Genetic Alterations and Personalized Medicine in Melanoma: Progress and Future Prospects

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High-throughput sequencing technologies are providing new insights into the genetic alterations involved in melanomagenesis. It appears likely that most genetic events important in the pathogenesis of melanoma will be discovered over the next few years. Genetic analysis is also increasingly being used to direct patient care. In parallel with the discovery of new genes and the elucidation of molecular pathways important in the development of melanoma, therapies targeting these pathways are becoming available. In other words, the age of personalized medicine has arrived, characterized by molecular profiling of melanoma to identify the relevant genetic alterations and the abnormal signaling mechanisms involved, followed by selection of optimal, individualized therapies. In this review, we summarize the key genetic alterations in melanoma and the development of targeted agents against melanomas bearing specific mutations. These developments in melanoma serve as a model for the implementation of personalized medicine for patients with all cancers.


The development of increasingly sophisticated molecular techniques over the last few decades has led to improvements in our understanding of the pathogenesis of cancers. Arguably, the most important recent technical advance has been the introduction of massively parallel (so-called “next-generation”) sequencing techniques, allowing comprehensive evaluation of the entire genome. Detailed genetic studies using massively parallel sequencing [including large multinational efforts such as The Cancer Genome Atlas project (1–4)] have clarified the prevalence of driver oncogenes and have identified unique genetically-defined subpopulations of melanoma. Furthermore, decreasing costs and increasing availability of massively parallel sequencing technologies are making it feasible to sequence individual patients’ tumors in search of actionable genetic alterations for the purpose of selecting therapy. Currently, standard targeted therapy for melanoma involves the use of single agents. Although initial response rates are promising, the development of tumor resistance has emerged as a major problem. Tumors harbor a landscape of concomitant genetic alterations, and strategies incorporating combinations of therapies targeting either the same or different signaling pathways are expected to provide greater efficacy. Some of these are already being investigated in early phase clinical trials (5). Treatment strategies similar to those successfully implemented in human immunodeficiency virus patients [in whom effective disease control is achieved by simultaneously using multiple medications with different targets (6)] are likely to become the standard-of-care in most metastatic malignancies.

Genetic Alterations in Melanoma

Chromosomal Alterations

DNA Copy Number Alterations in Cutaneous Melanoma.

Recognition of individual chromosomal alterations in cutaneous melanoma, such as losses of the CDKN2A locus on chromosome 9p (7–9) and the PTEN locus on chromosome 10q (10–12), was followed by the discovery of widespread chromosomal alterations using the then newly developed technique, comparative genomic hybridization (CGH) (13). In contrast with earlier studies, CGH allowed the first detailed analyses of primary tumors. CGH enables detection of DNA copy number alterations across the entire genome and has the added advantage that it can be successfully applied to formalin-fixed, paraffin-embedded tissues. Bastian et al. (13) found that chromosomal alterations were virtually absent in nevi but were frequent in melanoma. They included losses of chromosomes 9p (81%) and 10q (63%), focal losses in chromosomes 6q and 8p, and gains or amplifications in chromosomes 1q, 2, 4q, 6p, 7, 8, 11q, 17, and 20. The patterns of chromosomal gains and losses differed between clinicopathologic subtypes of melanoma, such as acral lentiginous melanoma, mucosal melanoma, melanoma in severely sun-damaged (SSD) skin, and melanoma in non-SSD skin (14). Gains of CDK4 (chromosome 12q) were generally found to be mutually exclusive of gains of CCND1 (chromosome 11q) and associated with less frequent losses of CDKN2A (chromosome 9q). Differences between BRAF-mutant and NRAS-mutant tumors were also noted. BRAF-mutant tumors more frequently had losses of chromosome 10q at the PTEN locus. Tumors lacking BRAF and...
NRAS mutations harbored higher numbers of chromosomal alterations, in particular affecting the CCND1 and CDK4 loci. These findings have been validated in a number of other studies (15–17). Recently, assessment of copy number status of chromosomes 6 and 11 has been shown to provide independent prognostic information in cutaneous melanoma (18).

**Chromosomal Losses in Ocular Melanoma.** Ocular melanomas include conjunctival melanomas and uveal melanomas. Conjunctival melanomas harbor chromosomal alterations similar to those seen in cutaneous and mucosal melanoma (19). In contrast, uveal melanomas show a very distinct set of recurrent chromosomal alterations. These include losses of chromosomes 3, 1p, and 6q, as well as gains of chromosomes 6p and 8q (20–23). Chromosome 3 loss is a strong adverse prognostic factor in uveal melanoma (21). A recent study found that the disease-specific mortality rate for tumors with chromosome 3 monosomy was 75.1%, compared with 13% for tumors that were disomic for chromosome 3 (23).

**Gain-of-Function/Oncogenic Mutations**

Most cancers contain at least one (and often many) gain-of-function genetic event(s). These events may lead to continuous activation of translated proteins as a result of mutations. Alternatively they may result in overexpression of protein, commonly through amplification of genomic DNA. Combinations of these events (eg, concurrent KIT mutations and amplifications) may also occur.

**BRAF.** BRAF is one of three RAF genes. Similar to RAS genes, RAF was first identified as the cellular homologue of v-rafl, a gene found in a transforming murine retrovirus (24). The first isofrom detected was CRAF (24,25). Vertebrates carry two other RAF isoforms, ARAF and BRAF (26–29). RAF proteins are downstream of RAS and lead to activation of ERK1/2 (extracellular signal-regulated kinase) through MEK1/2 (Figure 1). In 2002, BRAF mutations were reported as a frequent event in human cancers, particularly melanoma (30). Although mutations can occur at a number of locations in the gene, the overwhelming majority (>90%) lead to substitutions of the valine residue in codon 600. The most frequent reported mutations are V600E (approximately 80%) and V600K (approximately 17%) (31,32), and less commonly V600D, V600G, and others (33). V600K mutations have been found to occur primarily in SSD skin of elderly patients (32). BRAF mutations appear to be an early event in tumorigenesis because they are also found in the majority of common acquired nevi (34). The presence of BRAF mutations has been associated with an unfavorable prognosis in patients with melanoma (35,36).

