Melanoma Biomarkers

Subjects: Dermatology

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Melanoma is the deadliest form of skin cancer and remains a diagnostic challenge in the dermatology clinic. Here, we categorize and review known melanoma diagnostic biomarkers into five categories including visual, histopathological, morphological, immunohistochemical, and serological/molecular biomarkers.

melanoma biomarkers skin cancer benign nevi

1. Introduction

The consequences of missing a malignant melanoma are grave. As such, many biopsies are needlessly performed on clinically suspicious but still benign lesions to rule out melanoma. In fact, it has been shown that for every positive case of melanoma, there are 15 to 30 biopsies of lesions later proven to be benign[1]. Thus, the current method for melanoma detection has placed a significant economic burden on the healthcare system. At present, melanoma diagnosis is based on clinical examination and the ABCDE evaluation by specialists, followed by the selection of lesions that look different than the majority of existing moles on the body, dermoscopy and total body photography, excisional biopsy, and histopathologic examination by an expert dermatopathologist, and less often molecular analysis, genetic analysis, testing when indicated, and a multidisciplinary approach when indicated.

It is estimated that $32,594 dollars are spent for each melanoma detected[2]. Due to the increasing incidence of melanoma and the high cost of melanoma detection, there is a public health need for skin cancer screening with precise, cost-efficient methods. Particularly useful would be a non-invasive imaging technique to aid in melanoma diagnosis and the decision to biopsy.

Melanoma diagnostic biomarkers can be categorized into five categories including visual, histopathological, morphological, immunohistochemical, and serological/molecular biomarkers. Visual biomarkers are the specific features of melanoma that dermatologists recognize on the patient with a naked eye or with the use of a dermatoscope. Histopathology of melanoma refers to the features that pathologists and dermatopathologists look for under the microscope after a biopsy of a suspicious lesion has been performed. The morphologic features of melanoma refer to the overall layer architecture and cellular structure of the lesions. Immunohistochemistry refers to a method of staining lesions for specific key markers, which aid in differentiating benign from malignant lesions. Lastly, serological/molecular markers refer to markers that can be detected in the peripheral blood or serum as indicators for melanoma.

2. Melanoma Progression

The transition from normal healthy skin to melanoma is a topic that has been studied and debated for years. Cutaneous melanoma originates from melanocytes located in the basal layer of the epidermis. Melanocytes comprise only 1% to 2% of epidermal cells but produce all of the melanin in the skin. Melanin production is stimulated by melanocyte stimulating hormone (MSH) released from keratinocytes via a p53-mediated mechanism in response to ultraviolet (UV) light[3][4].

There are two common types of melanin found in humans: (1) eumelanin—a brown-black pigmented melanin found in darker-skinned people, and (2) pheomelanin—a yellow-red pigmented melanin responsible for red hair and freckles[3]. Eumelanin has the ability to protect DNA more effectively than pheomelanin, absorbing more efficiently the harmful UV radiation and converting it to heat through a chemical process known as internal conversion (a process lacking in pheomelanin)[3]. This mechanism likely contributes to the higher incidence of skin cancer and melanoma observed in lighter-skinned individuals than in darker-skinned individuals.

Cells typically respond to UV radiation-induced DNA damage in one of two ways: the cell either repairs the DNA or initiates apoptosis (rarely they undergo necrosis or mitotic catastrophe)[5]. DNA is repaired by a number of cellular mechanisms including direct repair, nucleotide and base excision repair, and recombinational and cross-linked repair[6]. However, these mechanisms are error-prone processes that can potentially lead to the formation of mutations resulting in melanoma formation[3]. UVB radiation damages pyrimidines, leading to the formation of cyclobutene pyrimidine dimers and (6-4) photoproducts[7]. Repeated carcinogenic exposure from UV light results in an accumulation of mutations within the skin. Invasive melanoma contains a larger number of UV-related mutations compared to those found in benign nevi[8]. In addition, inherited conditions such as xeroderma pigmentosum (XP), congenital melanocytic nevi, familial atypical multiple moles and melanoma (FAMMM) syndrome, and *BRCA2* mutation all provide evidence for a genetic predisposition to the development of melanoma[9][10].

