Diagnostic and Prognostic Biomarkers in Melanoma: Current State of Play

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Introduction

Melanoma is the most deadly skin cancer. The incidence and mortality rates of this tumor have been increasing over the last number of decades. Besides clinical and histopathological characteristics (i.e., anatomic site and subtype of the primary tumor, Breslow thickness, ulceration, vascular invasion, mitotic index), an increasing variety of molecular markers have been identified, providing the possibility of a more detailed diagnostic and prognostic categorization of melanoma. Recently published gene expression and proteomic profiling data indicate new candidate molecules involved in melanoma pathogenesis, which are currently being validated. This ongoing process of biomarker identification and validation is resulting in a rapidly changing molecular view of cutaneous melanoma, which holds the promise of improving our diagnostic and prognostic classification systems, as well as identifying therapeutic targets. In this chapter, we provide a comprehensive overview of the currently known serological and immunohistochemical biomarkers in melanoma.

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Tumor Tissue-Based Biomarkers

Cutaneous melanoma develops in three sequential stages (i.e., radial growth phase, vertical growth phase and metastases). The prognosis in any stage is only partially explained by morphological and histopathological parameters, such as primary tumor localization, patient gender and age, mitotic rate, tumor thickness and ulceration. Moreover, while some parameters seem to reflect merely the tumor burden, others, such as ulceration, appear to be intrinsically related to tumor biology. Additional technologies that help to assign patients to specific risk groups include immunohistochemistry, gene expression profiling, comparative genomic hybridization, and gene mutational analysis.

For diagnostic purposes, a small panel of melanocytic lineage markers (i.e., S100, MART-1, and gp100/HMB45) is sufficient to discriminate melanoma from non-melanocytic skin cancer. However, no marker has proven useful in distinguishing spindle cell/desmoplastic melanoma from other tumors. Ki-67 remains the most useful adjunct in distinguishing benign from malignant melanocytic tumors [1].

For prognostic classification, the situation is more complex. The transformation from benign melanocytes to metastatic melanoma results from a combination of genetic alterations contributing to the hallmarks of cancer (i.e., uncontrolled proliferation, unlimited replicative potential,

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apoptosis resistance, invasion, and angiogenesis). Several marker molecules involved in these genetic alterations have been identified, and their expression in primary melanoma has been studied and correlated with prognosis. Table 2.1 summarizes the most important tissue biomarkers known for melanoma, whose abnormal expression is associated with patient prognosis. It is likely that the most detailed prognostic classification for melanoma will not result from analysis of one biomarker, but rather from a panel of multiple biomarkers in this list.

In a recent retrospective study, primary melanomas (for which long-term clinical follow-up was available) were analyzed using a cDNA expression microarray [22]. The authors described a signature of 174 genes that identified patients at risk of developing distant metastasis. From these 174 genes, 141 were underexpressed and 33 overexpressed in tumors whose host remained free of metastasis for 4 years. Thirty of these 174 genes had already been studied in melanoma; these genes are involved in cell cycle regulation (CKS2, CDC2, CCNB1, CENPF, and DHFR), mitosis

Table 2.1 Immunohistochemical markers of melanoma associated with impaired prognosis

	Association with impaired prognosis	References
Melanocyte lineage/differentiation antigens		
gp100/HMB45	Increased expression	Niezabitowski et al. [2]
Tumor suppressors/oncogenes/signal transducers		
AP-2 (activator protein-2alpha) transcription factor	Loss of nuclear AP-2 expression	Berger et al. [3]
bcl-6	Expression	Alonso et al. [4]
c-Kit	Expression	Janku et al. [5]
c-met	Expression	Cruz et al. [6]
c-myc	Increased expression	Kraehn et al. [7]
CYLD	Decreased expression	Massoumi et al. [8]
EGFR (epidermal growth factor receptor)	Increased expression	Udart et al. [9]
ERK (extracellular signal-regulated kinase)	Absence of cytoplasmic ERK activation	Jovanovic et al. [10]
HER3	Increased expression	Reschke et al. [11]
HDM2 (human homologue of murine mdm2)	Increased expression	Polsky et al. [12]
ING3/ING4	Decreased nuclear expression	Wang et al. [13]
MITF (microphthalmia-associated transcription factor)	Gene amplification	Ugurel et al. [14]
$P16^{INK4A}$	Decreased expression	Mihic-Probst et al. [15] Alonso et al. [4]
p-Akt (activated serine-threonine protein kinase B)	Increased expression	Dai et al. [16]
pRb (retinoblastoma protein)	Inactivation due to protein phosphorylation	Roesch et al. [17]
PTEN	Decreased expression	Mikhail et al. [18]
SNF5	Loss of expression	Lin et al. [19]
Cell cycle-associated proteins		
Cyclin A, B, D, E	Increased expression	Florenes et al. [20] Florenes et al. [21]
Geminin	Increased expression	Winnepenninckx et al. [22]
Ki-67 (detected by MIB-1)	Increased expression	Gimotty et al. [23] Alonso et al. [4] Ostmeier et al. [24]
$P21^{CIP1}$	Decreased expression	Alonso et al. [4]
PCNA (proliferating cell nuclear antigen)	Increased expression	Winnepenninckx et al. [22]

