REVIEW

Editorial Process: Submission:12/29/2024 Acceptance:10/09/2025 Published:10/16/2025

Omics in Cutaneous Melanoma

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Abstract

The advancement of multidimensional omics technologies holds immense promise for the future of medical treatment, particularly in addressing a wide range of human illnesses. Melanoma, which ranks among the most aggressive malignant pathologies affecting the skin, is a complex and heterogeneous oncological condition. There exist mutations that are tightly intertwined with the biological behavior of tumors, significantly influencing the course and outcome of the disease. Specifically, a subset of these mutations has been identified as mutually exclusive, involving specific signaling molecules and signaling cascades. Simultaneously, it has now been well established that inactivation of one component can activate alternative signaling pathways, ultimately leading to a more pronounced intensification of carcinogenesis. Consequently, this study not only reveals the impact of transcription factors and growth factors on carcinogenesis, but also emphasizes the importance of non-coding RNA (microRNAs), which constitute a unique set of biomarkers that determine the biological and molecular characteristics of tumors. It is important to note that genomic, transcriptomic, and proteomic profiling of tumors do not provide a complete assessment of their invasive and metastatic potential. The article provides contemporary insights into multimodal approaches for identifying molecular subtypes of melanoma.

Keywords: Melanoma- oncogenesis- microRNA

Asian Pac J Cancer Prev, **26 (10)**, 3519-3529

Introduction

Melanoma is the most aggressive form of skin cancer, accounting for the smallest number of epithelial cancers, but it also causes the majority of deaths from skin cancer worldwide [1]. According to data provided on the website https://worldpopulationreview.com/country-rankings/skin-cancer-rates-by-country, melanoma is the most common type of skin cancer worldwide. It is a complex disease that arises from a combination of genetic mutations, changes in cellular signaling pathways, metabolic processes, and oxidative stress. These factors lead to abnormal growth of melanocytes and disruption of their normal function, causing them to die [2, 3]. Melanoma, a type of skin cancer, remains poorly understood. Despite the availability of advanced tools and technologies such as artificial intelligence, diagnosis is still imperfect and mortality rates remain high. Molecular processes underlying melanoma transformation are complex and include various stages. Activation of signaling pathways and autophagy initiation are key aspects of melanoma development and tumor growth. Due to the high prevalence of the disease and limited effectiveness of treatments, melanoma is a critical issue in modern oncology [4, 5]. At present, there is a lot of attention on genomic, transcriptomic and epigenetic markers that determine the specific molecular features in melanoma.

Omics in molecular grouping of the cutaneous melanoma

The vast majority of melanomas that arise in the skin are characterized by mutations in either the *BRAF* or *NRAS* genes. Specifically, *NRAS* mutations are more prevalent in cases where the skin has been chronically exposed to sunlight. Additionally, approximately 20–30% of certain subtypes of melanomas have been identified to harbor activating mutations in the KIT gene. The contemporary classification of melanoma of the skin is a multidimensional process that entails discerning the various elements that contribute to the progression of neoplastic processes. The genomic classification is predicated on the patterns of gene mutations that occur most frequently, including those in the *BRAF, RAS, NF1* genes, and the wild-type (WT) gene [6].

Two distinct molecular subtypes of melanoma have been identified, designated as C1 and C2. By comparing these subtypes, a model for predicting risk of ferroptosis, known as FPRS, has been developed. The C1 subtype is

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associated with a poor prognosis, characterized by a low infiltration of immune cells, an increased frequency of homologous recombination defects, an altered fraction, as well as amplified and deleted events involving gene copy numbers [7].

Moreover, a new pattern has emerged in the context of genes related to PANoptosis. PANoptosis is a recently identified form of programmed cell death characterized by inflammation, encompassing features of pyroptosis, apoptosis, and necroptosis. By combining the GTEx and TCGA databases, Zhong L et al. identified 14 genes that are associated with PANOptosis, called PAGs. The identified analyzes PAG characteristics that effectively predict the clinical outcomes for melanoma patients [8].

To explore the underlying mechanisms of prognostic variability, new insights into the role of PANoptosis in personalized assessment of molecular subtypes in cutaneous melanoma have been found. Moreover, a nomogram based on seven tumor-specific genes, taking into account tumor stage, has been reported to demonstrate favorable prognostic ability in patients with melanoma. The selection of these seven genes *BCAN, CFAP61, CXCL13, KIT, KRT17, PLA1A,* and *PPP1R3C* enabled the development of a risk score model [9]. It is noteworthy that patients categorized as high-risk demonstrated a significantly lower survival rate compared to those classified as low-risk.

