Marketers and Tissue Resources for Melanoma: Meeting Report

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Abstract

The Markers and Tissue Resources for Melanoma meeting convened by the Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, Specialized Programs of Research Excellence at the Organ Systems Branch of the National Cancer Institute (NCI), and the Melanoma Research Foundation was held in Gaithersburg, MD on October 2005. The meeting reviewed the current status of biomarkers for early- and advanced-stage melanoma and addressed some of the challenges scientists and clinicians face as they unravel the biology of melanoma and try to apply these findings to patient care. Specifically, the participants focused on molecular changes associated with melanoma progression, potential diagnostic and prognostic markers emerging from molecular profiling studies, and new treatment targets for current and future clinical trials. They also highlighted the ongoing challenges about translational research in melanoma, including availability of tissue resources, and summarized the status of nevus and melanoma tissue microarrays, recently developed as a collaborative project between the melanoma research community and the NCI. The meeting report is intended to provide a perspective on emerging scientific approaches in translational research that can enhance the progress in discovery and validation of markers for melanoma. (Cancer Res 2006; 66(22): 10652-7)

Introduction

The rate of new cases of melanoma has been rapidly increasing for many years in the United States and worldwide (1). In the United States alone, an estimated 62,190 new cases of melanoma will be diagnosed in 2006. When melanoma is diagnosed at an early stage [i.e., when the disease is confined to the epidermis and/or superficial dermis (radial growth phase; RGP)], surgical resection of the tumor with a wide and deep margin has a favorable cure rate. However, when melanoma progresses to the vertical growth phase (VGP), which involves invasion deep into the dermis, the prognosis becomes severe, and the current 5-year survival rate for patients with metastatic melanoma stage III and IV is 24% to 69% and 7% to 19%, respectively (2).

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Challenges in Clinical Management of Melanoma

Most melanomas are detected by macroscopic examination, and most diagnoses of melanoma are made with great specificity and reproducibility. Furthermore, clinical features, which include asymmetry, border irregularity, color variegation, and diameter, referred to as the ABCD system (3), are usually sufficient to identify early lesions. However, histopathologic features may not be indicative of tumor aggressiveness (4) and some melanomas and nevi lack the typical characteristics (5). In addition, currently available adjuvant melanoma therapy is associated with small improvement of survival, and markers of resistance to standard therapies would allow selecting patients who benefit from it and those who potentially would respond to alternative therapy before tumor recurs. Focusing efforts on specific challenges, to improve diagnosis, prognosis, and treatment of melanoma could have far-reaching implications on clinical melanoma management.

These challenges are: (a) Although Breslow thickness of the primary tumor remains the most powerful independent prognostic factor (6), in some cases, it has not been an accurate indicator of biological behavior of melanoma. A minority of patients with thin melanomas (<1 mm) will develop metastatic disease (7). Thus, predicting which thin melanomas and intermediate lesions (2-4 mm) are at risk for metastasis to the regional nodes and beyond is a major challenge. Therefore, additional prognostic variables with improved specificity to predict survival may prove particularly useful for stage I and II melanoma patients with lesions initially considered low risk. (b) Sentinel node (SN) status has been a powerful tool to predict future distant disease. However, because not all patients with SN-positive tumors will develop distant metastases and not all node-negative patients are cured, better surrogates for predicting metastases are needed (8). Molecular markers to detect submicroscopic levels of melanoma cells in SN that can be missed by routine histopathologic methods might help to identify early-stage melanoma patients with poor prognosis (9). (c) There is currently no standard approach for measuring the cutaneous margin of excision or for pathologic assessment of the margin, especially for melanomas thicker than 2 mm. Markers allowing to establish optimal excision margins would reduce risk of recurrence, especially in patients with deeper tumors (10). (d) Some melanomas lack typical diagnostic criteria and are difficult to recognize in the early stages. For example, ~5% of all melanomas are nonpigmented (5). Consequently, amelanotic melanomas are sometimes mistaken for basal cell or squamous cell carcinomas, or seborrheic keratoses. In addition, nodular melanomas often fail to fulfill the ABCD diagnostic criteria and are more likely than superficial spreading melanomas to lack pigmentation (11). (e) For subsets of cases of precursor lesions and melanomas, a specific and reproducible histologic diagnosis is difficult to achieve. The categories of melanocytic lesions that do not display the classic characteristics include cellular blue nevi, plaque-type blue nevi, sclerosing dermal nevi, dermal Spitz nevi, deep...
Markers that predict response to particular agents and to monitor response to treatment would allow individualization and adapting course of the therapy, which is of increasing importance in the context of novel adjuvant therapies that are on the horizon.