**NRAS.** Soon after the identification of NRAS as a RAS family oncogene (37,38), it was found to be mutated in melanoma cell

![Figure 1. Common signaling alterations in cutaneous melanoma. This figure illustrates some of the most common signaling proteins involved in melanoma pathogenesis. Therapeutic agents targeting specific events are shown on the left. Genetic events associated with resistance to BRAF inhibitors such as vemurafenib and dabrafenib are depicted in red. Akt = v-akt murine thymoma viral oncogene homolog; amp = amplification; BRAF = v-Raf murine sarcoma viral oncogene homolog B; COT = mitogen-activated protein kinase kinase kinase 8 (MAP3K8); CRAF = v-Raf-1 murine leukemia viral oncogene homolog 1 (RAF1); del = deletion; ERK = extracellular signal-regulated kinase; IGF-R1 = insulin-like growth factor 1 receptor; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MEK = MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) kinase; mut = mutation; NF-1 = neurofibromin 1; NRAS = neuroblastoma RAS viral oncogene homolog 1; PDGFRβ = platelet-derived growth factor receptor beta; PI3K = phosphoinositide 3-kinase; PTEN = phosphatase and tensin homolog; Ras = retrovirus-associated sequence oncogene; RTK = receptor tyrosine kinase.](https://academic.oup.com/jnci/article-abstract/106/2/djt435/2518210)
NRAS mutations occur in 15% to 20% of melanomas (41–44). Mutations in the other two RAS family members, HRAS and KRAS, are less common (1%–2%). Mutations in RAS genes typically affect codons Q61, G12, or G13. All of these mutations lead to GTPase inactivation, resulting in constitutive GTP binding and activation of the protein. RAS activation leads to multiple downstream signaling events. The most well recognized oncogenic downstream signaling events are phosphorylation and activation of PI3K (phosphatidylinositol 3OH-kinase) and the PI3K/PI4K pathway, as well as RAF, leading to mitogen-activated protein (MAP) kinase signaling through the RAS/RAF/MEK/ERK signaling cascade (Figure 1). Clinically, the presence of NRAS mutations is associated with primary tumors of greater thickness than comparable BRAF-mutant, BRAF–wild-type or NRAS–wild-type melanomas (43) and with a poorer prognosis in metastatic disease (42).

**KIT**. KIT is a type III transmembrane receptor tyrosine kinase. Classical activation occurs by ligand binding, leading to receptor dimerization, and autophosphorylation of tyrosine residues. Downstream targets activated by KIT are the MAP kinase, PI3K/AKT (phosphatidylinositol 3 kinase), and JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathways.

KIT mutations in melanoma illustrate the rationale for personalized medicine and stratified therapies in melanoma. A number of clinical trials initially tested imatinib, an oral tyrosine kinase inhibitor also targeting KIT, in metastatic melanoma and reported poor efficacy, with only selected patients showing responses (45–47). Subsequently, it was found that the frequency of KIT mutations varies (2%–21%) depending on melanoma subtype (48–50). KIT mutations and amplifications are primarily found in mucosal and acral melanomas (10%–20% of melanomas at these sites), and less commonly in melanomas in SSD skin (49,50). Larger studies that selectively treated patients with detected KIT alterations showed responses to imatinib in KIT-mutant tumors, primarily those with mutations in exon 11 (L576P) and exon 13 (K642E) (51–53). Tumors solely harboring KIT copy number increases (but lacking KIT mutations) responded poorly to treatment (52).

**GNAQ/GNA11**. GNAQ and GNA11 are two members of the Gq family of G proteins. They share 90% homology at the amino acid level (54). G proteins exist as heterotrimers of alpha, beta, and gamma subunits (55). Physiologic activation occurs through receptor ligand binding, leading to GTP loading of Gqα and Gqα11 (translated proteins of GNAQ and GNA11, respectively) and their dissociation from the G protein heterotrimer complex. Well-recognized downstream signaling events of Gq and Gqα11 are activation of phospholipase C beta, which leads to activation of protein kinase C (PKC) and diacylglycerol formation, as well as activation of Rho (56) (Figure 2).

Mutations in GNAQ and GNA11 occur in 80% to 90% of uveal melanomas (57,58). Mutations are also frequent in blue nevi and central nervous system melanocytomas (59,60) but are very rare in cutaneous melanomas (<1%) (57). The most frequent mutations found in both genes are exon 5 Q209 mutations (~90%) and exon 4 R183 mutations (approximately 5%). All mutations lead to inhibition of GTPase function and a constitutively GTP-bound, activated protein (61). To date, the recognition of these mutations has not translated to successful treatment with targeted therapies, but clinical trials with PKC and MEK inhibitors as well as other agents are in progress.

**Loss of Function/Tumor Suppressor Genes**

Tumor suppressor genes are genes whose inactivation in tumor cells leads to a proliferative advantage. Mechanisms leading to loss of function of tumor suppressor genes include loss of the gene locus, nonsense or frameshift mutations, and altered epigenetic regulation (ie, promoter hypermethylation), all of which result in loss of functional protein expression.

**CDKN2A**. The first gene locus linked to familial melanoma was found to be located on chromosome 9p (7). Later studies of this locus identified CDKN2A, a gene regulating the cell cycle (8,9,62) and having alternate reading frames coding for two proteins, p14ARF and p16INK4a (63). p16INK4a controls the cell cycle by negatively regulating cyclin-dependent kinases (CDKs) 4 and 6, thereby blocking phosphorylation of the retinoblastoma protein (Rb) (64,65). Phosphorylation of Rb results in release of the E2F transcription factor, allowing the cell cycle to continue from G1 to S phase (66). p14ARF inhibits MDM2, a ubiquitin ligase that targets p53 for pro teaseal degradation. One function of p53 is to induce p21, which inhibits CDK2-induced and cyclin E–induced phosphorylation of Rb (66) (Figure 3).
CDKN2A mutations are the most frequent genetic events underlying familial melanoma susceptibility and have been reported in the germline of 8% to 57% of familial melanoma cases (67–69). CDKN2A is also the most frequently affected tumor suppressor gene in sporadic melanoma (14). CDKN2A losses, often biallelic, are found in 50% to 80% of sporadic melanomas (13,15,70), and inactivating mutation or gene silencing promoter methylation has been described in 9% to 28% of tumors (70).