(continued)

Table 2.1 (continued)

	Association with impaired prognosis	References
Regulators of apoptosis		
APAF-1 (Apoptotic protease activating factor-1)	Decreased expression	Fujimoto et al. [25]
Bak	Decreased expression	Fecker et al. [26]
Bax	Decreased expression	Fecker et al. [26]
bcl-2	Increased expression	Tas et al. [27]
Survivin	Increased expression	Tas et al. [27]
Molecules involved in angiogenesis		
LYVE-1 (lymphatic vascular endothelial hyaluronan receptor-1)	Increased expression	Dadras et al. [28]
PTN (pleiotrophin)	Increased expression	Wu et al. [29]
Molecules involved in cell adhesion and motility		
Beta-catenin	Loss of nuclear staining	Bachmann et al. [30]
CEACAM1 (carcinoembryonic-antigen-related cell-adhesion molecule 1)	Increased expression	Thies et al. [31]
Dysadherin	Increased expression	Nishizawa et al. [32]
E-cadherin	Decreased expression	Andersen et al. [33]
Integrins beta1 and beta3	Increased expression	Saalbach et al. [34]
MMPs (matrix metalloproteinases)	Increased expression	Redondo et al. [35]
Osteonectin [also termed BM40 or SPARC (secreted protein, acidic and rich in cysteine)]	Increased expression	Massi et al. [36]
P-cadherin	Strong cytoplasmic expression	Bachmann et al. [30]
Immunoregulators		
HLA allele frequency	Specific expression	Luongo et al. [37] Ostmeier et al. [24]
Others		
ALCAM/CD166 (Activated leukocyte cell adhesion molecule)	Increased expression	Swart et al. [38]
CXCR4 receptor	Increased expression	Scala et al. [39]
HSP90 (heat shock protein 90)	Increased expression	McCarthy et al. [40]
MCM4 and MCM6 (minichromosome maintenance complex component 4 and 6)	Increased expression	Winnepenninckx et al. [22]
Melastatin	Decreased expression	Duncan et al. [41]
Metallothionein	Increased expression	Weinlich et al. [42]
NCOA3 (nuclear receptor coactivator 3)	Increased expression	Kashani-Sabet et al. [43]
Nestin	Increased expression	Bakos et al. [44] Piras et al. [45]
Nodal	Increased expression	Strizzi et al. [46]
Nuclear 8-hydroxy-2′-deoxyguanosine	Increased expression	Murtas et al. [47]
Osteopontin (OPN, SPP1)	Increased expression	Rangel et al. [48] Kashani-Sabet et al. [43]
RGS1 (regulator of G-protein signaling 1)	Increased expression	Kashani-Sabet et al. [43]
Sox9 (sex determining region Y-box 9)	Increased expression	Bakos et al. [44]
TA (telomerase activity)	Increased expression	Carvalho et al. [49]

(HCAP-G and STK6), mitotic spindle checkpoint (BUB1), inhibition (BIRC5) or stimulation (GPR105) of apoptosis, DNA replication (TOP2A, RRM2, TYMS, PCNA, MCM4, and MCM6), stress response (GLRX2, DNAJA1, HSPA4, HSPA5, HSPD1, and TXNIP), ubiquitin cycle (SIP), actin and calmodulin binding (CNN3), intracellular signaling (STMN2), negative regulation of the Wnt signaling pathway (CTNNBIP1), inhibition of MITF expression (EMX2), regulation of proteolysis (TNA), testis cancer (CML66), and metastasis suppression (NME1). The authors speculated that the use of immunohistochemistry with antibodies directed against corresponding encoded proteins would facilitate improved prognostication of melanoma patients, and thereby allow for treatment stratification. In particular, determination of karyopherin-alpha2, MCMs (minichromosome maintenance proteins), geminin and PCNA could be used to screen for melanoma patients with poor clinical outcome.