**Barriers to Markers Development for Melanoma**

Melanoma research and translational studies, in particular, have been hampered by limited access to large numbers of melanoma tissue samples with associated clinical information that permit discovery and validation of clinically useful markers. The development of the tissue microarray (TMA) approach has opened new possibilities for high-throughput molecular profiling of tumors. TMA allows simultaneous evaluation of hundreds of individual tissue sections and overcomes time-consuming and assay reproducibility aspects associated with conventional immunohistochemistry.

The National Cancer Institute (NCI) recognized the need for a multicenter effort in melanoma tissue collection and in 2004 convened a Melanoma Resource Workshop to identify available tissue resources for melanoma research. As an outcome from the workshop, melanoma tissue samples representing different stages of melanoma progression (nevi, primary melanomas, and local and visceral metastases) were collected at several institutions in the United States and the melanoma progression TMA was constructed.

Despite the fact that multiple melanoma TMAs have been successfully generated in several academic institutions and the NCI, many reasons account for the difficulty in accessing melanoma tissue specimens for research and clinical studies on a wider scale. (a) First, a major problem is obtaining tissue, even formalin-fixed paraffin-embedded samples, from thin primary tumors because the vast majority of cases are diagnosed by excisional biopsy done in a dermatologist’s or primary care provider’s office, not in an academic setting. Consequently, little primary tumor tissue has been made available to the melanoma research community. (b) Second, thin melanomas presently account for up to 75% of all newly diagnosed cases and between 5% and 10% will eventually develop regional or distant metastases. Because only a small fraction of thin lesions are available for research analyses, a large number of node-negative patients and hence relatively uninformative cases are needed to do an adequately powered study. (c) Because clinical outcome-related research requires tissue specimens in sufficiently large numbers and with long follow-up data to allow statistically valid analyses, most studies are limited by small sample sizes, single-institution selection bias, and limited follow-up data. (d) To reduce a sampling error rate attributable to tissue heterogeneity, a higher number of cores per tumor are required for melanoma than for other tumors to achieve high concordance with full sections. High concordance of melanoma TMA core biopsies with full sections has been shown in quadruplicates. (e) Variability in tissue depth of melanoma specimens from the different stages of tumor progression affects TMA availability because the number of sections that can be cut from the array block are limited by thin specimens. One of the solutions for these problems is construction of separate arrays for early lesions and metastasis. (f) Although most standard immunohistochemical analysis is based on readings that distinguish between positive and negative categories, in melanoma, subcellular localization may be important in interpretation of marker significance. In addition, stronger correlation with clinical outcome was found when patients were stratified according to staining intensity. Therefore, a higher degree of complexity might be required in evaluation of clinical validity of marker expression in melanoma.

Recognizing the significance of improvement of clinical management in melanoma, the Cancer Diagnosis Program (CDP) and Specialized Programs of Research Excellence (SPORE) at the NCI organized in October 2005 a meeting to review the progress in marker development in melanoma. Another charge to participants was to further discuss the tissue resources availability for high-throughput screening to ascertain the clinical value of the markers in predicting outcome in melanoma patients and potential targets for therapy. The meeting was moderated by M. Thurin and J.W. Fountain (CDP and SPORE Program, respectively, NCI, Rockville, MD) and chaired by D. Becker (University of Pittsburgh, Pittsburgh, PA). Four sessions were chaired by D. Becker, M.C. Mihm (Harvard Medical School, Boston MA), S.M. Hewitt (NCI, Bethesda, MD), and V.K. Sondak (University of South Florida, Tampa FL). Attendees consisted of 56 experts in the field, including 18 speakers (Appendix 1) as well as NIH representatives. The report summarizes discussion and recommendations emanating from this meeting.