PTEN. PTEN functions as a tumor suppressor by inhibiting PI3K signaling. PTEN's lipid phosphatase dephosphorylates PI3K 3-phosphoinositide products, leading to inhibition of different signaling pathways, including AKT (Figure 1). PTEN was initially reported to be lost or mutated in 43% of melanoma cell lines and 38% of primary melanomas (12). More recent studies have reported losses in 63% to 70% of melanomas (13,15). Epigenetic silencing of PTEN has also been described in melanoma (71,72). Induction of melanoma by mutant BRAF and PTEN loss has been shown in mouse models (73). In human tumors, PTEN losses are more frequently identified in BRAF-mutant than in NRAS-mutant melanomas (14,15). This is consistent with NRAS mutations already resulting in activation of the PI3K/AKT pathway which is not the case for BRAF mutations.

NF1. NF1 is a tumor suppressor gene that is inactivated by germline mutations in patients with type 1 neurofibromatosis (74–76). It is inactivated in a number of malignancies, including lung adenocarcinomas, neuroblastomas, and glioblastomas (1,77–79). NF1 encodes the protein neurofibromin, which interacts with RAS and negatively regulates its function by inducing hydrolysis of RAS-bound GTP to GDP (80). Functional inactivation of NF1 thus leads to activation of RAS and its downstream signaling pathways, including the MAPK, PI3K/AKT, and mTOR pathways (81,82).

Two recent studies showed that NF1 may play an important role in the pathogenesis of BRAF-mutant melanomas, as well as in tumors resistant to BRAF inhibitors (83,84). Although loss of NF1 in BRAF-mutant tumors led to resistance to certain BRAF inhibitors (ie, PLX4720) and MEK inhibitors, tumors were still responsive to treatment with either the combination of a MEK and mTOR inhibitor, irreversible RAF inhibitor (AZ628), or an ERK inhibitor. Therefore, determining NF1 status in melanomas may be important for making treatment decisions.

BAP1. BAP1 (BRCA1-associated-protein 1) was first described as a BRCA1 binding partner that inhibited cell growth (85). The deubiquitinase activity and nuclear localization of BAP1 was shown

Figure 3. Alterations in mechanisms of cell cycle control. CDKN2A protein products p14 (p14ARF) and p16 (p16INK4A) inhibit progression of the cell cycle through independent mechanisms. p16 inhibits cyclin D1 (CCND1)-dependent activation of cyclin dependent kinase 4 and 6 (CDK4, CDK6) and thus prevents the phosphorylation of RB1. Phosphorylated RB1 leads to its dissociation from E2F and cell cycle progression. p14 inhibits the function of MDM2, which normally ubiquitinates p53, targeting it for degradation by the proteasome. p53 induces p21 expression, which inhibits cell cycle progression both through inhibition of CCND1 and CDK4/6 as well as CDK2 and CCNE1. Removal of both p14 or p16 results in unregulated increases in cell cycle progression. CCND1 = cyclin D1; CCNE1 = cyclin E; CDK2 = cyclin-dependent kinase 2; CDK4 = cyclin-dependent kinase 4; CDK6 = cyclin-dependent kinase 6; MDM2 = MDM2 oncogene, E3 ubiquitin protein ligase; E2F = E2F transcription factors; p = phosphate; RB1 = retinoblastoma 1; ubi = ubiquitin.
to be relevant for BAP1-mediated tumor suppression (86). Further studies will be required to delineate the functional role of BAP1 in tumor formation.

BAP1 was originally identified in breast and lung cancer cell lines (85). Recently, inactivating mutations of BAP1 were described in 84% of metastazing uveal melanomas (87). Other reports have identified losses or inactivating mutations in a number of other cancers, including breast carcinoma (88), renal cell carcinoma (89), and mesothelioma (90,91). BAP1 loss plays an important role in uveal melanomas, but it has also been reported in cutaneous melanocytic tumors, including melanomas (60,92). Germline mutations in BAP1 predispose to the development of several different tumors, including distinctive epithelioid melanocytic tumors of the skin (92), uveal melanoma (93), mesothelioma (94), cutaneous melanoma (92), and others.

**Gene Expression Profiles in Melanoma**

Gene expression profiling has become a useful tool for the clinical management of patients with certain human cancers, such as determining treatment options in breast cancer (95) or prognosis in uveal melanoma (96–98). Several gene expression profiling studies of cutaneous melanoma have been performed. One of the first large studies analyzing RNA expression profiles was published in 2000 (99). Other studies identifying different gene expression sets followed (100,101), and recently, immune response–related genes have gained interest. A study of stage IV melanomas found low expression of an immune response–related gene signature to be associated with poor prognosis (102). Immune-related genes were also prominent in a 46-gene panel, which, when coupled with other clinicopathologic parameters, allowed more accurate prognostic assessments in stage III melanoma patients (35). There have been many other gene expression studies that are reviewed in detail elsewhere (103–105).

Despite these promising findings, gene expression profiling for cutaneous melanoma has not become a routine part of clinical management of melanoma patients. The main hurdle is that identified individual genes and gene expression signatures varied between studies and proved to be substantially less robust in follow-up studies (103–105). Reasons for variability in the results include methodological differences such as differences in the array systems, tumor characteristics, and tumor samples (issues related to tumor purity or to frozen vs paraffin-embedded tumors).

However, gene expression profiling of immune response–related genes (to determine how patients will respond to immunotherapy) is the subject of recent attention (35,102,106,107) and may yet prove to be clinically useful.

**Recently Identified and Incompletely Understood Genetic Events**

Remarkable progress has been made over the past two decades in unveiling the genetic landscape of melanoma. Many key genetic alterations (Figure 4) and oncogenic mutations (Figure 5) in melanoma have been recognized and their roles in tumorigenesis have been characterized. With the recent publication of a number of massively parallel sequencing studies of melanoma, new candidate genes have been described that are yet to be functionally defined and whose clinical relevance in terms of treatment potential are