In another recent study, Gould Rothberg et al. used a multimarker prognostic assay to help triage patients at increased risk of recurrent melanoma [50]. Protein expression for 38 candidate biomarkers relevant to melanoma oncogenesis was evaluated, using an automated quantitative analysis (AQUA) method for immunofluorescence-based testing in formalin-fixed paraffin-embedded (FFPE) specimens. A favorable prognosis was predicted by the expression of ATF2, p21(WAF1), p16(INK4A), beta-catenin and fibronectin. Primary tumors that met at least four of these five conditions were considered a low-risk group, and those that met three or fewer conditions formed a high-risk group for metastasis development.

Similarly, genetic abnormalities have recently been recognized to influence the prognosis of cancer patients. Indeed, a new classification system for melanoma that combines genetic aberrations with histomorphological characteristics has been proposed by Bastian et al. [51–53]. Of note, MITF gene copy number in tumor cells seems to be a useful prognostic marker in metastatic melanoma [14].

Moreover, it has recently been shown that an *in vitro* ATP-based chemosensitivity assay helps to differentiate between chemosensitive and chemoresistant melanoma patients, and can be used as a biomarker of chemotherapy response and survival outcome. A phase II study evaluating this assay in 53 patients with metastatic melanoma, followed by sensitivity-directed individualized chemotherapy, demonstrated that the chemosensitivity profile of an individual patient (reflected by the best individual chemosensitivity index [BICSI]) correlated with therapeutic outcome [54]. A surprisingly high proportion (~40%) of the investigated patient cohort were classified as chemosensitive, the remaining (~60%) classified as chemoresistant. Objective response was reported as 36.4% in chemosensitive patients compared to 16.1% in chemoresistant patients ($p=0.114$); progression arrest (CR + PR + SD) was 59.1% versus 22.6% ($p=0.01$). Chemosensitive patients showed an increased overall survival of 14.6 months compared to 7.4 months in their chemoresistant counterparts ($p=0.041$).

Serological Markers

Despite a large research effort, the prognosis of metastasized melanoma is still poor, and best results have been achieved in cases when the tumor is still amendable to surgical intervention. Thus, the search for reliable methods to detect early metastases and identify patients with high risk of disease progression who should undergo more vigorous follow-up is of major importance. Serological markers for tumor progression combine several advantages, such as the ease of obtaining serum samples and the availability of numerous methods to detect small molecules or proteins that correlate with tumor burden. Accordingly, several serological biomarkers have been established. In a number of European countries, the melanocyte lineage/differentiation antigens S100-beta and melanoma inhibitory activity (MIA) are routinely used for early detection of tumor relapse or metastasis during follow-up of melanoma patients (Table 2.2). Both

Table 2.2 Serologic markers of melanoma

	Serologic marker	References
Melanocyte lineage/ differentiation antigens	S100-beta	Guo et al. [55] Schultz et al. [56] Hauschild et al. [57] Krahn et al. [58] Garbe et al. [59]
	MIA (melanoma inhibitory activity)	Bogdahn et al. [60] Blesch et al. [61] Bosserhoff et al. [62] Stahlecker et al. [63] Garbe et al. [59]
	Tyrosinase 5-S-Cysteinyldopa L-dopa/L-tyrosine	Agrup et al. [64] Wimmer et al. [65] Stoitchkov et al. [66]
Proangiogenic factors	VEGF (vascular endothelial growth factor) BFGF (basic fibroblast growth factor) IL-8 (interleukin-8)	Ugurel et al. [67] Ugurel et al. [67] Ugurel et al. [67]
Molecules involved in cell adhesion and motility	sICAM-1 (soluble intracellular adhesion molecule 1)	Hirai et al. [68] Vuoristo et al. [69]
	sVCAM (soluble vascular cell adhesion molecule 1)	Franzke et al. [70] Vuoristo et al. [69]
	Matrix metalloproteinases (MMP-1 and MMP-9) Tissue inhibitor of metalloproteinases (TIMP-1 and TIMP-2)	Nikkola et al. [71] Yoshino et al. [72]
Cytokines and cytokine receptors	IL-6 (interleukin-6) IL-10 (interleukin-10) sIL-2R (soluble interleukin-2-receptor)	Mouawad et al. [73] Dummer et al. [74] Nemunaitis et al. [75] Boyano et al. [76]
HLA molecules	sHLA-DR (soluble HLA-DR) sHLA-class-I (soluble HLA-class I)	Rebmann et al. [77] Westhoff et al. [78]
Others	LDH (lactate dehydrogenase) CRP (C-reactive protein) Albumin TuM2-PK (tumor pyruvate kinase type M2) CD95 (Fas) YKL-40	Sirott et al. [79] Deichmann et al. [80] Sirott et al. [79] Ugurel et al. [81] Ugurel et al. [82] Schmidt et al. [83] Schmidt et al. [84]
	CYT-MAA (cytoplasmic melanoma-associated antigen) HMW-MAA (high-molecular-weight melanoma-associated antigen) sULBP2 (soluble UL16 binding protein 2) TA90IC (tumor-associated antigen 90 immune complex) Serum amyloid A anti-HERV-K antibodies	Vergilis et al. [85] Vergilis et al. [85] Paschen et al. [86] Faries et al. [87] Findeisen et al. [88] Hahn et al. [89]

