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Seminars in Cutaneous Medicine and Surgery

Pathways to Melanoma

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Melanoma is one of the most aggressive and yet poorly understood of human malignancies. Advances in genomics has allowed a more nuanced understanding of the disease, moving beyond the traditional dysplastic nevus-to-melanoma model and identifying multiple divergent oncogenic pathways leading to melanoma. An understanding of the molecular mechanisms driving melanoma has opened the doors for the development of targeted therapeutic approaches. As we enter the era of personalized medicine, it will be critical for clinicians to both appreciate and be able to determine the molecular profile of their patients' melanoma because this profile will guide risk stratification, genetic counseling, and treatment customization. A review of the divergent pathways of melanoma development is presented here, with a particular emphasis on recently identified mutations, and their implications for patient care.

Semin Cutan Med Surg 29:210-217 © 2010 Published by Elsevier Inc.

Melanoma remains one of the most aggressive of human malignancies. The cancer ranks as the sixth most common cancer in American men and women, the second most common cancer in patients between the ages of 20 and 35, and the leading cause of cancer death in women ages 25 to 30 years.[1] The incidence of melanoma has increased more rapidly than that of any other cancer in the past century,[2,3] yet our ability to treat disseminated disease has lagged behind our options for other malignancies. Predicted 1-year survival for stage IV disease ranges between 41% and 59%.[4] Despite the major socioeconomic impact of the disease on our young population,[5] our understanding of the epidemiologic risk factors and oncogenic potential of the melanocyte on a cellular and molecular basis has been relatively limited.

However, in the past several years, our ability to sequence and analyze the human genome has led to profound discoveries in the molecular pathogenesis of melanoma. Research to date suggests that not all melanomas are created equal. Tools such as genome-wide association studies and linkage analysis have allowed us to identify important differences between melanomas on the basis of anatomic location, degree of sun exposure, and individual susceptibility.[6] Molecular pathways specific to melanoma subtypes have been described and these findings have been translated into clinical benefit. Biomarkers for these pathways have been identified, and drugs targeting several of these pathways have emerged and shown clinical potential.

In this review, we outline a current understanding of the heterogeneity of melanoma as manifest through divergent etiologic pathways of melanoma development. We highlight the role and our understanding of *RAS*, *BRAF*, *PTEN*, *KIT*, *GNAQ*, and *EWF-ATF1* mutations that appear central to these divergent pathways. Finally, we discuss the potential implications for patient care as our understanding of these various pathways grows.

Nevus and Non-Nevus Pathways to Melanoma

The traditional Clark model of the progression of melanoma emphasized the stepwise transformation of melanocytes to melanoma, from the formation of nevi to the subsequent development of dysplasia, hyperplasia, invasion, and metastasis.[7] However, this ordered stepwise progression from melanocyte to mole to melanoma is relatively uncommon. Bevona et al[8] in 2003 found that only 26% of melanomas arise from nevi, of which 43% arose from dysplastic nevi. They estimated the annual rate of any given mole transforming into melanoma to range from 1 in 200,000 for patients younger than 40 years, to 1 in 33,000 for men older than 60 years. The finding that most cutaneous melanomas arise from normal-appearing skin at least suggests alternative pathways that bypass the nevus as intermediary or, as has been proposed that they derive from transformed melanocyte stem

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1085-5629/10/$-see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.sder.2010.10.004