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**Figure 4.** Summary of key genetic alterations in melanoma. The distribution of genetic events in different types of melanoma is shown. The **top panel** shows classic gain-of-function events that are frequently mutually exclusive. Below this, frequent additional genetic events in terms of tumor suppressor losses or **TERT** expression gains are shown. The **panel at right** shows the distribution of gene mutations in uveal melanoma. Genetic alterations in uveal melanoma have strong prognostic value (as noted below the genes in the figure). * refers to activating mutations for **TERT**, which should not affect the gene directly but are in the promoter region. Although many genetic events depicted are predominantly mutually exclusive, many can occur concurrently in individual cases. Mucosal melanoma (not shown here) is genetically similar to acral melanoma. Gains or mutations of **CDK4**, **CCND1**, and **KIT** are not always mutually exclusive; however, they more frequently occur in **BRAF**– and **NRAS**–wild-type tumors (14,50,109). **CDK4** gains are associated with lower amounts of **CDKN2A** losses (14). This figure represents a simplification of the genetic landscape of melanoma, and the interested reader is referred to references cited in the text for more detail. **BAP1** = BRCA1 associated protein 1; **BRAF** = v-Raf murine sarcoma viral oncogene homolog B; **CCND1** = cyclin D1; **CDK4** = cyclin-dependent kinase 4; **CDKN2A** = cyclin-dependent kinase inhibitor 2A; **SF3B1** = splicing factor 3b, subunit 1; **EIF1AX** = eukaryotic translation initiation factor 1A, X-linked; **GNAQ** = guanine nucleotide-binding protein subunit alpha-11; **GNA11** = guanine nucleotide-binding protein, q polypeptide; **KIT** = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; **NRAS** = neuroblastoma RAS viral oncogene homolog; **PTEN** = phosphatase and tensin homolog; **SF3B1** = splicing factor 3b, subunit 1; **TERT** = telomerase reverse transcriptase.
in SWI/SNF family member genes mutation is the SWI/SNF complex (group that is involved in melanoma development and progression). One chromatin remodeling approaches have also unveiled a number of mutations in genes coding linked to signaling pathways, massively parallel sequencing these mutations in melanoma.

In addition to genetic alterations affecting proteins directly linked to signaling pathways, massively parallel sequencing approaches have also unveiled a number of mutations in genes coding for chromatin remodeling proteins. Chromatin remodeling often involves modification of histones—for example, by addition of or removal of covalently bound methyl, acetyl, or ubiquitin residues (118). Proteins involved in chromatin modification are grouped into functional families, often playing critical roles in normal tissue development and cell differentiation. One chromatin remodeling group that is involved in melanoma development and progression is the SWI/SNF complex (119,120). Inactivating mutations in SWI/SNF family member genes ARID1A, ARID1B, ARID2, and SMARCA4# were reported in 16 of 121 melanomas (109). EZH2 murine sarcoma viral oncogene homolog B; GNA11 = guanine nucleotide-binding protein subunit alpha-11; GNAQ = guanine nucleotide-binding protein, q polypeptide; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; Non-SSD = melanoma arising in nonseverely sun-damaged skin; NRAS = neuroblastoma RAS viral oncogene homolog; SSD = melanoma arising in severely sun-damaged skin.

Distribution of Mutations in Terms of Functional Groups
The functional consequences of genetic events tend to dictate whether they coexist in the same tumor or whether they are mutually exclusive. In general, melanocytic tumors harbor only one gene alteration activating the MAP kinase pathway—for example, BRAF, NRAS, KIT, or NF1 in cutaneous melanoma (14,83,108,109) or GNAQ or GNA11 in uveal melanoma, blue nevi, and central nervous system melanocytomas (57,59,124). A similar pattern is seen with regard to genetic alterations influencing the cell cycle (Figure 3). Losses and mutations of CDKN2A, leading to loss of p14 and p16, and gains of CDK4 and MDM2 (located within a few megabases of each other) have very similar functional consequences, which explains why these events rarely coexist in the same tumors (especially homozygous CDKN2A losses) (14,109). Both CCND1 and CDK4 copy number increases are seen primarily in tumors lacking BRAF or NRAS mutations (14,109), arguing that additional events that deregulate the cell cycle are required in BRAF-wild-type and NRAS-wild-type tumors. PI3K/AKT signaling is activated downstream by NRAS and KIT mutations but not by BRAF mutations (Figure 1). Not surprisingly, PI3K/AKT pathway alterations, including frequent PTEN losses or rarely PIK3CA or PIK3R1, or 3 mutations (109,125), are most commonly identified in BRAF-mutant melanoma. These examples still not understood. Examples include putative activating driver mutations in genes such as PPP6C, STK19, RAC1 (108,109), and TRRAP (110). Mutations in ERBB4 have been described in up to 19% of melanomas, with functional studies describing an activating effect (111). Alterations currently presumed to have an inactivating function include those in PREX2 (112), which have regulatory effects on PTEN and the PI3K/AKT pathway, as well as those in MAP3K5 and MAP3K9 (113), which are involved in the MAP kinase signaling pathway.

Two recent reports found activating mutations in the telomerase reverse transcriptase (TERT) promoter in up to 71% of cutaneous melanomas (114,115). The mutations result in a two- to fourfold increase in gene expression. Telomerase overexpression allows neoplastic cells to continuously proliferate without entering senescence or apoptosis by maintaining telomere length and avoiding chromosomal instability. TERT promoter mutations have also been found to be frequent in conjunctival but not uveal melanomas (116). Further studies are required to fully elucidate the role of these mutations in melanoma.

Figure 5. Prevalence of oncogene mutations in melanoma subtypes. The most common activating gene mutations known to occur in different melanoma subtypes are shown. BRAF, NRAS, GNAQ, and GNA11 refer to percentage of tumors harboring activating mutations. Percentages of KIT shown refer to either copy number increases or mutations. Ocular (conjunctival and uveal) melanomas are shown on the right. Data are taken from (19,50,57,209,210). BRAF = v-Raf murine sarcoma viral oncogene homolog B; GNA11 = guanine nucleotide-binding protein subunit alpha-11; GNAQ = guanine nucleotide-binding protein, q polypeptide; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; Non-SSD = melanoma arising in nonseverely sun-damaged skin; NRAS = neuroblastoma RAS viral oncogene homolog; SSD = melanoma arising in severely sun-damaged skin.
illustrate the impact of functional consequences on the patterns of genetic alterations in melanocytic tumors.

**Genotype–Phenotype Associations in Melanoma**

*BRAF* mutations in melanoma are associated with younger patient age and with anatomic location on trunk and lower extremities (126–128). Histologically, *BRAF* mutations are commonly associated with superficial spreading melanomas (126,129) and with the presence of melanin pigment in melanomas (127). They are also associated with thinner tumors with lower tumor mitotic rates and proliferation indices (127). There is an inverse correlation between the degree of dermal solar elastosis (a histologic correlate of damage related to cumulative sun exposure) and the frequency of *BRAF* mutations, especially *BRAFV600E* mutations (32,126,128,130). This may be because the relative proportion of *BRAFV600E*-mutant melanomas is lower in anatomic sites with high levels of sun exposure, where melanomas that arise through other mechanisms [such as *BRAFV600K* (32) and *KIT* mutations (50)] associated with high ultraviolet exposure are more common.

