Laboratory Investigation (2017) 97, 630–635

PATHOBIOLOGY IN FOCUS

Malignant melanoma of sun-protected sites: a review of clinical, histological, and molecular features

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In most cases of cutaneous melanoma, ultraviolet (UV) radiation is recognized as a prominent risk factor. Less is known regarding the mechanisms of mutagenesis for melanoma arising in sun-protected sites, such as acral and mucosal melanoma. Acral and mucosal melanoma share many common features, including a late age of onset, a broad radial growth phase with prominent lentiginous growth, the presence of field cancerization cells, and, in most cases, lack of a precursor nevus. In addition to early chromosomal instability, many of the same genes are also involved in these two distinct melanoma subtypes. To better understand non-UV-mediated pathogenesis in melanoma, we conducted a joint literature review of clinical, histological, and molecular features in acral and mucosal melanoma. We also reviewed the current literature regarding aberrations in *KIT*, *PDGFRA*, *TERT*, and other commonly involved genes. By comparing common features of these two subtypes, we suggest potential mechanisms underlying acral and/or mucosal melanoma and offer direction for future investigations.

Laboratory Investigation (2017) **97,** 630–635; doi:10.1038/labinvest.2016.147; published online 16 January 2017

INTRODUCTION

Our understanding of melanoma has grown in the last decade to include molecular subtypes, in which different levels of sun exposure lead to distinct sets of genetic changes.[1] In the majority of cases of cutaneous malignant melanoma, chronic or intermittent sun exposure is recognized as a prominent risk factor. In uveal melanoma, the role of ultraviolet (UV) light is more controversial, but likely contributes to at least a subset of cases, as evidenced by UV-signature mutations in *GNAQ* and *RAC1*.[2–4] For melanomas arising in sun-protected sites, including acral and mucosal melanomas, there are presumably other mechanisms that lead to mutagenesis through distinct biological pathways.

Acral lentiginous melanoma (ALM) and mucosal melanoma account for approximately 1.5 and 1.3% of cases of melanoma, respectively. More broadly, 'acral melanoma' serves as an anatomical term for any histologic subtype of melanoma occurring on the palms, soles, or subungual regions. The most common histologic subtype of acral melanoma is the acral lentiginous type, which has a broad radial growth phase with atypical melanocytes filling the basal layer of the epithelium.[5,6] Primary mucosal melanomas arise from any mucosal surface of the body, most commonly the head and neck, anorectum, and vulvovaginal mucosa.[7]

We conducted a joint literature review of clinical, histological, and molecular features in acral and mucosal melanomas. By understanding the common mechanisms underlying these two subtypes of non-ultraviolet-related melanoma, we hope to better our understanding of non-UV-mediated pathogenesis.

CLINICAL

Compared to most cutaneous melanomas, non-cutaneous melanomas have distinct epidemiologic and clinical features. In total, an estimated 76 380 new cases of melanoma will be diagnosed in 2016.[8] This reflects an upward trend, with the number of new cases of cutaneous melanoma increasing by ~1.4% annually over the past decade. In contrast, the incidence of mucosal melanoma has remained stable over this time period.[9]

Overall, cutaneous melanoma is most frequently diagnosed among people age 55–64, with a median age of 63.[8] Incidence rates are higher in women than men before age 44, with a peak difference at age 20–24.[10] By age 65, however, rates in men approximately double those in women.[11] This clinically relevant bimodal distribution suggests a broad age range for patients diagnosed with cutaneous melanoma, such that the development of cutaneous melanoma in patients, particularly

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Received 14 September 2016; revised 22 November 2016; accepted 6 December 2016

women under age 50, is not unusual. This predilection for males later in life is in contrast to mucosal melanomas, which are approximately two times more common in women, and have a median age of onset of 70.[12] Acral melanoma is similarly diagnosed in an older patient population, with most cases presenting in the seventh decade of life, and a female predominance noted in subungual variants.[13,14] Hence, unlike cutaneous melanoma in sun-exposed sites, both of these melanoma subtypes occur relatively infrequently in younger individuals.[12] Though it is well recognized that non-Hispanic whites with a fair complexion are generally at the greatest risk for melanoma, neither acral nor mucosal melanoma has a predilection for a particular racial or ethnic group. In fact, these subtypes represent a disproportionally high percentage of melanomas in blacks, Asians, and Hispanics, owing to the overall low incidence of sun-related melanomas in these groups.[15,16]

