 patients with acral melanoma treated with nivolumab or pembrolizumab; an overall response rate (ORR) of 32 % was reported, similar to reported rates with melanoma in general [79]. With a median follow up of 20 months, however, the progression free survival (PFS) of 4.1 months was lower than generally observed at 6–7 months in advanced melanoma. In a more recent retrospective review of 193 acral melanoma patients treated with pembrolizumab or nivolumab in Japanese centers, ORR was only 16.5 %, with worse outcomes in patients with subungual melanoma as compared to palm/sole melanomas [80]. A recent Chinese phase I trial explored anti-PD-1 therapy (toripalimab) in 22 patients with acral or mucosal melanomas, with a response rate of 18.2 % [81]. Considering the aforementioned evidence showing the number of tumor-infiltrating lymphocytes (TILs) to be lower in acral vs. cutaneous melanomas [82], lower PD-L1 expression in acral melanoma than other melanoma subtypes [71], and a lower somatic mutation rate in acral melanoma [54], it is possible these factors may play a role in the somewhat lower ORR and shorter progression-free survival (PFS) observed in acral melanomas. There are ongoing clinical trials exploring immunotherapy in advanced acral lentiginous melanoma, such as a biomarker study of the ipilimumab + nivolumab combination in these patients (NCT02978443). In the adjuvant post-surgery setting, nivolumab or pembrolizumab monotherapy up to a year is FDA-approved following surgical resection of stage 3 or 4 melanoma, and patients with acral melanoma are offered this treatment as well. In the recent phase II CheckMate 172 trial, a total of 1008 patients with rare melanoma subtypes were treated with Nivolumab after progression on Ipilimumab [83]. Among these patients, 723 were non-acral cutaneous melanomas, 55 were acral melanoma patients, 103 were ocular melanoma and 63 were mucosal melanomas. No differences were observed in the incidence of grade 3 treatment-related AEs among melanoma subtypes or compared with the total population. At a minimum follow-up of 18 months, for non-acral cutaneous melanoma and acral cutaneous melanoma, the median overall survival was comparable (at 25.3 and 25.8 months, respectively) with comparable 18-month overall survival rates (of 57.5 % and 59.0 %, respectively), whereas those with ocular and mucosal melanoma had worse survival outcome [83].

Identifying biomarkers associated with patients' response to immune checkpoint inhibitors has been a major focus of cancer research in general. In a recent study of 32 Japanese melanoma patients (with the breakdown of 15 acral and 17 mucosal melanomas in the cohort), it was found that IDO expression level in the tumors was associated with better response to anti-PD-1 therapy while IDO expression in peritumoral inflammatory

mononuclear cells was not associated with the response [84]. In addition, positive IDO expression in tumors was significantly associated with better PFS while positive PD-L1 expression level (≥5 % staining) had similar trend without statistical significance (p = 0.21). Furthermore, in the multivariable Cox regression model after adjusting for LDH and ECOG performance status, lower IDO expression was still significantly associated with poor PFS outcome.

The discovery of activating *BRAF* mutations in the majority of cutaneous melanomas led to the development of BRAF-specific inhibitors, including vemurafenib, dabrafenib and encorafenib [85]. In preclinical models, inhibition of BRAF led to growth arrest, apoptosis induction, and the regression of melanoma xenografts [86,87]. In the clinic, the BRAF inhibitors had impressive single-agent activity, followed by the onset of resistance after progression-free survival of ~6 months. Correlative and lab-based studies demonstrated that recovery of signaling through the MAPK pathway was the major mechanism of therapeutic escape from BRAF inhibitor targeted therapy [34,88–91]. The use of BRAF inhibitor monotherapy was quickly superseded by the development of BRAF-MEK inhibitor combinations (vemurafenib-cobimetinib, dabrafenib-trametinib, encorafenib-binimetinib), which were more effective at suppressing MAPK activity and led to markedly improved clinical responses [92,93].

With this trend in mind, BRAF targeted therapy has also been evaluated in patients with *BRAF*-mutant acral melanoma. There is evidence that BRAF inhibitor monotherapy has similar activity in *BRAF*-mutant acral melanoma to that seen in cutaneous melanoma, with a recent report of 13 Chinese BRAF-mutant acral melanoma patients treated with vemurafenib reporting an overall response rate of 61.5 % with a PFS of 5.4 months [94]. In a cohort of 27 Korean patients with *BRAF*-mutant acral melanoma, treatment with dabrafenib-trametinib combination therapy (n = 11) or vemurafenib monotherapy (n = 16) led to a response rate of 79 % with a PFS of 9.2 months [95].These findings, and the observed improved durations of response to the BRAF-MEK inhibitor combination, matched those seen in *BRAF*-mutant cutaneous melanoma.