A number of oncogenic mutations in melanoma are prognostically relevant. *BRAF* mutations were found to be poor prognostic markers in patients diagnosed at stage III or IV (35,36). Studies have also shown worse prognosis for NRAS-mutant tumors at stage III or IV (35,42). Similarly, the presence of *KIT* mutations or alterations was shown to be associated with decreased overall survival in a large study of Asian patients (48). Correspondingly, another study found *KIT*-mutant stage IV melanomas to have a worse prognosis than comparable *KIT* wild-type tumors (131).

Based on a detailed morphological study of a large number of melanomas with known *BRAF* and NRAS mutation status, Viros et al. (128) proposed histological features that could predict *BRAF* (but not NRAS) mutation status. These features included upward migration and nest formation of intra-epidermal melanocytes; epidermal thickening; demarcation of the melanocytic proliferation; and larger, rounded, pigmented melanocytes. By integrating the findings of such studies, the traditional histological taxonomy of melanomas could be improved, thereby yielding a more biologically relevant and therefore clinically useful classification. Although Viros at al. (128) showed some associations between mutation status and morphological features, the associations are not strong enough or universal enough to accurately infer genotype from phenotype or vice versa. Detailed histopathologic evaluation and *BRAF* mutation analysis by DNA or immunohistochemistry analysis remain the standard of care. As more genetic alterations (and their clinicopathologic correlates) are identified in melanoma, further refinements of the integrated genetic–morphological classification will be possible, allowing better prognostic and therapeutic stratification of melanoma patients.

**Personalized Medicine and Melanoma**

**Genetic Susceptibility to Melanoma**

The percentage of melanomas occurring in melanoma-prone families is on the order of approximately 10% (132,133). The most common susceptibility gene is the previously described *CDKN2A* (7), accounting for 8% to 57% of disease susceptibility (67–69).

Germline *CDKN2A* mutations more frequently affect p16; however, cases harboring selective alteration of p14 have also been described (134,135). Another melanoma susceptibility gene is cyclin-dependent kinase 4 (*CDK4*) (136). *CDK4* binds with p16, with both regulating the downstream protein retinoblastoma. *RB1* mutation carriers are also at increased risk of developing melanoma (137). However, *CDK4* and *RB1* germline mutations in melanoma are rare events. Other genetic events shown to predispose to melanoma are inactivation of *BAP1* (92) (in particular in uveal melanoma and less frequently in cutaneous melanoma) and *TERT* promoter mutations, which were described in one family with very high penetrance for cutaneous melanoma at an early age (114). Relatively recently, *MITF* mutations impairing the protein’s physiologic sumoylation have been described as an intermediate risk factor (138,139). The identified *MITF* E318K alteration led to gene expression profile changes with altered regulation of *MITF* targets and a biological gain-of-function effect with mutant cells showing increased clonogenicity, migration, and invasion (138,139). The most prevalent low-risk genetic factors for melanoma are *MCIR* variants (140). Large numbers of *MC1R* polymorphisms exist and influence skin pigmentation (141). The risk differs depending on the variant and is additive when multiple inactivating variants are present. Although originally linked primarily to sun exposure, recent experimental evidence suggests that *MCIR* variants also increase melanoma risk independent of ultraviolet exposure (142).

**Diagnosis**

The majority of melanocytic tumors are readily diagnosed by histopathologists as benign or malignant on the basis of their morphological features. However, in a few cases, melanocytic tumors present an ambiguous histological picture and exhibit features seen in both benign and malignant tumors. In these cases, ancillary genetic tests can be helpful in determining whether a tumor should be categorized as benign (nevus) or malignant (melanoma).

**Comparative Genomic Hybridization.** CGH allows assessment of chromosomal copy number changes across the entire genome (13). The technique has been refined over the years and is currently array-based, with high resolution and standardized user-friendly software (Figure 6). One of the main caveats is that the tumor cell population analyzed has to be relatively pure. Should higher percentages of surrounding non-tumor tissue contaminate the sample, chromosomal alterations may be missed. In cases where little tumor tissue is available, or when it is heavily admixed with normal tissue, fluorescence in situ hybridization (FISH) may be a helpful alternative.

**Fluorescence In Situ Hybridization.** FISH as a diagnostic tool in melanoma is based on assessment of loci known to harbor chromosomal alterations that were identified by CGH. Probes detecting commonly altered loci were tested in various combinations on cohorts of melanocytic tumors with known outcomes (143). The major advantage of FISH is that it is done on histologic slides, allowing assessment of morphology, which in contrast to CGH enables analysis of small or dispersed amounts of tumor tissue. The initial set of commercially available probes was directed at 6p25 (RREB1), 6q23 (MYB), Cep6 (centromere 6), and 11q13 (CCND1) (Figure 6).
Sensitivity and specificity reported in the initial study and two validation studies ranged from 83% to 86.7% and 90% to 95.4%, respectively (143–145). Further studies recommended either adding a 9p21 probe (which harbors the CDKN2A locus) (146) or altering the probe set to a combination of 9p21, 6p25, 11q13, and 8q24 (147) to increase sensitivity and specificity, in particular for spitzoid tumors. In summary, FISH is a useful tool for assessing melanocytic tumors, and there are ongoing efforts by different groups to further improve the sensitivity and specificity of the technique (146–148).

CGH and FISH are useful supplemental diagnostic tools in assessing borderline melanocytic lesions. They can be particularly helpful for pediatric melanocytic lesions, where making a distinction between a benign spitzoid lesion and a melanoma can be very difficult (149,150). These tests are routinely used in a number of centers worldwide. In some histologically ambiguous tumors that are deemed to be borderline (“of uncertain malignant potential”), CGH or FISH reveals a profile of genetic alterations that allows definitive assessment of whether the tumor is benign or malignant and aids management of affected patients. For example, the absence of copy number alterations points to a benign tumor, whereas the presence of numerous alterations favors malignancy (13). However, other cases show an ambiguous profile of genetic alterations, which precludes definitive distinction of benign and malignant tumors.