In the context of cancer research, the presence or absence of specific genetic alterations can provide valuable insights into the functional interactions within cellular systems. Numerous examples of mutual exclusivity have been reported, involving well-known genes associated with cell cycle regulation and growth factor signaling. These include less well-studied regulators of Hedgehog signaling, as described by Canisius S. in 2016. Melanoma, a highly heterogeneous malignancy, presents an unpredictable clinical course. Analysis of this data reveals recurring driver mutations, with instances of mutually exclusive genetic interactions involving two genes that rarely or never occur together. Moreover, there is a dearth of concurrent genetic events [10].

In 2023, Birkealv et al. compared copy number data from the melanoma core dataset with whole-genome CRISPR sequencing results, indicating interferon regulatory factor 4 (IRF4) as a key element in the melanoma development process [11].

It has been shown that melanomas, regardless of their gene expression profile (GEX), can be divided into genomic subtypes based on alterations in the mitogen-activated protein kinase (MAPK) signaling pathway [12]. A comprehensive understanding of the intricate cellular and molecular processes that underpin the ongoing co-evolution of the immune system and tumors could pave the way for the rational design of combined therapies targeting specific signaling pathways and cellular mechanisms involved in immune evasion [12].

Omics sciences, encompassing the large-scale analysis of various biological molecules such as DNA, RNA, proteins, and metabolites, play a pivotal role in advancing our understanding of melanoma and have the potential to significantly enhance patient outcomes [13].

The microenvironmental characteristics of HLA-DR-positive metastatic melanoma specimens were explored using a comprehensive multi-omics approach [14]. Melanoma is a highly aggressive skin cancer. Feature selection is employed to detect metastatic biomarkers in both long non-coding RNA (lncRNA) and messenger RNA (mRNA) datasets [15].

The Gene Set Enrichment Analysis, combined with RNA-Seq data obtained from the TCGA and GTEx databases, confirmed the overall trend of downregulation of proteins involved in the cytoskeleton [16]. By integrating components identified in mRNA and miRNA data, this method helps to elucidate the biological functions of microRNAs, which would otherwise be elusive [17]. The field of managing metastatic melanoma has undergone significant transformation due to recent advancements in multi-omics analysis [18].

A novel approach has been developed to elucidate the differential expression patterns of miRNA gene subtypes between tumoral and benign nevi in individuals with melanoma, with the aim of identifying clinically significant correlations that can serve as reliable biomarkers for evaluating tumor staging and progression [19].

The identification of microRNAs (miRNAs) offers great promise for the development of non-invasive and cost-effective diagnostic tools. These tools can potentially guide therapeutic interventions and improve patient outcomes in melanoma management [10].

The role of transcriptional, growth factors and microRNAs in the development of melanomas

A comprehensive review of the literature was conducted to investigate the potential role of miRNAs in melanoma development. The results of the analysis of the conducted research to determine the concentration of microRNA in the blood with the aim of using certain types of them as prognostic and diagnostic markers, as well as to identify the role of microRNA in melanogenesis are presented in Table 1.

Several miRs, including miR-126-5p, miR-134-5P, and miR-145-p (among others), have been associated with specific mechanisms involved in tumorigenesis of melanoma [see references 20-30]. miR-126-5p is a miRNA that is located within an intron and functions as a tumor suppressor in various types of cancers [27]. The miR-126-5p targets the *MDH1* gene, which encodes for malate dehydrogenase 1 (*MDH1*), an isoenzyme of the malate-aspartate shuttle, essential for energy metabolism in tumor cells [20].

The miR-134-5p tumor suppressor regulates a region of the *PCDH9* gene. This gene encodes for a protein called protocadherin 9. When expressed in excess, this protein can inhibit the activity of *RAC1, MMP2*, and *MMP9*, as well as enhancing the activity of Pyk2 and cyclin D1. The *PCDH9* overexpression is a key mechanism that inhibits melanoma progression [28]. The region of the MIG1 gene, which is activated in taurine, regulates the expression of miR-145-5p by decreasing its concentration. miR-145-5p functions as a regulator of SOX2 by targeting its binding site, and by inhibiting miR14, TUG1 promotes positive regulation of SOX. This results in an increase in