proteins show high (but not exclusive) specificity for melanoma cells, and both correlate with the patient's tumor load.

The S100 protein is a 21-kd thermo-labile acidic dimeric protein which was originally isolated from the central nervous system. It consists of two subunits, alpha and beta in any pairing (i.e., alpha/alpha, alpha/beta, and beta/beta). It affects the assembly and disassembly of microtubules and also interacts in a calcium-dependent manner with p53, the product of a tumor suppressor gene. The beta subunit is expressed by cells of the central nervous system as well as cells of melanocytic lineage. Initially, the presence of S100-beta in the cerebrospinal fluid was used as a marker of central nervous system damage [90]. More recently, it was observed that S100-beta was elevated in the serum of melanoma patients [55].

MIA was originally detected in melanoma cell culture supernatants [60], and has been shown to exert an important role in cell-matrix-interaction and metastasis [61].

Studies comparing both these serum markers have demonstrated that S100-beta is superior to MIA as an early indicator of tumor progression, relapse or metastasis [58, 91]; hence, S100-beta is more often used in this setting [92]. Both markers have been shown to be useful prognostic markers in melanoma patients with distant metastases [56, 57], but have failed to provide prognostic significance in early stages of melanoma, especially in patients who are tumor-free after surgical excision [63]. Moreover, S100-beta fails to identify patients with lymph node micrometastases detected by sentinel lymph node biopsy [93]. Nonetheless, the correlation of serum S100 concentration with tumor load makes it a useful marker for monitoring therapeutic response in patients with advanced metastatic melanoma [57].

The strongest prognostic serum biomarker in advanced metastatic melanoma is lactate dehydrogenase (LDH), a nonspecific marker that indicates high tumor load in a variety of human tumors, including melanoma. Studies comparing LDH, S100-beta and MIA, using multivariate data analysis, showed that LDH was the strongest independent prognostic factor in stage IV melanoma patients [91]. Due to its high prognostic significance, in addition to its easy and cost-efficient detection, serum LDH is the only molecular marker that has been incorporated into the current melanoma staging and classification system of the American Joint Committee on Cancer (AJCC) [94]. In fact, it serves as a stratification parameter in most randomized clinical trials that test therapeutic interventions in advanced melanoma, and may also be used to monitor therapeutic response in these patients.

Other potential serum biomarkers have been reported to correlate with tumor load and disease progression in melanoma. These are related to different characteristic features of melanoma, such as melanocytic differentiation (i.e., tyrosinase), tumor angiogenesis (i.e., VEGF, bFGF, IL-8), cell adhesion and motility (i.e., ICAM-1, MMPs), cytokines and their receptors (i.e., IL-6, IL-10), antigen presentation (i.e., HLA molecules), tumor cell metabolism (i.e., TuM2-PK), apoptosis (i.e., Fas/CD95), and many others (Table 2.2). However, none of these markers has been demonstrated to be superior to S100-beta or LDH in reflecting the prognosis of patients with advanced stage disease. Moreover, these markers have also failed to be of prognostic relevance in early-stage tumor-free patients.

An innovative approach to identify novel, potentially better serological biomarkers in melanoma patients is serum proteomic profiling. This methodology offers the possibility of screening the whole serum proteome for markers which correlate with different criteria, such as prognostic significance and prediction of therapeutic response. Using this technology, marker proteins from thematic fields, that are different to those mentioned above, might be found and subsequently validated for their clinical utility. Studies have shown that stage I and stage IV melanoma patients can be differentiated by their serum proteomic profiles [95]. Another recent proteomic profiling study reported the identification of serum amyloid A as a new prognostic serum biomarker in melanoma patients [88].

Perspective

Melanoma is a highly aggressive form of skin cancer which is difficult to treat once the tumor has metastasized beyond the locoregional area. Established biomarkers include the morphological and histopathological characteristics of the primary tumor. More recently, molecular biomarkers have been identified, facilitating more detailed diagnostic and prognostic categorization of melanoma patients and allowing for stratified or even personalized therapy.

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