**Targeted Therapies (Tables 1 and 2)**

**BRAF Inhibitors.** The emergence of specific, clinically effective inhibitors of V600-mutant BRAF is a major landmark in the field of personalized medicine. Clinical efficacy of the first compound (now known as vemurafenib) was reported in 2010 (151,152), a mere 8 years after the identification of BRAF mutations in melanoma (30). In a number of clinical trials, vemurafenib has shown remarkable early responses in patients with BRAF-mutant metastatic melanoma. The phase III BRIM-3 (BRAF in Melanoma) trial compared vemurafenib with standard chemotherapy treatment with dacarbazine. Response rates were 48%, with a median progression-free survival (PFS) of 5.3 months in the vemurafenib group, compared with a 5% response rate and 1.6-month median PFS for dacarbazine (153). Because of the sizable clinical benefit, the study was halted ahead of schedule and vemurafenib was approved by the US Food and Drug Administration (FDA) in 2011. Dabrafenib is another selective BRAF V600 inhibitor, now also FDA approved for the treatment of BRAF V600-mutant melanoma (154). A phase III trial of dabrafenib in melanoma reported treatment responses similar to the vemurafenib trial, with a median PFS of 5.1 months in the dabrafenib-treated group and 2.7 months in the dacarbazine-treated group (155).

Side effects of both these BRAF inhibitors are similar, although photosensitivity appears to be more severe with vemurafenib. A frequent event is the development of verruciform keratoses (up to 49%) and cutaneous squamous cell carcinomas particularly of the keratoacanthoma type (approximately 25%) (153,156,157). Additionally pruritus, acneiform eruptions and hyperkeratosis of the hands and feet can occur (overall approximately 31%). Noncutaneous side effects reported are arthralgia (approximately 21%), liver enzyme increases (approximately 6%), and nausea (approximately 8%) (153,157).

**MEK Inhibitors.** MEK is downstream of BRAF and RAS, and a number of inhibitors blocking MEK activation have been developed. A promising drug is trametinib (158–160). A phase III trial in BRAF-mutant metastasized melanoma patients showed a median PFS of 4.8 months in the trametinib group compared with 1.5 months for chemotherapy (paclitaxel or dacarbazine) (161). Limiting side effects were diarrhea, skin rashes, and ocular toxicity, in particular serous retinopathy (158,159). Based on these findings, the US FDA has recently approved trametinib for unresectable or metastatic melanoma that has not been previously treated with a BRAF inhibitor. Combination therapy, combining trametinib with

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**Figure 6.** Assays analyzing DNA copy number alterations in determining whether melanocytic tumors are benign or malignant. A) Examples of fluorescence in situ hybridization of melanomas showing copy number gains of CCND1 and RREB1 (images courtesy of Drs Tina Selinger and Sandra O’Toole). B) Comparative genomic hybridization profiles of a benign nevus (top) and malignant melanoma (bottom) with corresponding histological pictures shown on the left. Whereas the nevus shows no alterations of chromosome numbers, the melanoma presents gains of 6p, 8q, and 10p, as well as losses of 6q, 9p, and 10q (images courtesy of Dr Thomas Wiesner). CCND1 = cyclin D1; RREB1 = ras responsive element binding protein 1.
### Table 1. Recently introduced therapies for melanoma*

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Melanoma mutation profile</th>
<th>Medication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>BRAF V600</td>
<td>Vemurafenib Dabrafenib</td>
<td>Development of proliferative cutaneous lesions (e.g., verruciform keratoses, keratoakanthomas, squamous cell carcinomas, acneform eruptions, other skin rashes, arthralgias, photosensitivity, panniculitis, elevated liver enzymes, nausea)</td>
</tr>
<tr>
<td>MEK</td>
<td>BRAF BRAF</td>
<td>Trametinib MEK162</td>
<td>Diarrhea, acneform dermatitis and other skin rashes, peripheral and facial edema, ocular toxicities (e.g., dry eyes, blurred vision, and reversible central serous retinopathies, creatine phosphokinase increases)</td>
</tr>
<tr>
<td>NRAS</td>
<td>NRAS WT</td>
<td></td>
<td>Blood formation deficits (including neutropenia, thrombocytopenia, anemia), gastro-intestinal symptoms, edemas, liver enzyme and bilirubin level increases, skin rashes</td>
</tr>
<tr>
<td>KIT</td>
<td>KIT</td>
<td>Imatinib Nilotinib Sunitinib Danatinib Pipilimunab (Tremelimumab)</td>
<td>In particular autoimmune diseases (e.g., colon [diarrhea, colitis], endocrine [thyroiditis, hypophysitis, adrenal gland insufficiency, hypopituitarism], hepatic, renal, lung, cutaneous [pruritus, rash, vitiligo], ocular)</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>All melanomas</td>
<td>Ipilimumab (Tremelimumab)</td>
<td></td>
</tr>
<tr>
<td>PD-1</td>
<td>All melanomas</td>
<td>Nivolumab (MK-3475 BMS-936559)</td>
<td>Autoimmune diseases Comparable spectrum to CTLA-4 antibodies, but potentially milder</td>
</tr>
</tbody>
</table>

* BRAF = v-Raf murine sarcoma viral oncogene homolog B; CTLA-4 = cytotoxic T-lymphocyte antigen-4; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MEK = MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) kinase; NRAS = neuroblastoma RAS viral oncogene homolog; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death 1 ligand 1; WT = wild-type for BRAF and NRAS.