Unlike non-melanoma skin cancers (NMSC), melanoma can develop in areas that rarely receive sun exposure, such as the palmar surfaces of the hands and feet, and mucosal surfaces[11]. These melanomas are understood to have distinct oncogenic mutations uncommon in melanomas in areas of chronic ultraviolet (UV) exposure. One study found that melanomas located in areas of minimal sun exposure commonly displayed mutations in *BRAF* or *NRAS,* while melanomas in chronically sun exposed areas are most commonly associated with mutations in *TP53*, evidencing that melanoma is a heterogeneous disease stemming from genetic risk factors and accumulated environmental exposures[11][12].

Recently, the thought of a simple linear progression from nevus to melanoma in situ does not appear to occur[8]; rather, it is the result of an accumulation of multiple different mutations[13]. It has been found that melanoma associated mutations can be either somatic or due to environmental factors that are acquired over time[14]. In order to transform from benign nevus to melanoma, multiple mutations or “hits” must occur. Tsao et al. found that there is a 0.03% (men) and 0.009% (women) lifetime risk of a mole that is present by age 20 to later transform into cutaneous melanoma by age 80[15]. In the work by Bastian, he suggests that there is an inciting oncogenic event that is often a gain of function mutation involving one of the following: *NRAS*, *HRAS*, *BRAF*, *KIT*, *GNAQ*, *GNA11*, *ALK*, *ROS1*, *RET*, and *NTRK1*[13]. Given that 30% of cutaneous melanoma arise near a nevus, often with the

BRAF^{V600E} mutation[16], the initial oncogenic mutation is helpful in separating different lesions such as congenital nevi, pigmented lesions on chronic sun damaged (CSD) skin, non-CSD skin pigmented lesions, spitz tumors, and blue nevi[13]. Secondary and tertiary oncogenic events usually involve a loss of tumor suppressor genes such as *CDKN2A, TP53, PTEN,* or *BAP1*, and these can be used for determining disease progression within classes[13].

Melanomas can be sorted into two categories based on the skin on which they arise: CSD and non-CSD. CSD melanomas develop on skin showing solar elastosis, deterioration of the dermal elastic fibers, and they are often found in individuals >55 years old after years of UV radiation often on the head and neck, while the non-CSD melanomas usually affect individuals <55 years old in areas with intermittent sun exposure such as the trunk[17]. Non-CSD melanomas are often superficial spreading melanomas that can develop within a previous nevi in younger patients[18]. Non-CSD melanomas are often associated with *BRAF*^{V600E} mutations that are found in common nevi as well, while CSD melanomas are often seen to have *NF1, NRAS,* or *BRAF*^{nonV600E} mutations[17][19].

Within a nevus, limited proliferation occurs due to the initiating mutation. If additional mutations are acquired such as *TERT* promoter mutations on both non-CSD and CSD skin, this results in further proliferation toward melanoma[19]. The characteristic histologic pagetoid growth pattern is associated with non-CSD melanoma with *BRAF*^{V600E} mutations[17]. In contrast, melanocytes with high cumulative sun exposure can result in the formation of lentigo maligna with its characteristic lentiginous growth pattern that can cover several centimeters of skin for years before generating a nodule and becoming invasive, making it more common in older individuals with years of sun damage[17]. Ultimately, loss of function in *CDKN2A* or *SWI/SNF* primes lesions to become invasive, with mutations in *PTEN* and *TP53* promoting complete invasion[19]. As found in the study by Colebatch et al., a simple linear progression from nevus to invasive melanoma does not appear to occur, but instead, different branches of mutations occur later in the progression of melanoma with a resultant heterogeneity of neoplasms[8].

