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Review

Biomarkers in Melanoma: Lessons from Translational Medicine

Elizabeth I. Buchbinder[1,*] and Keith T. Flaherty[2]

The treatment landscape for advanced melanoma has been rapidly evolving. As new therapies become available, there is a need for better biomarkers to detect disease, guide patient selection, and monitor for response. The use of tumor genetics has been able to predict responses to targeted therapy in melanoma. However, the role of biomarkers in melanoma detection, monitoring, and immunotherapy has been less successful and is still being defined. Translational studies in many areas of melanoma are being performed to identify biomarkers and validate their clinical role. In this review, we examine the status of biomarkers in melanoma and areas of future development.

Trends

While most patients who are diagnosed with melanoma do not have metastatic disease, there is a high risk of recurrence. This leads to a large need for better prognostic tests and biomarkers to help detect melanoma earlier in recurrence.

Biomarkers have a large role in guiding targeted therapy in melanoma treatment and to help examine mechanisms of resistance.

As immunotherapy in melanoma becomes more advanced, so does the need for biomarkers to guide treatment selection and predict toxicity.

Biomarkers in Melanoma

Biomarkers can be used in many ways in the treatment of cancer. Blood tests such as the prostate-specific Antigen (PSA) in prostate cancer or alpha-fetoprotein (AFP) in liver cancer can be diagnostic of malignancy and predictive of how a patient is doing on therapy. Genetic testing, looking for specific mutations, such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) in colon cancer or anaplastic lymphoma kinase (*ALK*) in lung cancer can guide therapy selection. In addition, biomarkers can be prognostic, as is the presence of human papillomavirus (HPV) in head and neck cancer. A biomarker can be anything from a serum protein, detectable genetic alteration, pathology finding, or imaging finding that helps predict the presence of disease or guide therapy for a disease.

The use of biomarkers has had mixed success in the treatment of metastatic melanoma. Tumor genetic testing has a proven role predicting response to targeted therapy. However, in other areas of biomarker development, studies have fallen short. There remains no blood test that can be used diagnostically to detect melanoma occurrence or recurrence, although lactate dehydrogenase (LDH) and S-100B can be useful for monitoring. In addition, with the current widespread use of immunotherapy in melanoma, there is a huge need to identify biomarkers that may be useful in predicting immunotherapy responses and toxicity. In this review, we examine the past, current, and future role of biomarkers in melanoma detection, treatment selection, and treatment monitoring.

Biomarkers of Recurrence

Most patients diagnosed with melanoma present with resectable disease, but after surgery have a lifetime risk of systemic recurrence. Detecting early recurrence in these patients is important, but our tools to do so are limited. LDH was initially observed to be an indicator of hepatic metastasis in malignant melanoma [1,2]. Subsequently, it became clear that LDH could be an indicator of disease recurrence with a sensitivity of 72% and specificity of 97% [3]. Studies showed that elevated LDH was the first indication of recurrent disease in 12.5% of patients [3]. In addition, LDH is a prognostic factor in melanoma, with elevated levels predicting a shorter

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[2]Department of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA

*Correspondence: elizabeth_buchbinder@dfci.harvard.edu (E.I. Buchbinder).

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survival and lower response rates to therapy [4]. The LDH trend may also be useful as a marker during treatment to predict early response or progression [5].

Another potential biomarker of melanoma recurrence is serum S-100B levels. The mean serum concentration of S-100B correlates with melanoma stage and has been shown to be an independent prognostic marker [6]. S-100B has also been proposed to be a potential predictor of finding melanoma in additional lymph nodes after an initial sentinel lymph node is found to have melanoma [7]. However, serum S-100B has not been widely adopted in clinical practice or incorporated into staging and decision-making algorithms.

There has been work to develop blood-based assays, including RT-PCR to detect v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations in circulating tumor cells (CTCs) and those that detect ctDNA [8–10]. These assays need to be validated further and are only useful in patients with detectable DNA mutations at the time of initial melanoma diagnosis. There are also efforts to detect circulating exosomes that contain the melanoma biomarkers MIA, S-100B, and TYRP2 [11]. Further work to determine the utility of these assays in the clinic is ongoing.

Biomarkers in Targeted Therapy

Biomarkers have a clear role in the world of targeted therapy for melanoma. Characterization of melanoma genomes has led to a better understanding of the mutations driving growth and of disease subtypes [12]. The Cancer Genome Atlas Network published DNA, RNA, and protein analysis from 333 melanomas and created a classification structure based on *BRAF*, *RAS*, and *NF1* mutational status [13] (Table 1).

BRAF

BRAF has been established as the most important mutated gene for which all patients with advanced melanoma should be tested. The most common mutations observed are the *BRAF* V600E/K mutations, which are observed in 40–60% of patients and lead to increased activation of the MAP kinase pathway [14,15]. BRAF blockade therapy with vemurafenib or dabrafenib leads to an improved overall survival in patients with mutations. These agents are highly selective RAF inhibitors that target BRAF V600 mutated kinase domains. Paradoxically, these agents lead to MAP kinase activation in BRAF wild-type (WT) cells, likely through binding to normal CRAF and BRAF [16,17].

Table 1. Biomarkers in Melanoma-Targeted Therapy.

Biomarker	Frequency	Therapeutic Intervention	Refs
BRAF V600 E/K	40–60%	Vemurafenib or dabrafenib (usually combined with MEK inhibition with cobimetinib or trametinib)	[14–26]
BRAF (non-V600E/K)	5%	Trials looking at BRAF inhibition with vemurafenib or dabrafenib with or without MEK inhibition	[27,29,30]
NRAS	20%	MEK inhibition + –CDK 4/6 inhibition	[31–33]
NF1	46% of BRAF and NRAS WT	MAPK inhibition being evaluated	[34]
KIT	28–39% of mucosal, acral, or chronic sun-damaged skin	Imatinib or other KIT-targeted tyrosine kinase inhibitors have shown activity in patients with specific mutations	[12,35–38]
GNAQ/GNA11	80% of uveal melanoma	MEK inhibition had initial promising results, but failed to show efficacy in Phase III testing	[40–43]
TP53/CDKN2A	11%	Early clinical testing is underway	[44–47]

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