### Table 2. Selection of clinical trials applying individual or multiple targeted agents in melanoma*

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Melanoma mutation profile</th>
<th>Target(s)</th>
<th>Study phase</th>
<th>Status</th>
<th>Trial No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib Bevacizumab</td>
<td>BRAF</td>
<td>BRAF VEGF</td>
<td>Phase II</td>
<td>Enrolling</td>
<td>NCT01495988</td>
</tr>
<tr>
<td>Vemurafenib PX-866</td>
<td>BRAF</td>
<td>BRAF P13K</td>
<td>Phase I+II</td>
<td>Enrolling</td>
<td>NCT01616199</td>
</tr>
<tr>
<td>Vemurafenib XL888</td>
<td>BRAF</td>
<td>BRAF HSP90</td>
<td>Phase I</td>
<td>Enrolling</td>
<td>NCT01657591</td>
</tr>
<tr>
<td>LGX818 vs LGX818 MEK162 vs Vemurafenib</td>
<td>BRAF</td>
<td>BRAF</td>
<td>Phase III</td>
<td>Enrolling</td>
<td>NCT01909453</td>
</tr>
<tr>
<td>LGX818 + MEK162 or LEE011 or BGJ398 or BKM120 or INC280</td>
<td>BRAF CDK4/6 FGFR P13K c-Met</td>
<td>BRAF MEK BRAF</td>
<td>Phase II</td>
<td>Not yet enrolling</td>
<td>NCT01820364</td>
</tr>
<tr>
<td>Tramatenib GSK2141796</td>
<td>BRAF wild-type</td>
<td>MEK AKT</td>
<td>Phase II</td>
<td>Not yet enrolling</td>
<td>NCT01941927</td>
</tr>
<tr>
<td>Pimasertib vs DTIC MEK162 LEE011</td>
<td>NRAS</td>
<td>MEK</td>
<td>Phase II</td>
<td>Enrolling</td>
<td>NCT01693068</td>
</tr>
<tr>
<td>MEK162 LEE011</td>
<td>NRAS CDK4/6</td>
<td>MEK</td>
<td>Phase I+II</td>
<td>Enrolling</td>
<td>NCT01781572</td>
</tr>
<tr>
<td>MEK162 BKM120</td>
<td>NRAS or BRAF</td>
<td>MEK P13K</td>
<td>Phase I</td>
<td>Enrolling</td>
<td>NCT01363232</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>KIT</td>
<td>KIT</td>
<td>Phase II</td>
<td>Enrolling</td>
<td>NCT01099514</td>
</tr>
<tr>
<td>Masitinib vs DTIC</td>
<td>KIT</td>
<td>TKI KIT</td>
<td>Phase III</td>
<td>Enrolling</td>
<td>NCT01280565</td>
</tr>
</tbody>
</table>

* (Table continues)
the BRAF inhibitor dabrafenib, has proven to be even more promising on the basis of improved efficacy as well as suppression of some BRAF inhibitor–associated phenomena, such as cutaneous squamous cell carcinomas (5). Median PFS for patients receiving both dabrafenib and trametinib was 9.4 months compared with 5.8 months for dabrafenib alone. A complete or partial response was observed in 76% of patients receiving both agents, compared with 54% for those receiving only dabrafenib. This represents the best result for targeted therapies in melanoma to date. The combination treatment group experienced more frequent systemic side effects, including pyrexia (71%), chills (58%), fatigue (53%) and vomiting (40%), than the group receiving monotherapy (26%, 17%, 40%, and 15%, respectively), but cutaneous side effects including hyperkeratosis, alopecia, and cutaneous squamous cell carcinoma were less frequent (9% vs 30%; 5% vs 34%; and 7% vs 19%, respectively).

Results from a phase II trial of another MEK Inhibitor, MEK162 were published recently (162). Median PFS was 3.7 months for the NRAS-mutant group and 3.6 months for the BRAF-mutant group; in both groups a partial response (PR) was achieved in 20% of patients. In BRAF-mutant melanoma, MEK inhibitors show somewhat inferior results to those for BRAF inhibitors. However, the MEK162 study also showed efficacy of a MEK inhibitor in NRAS-mutant tumors (162).

In summary, it appears that for BRAF-mutant tumors, MEK inhibitors perform less well than BRAF inhibitors when used as monotherapy and are likely to show greater benefit when used in combination with BRAF inhibitors. However, MEK inhibitors currently represent the first targeted therapeutic agents to show benefit in NRAS-mutant tumors.

**KIT Inhibitors.** Initial trials using KIT inhibitors involved unselected patient cohorts and, not surprisingly, showed poor results (45, 47, 163). Studies selectively targeting patients whose tumors harbor KIT alterations have shown considerably more promise. The most frequently used agent for treatment of melanomas with...
KIT alterations has been imatinib. Although initial case studies reported dramatic responses to imatinib (164,165), larger studies have shown less promising results (51,52). Three phase II trials showed a median PFS of approximately 3 months [3.5 months (51), 3.7 months (53), and 12 weeks (52)]. In one study there were two complete responses with two durable and two transient PRs in 25 patients (52); in the other studies, there were 10 PRs and 13 cases of stable disease (SD) in 43 patients (51) and five cases of SD and seven PRs in 24 patients (53), with an overall PFS of only 3.5 or 3.7 months, respectively. The Guo et al. trial did, however, find that in patients with either SD or PR, PFS and OS were 9 months and 15 months, respectively, compared with 1.5 and 9 months, respectively in nonresponders (51). In all studies, the majority of patients responding to therapy had tumors characterized by exon 11 and 13 mutations (ie, L576P and K642E). Other inhibitors targeting KIT that have been used are sorafenib, sunitinib (131), dasatinib (166), and nilotinib (167). All studies to date have shown limited success, with therapeutic benefits only seen in some cases. Tumors with increased copy numbers of KIT but lacking mutations generally respond poorly. It is hoped that the development of novel inhibitors showing effects on tumors harboring KIT mutations as well as copy number increases will improve therapeutic options for patients with KIT-aberrant melanomas. Although the results vary, imatinib is currently a treatment option that should be considered for patients with metastasized KIT-mutant melanomas, in particular those harboring L576P or K642E mutations.

Resistance to Targeted Therapies. Virtually all tumors treated with BRAF inhibitors become resistant to therapy at some point. Many different mechanisms have been described, such as additional alterations in the MAP kinase pathway, including NRAS (168) and MEK (169) mutations, as well as splice variations or amplifications of BRAF (170–172) or CRAF (173). Losses of NF1 (83,84), as well as increased expression of COT (174) have also been described. Upregulation of receptor tyrosine kinases such as PDGFRβ (168) and IGF-1R (175), have also been shown to lead to resistance, primarily through activation of the PI3K/AKT pathway. Activation of this pathway by losses of PTEN (176) has also been described as a resistance mechanism. Changes in cell cycle control, in particular overexpression of CCND1, have been associated with resistance to BRAF inhibitors (177). Recently, hepatocyte growth factor signaling through its receptor cMET was shown to mediate BRAF inhibitor resistance (178,179). These data also imply that stromal and microenvironmental factors could play an underappreciated role in resistance. Although BRAF inhibitors are very useful in the management of BRAF-mutant stage IV melanoma patients (approximately half of all patients with cutaneous melanoma are BRAF-mutant), an ongoing challenge is to prevent or circumvent resistance to BRAF inhibitors by using combination therapies that target one or more of the resistance mechanisms. Scaffolding proteins necessary for MAP kinase pathway signaling could prove to be valuable additional therapeutic targets. Considerable therapeutic effects were seen upon inhibition of the scaffold protein MAP kinase interaction, even in BRAF inhibitor-resistant cell lines (180).