3. Melanoma Biomarkers

3.1 Visual

Differentiating a benign nevus from cutaneous melanoma is first done through visual inspection. Visual criteria for melanoma detection include the ABCDE criteria of asymmetry, border irregularity, color variation, diameter (>6 mm), and evolution, with “E” being officially added in 2004[20]. Thomas et al. found that using two criteria in combination leads to sensitivity of 89.3% and specificity of 65.3%, while utilizing three criteria brings sensitivity to 65.55% and specificity to 80%[21][22]. Identifying visual features can be difficult with lesions that are not pigmented such as nodular amelanotic melanoma[22]. Dermoscopy or dermatoscopy is a method of examining the skin using skin surface microscopy. Russo et al. presented a seven-point checklist of melanoma used in dermoscopy including (I) atypical network (indicating two types of pigment networks), (II) blue whitish veil (irregular area with blue pigmentation), (III) atypical vascular pattern (dotted and hairpin vessels indicating neoangiogenesis), (IV) atypical dots/globules (indicating clumps of melanocytes), (V) irregular streaks (indicating melanocytic nests in rete ridges), (VI) irregular blotches (pigmented keratinocytes or pagetoid melanocytosis), and (VII) regression structures

(corresponding to thin epidermis and few melanophages)[23]. In dermoscopy of acral lesions, benign lesions often show a parallel furrow pattern (linear pigmentation in furrows of the sole) in comparison to malignant lesions with parallel ridge pattern (parallel band-like pigmentation in ridges of the sole (gold standard for diagnosing volar melanocytic nevus and malignant melanoma)[24].

3.2. Histopathology

While visual examination is limited to the horizontal plane of view (surface of the lesion), the next logical step is to examine the lesion in the vertical plane[25]. This is done by either a pathologist or dermatopathologist who analyzes the biopsied specimen stained with hematoxylin–eosin (H&E) staining to allow for the visualization of structures from the epidermis through the reticular dermis and subcutaneous tissues[26]. Criteria for the diagnosis of melanoma includes overall asymmetry and poor circumscription, poor or variably sized nests, single cells predominating over nests, upward scatter of melanocytes and nuclear pleomorphism, and morphologic changes of the nucleus and cytoplasm. Pathologists do have a set of mandatory histopathological qualities of melanoma that must be included in the pathology report of a melanoma including ulceration, mitotic rate, regression, lymphovascular invasion, perineural invasion, Breslow thickness, satellitosis, and status of surgical margins[27].

3.3. Morphology

Morphologic features can be examined through different non-invasive imaging modalities including Optical Coherence Tomography (OCT), Reflectance Confocal Microscopy (RCT), and Ultrasonography (see the complete list of these imaging modalities in [26][28][29][30][31], including quantitative dynamic infrared imaging, hyperspectral imaging, multispectral imaging, electrical impedance spectroscopy, and photoacoustic imaging (both microscopy and tomography)[32][33][34][35][36][37]. Raman spectrometry, real-time elastography, terahertz pulse imaging, multiphoton imaging, magnetic resonance imaging, positron emission tomography, fiber diffraction, Fourier transform infrared spectroscopy, and reflex transmission imaging. It should be noted that many of these imaging modalities are in the investigational phase (see [38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62]); i.e., they are not regularly used in clinical practice as of yet, but they could provide promising options in the future when they are better understood and accessible.

Rajabi-Estarabadi et al. reviewed the literature on the use of OCT to detect morphologic features of melanoma. These features included architectural disarray, stromal reaction, atypical melanocytes, vertical location of atypical melanocytes, pagetoid spread, junctional nests, and dermal nests[62]. Vessel morphology can also be examined through the use of speckle variance optical coherence tomography (SV-OCT) to detect the irregular organization of vessels found in melanoma[62].

Reflectance Confocal Microscopy (RCT) is another non-invasive method to study skin cancer in vivo. RCT also allows for visualization of the tissue microstructure in tumorous lesions. Morphologic biomarkers such as pagetoid melanocytes can be detected by RCT[63]. Other morphologic features detected by RCT are broken down by skin layers by Waddell et al.[64]. In the superficial epidermis, atypical honeycomb pattern, atypical cobblestone pattern,

and pagetoid cells are often seen in melanomas. In the basal cell layer and the dermo-epidermal layer (DEJ), cellular atypia, nonedged dermal papillae, and a disarranged DEJ can be appreciated. Lastly, the upper dermis can have cells distributed in sheet-like structures and sparse nests composed of round or pleomorphic cells[64].