**Session 1. Emerging markers from molecular profiling studies. Chair: Dorothea Becker.** Rapidly expanding knowledge about molecular mechanisms underlying development and progression of melanocytic tumors has already contributed to the search for potential markers, which was reviewed recently (18). During the meeting, the results of recently conducted high-throughput studies, such as comparative genomic hybridization and gene and protein expression profiling, provided several candidate molecules that upon clinical validation could serve as markers for diagnosis and prognosis and as therapeutic targets in melanoma.

Boris Bastian and colleagues [University of California San Francisco (UCSF), San Francisco, CA] provided experimental evidence for the existence of distinct genetic pathways in development of melanoma depending on the anatomic site of origin and levels of sun exposure. The data showed significant differences in regional changes in the number of copies of DNA and mutation frequencies in the BRAF oncogene between melanomas from skin with and without chronic sun-induced damage, and acral and mucosal melanomas (19). In particular, ~80% of melanomas from skin without chronic sun damage carried mutations in BRAF or NRAS oncogenes, whereas the majority of melanomas in the other three groups did not exhibit these mutations. Furthermore, melanomas with wild-type (WT) BRAF or NRAS frequently exhibited increases in the number of copies of the genes for cyclin-dependent kinase (CDK) 4 and the regulatory subunit of CDKs cyclin D1 (CCND1), downstream components of the RAS-BRAF signaling pathway (19). The data implicate CDK4 and CCND1 as independent oncogenes in melanoma without mutations in BRAF or NRAS.

Mohammed Kashani-Sabet (UCSF) summarized the results from a gene expression profiling study that compared nevi, primary melanomas, and metastatic melanoma (20). Unsupervised hierarchical clustering analysis separated nevi and primary melanomas.

Furthermore, metastatic melanomas were found to exhibit two different patterns of gene expression. These results imply that different diagnostic markers and therapy targets could be identified for these two subtypes of melanoma.

Dorothea Becker described the evidence for the existence of two distinct molecular profiles associated with the melanoma...
progression pathway based on the whole-genome expression microarray analysis of tissues ranging from normal skin to melanoma-positive lymph nodes (21). One expression pattern termed an “early stage” was specific for benign and atypical nevi, and early stage melanoma. The other pattern termed “advanced stage” characterized VGP melanoma, metastatic growth phase (MGP) melanoma, and MGP melanoma–positive lymph nodes. The data revealed that significant molecular changes occur at the border of transition from early to advanced stage melanoma. Two major gene groups associated with this switch were genes involved in mitotic cell cycle regulation and cell proliferation. Osteopontin emerged as leading the list of the top 50 genes that undergo the most profound up-regulation in VGP melanoma.

Focusing on aspects pertaining to mechanisms of immunomediated rejection of cancer, Francesco Marincola (NCI, Bethesda, MD) discussed the results of an expression array profiling study conducted in his laboratory, which showed that melanoma metastases likely to respond to immunotherapy have different genetic profile than those unlikely to respond (22). The transcriptional profile differs particularly with respect to expression of immunologically relevant genes that predispose to immune rejection in an otherwise tolerant host immune system. In addition, Dr. Marincola discussed gene profiling analysis of tumors from patients treated with different immunotherapy modalities, such as interferon (IFN)-α, interleukin (IL)-2, or Toll-like receptor 7 agonists, which showed common immunologic pathways that seem to be necessary for immune rejection (23). The identified signatures can have predictive significance to prospectively stratify patients for different therapies, vaccine therapy in particular.