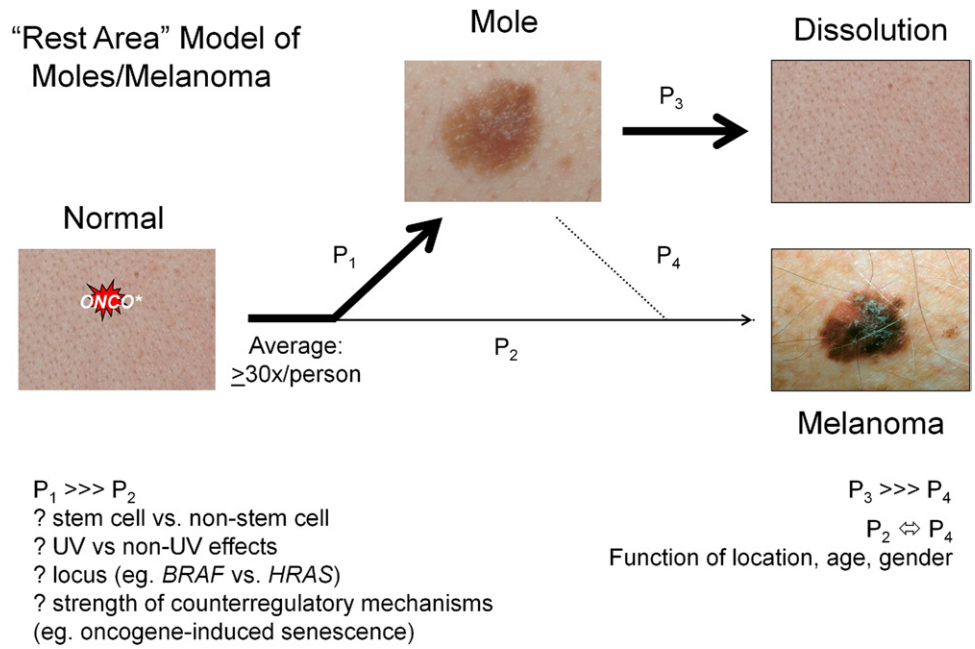

Figure 1 "Rest area" model of moles and melanoma. The oncogenic transformation of melanocytes is dependent on genetic factors, germ-line predisposition and the interplay with environmental factors, most notably UV exposure. Transformed melanocytes develop into nevi with a certain probability defined as P1; the vast majority of moles remain at this "rest stop," eventually undergoing senescence and dissolution with a high probability (P3). Rarely, these nevi go on to develop into melanomas with a much lower probability (P4).

An oncogenic change, in the proper context, can also lead to de novo melanomas with a certain probability (P2); however, given the large number of moles relative to nevi, P1 is much greater than P2. Likewise, since most moles disappear rather than transform into cancer, P3 is much greater than P4. The path of melanoma development is influenced by location on the body, age and other unknown factors.

cells or de-differentiated mature melanocytes.[9,10] Evidence from epidemiologic studies suggests a more complex model of pathways to melanoma determined by genetic factors, germ-line predisposition, and the interplay with environmental factors, most notably ultraviolet (UV) exposure (Fig. 1).

In such a schematic, a divergent pathway model for the development of cutaneous melanoma suggests a fundamental divide between individuals with inherent genetic susceptibility for melanocyte proliferation (who would be expected to require less solar damage and develop melanomas on intermittently sun-exposed body sites, such as the trunk), and individuals with inherently low propensity for melanocyte proliferation (who would be expected to require chronic UV exposure to drive formation of melanoma on habitually sun-exposed areas, such as the face and neck).[11]

Certainly, a genetic predisposition for the development of melanoma and nevi, especially clinically atypical variants, is well-established and recognized since the 19th century.[6] A familial predisposition, defined as 2 first-degree relatives with melanoma, is found in 10%-13% of melanoma cases.[12] Two autosomal-dominant high-susceptibility loci were first identified in clusters of families with melanoma in the mid-1990s: cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and cyclin-dependent kinase 4 (*CDK4*). Located on chromosome 9p21, the *CDKN2A* locus encodes 2 tumor suppressor proteins, p16 and p14, which both act to arrest the cell cycle. Inactivation of *CDKN2A* through deletion, mutation, or promoter silencing leads to uncontrolled cell proliferation. Mutation penetrance, defined as the risk of observing a disease over time given a certain genotype, is probably influenced by UV exposure because the risk of melanoma among *CDKN2A* mutation carriers varies across continents, populations, and age; overall, the estimated disease risk for individuals carrying *CDKN2A* mutations is 30% by 50 years of age and 67% by 80 years of age.[13] *CDKN2A* mutations have also been associated with pancreatic cancer, uveal melanoma, and nervous system tumors.[12] Germ-line mutations in *CDK4*, located on chromosome 12q13, have only been identified in a limited number of families worldwide to date. Together these genes account for approximately 30%-40% of familial melanoma cases and describe only a very small portion of all melanomas.[6] These results suggest that other undiscovered high-risk alleles are likely to exist or that some of the observed familial clustering may be attributable to the cumulative risk from a concurrence of low-to-moderate risk loci.