HISTOLOGICAL

The most characteristic histologic feature of acral lentiginous and mucosal melanoma is broad lentiginous growth. This refers to a predominantly single-cell pattern of growth of melanocytes along the dermal-epidermal junction with minimal, if any, nests in the early stage.[17] While this is the most common pattern in melanoma from acral sites, other histologic subtypes, including superficial spreading (SSM) and nodular (NM), can arise in these regions. In previous population-based studies, ALM was described in 45–53% of cases, while NM (8–27%) and SSM (20–39%) were relatively less frequent.[18–20] Lentigo maligna melanoma (LMM) is rarely reported, and in a study of 51 plantar malignant melanomas, accounted for 0% of cases.[20] ALM characteristically undergoes irregular horizontal spread during a radial growth phase that lasts ~2–3 years before a vertical growth phase begins.[21] (Figure 1) Clinically, this is supported by the development of broad pigmented patches and an average size of 3 cm at diagnosis.[22]

A broad lentiginous growth pattern is the most common histopathologic pattern in mucosal melanomas as well. In a case series of 55 melanomas arising on a variety of mucosal surfaces (lip, oral cavity, nasal cavity, esophagus, ano-rectal areas, genitourinary areas, and conjunctiva), the authors concluded that lentiginous growth was the prominent pattern for nearly all tumors in the radial growth phase.[17] In a smaller series of 13 mucosal melanomas from similarly diverse anatomic sites, the authors reported more varied histology, including 58% lentiginous, 23% NM, and 15% SSM.[23] A similar distribution was found among 198 melanomas isolated to the vulvar region, in which 57% were lentiginous, 22% NM, 12% unclassified, and 4% SSM.[24] Lentigo maligna melanoma does not occur on sun-protected mucosal surfaces but may occur on the keratinized sun-exposed surface of the lip, although the incidence is not well documented. Hence, the histologic patterns in acral and mucosal melanoma have many similarities. Importantly, both have a significantly lower frequency of SSM than other cutaneous sites, in which SSM is the predominant subtype. We suggest this is related to the degree of UV exposure. While UV plays a prominent role in most cutaneous sites, mucosal sites are nearly 100% UV protected (other than the external lips), and acral sites are highly UV protected by clothing or anatomical positioning away from direct sunlight.

Another similarity between mucosal and acral melanomas is infrequent evidence of a precursor nevus. Precursor nevi are found in association with melanoma in 30–33% of cases overall.[25] Based on current estimates in the literature, we believe that only ~10% of acral or mucosal melanomas arise in association with a precursor nevus. In 55 mucosal melanomas described by Saida *et al.*,[17] no single case demonstrated the presence of an associated nevus in the

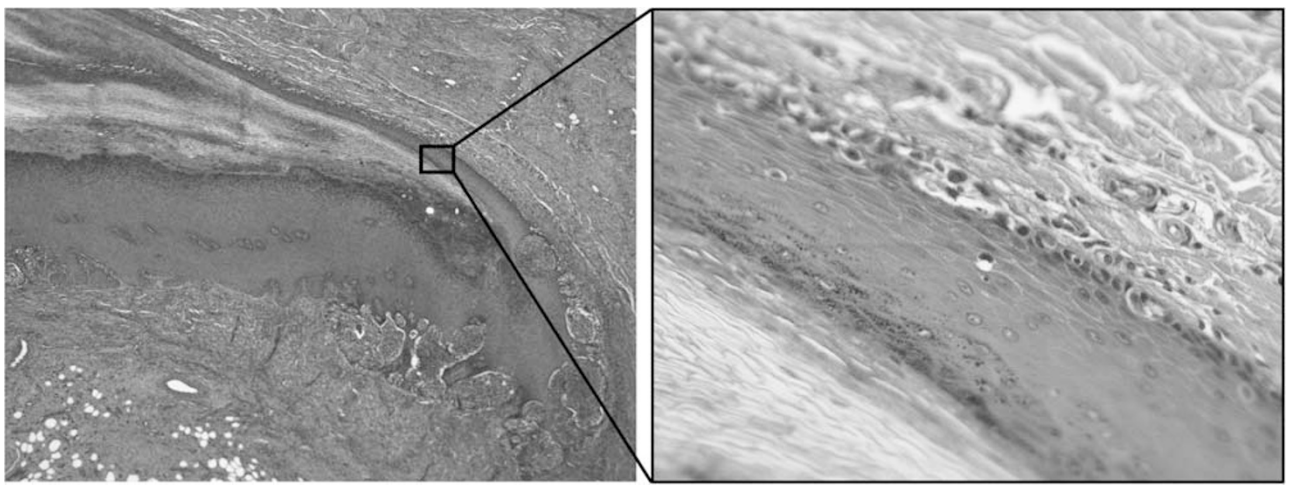

Figure 1 Subungual melanoma. (**a**) Low-power magnification demonstrates bulky melanoma tumor at the nail matrix. (**b**) At higher power, single atypical melanocytes consistent with field cancerization cells are noted in the proximal nail fold, distal from the main tumor mass.