Ruth Halaban (Yale University School of Medicine, New Haven, CT) described a first series of studies that involved probing of commercially produced protein microarrays with sera from patients with metastatic melanoma. The data showed that protein arrays can identify serum antibodies to known melanoma antigens, such as human cancer testis antigens NY-ESO-1 and MAGE-A4 and melanocyte differentiation antigen Rab38. In addition, the results suggested that a considerable number of serologic responses occur to a variety of antigens, none of which were detected previously by other techniques, and that these antigens may be relevant to the active disease. These novel antigens and profiles may help identify biomarkers to develop assays for detecting and monitoring melanoma.

Session 2. Markers with potential for staging, prognosis, and diagnosis of melanoma. Chair: Martin C. Mihm. Martin C. Mihm opened the session with a brief review of the status of markers from the literature, with the example of the work by Alonso et al. (24), who used a TMA for evaluation of progression markers with specimens from RGP and VGP and metastatic melanoma. Of the markers tested, the ones that were most associated with patients’ death were the absence of CDK inhibitor 2A (p16) or the presence of an oncogene product and transcriptional repressor BCL-6, along with an increase in proliferation marker Ki-67 and CDK inhibitor 1A (p21).

Another group of markers included α,β3 integrin, whose lack of expression has been reported to show a survival benefit. This important integrin reacts with fibronectin among other molecules and is associated with increased motility. A recent report has shown its interaction with T-cell antigen THY1 that is expressed on activated endothelial cells. Thus, the integrin not only reacts with stroma but also may facilitate extravasation (25, 26). Next, the cadherins and their role as adhesion molecules were discussed. E-cadherin is expressed on keratinocytes and melanocytes and is apparently the major adhesion molecule between the epidermis and the keratinocytes. The loss of its expression on melanocytes is associated with up-regulation of melanoma cell adhesion molecule (MCAM) and α,β3 integrin and transition to RGP. E-cadherin loss is a certain sign of transformation of cells from the RGP to VGP. N-cadherin, on the other hand, is expressed on fibroblasts, endothelial cells, and VGP melanoma cells. The cadherins are important markers of progression (27).

Increased expression of activated extracellular signal-regulated kinase (ERK)-1 and ERK-2 is associated with malignant potential and it may be important in melanoma progression. Inhibition of this signaling pathway may be useful as a treatment target (28).

Chemokines have many functions with regard to host response, growth, and invasion. The expression of the CCR4, CCR7, and CCR10 chemokine receptors are associated with metastasis of melanoma cells (29). Melanoma cells have been shown to express high levels of mRNA for these receptors when compared with normal melanocytes. A study of these specific receptors could prove useful to differentiate tumors that are only tumorigenic and do not express these molecules, as opposed to those that express them and can metastasize (30).

Melastatin (TRPM1) is a member of one of the families of putative calcium channel proteins that are related to the transient receptor potential superfamily (TRPM). Its mode of action is not clearly understood, but its expression is related to microphthalmia-associated transcription factor (MITF) function. The presence of melastatin expression diffusely in a primary melanoma is associated significantly with a better survival than when it is lost. It is strongly expressed in atypical nevi, less so in vertical than in RGP, and is absent in metastatic melanoma. This molecule is certainly a candidate for study as a prognostic marker (31).

A recent review has shown that the presence of intratumoral lymphatics is highly associated with metastatic disease in melanoma (32). Lymphatic vessel endothelial hyaluronic acid receptor-1 (LYVE-1) was used to detect the intratumoral lymphatics, an increase of which, compared with melanomas without these structures, was associated with diminished disease-free and overall survival.