Although UV exposure is well-established as the major modifiable risk factor for the development of melanoma, the relationship between UV exposure and development of melanoma is not entirely straightforward. If one presumes a stepwise progression from melanocyte to melanoma based on the sequential accumulation of genetic events, the finding that melanomas frequently occur in locations that are more often covered by clothing, and that indoor workers have been shown to have greater rates of melanoma than outdoor work-

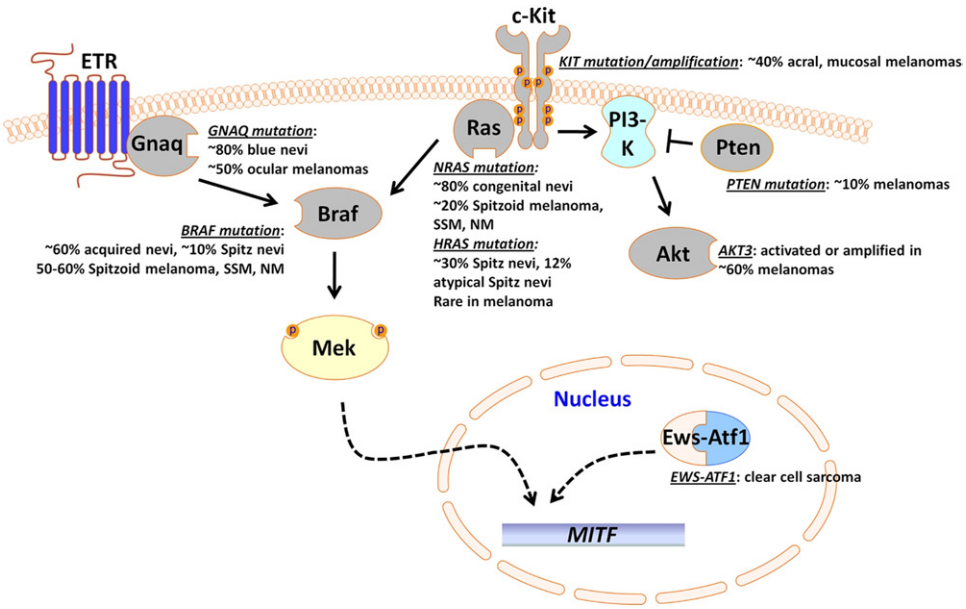

Figure 2 Molecular alterations in nevi and melanomas overlap. Activation of Ras, a GTPase that lies on the inner surface of the cell membrane, occurs via receptor tyrosine kinases (ie, KIT) binding ligand, or by integrin adhesion to extracellular matrix.[13] GTP-bound RAS induces signaling cascades that activate both the MAP kinase pathway, which mediates cell growth, differentiation, and the induction of the microphthalmia transcription factor (*MITF*) gene, as well as the Akt pathway, which is responsible for inhibition of apoptosis. The Ref family of serine/threonine protein kinases regulates the MAP kinase cascade. Phosphatidylinositol 3-kinase (P13K) phosphorylates phosphoinositides, which then bind to AKT, and mobilize the protein kinase to the cell membrane. Pten acts as a phosphatase to dephosphorylate the phosphoinositides and impede their membrane-localizing effect on Akt. In uveal melanomas, mutations in *GNAQ* can lead to activation of a separate cascade mediated by ETR, endothelin receptor; GNAQ, guanine nucleotide-binding G(q) subunit alpha. In clear cell sarcomas, the EWS-ATF1 fusion product transcriptionally up-regulates MITF, which results in increased pigment synthesis. Known mutated proteins in melanoma are shown in gray.

ers is paradoxical.[14,15] There is also consistent evidence that demonstrates melanoma incidence rates on sun-exposed and unexposed body areas have different age peaks.[16-18] These data reveal the complexity of the relationship between UV exposure and melanoma and provides support for the notion that melanomas arise through different pathways.