High-frequency ultrasound (HFUS) has also been utilized in the diagnosis of melanoma[65]. Dinnes et al. found in their analysis that melanotic lesions appear hypoechoic, homogenous, and well defined on ultrasound[65]. Doppler ultrasound can be utilized to assess tumor vascularity by characterizing vascularization and the number of vascular pedicles present[66]. Giovagnorio et al. found that hypervascularity had a sensitivity of 90% and specificity of 100% in contrast to the benign lesions that showed hypovascularity with a sensitivity of 100% and specificity of 90% [89]. Strain elastography can be utilized to assess tumor stiffness, which is likely due to increased cellularity and tumor infiltration, as noted by Botar et al.[66].

One of the parameters that can be well studied using the above-mentioned modalities is the depth of the tumor in skin. The depth of tumor invasion correlates with the thickness of the tumor, which is strongly related to prognosis. Thickness of the tumor assists in the staging of the melanoma, which is based off of Breslow's Depth, which was updated in 2017 in the 8th Edition of the AJCC Cancer Staging Manual. The depth is measured from the epidermal granular level to the deepest level of invasion[67]. The stages are as follows T1: ≤1.0 mm, T1a: <0.8 mm with no ulceration, T1b: 0.8–1.0 mm with or without ulceration or <0.8 mm with ulceration, T2: 1.01–2.0 mm, T3: 2.01–4.0 mm, and T4: >4.0 mm. Additionally, mitotic rate is no longer in the T category[67].

3.4. Immunohistochemical Stains

When the limitations of histologic examination are reached, special stains and immunohistochemical analysis provides tools to differentiate malignant lesions from benign nevi. Multiple targets have been noted in several reviews including but not limited to S100, Gp100, Anti-MART-2, Anti Melan-A, CSPG4 (Chondroitin Sulfate Proteoglycan 4), pHH3, and p16[68][69][70]. A comprehensive list of immunohistochemical biomarkers is given in the review by Abbas et al.[70]. As noted by Eisenstein et al., these biomarkers indicate the existence of melanoma, as opposed to separating it from other cancer types[69]. While there are many immunohistochemical markers that are currently known, we have focused on several of the most clinically utilized markers, as well as several markers that are utilized for the discernment of ambiguous lesions. These biomarkers include S100, HMB 45, Ki-67, Melan A (MART1-Melanoma antigen recognized by T cells 1), Chondroitin Sulfate Proteoglycan 4 (CSPG4), Tyrosinase, PNL2, MITF (Microphthalmia transcription factor), SOX10, MC1R (Melanocortin 1 Receptor), PRAME (preferential expressed antigen in melanoma), pHH3, and p16.

S100 is a protein family with at least 25 identified members encoded by many genes, but most are located on chromosome 1q21 in a region called the epidermal differentiation cluster. These proteins have a known expression in melanoma[71]. S100 is involved in multiple cellular processes including cellular growth, cell cycle progression, cellular motility, calcium homeostasis, transcription, and protein phosphorylation[72][73]. Eisenstein et al. reported 90% sensitivity in the immunohistochemistry (IHC) stain of S100 in primary and metastatic lesions of melanoma[69]. This is in agreement with the work done by Nonaka et al., finding that S100 is the most sensitive marker for

melanoma, particularly with the subtypes S100A1, S100A6, and S100B[74]. In their study[74], more than 90% of the malignant melanomas were found to express these proteins; S100A1 specifically was present in all types of melanomas but was not present in neurofibromas, schwannomas, or malignant peripheral nerve sheath tumors [72][74]. In contrast, S100A6 was strongly and diffusely positive in the junctional and dermal components of 100% (42/42) studied spitz nevi, positive in 56% melanocytic nevi (41/73), but only positive in 33% (35/105) of the dermal components of melanomas in the study done by Ribé and McNutt[75]; therefore, they proposed the idea of utilizing S100A6 for the differentiation of Spitz nevus from melanoma[75].

HMB 45 is a monoclonal antibody against PMEL17, which is also called gp100 and plays a role in the organizational structure of melanoma[72][76]. While it can stain positively in nevi, the stain is usually limited to the epidermal and papillary dermal melanocytes in benign nevi[77], while in primary melanoma, the staining pattern is in both the superficial and the deep melanocytes of the lesion[72]. HMB 45 could be particularly useful in combination with Ki-67[72][77][78], which is discussed as an additional marker in this manuscript. In the past, there was discussion in regard to false positive results in other forms of cancer, but currently, Ordóñez states that other tumors such as epithelial, lymphoid, glial, and mesenchymal origin tumors are negative[72]. However, HMB 45 can be seen in other tumors such as angiomyolipoma, lymphangiomyomatosis, and the clear cell “sugar” tumor, and it has also been seen to be positive in post inflammatory hyperpigmentation, making it less reliable as a melanoma marker according to the review by Eisenstein et al.[68][69].