Several other markers, all capable of study in paraffin-embedded tissue, were discussed. The markers included the transcription factors, such as nuclear factor-κB (NF-κB) and cyclic AMP-responsive element binding protein (CREB), both of which have been strongly associated with tumor progression to the VGP by favoring angiogenesis and promoting escape from apoptosis (33, 34). Signal transducer and activator of transcription (STAT) 3 was mentioned because of its promotion of metastasis through overexpression of the matrix metalloproteinase 2 (MMP-2), activation of vascular endothelial growth factor (VEGF) and angiogenesis, and as a key regulator of immune surveillance (35). Dr. Mihm emphasized the importance of studying osteopontin that has been associated with invasiveness in melanoma among other prognostic effects (36). He also mentioned CD4+CD25high regulatory T cells expressing the forkhead box protein P3 (FOXP3) transcription factor that are found in metastatic lymph nodes. These cells might be evidence of inhibition of the antitumoral CD8 response and could present a target for the treatment of melanoma patients (37).

Following discussion from the panel and the floor, Lyn Duncan (Harvard Medical School) assembled a list of markers to be con-
markers chosen as most useful for histologic diagnosis. p16 was chosen as helpful in evaluating for the familial trait and thus had diagnostic and progression importance. For similar reasons, p21 was chosen as most useful for histologic diagnosis. p16 was considered for future testing. (a) Among diagnostic markers, the MITF was considered in the progression of the tumor from RGP to VGP, the markers chosen included Ki-67, melanatin, MITF, α3β1 integrin, β-catenin, IL-6 receptor, STAT1/STAT3, phosphatase and tensin homolog suppressor gene (PTEN), protein kinase B (AKT), phosphorylated ERK, 90-kDa tumor-associated glycoprotein antigen (TAG90), osteopontin, MCAM, activating protein 2 transcription factor (AP-2), p300 histone acetyltransferase/CREB-binding protein transcriptional coactivators (CRP), and inducible nitric oxide synthase (iNOS). (b) As far as angiogenesis was concerned, three markers were chosen, VEGFA and VEGFC and lymphatic endothelium marker D2-40. It was noted that osteopontin in addition to invasion has a very marked effect on stimulating angiogenesis. (c) There was a group of other markers chosen because of possible multiple effects and these included hypoxia-inducible factor-1 (HIF-1), p65 subunit of NF-κB transcription factor, CD9 or tetraspan adhesion molecule (TM4SF), and c-KIT proto-oncogene-encoded tyrosine kinase receptor that could serve for classification of patients into subgroups with different probability of disease recurrence following therapy with c-KIT inhibitors.

It was recommended that the expression of these markers be further evaluated to determine their significance in melanoma progression and prediction of outcome using available melanoma TMAs. Consequently, it is expected that this analysis will successfully identify new candidates for clinical validation of markers and potential targets for therapy.

Session 3. TMA for marker studies in melanoma. Chair: Stephen Hewitt. Multiple presentations discussed the utility and limitations of using TMAs in melanoma research. The numerous melanoma TMAs lack a standardized design approach, related to lack of tissue available for research, and the lack of a biomarker on which to base the design, compared with breast and prostate cancer TMAs, where tissue sampling to match whole sections for predictive biomarkers has been worked out. Although TMAs reduce the number of variables in immunohistochemical analysis, such as antigen retrieval, differences in staining conditions, etc., which generate results that cannot be compared between different studies, it does not eliminate variability of scoring by a pathologist. These scoring methods are subjective and thus contingent to variability even in controlled settings, in which positive and negative controls are used (38).

David Rimm (Yale University School of Medicine) presented efforts at automated image analysis with the Automated Quantitative Analysis (AQUA) system that he developed (39). The AQUA is a fluorescence-based system that detects the expression of the antigen by measuring the intensity of antibody-conjugated fluorophores within subcellular compartments (nucleus, cytoplasm, and plasma membrane). AQUA provides continuous and reproducible quantitative scores of the marker expression in the tissue sample across the dynamic range. This approach offers promise in understanding the relevance of different proteins, either alone or in combination, with outcome. The data showed that multiple markers or ratio of markers, such as p16, p21, and Ki-67, can predict survival of melanoma patients. The algorithm did not show advantage over Breslow depth but in melanomas thicker than 1 mm allows separating patients into two groups with good and bad overall survival. In addition, the specific subcellular compartment where the marker is expressed is of crucial importance for correlation with the clinical variables, such as outcome, a correlation that conventional immunohistochemistry does not provide (39).