Epidemiologic Evidence for Distinct Pathways

More specifically, epidemiologic studies have investigated the association between nevus count and melanoma risk by body site. Several investigators reported nevus counts to be more strongly associated with melanomas of the trunk and legs than that of the head or upper extremities.[19-22] Notably, Bataille et al[23] reported that patients with melanoma of the head and neck had fewer nevi and more solar keratoses than patients with melanoma of the trunk or legs. Randi et al[24] published a case-control study that reported the risk of melanoma of the trunk was associated with nevi, particularly with atypical nevi, which were more likely to occur on the trunk. Olsen et al[25] confirmed these findings in a large-scale pooled retrospective study of case-control studies of melanoma in women. They showed higher nevus count on the arm to be associated with increased risk of melanoma of the trunk and limbs but not of the head and neck. Finally, several studies have reported that melanomas arising on the trunk are more likely to arise within a nevus than melanomas of the head and neck, suggesting that nevi may be precursors for a subset of truncal melanomas.[26,27]

Genetic Relationships Between Nevi and Melanoma

Studies from molecular genetics support the notion of divergent and convergent etiologies for melanoma and nevus development. Many of the oncogenic mutations initially identified in melanomas have also been detected in benign melanocytic proliferations (Fig. 2). This finding suggests that pigmented nevi and melanomas share some common molecular triggers that could define a "proliferative" pathway, ie, melanoma in the setting of a large number of moles. In the ensuing section, we provide a synopsis of genetic changes that have been uncovered in melanocytic tumors, both benign and malignant.

By using array-based comparative genomic hybridization, Curtin et al[28] studied melanomas from 4 anatomic locations—acral, mucosal, skin with chronic sun damage, and skin without chronic sun damage—and were able to scan and

compare melanoma genomes. They demonstrated that cutaneous melanomas arising on skin without chronic sun-induced damage had frequent somatic mutations in *BRAF* and *NRAS* genes, whereas melanomas arising on skin with chronic sun-induced damage had infrequent mutations in *BRAF* and frequent increases in the number of copies of the *CCND1* gene. The statistically significant differences in chromosomal aberrations and frequency of mutation of specific genes suggest that there are distinct subtypes of melanoma which arise by divergent routes, in response to different influences. A number of further studies have reported similar differences in genetic and molecular profiles of melanomas by anatomic site.[29-31] Specifically, Thomas et al[32] found that people with large numbers of nevi on the back were more likely to have melanoma with *BRAF* or *NRAS* mutations than those with low nevus counts on the back, and that *BRAF*-mutant melanomas are associated with an increased ability to tan. However, the mechanisms responsible for these diverse genetic profiles and for these seemingly divergent etiologic pathways for melanoma remain unclear.

RAS

The RAS family of small G proteins is among the most ubiquitously altered genes in cancer. There are 3 common members of the RAS family: *HRAS*, *KRAS*, and *NRAS*. *NRAS* mutations are found in a significant subset of melanomas, and they tend to occur in melanomas arising from intermittently sun-exposed skin (Fig. 2).[28,33] *NRAS* and *BRAF* appear to be mutually exclusive mutations, which fits with the finding that each is sufficient to constitutively activate the mitogen-activated protein (MAP) kinase pathway. Bauer et al[34] found that 26 of 32 truly congenital nevi harbored *NRAS* mutations while none had *BRAF* mutations. Their results suggest the role of UV exposure in development of *BRAF* mutation, as most melanocytic nevi develop on sun-exposed skin during childhood and adolescence, and commonly harbor *BRAF* mutations or, less frequently, *NRAS* mutations.[35,36] At the same time, they posit that UV exposure does not play a role in the development of *NRAS* mutations, as these mutations occurred while in utero.

Also lending insight into the role of RAS in pathways to melanoma is a study by Bastian, et al. They examined 102 Spitz nevi and found copy number increases of chromosome 11p. In 12 cases, they found copy number increases involving the *HRAS* gene, which is located on 11p. Further sequential analysis demonstrated oncogenetic mutations in *HRAS* in 8 of these 12 cases and rarely in cases without increased copy number. This subset of cases demonstrated several histologic features that overlap with those of melanoma. The authors proposed that *HRAS* activation in the absence of additional genetic alterations led to the partially transformed melanocytes into a growth-arrested state.[37]

BRAF

Much attention has been focused on the *BRAF* gene and its role in nevus and melanoma formation. The *BRAF* gene encodes a protein belonging to the ref/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/extracellular signal-regulated kinase signaling pathway, which affects cell division, differentiation, and secretion. *BRAF* is highly expressed in neuronal tissue and melanocytes and is not likely an inherited cancer predisposition gene.[38] Individuals with germ-line *BRAF* mutations develop cardio-facio-cutaneous syndrome, which is not known to be associated with an increased risk of cancer or melanoma.[39,40]