The overarching challenge will be to personalize and combine available therapeutic options based on anticipated mechanisms of resistance relevant to each patient's tumor. Similarly, although individual cases have been reported showing long term responses (>1 year) to imatinib (164), most melanomas showing initial responses to KIT inhibitors became resistant, frequently within a matter of months (51–53). Resistance to KIT inhibitors has been examined mainly in nonmelanoma tumors, in particular, gastrointestinal stromal tumors, in which resistance is primarily due to the emergence of secondary mutations affecting drug binding or accessibility to the ATP binding pocket (181–184). In melanoma, KIT inhibitor resistance has been reported to be associated with activation of the PI3K/AKT/mTOR pathway (161), presence or emergence of NRAS mutations (53,131), and KIT copy number increases (53). A recent study found that melanoma cell lines harboring mutations resistant to certain KIT inhibitors were still sensitive to other RTK inhibitors (185). Additionally, joint MAPK and PI3K/AKT inhibition also proved effective. Hopefully these treatment options will prove beneficial in the clinical setting.

Tumor Heterogeneity and Its Implications for Implementation and Efficacy of Targeted Therapies. The increasing sophistication of techniques for analysis of cancer genomics has revealed the considerable heterogeneity that exists within tumors (186–189). Although some common alterations exist (particularly in terms of mutations in major driver oncogenes and tumor suppressor genes), the pattern of other alterations in many other genes is highly variable between individual tumors, resulting in considerable intratumoral heterogeneity (188,190,191). This heterogeneity may result from events that are positively selected during tumor progression and are influenced by a variety of factors, including the host's genome, epigenetic influences, tumor microenvironment, immunologic factors, and therapeutic interventions. Metastatic tumors, although originating from one or more clones of a primary tumor, continue to evolve after colonization of distant sites, thereby developing even greater levels of intratumor heterogeneity. Finally, it appears that tumor cells from some metastases may colonize (“self-seed”) their primary tumor of origin (192,193), potentially adding to the diversity of genomic alterations in these tumors.

Heterogeneity within tumors raises a number of important issues. From the discovery standpoint, the results of analysis of tumors will be heavily influenced by the area(s) of tumor that are sampled for analysis. Although early genetic events that are present in the vast majority of tumor cells are likely to be detected irrespective of sampling sites, subsequent events that may be restricted to smaller clones within the tumor are unlikely to be detected unless the tumor is widely sampled and sequenced at very high depth. The emerging approach of sequencing DNA from single cells obtained from different sites in the tumor might help in addressing these issues (187).

Clinically, intratumor heterogeneity has implications for detection of genetic events and for targeted therapy. Detection of early events that are targetable (such as the BRAF oncogenic mutation in melanoma) is unlikely to be a problem, given their widespread occurrence in tumor cells. However, this may not be the case for newly discovered targetable genetic events that occur in discrete clones or regions of tumors. Tumor sampling may have a major influence on whether all actionable genetic alterations within a tumor will be detected, and therefore on whether the most appropriate therapy will be offered to patients. Furthermore, genetic alterations that confer resistance to certain targeted therapies may only be present...
The recent identification of TERT promoter mutations leading to increased expression of telomerase in up to 71% of cutaneous melanomas (114,115) shows that highly relevant pathogenetic mutations do not have to affect protein coding regions but may also be found elsewhere (eg, in regulatory DNA domains).

One of many promising ongoing research efforts is focusing on improving the targeted therapy options for metastatic melanoma patients with BRAF wild-type tumors. The Stand Up To Cancer initiative aims to perform massively parallel sequencing of BRAF wild-type melanomas and testing of a panel of targeted drugs on cell lines in vitro and in vivo (201). The aim is to quickly translate successful experimental therapeutic approaches to the clinic, with patients receiving a personalized selection of the tested therapeutic modalities based on the sequencing profiles of their tumors.

Large sequencing studies have identified several novel genetic alterations in melanoma (108,109), and additional mutations will inevitably be identified. Nevertheless, much remains to be understood about the genetics of melanoma. For example, most published genetic studies to date are based on whole-exome sequencing. The recent identification of TERT promoter mutations leading to increased expression of telomerase in up to 71% of cutaneous melanomas (114,115) shows that highly relevant pathogenetic mutations do not have to affect protein coding regions but may also be found elsewhere (eg, in regulatory DNA domains).

The role of epigenetic factors in melanoma pathogenesis is yet to be fully elucidated. Mutations, copy number alterations, or altered expression levels of chromatin remodeling proteins such as SWI/SNF and polycomb complex family members have been identified in melanoma (109,119–123), clearly arguing for deregulated chromatin remodeling processes playing a major role. Alterations in DNA methylation have been described, and include hypomethylation, leading to aberrant gene expression (202), and focal CpG island hypermethylation, which is generally associated with gene downregulation (203,204). Noncoding RNAs, both short (eg, microRNAs) (113,205) and long (206,207), are known to be aberrantly expressed in melanoma and play as yet incompletely defined roles in pathogenesis.

Comprehensive DNA and RNA analysis has become readily available, but analyzing widespread protein expression levels, modifications, and interactions is still difficult. Current experimental approaches elucidating the functional consequences of individual genetic events have proved extremely useful, but they are often laborious and time consuming. Gaining a functional understanding of the mechanistic roles that newly identified genetic events play in melanocytic neoplasia will be important for developing satisfactory therapeutic approaches.

As a consequence of the aforementioned advances, there is great optimism for the future prospects of melanoma patients. Genetic
advances have enabled the identification of many relevant pathogenetic events and have already led to the successful introduction of targeted therapies that represent the first effective agents in patients with metastatic melanoma. Although resistance to single-agent therapies almost always develops quickly, novel compounds targeting various signaling pathways are in development. Personalized genetic analysis of tumors and individualization of selected therapeutic modalities based upon these results are already a reality. At present, this process most often involves sequencing individual genes (eg, BRAF) and applying individual therapies (such as vemurafenib). However, sequencing an array of genes or the entire genome in parallel is already technically possible and quickly entering routine clinical practice. It is very likely that within the next few years selecting multiple therapeutic agents from a library of compounds based on the genetic makeup of individual tumors will become commonplace, thus realizing the potential of personalized medicine.

References


B-RAF(V600E) inhibition by RTK or N-RAS upregulation.


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