Alexander Lazar [University of Texas M.D. Anderson Cancer Center (MDACC), Houston, TX] discussed the efforts in construction of melanoma progression TMA that he and his colleagues constructed at MDACC. Their experience echoes that of other groups working with TMAs in melanoma. Melanoma lesions, because of small size of primary tumors and the nature of infiltration of metastatic lesions, make construction of melanoma TMAs challenging, and optimal sampling strategies (core size and number) are not clear. Further, the following methodologic concerns remain: (a) specimen quality, (b) performance of assays, and (c) challenges in interpretation. All of these problems can be overcome; however, they highlight the challenges in molecular assays on clinical specimens.

Catherine Ball (Stanford University School of Medicine, Stanford, CA) presented a database platform for the analysis of data generated by TMA studies. It supports the design of TMAs, serves as a platform for data storage and analysis, and allows integration of data acquired by automated image analysis and presentation of images for histopathologic evaluation via a computer screen rather than microscope. An additional advantage to this database platform is the fact that other groups can use it and that data can be shared via the Internet.

Kevin Dobbin (NCI, Rockville, MD) spoke about statistical concerns in the design of TMAs. TMAs are clearly enabling biomarker development; however, the deficiencies in TMA design and analysis remain. He emphasized that whenever possible, design and use of TMAs ought to be modeled along variables used in clinical trials because this may be important in showing the prognostic and predictive roles of individual biomarkers. Furthermore, other TMAs and possibly clinical specimens should be used to validate results from an initial TMA-based study. He also cautioned against overanalysis of TMAs. Whenever multiple markers are analyzed, it is essential to increase the number of samples or reduce the P that is considered statistically significant.

Discussion focused also on multi-institutional prospective collection of tissue for the construction of melanoma TMAs. The issues included obtaining material transfer agreement from each institution, standardization of protocols for patient enrollment, clinical data to be acquired, and specimen handling. Current challenges include the nonstandardized approach to immunohistochemistry, with different reagents, methods of antigen retrieval, and other technical aspects of the assay that can result in findings not being reproduced in the hands of other laboratories or on other specimen cohorts. Other challenges include the issue of scoring immunohistochemical results and standardized quantitative interpretation of staining data and their combined relationship with clinical and pathologic features.

Session 4. New targets for melanoma treatment. Chair: Vernon K. Sondak. Vernon K. Sondak described another clinical scenario where new biomarkers could be highly relevant and have an immediate effect on melanoma treatment. This clinical scenario concerns the adjuvant therapy of melanoma. The 1-year high-dose IFN-α is a current Food and Drug Administration–approved adjuvant therapy for patients at high risk of recurrence of melanoma. This regimen is toxic, lengthy, and associated with
only a small gain in absolute survival, if any. New biomarkers could help in several ways: (a) Reliable predictors of favorable outcome could identify patients with a good prognosis, who could then be spared adjuvant IFN-α. (b) Predictors of resistance to therapy could permit patients to forego ineffective therapy with IFN-α and enter into clinical trials of new agents. (c) Improved biomarkers of susceptibility to IFN-α toxicity could avoid the currently used one-size-fits-all dosing approach and allow tailored dosing to maximize therapeutic benefit while minimizing toxicity.

Scott Saxman (NCI, Rockville, MD) discussed a current approach at Cancer Therapy Evaluation Program (CTEP), NCI to integrate biomarker studies into ongoing clinical trials for patients with advanced-stage melanoma using “targeted therapies.” CTEP has launched a program to evaluate combinations of targeted therapies, centered on three nonexclusive strategies: (a) maximize target inhibition by directing two inhibitors to the same target; (b) maximize inhibition of a pathway by using inhibitors of two different points on the same pathway; and (c) target multiple cellular mechanisms/pathways. The initiative involves standardization of tissue/blood collection, processing, and storage and analyses across trials to ensure that there are sufficient numbers of samples to show correlations between potential predictive markers and patient outcomes. Central collection and analyses should reduce variability and improve the number of samples available for analyses: two elements that caused problems in identifying important predictive markers from correlative studies conducted in prior clinical trials. The markers and assays will be determined by consensus of experts.