lamina propria or surrounding epithelium. Similarly, in a large series of vulvar melanomas, pre-existing nevi occurred in the minority of cases (11/198). Interestingly, melanomas with a precursor nevus in this study occurred exclusively on hairy, rather than glaborous, skin and were primarily SSM.[24] Acral lentiginous melanoma is similarly thought to evolve primarily *de novo*, as there are few reports of ALM with a pre-existing lesion.[5,26] In a large cohort of 121 acral lentiginous melanomas, remnants of a nevus were found in just 3% of cases.[5] Other reports have suggested pre-existing nevi in 10–13% of ALM.[27,28] Even in studies reporting a higher prevalence of precursor nevi, such as in the series of 112 acral specimens evaluated by Kuchelmeister *et al.*,[29] precursor lesions were relatively less common in those with lentiginous growth patterns (10.4%) compared with SSM (17.6%). As UV-mediated DNA damage is the primary means by which nevi are transformed to melanoma, the relative infrequency of precursor nevi suggests alternate mechanisms of pathogenesis.

MOLECULAR

With recent efforts focused on the molecular characterization of melanomas with varying levels of sun exposure, several genes have been implicated as frequent targets in acral and mucosal melanomas. Mutations in *KIT*, a receptor tyrosine kinase, are estimated to occur in 14% of ALM and 23% of mucosal melanomas.[30–32] Our own group identified *KIT* mutations in 36.4% of melanomas of the female genital tract.[33] These mutations most commonly occur as missense substitutions in the region encoding the juxtamembrane domain, which are thought to promote constituitive activation of KIT and drive several downstream pathways, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase.[32] Additionally, many acral and mucosal melanomas may have focal gains or amplifications of *KIT* that result in increased kinase activity. Copy number gains or amplifications in *KIT* are seen in ~26% of acral and ~25% of mucosal melanomas.[34] In all, it is estimated that activation of KIT has a role in 36% of acral and 39% of mucosal melanomas, which is significantly more frequent than melanomas from intermittently sun-damaged skin of the trunk or extremities.[34]

KIT is an important gene for melanocytic development and migration, as supported by inactivating mutations in developmental disorders, such as piebaldism, that result in congenital amelanotic patches.[35,36] Recently, investigation into the molecular basis for local melanoma spread suggested a migratory advantage in *KIT* mutant melanocytes. This was supported by greater *in vitro* horizontal dispersion of *KIT* mutant cells on human dermis, as well as increased lateral migration of *KIT* mutant cells in a mouse xenograft model of early melanoma.[37] This migratory growth advantage appears to be separate and distinct from increased proliferation.[35,37] Thus, frequent *KIT* alterations in acral and mucosal melanomas may help to explain the clinical and histologic presentation of broad, single-cell lentiginous growth of melanocytes along the dermal-epidermal junction. Furthermore, the presence of a 'field effect,' defined as genetically abnormal cells beyond the histologically remarkable *in situ* event, suggests that KIT pathway activation is an early or initiating event that is followed by additional genetic alterations to form detectable lesions.[38]

Alterations in platelet-derived growth factor receptor α polypeptide (PDGFRA) have also been identified in melanomas from sun-protected sites. PDGFRA is a type III receptor tyrosine kinase. In a variety of cancers, gain-of-function mutations in *PDGFRA* can lead to ligand-independent activation and dysregulation of cell proliferation, differentiation, survival, and tumor progression.[39–42] In a large series of 351 melanomas, Dai *et al.* demonstrated an overall low frequency of *PDGFRA* mutations (4.6%), with a notably higher prevalence in acral (6.8%), mucosal (3.6%), and skin without chronic sun-induced damage (1.8%), compared to melanomas from chronically sun-damaged skin (0%). Mutations in *PDGFRA* were also found to be mutually exclusive with *KIT* mutations, and coincided with *BRAF* and *NRAS* mutations in the minority of cases.[43] Similar to KIT, PDGFRA is thought to play a role in melanocyte migration. The release of platelet-derived growth factor has been postulated as one mechanism by which melanocytes downregulate E-cadherin to 'escape' from epidermal keratinocytes.[44] Presumably, ligand-independent activation of PDGFRA could thus serve as one of the first steps in deregulated melanocyte proliferation.