As previously noted, activating mutations in *BRAF* are found in approximately one-half of all melanomas, with the significant majority arising in skin with intermittent sun exposure, compared with melanomas from chronically sun-exposed areas, acral, mucosal, and uveal melanomas, suggesting an inverse association with high levels of cumulative sun exposure.[28] The most common *BRAF* mutation (approximately 90% in clinical pathology samples) is the T1799A point mutation, in which a T → A transversion converts the canonical valine into a novel glutamic acid at the 600 position of the amino acid sequence; the $BRAF^{V600E}$ protein then becomes constitutively active.[41] The finding that *BRAF* mutations are common in both benign and dysplastic nevi argues that such mutations are not sufficient for malignant transformation of melanocytes.[42,43] However, it does suggest a role in the earliest stages of neoplasia.

As demonstrated by Bevona et al,[8] nevi are fundamentally growth-arrested and only rarely progress to melanoma. The introduction of a $BRAF^{V600E}$ mutation into melanocytes has been shown to induce senescence and cell-cycle arrest.[44] Wajapeyee et al[45] found that introduction of an insulin-like growth factor binding protein-7, *IGFBP7*, into melanoma cells with *BRAF* mutation slowed cell growth and triggered apoptosis. Furthermore, when given systemically, IGFBP7 suppressed growth of human tumors grafted into mice. Finally, the authors demonstrated that normal cutaneous melanocytes express low but present levels of IGFBP7 in contrast to the high levels expressed by *BRAF* mutation-containing nevi. Melanomas with *BRAF* mutations did not express detectable levels of IGFBP7. Thus, one component of melanomagenesis is escape from $BRAF^{V600E}$-mediated IGFBP7 restriction. In contrast to the findings of Wajapeyee et al, Scurr et al[46] recently demonstrated that BRAF signaling does not induce the expression of *IGFBP7* or its targets in human melanocytes or fibroblasts. In fact, they found no correlation between *BRAF* mutational status and IGFBP7 protein expression levels in the 22 melanoma cell lines, 90 melanomas, and 46 benign nevi examined. These seemingly contradictory results highlight the inherent difficulties in ascribing focal genetic aberrations to complex tumor phenotypes.

Studies in animal have demonstrated that concurrent inactivation of *Cdkn2a* permits transformation and the concomitant deletion of *PTEN* or *Trp53* results in the formation of invasive and metastatic melanoma in animal models.[47,48] Simultaneous activation of $BRAF^{V600E}$ and deletion of *Ink4A* can lead to invasive melanoma in mice. These findings support the human nevus observation that a $BRAF^{V600E}$ lesion, on its own, is not sufficient for malignant transformation of melanocytes.

What then is the relationship among UV exposure, *BRAF*

mutation, and melanoma? There is no clear answer with respect to the factors driving *BRAF* mutagenesis at the current time. However, one might speculate that melanocytes from "nevogenic" persons, who may also be prone to develop melanomas on intermittently sun-exposed skin, have an inherently increased susceptibility to *BRAF* mutagenesis and develop melanocytic proliferations in the setting of such an alteration. Epidemiologic studies and animal studies suggest that in this population, there may be a window of vulnerability to exposure to ultraviolet light early in life.[49,50] Arguing against a straightforward UV-mediated mechanism is the fact that the T → A transformation is not classically associated with UV photoproducts[51] and that genes, such as *BRAF* and *NRAS* are do not commonly show the typical UV "fingerprint" mutations (eg, CC → TT).[52-54] These observations highlight the uncertainty surrounding the factors driving *BRAF* changes, specifically the role of UV exposure in development of *BRAF* lesions. The gene-environment interaction between UV exposure and *BRAF* mutation is further complicated by evidence of gene-gene interactions—ie, germ-line melanocortin-1-receptor variants may regulate the somatic *BRAF* mutagenesis, nevus burden, and melanoma risk.[55-57]

