Prognostic Biomarkers in Melanoma: Tailoring Treatments to the Patient

Albert G. Wu, MS[1]; Carl V. Hamby, PhD[1,] Bijan Safai, MD DSc[2]

1 New York Medical College School of Medicine ● 2 Department of Dermatology, Metropolitan Hospital

Background and Purpose

In the era of genomics, the using large-scale screening assays to screen for a predetermined set of markers has largely rendered the idea of a single, tell-all biomarker an archaic notion. Genetic tests are already commercially available to aid clinicians with melanoma staging and diagnosis. Treatment options for melanoma have also evolved, with checkpoint inhibitors improving patient survival rates5 for late stage melanoma. However, therapeutic benefits vary from individual to individual, as studies have expressed a difficulty in anticipating patient response6, as well as the insufficiency of conventional response criteria for predicting therapeutic benefit7. This variation has driven the search for biomarkers which can serve as indicators of patient response to therapy. Recently, a number of studies have been able to uncover several genetic and protein markers that show statistically significant associations with mortality, improved clinical outcome, and melanoma progression. We aim to summarize and highlight these markers, which have the potential to aid in the development of individualized treatments for malignant melanomas in the future. of PC subtypes.

Objective:

▪To characterize the current state and progression of biomedical markers towards their utilization as prognostic indicators for patients with melanoma.

Methods

A literature search of the research repository databases PubMed and Google Scholar was conducted using the following inclusion criteria: Published within the last 10 years, and use of Overall Survival, Disease Progression, or Clinical Outcome as primary endpoints. Search terms included various permutations of “biomarkers”, “prognostic”, “immunologic”, “serologic”, “visual”, and “melanoma”. Results were evaluated for statistical power, results significance, and experimental design integrity.

NEW YORK MEDICAL COLLEGE
A MEMBER OF THE TOURO COLLEGE AND UNIVERSITY SYSTEM
School of Medicine

Results

Biomarker	Gene	Associations
Adenylyl cyclase-associated protein 2[8]	CAP2	Higher levels of expression were associated with poorer clinical outcomes.
CD169+ Cells[39]	---------	High numbers of cells were correlated with favorable overall survival
Human epidermal growth factor receptor[11]	HER4	Higher levels of expression were associated with shorter duration of progression free survival
Cancerous inhibitor of protein phosphate 2a[12]	CIP 2A	Higher levels of expression were associated with poorer clinical outcomes
Soluble CD73[40]	CD73	Higher levels of sCD73 enzyme associated with poorer clinical outcomes
Melanocortin Receptor 1[41]	MC1R	Presence of any variant of MCR1 was associated with poorer clinical outcomes.
S100B[42]	S100B	Higher levels of expression were associated with poorer clinical outcomes
Aldehyde Dehydrogenase 1[15, 16]	ALDH1	Higher levels of expression were associated with better prognosis
Micro RNA 16[23]	miR-16	Decreased Serum levels were associated with advancing melanoma stage.
Micro RNA 15[22]	miR-15b, miR-425	Increased serum levels prior to melanoma recurrence.
Micro RNA 206[21]	Mir-206	Decreased serum levels were associated with poor clinical prognosis.
Micro RNA 4633-5p[43]	miR-4633-5p	Differentially higher expression was associated with better clinical outcomes.
Micro RNA 330-5p[44]	miR-330-5P	Increased exosome concentration was associated with melanoma presence.
Micro RNA 10b	miR-10b	Increased in expression associated with metastasis.
BRCA-associated protein 1[41,45]	BAP1 (piris too)	Deficient BAP1 expression was associated with decreased survival.
Glucose-regulated protein of 78 kD[46]	BiP, GRP78	Increased expression of BiP/GRP78 with poor survival
Melanoma cell adhesion molecule[47]	MCAM/MUC18	Increasing MCAM/MUC18 intensity and cancer progression
β2-adrenergic receptor[48]	β2AR	Increased expression was associated with poorer clinical outcomes
Melanoma Inhibitory Activity[44]	MIA	Higher serum levels were associated with lower overall survival rates.
Krüppel-like factor[49]	KLF6	Higher protein levels were associated with lower 3-year survival rate.
Eukaryotic translation initiation factor 4E[50]	eiF-4E	Increased expression of eIF4E and phospho-eIF4E were associated with reduced survival and increased risk of death.
class III β-tubulin[51]	TUBB3	Decreased expression levels were associated with decreased overall survival and lower prognosis free survival.
D-dimers[52]	----------	Increased plasma levels were associated with poor overall disease outcome

The prognostic capabilities of clinical tests for malignant melanoma have made great strides over the last few years, with several serologic and immunohistochemical biomarkers being preliminarily linked to various measures of clinical prognosis. While clinical feasibility of a single sensitive and specific biomarker remains unfeasible, use of select combinations of tested biomarkers remain viable.

Immunohistochemical Markers

The wave of retrospective reviews in the last five years have brought up many immunohistochemical biomarkers associated with prognosis of malignant melanomas, many of which are summarized in the table. It is important to stress that many of these studies were limited by having small cohorts, using single centers, or studying rare variants of malignant melanoma. These initial findings will need to be replicated and expanded for any definitive claims to be made; however, they add to the pool of potential markers and therapeutic targets to be tested for future use. Markers evaluated include: Adenylate Cyclase Associated Protein (CAP 2), Epidermal Growth Factor (EGFR), Cancerous inhibitor of protein phosphate 2A (CIP2A), and Aldehyde dehydrogenases (ALDH)

Continued Results

Serum Markers

Serologic markers are extremely appealing as biomarker candidates as testing is less invasive and have relatively fast turnaround times[17,18]. Identification of new metabolites, antigens, and enzymes which could be used as a marker of disease progression and predictor of patient outcomes has driven research over the last few years. Another focus of research has been re-evaluation of classic biomarkers for their clinical utility and prognostic strength.

Biomarker Applications in Malignant Melanoma Treatments

Recently, the number of treatments for malignant melanoma has expanded. Immune checkpoint inhibitors, which harness T-cells to amplify immune system responses against tumors, have been extensively researched due to promising, long term clinical results. However, obstacles such as developed resistance and limited treatment scope make traditional chemotherapy the main option for many patients.

Biomarkers and Screening Assays

Biomarker assays and assessments that integrate multiple prognostic factors are an aspect of research focusing on combining and weighting current data to make the most accurate predictions on malignant melanoma diagnoses and prognoses2,18. Because melanomas often have different combinations of mutations and different levels of expression changes, these assays may be able to somewhat make up for skews in small patient cohorts and prove more consistent than tests based on a single biomarker.

Discussion & Conclusion

The prognostic capabilities of clinical tests for malignant melanoma have made great strides over the last few years. Diagnostic and prognostic genetic assays have begun to cross over from research to commercial applications, giving physicians additional tools during the early stages of diagnosis to optimize and individualize treatments. A significant number of biomarkers from many sources remain to be analyzed and tested, with the potential to improve upon and further optimize current tests. As novel treatments for melanoma continue to be developed, innovation must continue to isolate biomarkers which can help track their efficacy.