More recently, mutations in the promoter region of telomerase reverse transcriptase (*TERT*) have been reported in up to 50% of melanomas. *TERT* encodes a subunit of telomerase, the enzyme responsible for elongating the ends of chromosomes to maintain genomic integrity through cycles of replication.[30] The incidence and relevance of *TERT* mutations in ALM and mucosal melanoma are not yet well characterized. Some of the earliest studies in ALM have suggested a relatively low frequency of mutations (8.4%).[30] In mucosal melanomas, studies on *TERT* mutations are limited, but one study found an absence of *TERT* mutations in oral mucosal melanomas (0/39) and a low prevalence among sinonasal malignant melanoma (8%).[45,46] However, copy number gains in *TERT* are among the most common chromosomal aberration in acral melanomas, as they have been found in ~25% of cases.[47] Considering germline and somatic mutations in the *TERT* promoter, in addition to copy number alterations, it is likely that >30% of ALM have increased expression of TERT. While less is known regarding the frequency of *TERT* aberrations in mucosal melanoma, the many similarities between acral and mucosal melanoma would seem to suggest that future analyses will reveal a considerable percentage of cases with *TERT* involvement.

Though significant amplifications and copy number gains in *KIT* and *TERT* have been reported recently, chromosomal instability surrounding Cyclin D1 (CCND1) is most frequently described in acral and mucosal melanomas. CCND1

is the binding partner of CDK4, a serine/threonine kinase and central regulator at the G1-S checkpoint of the cell cycle. The activated CCND1/CDK4 complex promotes progression through the cell cycle by phosphorylation and subsequent inactivation of retinoblastoma protein. Copy number gains and amplifications of *CCND1* are detected in up to 45% of ALM and 10–31% of mucosal melanomas.[47–52] Similar to KIT, these are thought to occur early in the pathogenesis of melanoma, as increases in *CCND1* copy number have been detected beyond the histological margin of melanoma *in situ* in surrounding 'field cells.'[49,53] CCND1/CDK4 is negatively regulated by 1:1 binding with p16, a tumor-suppressor protein encoded by *CDKN2A*. Copy number gains in CDK4 or homozygous copy number losses in CDKN2A can alter this balance and lead to unconstrained cell cycle proliferation.[54] Indeed, Curtin *et al.*[1] found that acral and mucosal melanomas harbored significantly more *CDK4* amplifications and *CDKN2A* losses compared with other subtypes. Overall, chromosomal copy number gains and deletions are thought to occur earlier and more frequently in the pathogenesis of acral and mucosal melanomas, affecting 89 and 85% of cases, respectively.

INHERITED AND OTHER RISK FACTORS

Little is known about germline mutations that specifically predispose to acral or mucosal melanoma. However, up to 15% of patients with vulvar or vaginal melanoma provide a family history of melanoma, and some studies have shown germline mutations in melanocortin type I receptor gene and *CDKN2A* in these patients.[33,55] Currently, *CDKN2A* germline mutations are recognized as the most common germline mutation in melanoma. In families with three or more cases of melanoma, *CDKN2A* germline mutations are thought to predispose to approximately 40% of cases. Frequently, these patients are characterized by multiple primary melanomas, early onset of disease, and increased risk of pancreatic cancer.[56] Less than 1% of such families have been reported to harbor germline mutations in *CDK4*.[57] Recently, two families have been identified with germline *TERT* mutations.[56] Considering the importance of somatic alteration in *TERT* in acral melanomas, it would be of interest to further investigate the possibility of germline mutations in patients with acral and mucosal melanoma. There are no reports of *KIT* germline mutations leading to melanoma, despite nearly 40 individuals or kindreds with identified *KIT* mutations associated with gastrointestinal stromal tumors.[56,58,59]

Since exposure to UV radiation is unlikely to be a source of mutagenesis, there have been several attempts took to look at other environmental risk factors for the development of acral or mucosal melanoma. Two case-control studies identified previous trauma as having significant associations with acral melanoma. Among Australian patients, 20.1% with melanoma arising on the palms and soles reported a history of deep penetrative injury at the site, compared with 4.6% of healthy controls.[60] Similarly, among Paraguayan patients with plantar melanomas, the strongest association was found for reported injuries, which occurred in 50% of patients with plantar melanomas compared with 11% of controls.[61] In mucosal melanoma, there is no strong evidence that any environmental exposures or carcinogenic viruses are involved in pathogenesis. In a study of melanomas from sun-sheltered body areas, 41 samples were examined for the presence of human herpes virus DNA. The authors reported Epstein–Barr virus in 1 subungual melanoma, human herpes virus-6 in one melanoma from the nasal cavity, and cytomegalovirus in two separate samples from anal and nasal tracts.[62] Similarly, another group investigated 38 extracutaneous melanomas for the presence of polyomavirus, only to find that none of the samples from various mucosal sites tested positive for BKV, JCV, KIPyV, WUPyV, or MCPyV.[63] Instead, only modest associations without direct correlations have been established. For example, 66% of patients with mucosal melanoma arising on the larynx or pharynx report a history of smoking, and anorectal melanoma appears to be more common in patients with HIV.[16,64]