PTEN

The *PTEN* gene, located on chromosome 10, encodes a tumor suppressor protein and has also gained considerable attention as our understanding of melanoma pathogenesis has increased.[13] Mutations in *PTEN* are found in 10%-20% of primary melanomas[58] and have also been associated with thyroid, breast, and prostate cancer. Pten has lipid phosphatase activity, which prevents formation of intracellular signaling molecules required for conformational change activating the AKT protein kinase family.[59] Recent studies have demonstrated that activation of AKT pathway suppresses apoptosis[60,61] through several mechanisms, including phosphorylation and inactivation of proapoptotic proteins, such as BAD (ie, Bcl-2 antagonist of cell death),[62] and caspase-9,[63] as well as activation of nuclear factor-$\kappa\beta$.[64] DNA copy gain of the *AKT3* locus is found in 40%-60% of melanomas and results in activation of the Akt protein kinase. Further studies suggest that *AKT* may be able to transform melanocytes in hypoxic conditions.[65] Interestingly, *AKT3* expression correlates with melanoma progression.[66] Thus, inactivation of *PTEN* allows signaling through the Akt pathway, which contributes to aberrant cell growth and escape from apoptosis. Evidence suggests that there is cooperation between loss of *PTEN* and *BRAF* mutations.[67]

KIT

Melanomas that arise on acral surfaces (palms, soles, and nails) and mucosal surfaces seem to arise from a different etiologic pathway than their cutaneous counterparts. Although the frequency of melanoma varies among ethnic populations, acral melanoma is one of the few morphologic variants that occur with equal frequency across all races. Acral and mucosal melanomas are also 2 of the most aggressive melanoma subtypes.[68] Several recent investigations have demonstrated important distinctions in their developmental pathways. As alluded to previously, a molecular analysis of melanoma subtypes found that acral and mucosal melanomas have a higher frequency of somatic copy number alterations than cutaneous melanomas.[28] In addition, the MAP kinase cascade was not activated by the same mutations in each of the subtypes. Although *BRAF* mutations are highly prevalent (59%) in melanomas occurring on skin without chronic sun damage, *BRAF* mutations are significantly less frequent in acral and mucosal melanomas. *CDK4* and *CDKN2A* mutations are more common in acral and mucosal melanomas, but not present simultaneously as one would expect because the protein products of these 2 genes physically interact with one another.[28]

Given the finding that acral and mucosal melanomas have a low frequency of *BRAF* mutations, Curtin, et al sought to uncover an alternative mechanism for activating the MAP kinase cascade in these melanomas. In a follow-up series, the investigators identified a common region of copy number gain at chromosome 4q12 among acral and mucosal melanomas; this region contains several receptor tyrosine kinases (RTKs). Subsequent immunohistochemical studies comparing gene copy number and protein or RNA expression revealed that the *KIT* gene was most likely responsible for the changes at 4q12. c-Kit is an RTK that plays an important role in proliferation, development, and survival of melanocytes, hematopoietic cells and germ cells.[69] Pathogenic *KIT* mutations have been observed in a variety of tumors, including, gastrointestinal stromal tumors, seminomas, large cell carcinomas of the lungs, and certain acute myeloid leukemias.[70] Curtin et al[69] found mutations and/or copy number gains of *KIT* in 39% of mucosal melanomas, 36% of acral melanomas, and 28% of melanomas on chronically sun damaged skin, compared with 0% of melanomas on skin without sun damage. *KIT* mutations have also been shown to occur in up to 88% of oral mucosal melanomas[71] and 15% of anal melanomas.[72] Several of these *KIT* mutations affect the juxta-membrane domain of the gene. Similar *KIT* mutations have been described in gastrointestinal stromal tumors and appear to confer sensitivity to an RTK inhibitor, imatinib. In an ensuing trial, 4 patients with acral and mucosal melanomas and documented KIT mutations were treated with either imatinib or sorafenib and all showed tumor regression. However, all cases also showed increased rates of central nervous system progression, thought to be due to limited penetration of the drug into the brain.[73] Although not a curative option to date, the example illustrates the ultimate goal of tailoring individual patient therapy to results of a selective biomarker panel.