The observation that acral melanomas frequently harbor mutations and amplifications in the CDK4/CCND1 axis has suggested the possibility of using CDK4/6 inhibitors, which are already FDA-approved for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer in women who no longer benefit from endocrine therapy. A recent phase II trial applied palbociclib, a CDK4/6 inhibitor, in advanced acral melanoma patients with CDK pathway gene aberration (CDK4 or/and CCND1 amplification or/and CDKN2A loss). In the preliminary findings presented, three of 15 patients achieved tumor shrinkage at 8 weeks, including one with a confirmed partial response, with median PFS of 2.5 months [96]. There is a completed trial of a CDK inhibitor, dinaciclib, in advanced melanoma, including acral melanoma, with results still pending (NCT00937937).

The enrichment of *KIT* mutations in acral melanoma relative to other subtypes led to several clinical trials of targeted inhibition of this molecular. *KIT* molecular testing of tumor can be considered in patients with acral melanoma, particularly in patients refractory to frontline immunotherapy. Common *KIT* mutations are usually included in next generation sequencing

assays as well. Imatinib has been shown to induce apoptosis in melanoma cells with activating *KIT* mutations, and small molecular inhibitors like imatinib, nilotinib, and dasatinib that inhibit KIT and other tyrosine kinases, have been tested in trials of *KIT*-mutant or *KIT*-amplified melanoma [97,98]. In a study of 25 patients with predominantly mucosal or acral (n = 6) advanced melanoma, response rates were 29 %, with a higher benefit seen in *KIT*-mutated *vs KIT* amplified tumors [99]. In a phase II study of 42 patients with advanced *KIT*-mutant melanoma (20 with acral subtype), ORR of 26.2 % was observed, with median PFS of 4.2 months [100]. Ten of the 11 responding patients had exon 11 mutations, four of which with an L576 P mutation. In a smaller phase II study in 20 patients (4 acral) with advanced *KIT*-mutant melanoma, the response rate was 15.8 %, including in two patients with prior imatinib resistance [101]. In the first stage of a phase II trial of dasatinib in advanced melanoma (E2607), the response rate was only 5.9 % in 51 evaluable patients (13 with acral, 1 *KIT*-mutant acral melanoma). In the second stage with only *KIT*-mutant melanoma patients, 4 of 22 (18.2 %) patients (8 acral) had a partial response, while median PFS for all patients was only 2.1 months [102]. Thus, while initial enthusiasm for *KIT* inhibition has waned, it still may be considered in acral melanoma patients refractory to standard therapy.

8. Future perspectives

Acral melanoma is a rare subtype of melanoma that remains understudied. At present, the therapeutic strategies used to manage advanced acral melanoma are the same as cutaneous melanoma, despite the etiology of the two diseases being quite different. Although there are some signs from clinical studies that BRAF and MEK-inhibitors may be effective in acral melanoma, the majority of acral melanomas lack *BRAF* mutations and are not good candidates for that specific type of targeted therapy. Mutations in *KIT* are also found in only a minority of acral melanomas, and clinical results so far have been modest. It is likely that the further development of targeted therapies for acral melanoma could be a challenge, as many of the mutations identified are not therapeutically tractable. There remains however some potential to target the CDKN2A/CDK4/CCND1 axis through CDK4/6 inhibitors, and the results of these investigations are still pending.

Important differences also exist in terms of immunotherapy, with acral melanoma patients being less responsive to the immune checkpoint inhibitors than individuals with sun-exposed, cutaneous melanoma. These differences may be a consequence of the lower mutational frequency and therefore a lower neoantigen burden present in acral melanoma. Novel approaches to immunotherapy and targeted therapy in acral melanoma are urgently needed.

One limitation for the field has been the lack of good experimental tools with which to interrogate acral melanoma. Acral melanoma cell lines are much less numerous than those available for cutaneous melanoma and genetically-engineered mouse (GEM) models of acral melanoma are lacking. Over the past few years there has been some limited progress, with new models such patient-derived xenograft models (PDXs) becoming available for acral melanoma research. A recent effort led by researchers at the University of Pennsylvania and the Wistar Institute has generated 459 patient-derived xenografts (PDX) from 384 melanoma

patients, 15 of these from acral melanomas [103]. Twenty four cell lines were established from these PDXs, with two being from acral melanomas (WM4324: BRAF-V600E; WM4235: NRAS-Q61R). Unfortunately, these models are driven by the most common mutations found in cutaneous melanoma. It is clear that more cell lines and PDXs that represent the spectrum of mutational subtypes of acral melanoma are required in order for progress to be made. Another area of need is better early detection, surveillance strategies, and patient education to ensure that acral melanomas can be identified earlier through improved screening and public awareness. Acral melanomas typically arise on skin sites that are not frequently examined (*e.g.* on the soles of the feet) in populations with lower susceptibility to cutaneous skin damage (who may be therefore less concerned about cutaneous melanoma development). Improved public awareness and education will lead to early detection and surgical excision before metastases develop.