Table 1 Summary of gene aberrations and estimated frequency of involvement in melanomas of sun-protected sites

Gene	Acral melanoma	Mucosal melanoma
CCND1	45%	31%
KIT	36%	39%
PDGFRA	6.8%	3.6%
TERT	~30%	8–?%

CONCLUSION

In summary, our review of the literature suggests important clinical and histological similarities between acral and mucosal melanomas. Whereas cutaneous melanomas may be somewhat common in women before the age of 50, sun-protected subtypes are rarely diagnosed before the seventh and eighth decades of life. Histologically, acral and mucosal melanomas are characterized by a predominantly lentiginous growth pattern with a broad radial growth phase, frequent 'field cells,' and lower proportions of superficial spreading subtypes or precursor nevi.

On sun-exposed sites, the development of melanoma typically follows a large number of UV-induced mutations. These mutations commonly affect genes regulating the MAPK pathway, thereby leading to activation of the cell cycle and tumor proliferation. In the absence of UV-mediated events in mucosal and acral skin, a combination of (1) early chromosomal instability, characterized by copy number gains in *TERT*, *CCND1*, and *KIT*, and (2) non-UV-related activating mutations in *KIT* and *PDGFRA* lead to tumor proliferation (Table 1). Hence, it is the presence of early chromosomal copy number aberrations, with gains in select

oncogenes and deletions in select tumor suppressor genes, that allow melanocytes to overcome cellular senescence and undergo tumor proliferation.[65]

The activation of TERT provides cells with a growth advantage and the ability to avoid telomere shortening-induced senescence, which typically occurs after 100 0 00 rounds of replication. We postulate that the later onset of acral and mucosal melanomas suggests that increased TERT activity may be present at a very early stage or present in more slowly dividing, and possibly non-tumoral, cells. This hypothesis includes possible germline or early somatic mutations in *TERT* or other genes impacting TERT activity and is consistent with the lack of a precursor nevus in most cases of acral and mucosal melanoma. In contrast, melanomas that arise earlier in areas with intermittent sun exposure, and often from a precursor nevus, may be undergoing or completing a phase of rapid proliferation and thus reach telomere crisis in a much shorter time frame.

Mutations or copy number gains in *KIT* or *CCND1* have not been identified as a characteristic feature of any known variant of benign nevi. However, these alterations clearly lead to increased cellular proliferation. Genetic studies have revealed that sun-protected melanomas are characterized by early and frequent alterations in *KIT* and *CCND1* in melanocytic 'field cells' beyond the clinical or histological margin of a lesion, suggesting that these changes occur relatively early. Increased non-nevus-forming cellular proliferation through KIT or CCND1 could be a factor that leads to cells reaching critical telomere shortening and hence, provide a growth advantage for cells overexpressing TERT. These combined events, leading to increased proliferation with aberrantly elongated telomere ends, may lead to the early chromosomal instability that is so characteristic of non-UV-related melanomas.[66]

Multiple studies have suggested trauma as a possible factor for the development of acral melanoma. While these reports are retrospective and largely anecdotal, the association is mechanistically plausible. Trauma and cellular damage are known to activate the cell cycle. Recurrent activation could contribute to cells reaching critical telomere shrinkage at an earlier stage, and then manifest an otherwise unapparent selective growth advantage from increased TERT expression. In acral sites, activation may be trauma-related, while in mucosal sites, there may be an alternative mechanism, such as smoking, human papillomavirus, or other carcinogens that trigger dormant cells to reenter the cell cycle. These pathways are highly conjectural, however, and while some of the key oncogenes have been identified, there still remain many unknowns regarding the sequence of events and the factors that predispose to alterations in these genes.

ACKNOWLEDGMENTS
This work was supported by the IDP Foundation.

DISCLAIMER
This work is original and has not been previously published.

DISCLOSURE/CONFLICT OF INTEREST
Dr Gerami has served as a consultant for Myriad Genomics, DermTech Int. and Castle Biosciences, and has received honoraria for this. The remaining author declares no conflict of interest.

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