GNAQ

The most common primary eye tumor, uveal melanoma, arises from melanocytes of the choroid, cilliary body, and iris. Unlike cutaneous melanomas, which more frequently metastasize to lymph nodes, lung and brain, uveal melanomas often target the liver. Metastatic disease is aggressive, and there are no effective treatment options. Five-year disease specific survival is 70%.[74] Recent studies have shown that the

oncogenic pathways between uveal and cutaneous melanomas are different. For instance, uveal melanomas often lack activating and inactivating *BRAF* and *CDKN2A* mutations, respectively.[70] Although c-Kit expression has been found in up to 87% of uveal melanomas, there does not appear to be activating changes. In a phase II trial of uveal melanoma patients, no objective response was observed in 10 patients treated with high dose imatinib.[75]

Van Raamsdonk et al[76] have recently suggested that the development of uveal melanomas may be explained in part by mutations in *GNAQ*, a gene encoding the q class of G protein α-subunits, involved in transmitting signals between G protein-coupled receptors and their downstream pathways. They studied a wide variety of nevi and melanoma and found *GNAQ* mutations in 46% of uveal melanomas, as well as in 83% of blue nevi. Interestingly, *GNAQ* mutations were also found in nevus of Ota lesions, a known risk factor for uveal melanoma (1:400).[77] In accordance with previous studies, none of the uveal melanomas had mutations in *BRAF* or *NRAS*. All *GNAQ* mutations occurred at codon 209, and seem to cause constitutive activation by loss of GTPase activity. Once activated, Gnaq initiates several downstream pathways, including activation of protein kinase C family members which are then able to activate the MAP kinase pathway. The finding of constitutive activating mutations in *GNAQ* may therefore explain MAP kinase activation in uveal melanomas, in the absence of *BRAF* or *NRAS* mutations. Still, further studies are needed to explain the exact role of *GNAQ* and why some mutated lesions remain benign (blue nevi or nevus of Ota) and others progress to malignancy. Van Raamsdonk, et al hypothezise that like *BRAF* or *NRAS*, *GNAQ* is just one step in the oncogenic pathway.[76]

EWT-ATF1

Malignant melanoma of soft parts, also known as clear cell sarcoma of tendons and aponeurosis, is a rare tumor composed of nests of malignant cells that presents in the deep soft tissues and shares the same immunohistochemical pattern of melanocytes. Clinically, the tumor presents as a painful, slow growing, soft tissue mass, frequently around the knee or ankle of a young adult. Diagnosis is challenging as lesions can appear radiologically benign. Five- and ten-year survival is approximately 50% and 10%-20%, respectively, because of local recurrence and metastatic potential.[78] Although it is difficult to study because of its rarity, research into its oncogenic pathways, shows unique genetic alterations. Unlike cutaneous melanomas, these tumors lack *BRAF* or *NRAS* mutations.[79] Up to 80% of malignant melanoma of soft parts, harbor a t(12,22) (q13; q12) translocation that results in a fusion gene product with the Ewing sarcoma gene (*EWS*) and the activating transcription factor gene (*ATF-1*), a feature more suggestive of sarcoma lineage. Langezaal et al[78] studied primary cutaneous and uveal melanomas using reverse transcriptase polymerase chain-reaction or fluorescent in situ hybridization and demonstrated that none of these tumors contain a similar translocation. Davis et al[80] demonstrated that clear cell sarcomas harbor this translocation creating the *EWS-ATF1* fusion gene product, which subsequently occupies the *MITF* promoter thereby inducing pigment synthetic genes and eumelanization. Biologically, it appears that these tumor cells mimic melanocytes because of the high *MITF* expression that results from the *EWS-ATF1* fusion gene product.

Advances in our molecular understanding of melanoma and nevi reveal intricate genetic relationships between the two types of melanocytic tumors. Shared oncogenic mutations between nevi and melanoma suggest that all moles develop with an ambition to become autonomous and that regulatory mechanisms limit its replicative potential. Given the inordinate number of nevi compared to bona fide melanomas, the growth suppressive response (eg. oncogene-induced senescence) appears to be amazingly strong. Furthermore, if proliferation is indeed triggered by a similar mutagenic signal, this may explain the clinical and histologic overlap between nevi and early melanoma. It is clear that the pathway to melanoma is dependent on the global genetic context in which cancer-driving mutations arise.

Acknowledgments

This work was made possible by the generous donors to the MGH Millennium Melanoma Fund.

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