The development of new targeted therapies and immunotherapies for advanced cutaneous melanoma has already led to a 22 % reduction in the mortality rate [104]. This incredible progress has clearly demonstrated that great things can be achieved when strong translational science is supported and novel ideas can move rapidly into the clinic. We remain optimistic that this recent history, and the current research focus on rarer subtypes of melanoma, including acral melanoma, will continue to deliver impressive results for our patients.

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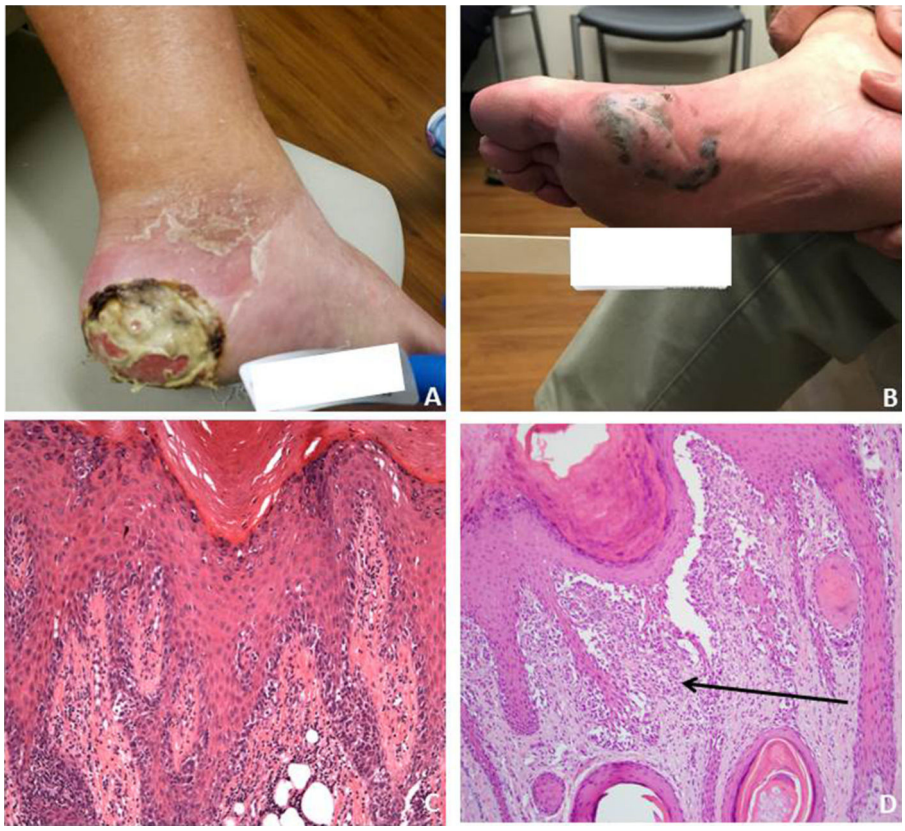

Fig. 1. Clinical Presentation of acral lentiginous melanoma.

A. Acral lentiginous melanoma of heel. Many lesions present as chronic ulcerations; note pigmented periphery which alludes to melanocytic nature of this lesion. **B.** Acral lentiginous melanoma of medial foot, status post incisional biopsy. This lesion demonstrates typical broad size with peripheral macular pigmentation and nodules where invasive tumor resides. **C.** Acral lentiginous melanoma *in situ*, demonstrating lentiginous growth of single, hyperchromatic polygonal melanocytes in confluent fashion within epidermis (H&E, 10x). **D.** Acral lentiginous melanoma with prominent involvement of adnexal structures. Arrow indicates early dermal invasion (H&E, 10x).

Table 1:

Summary of acral melanoma mutation studies.

Study	Year	Sequencing	Target	# Samples	BRAF (%)	NRAS (%)	KIT (%)	TERT promoter 10%)
Curtin [44]	2005	capillary	Targeted[a]	36	23	10	nd	nd
Krauthammer [37]	2012	NGS	WES	17	0	12	29	nd
Furney [54]	2014	NGS	WGS	5	40	0	40	0
Vazquez [45]	2016	capillary	Targeted[b]	61	10	8	21	9
Liang [13]	2017	NGS	WES, long-insert WGS	34	18	12	21	21
Hayward [12]	2017	NGS	WGS	35	23	11	9	10[c]
Yeh [46]	2019	NGS	Targeted (293, 365, or 511 genes)	122	21	28	12	5[d]

[a] Hotspot codon in BRAF, [NKH]RAS.

[b] Hotspot codon in BRAF, NRAS, KIT, PDGFRA, TERT, PDGFRA, TERT.

[c] Proportion estimated from 31 tested cases.

[d] Proportion estimated from 75 tested cases.