John Kirkwood (University of Pittsburgh) discussed the clinical experience with an antibody targeting αvβ6 integrin as treatment for metastatic melanoma (40). A total of 112 patients were treated in a randomized trial; there were no objective responses seen with the antibody alone, compared with a 13% response rate when the antibody was combined with dacarbazine. Progression-free survival averaged <3 months for the combination and <2 months for the antibody alone, yet overall survival for the antibody-alone group was 12.7 compared with 9.4 months for the combination group. No tissue biopsy studies were incorporated in this trial, so there is little guidance as to the cause of this effect or how/if this antibody should be developed for melanoma treatment.

Another clinical strategy, which targets BRAF, was described by Keith Flaherty (University of Pennsylvania School of Medicine, Philadelphia, PA). The small molecular agent, sorafenib (BAY 43-9006), targets both mutant and WT BRAF, VEGF receptor (VEGFR)-2 and VEGFR-3, c-KIT, and FLT3 tyrosine kinase receptor and, albeit not selectively, also inhibits another member of Raf family tyrosine kinases (CRAF) and platelet-derived growth factor receptor (PDGFR). Melanoma patients treated with sorafenib as a single agent in phase II trials had minimal evidence of clinical response but some possible prolongation of time to progression (41). However, dramatic results, including objective tumor remissions and a median time to progression of 8.8 months, were seen when sorafenib was combined with carboplatin and paclitaxel. The value of adding sorafenib to these two cytotoxic drugs is now undergoing testing in two large-scale randomized phase III trials. Interestingly, in limited correlative analyses, there has been no clear correlation between BRAF mutation status and response to chemotherapy alone or with sorafenib.

David Fisher (Harvard Medical School) described potential clinical applications of the transcriptional factor MITF as a biomarker or therapeutic target for melanoma (42). MITF regulates not only pigmentation enzymes but also melanocyte differentiation antigen (MART-1) and melastatin, as well as oncogene and apoptosis regulator BCL-2 and CDK2. Potentially, MITF could serve as a diagnostic and prognostic aid, as a factor to up-regulate immune antigens, and by enhancing pigmentation, as a potential melanoma prevention strategy.

Menasha Bar-Eli (University of Texas MDACC) described targeting MCAM as a therapeutic strategy (43). This cell adhesion molecule is expressed in melanomas and is associated with increased attachment to endothelial cells, decreased adherence to laminin, up-regulation of MMP-2 activity, and increased invasiveness of melanoma cells. These functional changes resulting from MCAM expression could contribute to the malignant phenotype in melanoma. Thus, MCAM expression may serve as a therapeutic target for melanoma treatment. A humanized antibody that blocks MCAM expression is currently evaluated in preclinical studies of melanoma and poised for use in future clinical trials.

Conclusions

Unraveling the molecular signatures of atypical nevi and early- and advanced-stage melanomas; implementing diagnostic and prognostic melanoma biomarkers; and identifying targets for effective melanoma therapy are the immediate goals of the melanoma research community. Although the data from high-throughput studies and individual markers point to greater complexity of melanomas than previously thought, a list of potential candidate markers was identified. These markers may prove useful for diagnosis, staging, and prognosis of melanoma and/or selection of therapy upon future evaluation. Further efforts of validating potential markers for clinical use will require large numbers of patients treated in a uniform fashion and for whom comprehensive follow-up data are available. To achieve this goal, multi-institutional collaborations in tissue collection and TMA generation will be necessary. As shown by recently held NCI-sponsored workshops as well as other important meetings focused on melanoma, the research and clinical communities have become increasingly interested in coordinating their future efforts to assure the progress.

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