Ki-67 is a non-histone nuclear protein and is useful as a marker of proliferation. Due to the detection of Ki-67 in all cell cycle phases except in the resting phase G_0, Ki-67 is thought to be a more useful marker of proliferation than mitotic rate[70]. Ki-67 is found to be positive in <5% of common nevi, while being positive in 13%–30% of melanoma tumor cells, with cases showing 100% nuclear positivity[70][79][80].

Melan A, also known as MART 1 (Melanoma antigen recognized by T cells-Cloned gene)[81] is found in both melanosomes and the endoplasmic reticulum, which aids in the processing and transportation of PMEL (premelanosome protein). PMEL is a key factor in the creation of melanosomes[82]. Rochaix et al. stated that “Immunohistochemical studies have shown Melan A expression in all (100%) dysplastic, junctional, intradermal, compound, Spitz, and congenital nevi, as well as in lymph node capsular nevi”[83]. Melan A is a highly sensitive marker that is not expressed in the dendritic cells of lymph nodes like S100 is, which makes Melan A an appropriate candidate for melanoma detection in lymph nodes. Melan A is also not expressed in histiocytes and is reported to be more sensitive than HMB 45[84].

Chondroitin Sulfate Proteoglycan 4 (CSPG4) is involved in tissue development and can be a transmembrane receptor allowing for melanoma motility. Campoli et al. showed that the expression of CSPG4 is seen in 70% of superficial spreading and nodular human melanomas at multiple stages of melanoma progression[69][85].

Tyrosinase is involved in melanin synthesis and is expressed in epidermal melanocytes as well as pigmented portions of the eye including the retina, iris, and ciliary body[72]. Tyrosinase is also expressed in junctional nevi as well as in the junctional zone of compound nevi, with decreasing expression in the deeper areas[86]. In the review

done by Ordóñez, he noted that tyrosinase has been seen to also be positive in clear cell sarcomas, pigmented neurofibromas, and a low percentage of angiomyolipomas[72].

PNL2 is a monoclonal antibody that does not have a target antigen known but reacts with normal melanocytes and neutrophils[83]. After Ordóñez performed multiple studies, he concluded that PNL2 is a highly sensitive and specific melanoma marker that is often positive in primary epithelioid melanomas and metastatic melanomas[72][83]. PNL2 has also been reported positive in clear cell sarcomas, renal angiomyolipomas, lymphangioleiomyomatosis, and melanocytic schwanommas[83][87].

MITF, the microphthalmia transcription factor protein, plays a role in the differentiation of neural crest-derived melanocytes, mast cells, osteoclasts, and optic cup-derived retinal pigment epithelium[88]. MITF-M is the melanocyte specific isoform that does the transcription regulation of genes and controls melanogenesis, cell survival, and differentiation[87]. Ordóñez found that the sensitivity and specificity of MITF is lower than other melanoma biomarkers. MITF is similarly expressed in Schwann cells, stromal fibroblasts, dermal scars, and some mesenchymal and neural spindle cell neoplasms, which can easily be mixed up with desmoplastic melanoma[87][89]. MITF lacks specificity, so it is not beneficial for use in differentiating epithelioid melanomas from carcinomas but does have the advantage of being expressed in the nucleus, making the interpretation of IHC easier to read[72].

SOX10 is involved in the embryonic determination of cell fate and is critical in the development and formation of melanocytes[90][91]. SOX10 is a sensitive biomarker for melanocytic tumors that can be expressed in both primary and metastatic melanomas[72][74]. SOX10 stains in a nuclear pattern and is not expressed in dendritic cells, making it more beneficial for lymph node staining [92][93]. SOX10 is not restricted to solely the melanocyte, and it is found in hepatocytes, renal tubular cells, adrenal medullary cells, and the myocardium[94].

Melanocortin 1 Receptor (MC1R) is a melanocyte-stimulating hormone receptor in the GPCR (G protein-coupled receptor) family that controls pigment and plays a large role in the skin phenotype and sensitivity[95]. In two studies reviewed by Ordóñez[94][96], MC1R was present in 100% of the 44 melanomas.

PRAME (preferential expressed antigen in melanoma) is a member of the cancer testis antigen family that has normal expression in the testis, ovaries, adrenals, endometrium, and placenta[97][98]. These proteins encode antigens that are subsequently recognized by T lymphocytes[97]. In a study done by Lezcano et al., they tested 110 melanocytic tumors with ambiguous features by PRAME immunohistochemistry (IHC) and cross-referenced them with fluorescent in situ hybridization (FISH) and single nucleotide polymorphism (SNP) array. They found agreement in PRAME IHC and final diagnostic interpretation in 102/110 samples (92.7%) [99]. In their previous study from 2018, Lezcano found that 88%–94% of non-spindle cell cutaneous melanomas showed nuclear immunoreactivity for PRAME in >75% of sampled cells. In comparison, benign nevi showed PRAME expression in 13.1% of the samples and was present in less than 50% of specimen cells[98]. These findings suggest the use of PRAME in the workup of ambiguous melanocytic lesions[99].

Other studied immunomarkers include pHH3 and p16. Tissue growth is identified when stained for pHH3 and correlates with mitosis specifically by looking at the phosphorylation of histone H3 [70][100]. There is some concern that pHH3 may overestimate mitoses in both melanocytes and nonmelanocytic mitoses in the tissue[70]. The product of the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene is p16 protein. In the review by Abbas et al., they found several studies that have shown a decrease in nuclear staining with p16 in melanomas (50%–98% show loss) and that p16 could be used for differentiating melanoma from spitz nevi[70].

3.5. Serologic/Molecular Diagnosis

In addition to studying markers within the tissue themselves, current research has shifted toward seeking out melanoma biomarkers within the serum. While LDH (lactate dehydrogenase) is the most widely known serum biomarker in melanoma as a strong prognostic factor[101], its use in diagnosis is limited. Deichmann et al. demonstrated that LDH is the most specific serum biomarker in melanoma with a 92% specificity and 79% sensitivity[102]. LDH is currently the only serum biomarker accepted by the American Joint Committee on Cancer staging system as having a prognostic value for melanoma[73]. Neagu et al. discussed research on microRNA. They showed that miRNA-200c, miRNA-205, and miRNA-23b were downregulated in melanoma, while miR-146a and miR-155 were upregulated[103][104]. Armand-Labit et al. did a study with miR-1246 and miR-185, finding them to be associated with metastatic melanoma. These microRNA biomarkers in the plasma have the potential to serve in early detection of melanoma[103][105].

S100B in the serum has also been seen to correlate with the clinical stage of melanoma according to Fagnart et al. [69][106]. S100B has a direct action on TP53, a known tumor suppressor, and the effect of S100B allows for increased tumor growth in melanoma[8][16]. In a study done by Guo et al., serum S100B was normal in healthy people, and it increased in those with melanoma. In stages I/II, 1.3% of people were found to have elevated levels. In stage III, 8.7% had elevated levels, and in stage IV, 73.9% of patients had elevated levels of serum S100B[107]. Weinstein et al. suggests that S100 is not beneficial in early melanoma detection, but it is better suited for evaluation in patients with advanced disease[73].

Another serologic test possibility on the horizon is the use of genetic screening for the identification and risk stratification of patients based on their likelihood of developing melanoma. This is especially pertinent in patients with conditions that predispose to the development of melanoma such as mutations in *PTEN* (Cowden syndrome), *TP53* (Li Fraumeni syndrome), and *multiple XP genes* (xeroderma pigmentosum)[108]. Other genes including *CDKN2A*, *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, and *TERT* are known for their high penetrance as predisposing mutations for melanoma[109]. While *CDKN2A*, *BRCA1* protein, and *CDK4* genes are known susceptibility genes that are considered to be high risk for melanoma, a well-established clinical utility for testing these gene must first be established[110]. The genetic biomarkers are a promising niche that we continue to better understand each year.

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