Table 1. MicroRNA Expression in the Blood of Patients with Skin Melanoma

microRNA	Expression	Functions	Source
miR-126-5p	There was an increase in the number of patients with stages I-IV melanoma compared to the control group	A potential biomarker for stage I-II melanoma.	20, 22, 30, 27
miR-129a-5p	The modulation of gene expression can be used to treat melanoma patients who exhibit resistance to BRAF inhibitors (BRAFi).	A suppressor of melanoma cell proliferation that binds to the SOX gene, making melanoma cells more sensitive to BRAFi	25, 31
miR-134-5p	There is a reduction in the expression of certain genes in stage 0 melanoma patients compared to healthy individuals.	A potential diagnostic biomarker	24, 28
miR-146a-5p	The expression of miRNA is differentially regulated in metastatic melanoma.	A predictive biomarker	39
miR-150-5p	The risk of recurrence increases as the disease progresses, and it is also higher in patients who are at a high risk of relapse.	The stratification of patients into high-risk and low-risk categories, as well as the prediction of recurrence.	32
miR-15b	There was a gradual increase in expression, which correlated with the progression of disease. Moreover, this increase was more significant in patients with high risk of relapse. Conversely, miR-15b showed a decrease in expression in patients who had high-risk melanomas.	The categorization of patients into high-risk and low-risk groups, as well as the prediction of disease recurrence.	33
miR-16	In stages I and II of the disease, the level of this parameter is lower than that in healthy individuals. Moreover, it also decreases in stages III and IV, compared to stages I and II. This parameter has a negative correlation with ulceration and tumor thickness, but a positive correlation with patient survival. Another study found that there was an increase in its expression in patients with stages I to IV, compared with healthy individuals.	A potential diagnostic and prognostic biomarker	34
miR-182-5p	A decrease in melanoma stages I-IV was observed in the patient group compared to the control group.	A potential diagnostic biomarker	35
miR-193b-3p	The incidence of the disease was higher in patients with stages I-IV compared to healthy individuals.	A potential diagnostic biomarker and a marker for the differential diagnosis of metastatic melanoma.	22
miR-197-3p	A decrease was observed in patients with stages I-IV compared to the healthy control group.	A potential diagnostic biomarker	22, 37
miR-200c-3p	There was a decrease in the expression of this marker in patients with stages I-IV, compared to healthy individuals. In addition, a further decrease was observed in expression in patients with stage III/IV compared to those with stage I/II.	A potential diagnostic and prognostic biomarker	22, 38
miR-203	A decrease in the expression was correlated with a decrease in overall patient survival. An increase in melanoma cell proliferation was associated with the upregulation of BRAF.	A potential prognostic biomarker	22, 40
miR-204-5p	The reduced expression was found to be linked with a faster cancer progression.	An oncogene suppressor.	22, 41, 42
	A reduction in the number of patients with stages I-IV was observed compared to healthy individuals. This reduction was particularly significant in patients with melanoma compared to those with benign nevi. A correlation was found between the T stage and Breslow's depth value	A potential diagnostic and prognostic biomarker	
miR-211	The lack of miR has been shown to inhibit the proliferation, tumorigenic potential, and invasive capacity of melanoma cells.	A prognostic biomarker is an essential tool for the accurate diagnosis of melanoma.	23, 25
miR-205-5p	The level of this parameter was found to be higher in patients with stages I-IV compared to healthy individuals. In contrast, it was lower in cases of melanoma compared to benign naevus.	A potential diagnostic biomarker	22, 43
miR-206	The expression of miR is significantly lower in melanoma patients than in healthy individuals. This decrease in expression is linked to more aggressive disease development and poor prognosis.	A potential diagnostic and prognostic biomarker	22, 44
miR-21	The expression of miR is significantly increased in various types of cancer, especially in melanoma. Increased levels in the blood indicate its high expression in metastatic melanoma tissues. When preoperative and postoperative samples were compared, a decrease in the levels of this gene in the blood was observed in the postoperative specimens.	The targeted FBXO11 protein promotes proliferation, migration, and inhibits apoptosis in A375 human melanoma cells. This is achieved through the inhibition of the activity of SPRY1, PDCD4, and PTEN proteins, as well as the stimulation of the ERK/NF-κB signaling pathway.	22, 45
miR-211-5p	The miR expression was found to be elevated in patients with stages I–IV compared to healthy individuals. This elevation correlates with an increase in tumor thickness, a decrease in differentiation, and higher T and N grades.	A potential diagnostic and prognostic biomarker is the target for the mammalian cell cycle regulator p27Kip1 in the melanoma cell line Me1402.	22, 46
miR-27a-3p	The expression of miR has been found to be significantly lower in patients with stages I-IV than in healthy individuals. This decrease is particularly noticeable in individuals with metastatic melanoma.	A potential diagnostic and prognostic biomarker	22, 47
miR-28-5p	A decrease was observed in patients with stages I-IV compared to healthy individuals.	A potential diagnostic biomarker	22, 48

Table 1. Continued

microRNA	Expression	Functions	Source
miR-301a-3p	The expression of miR is reduced in patients with stages I-IV, compared to healthy individuals. It also exhibits differential expression in metastatic melanomas.	A potential diagnostic and prognostic biomarker	22, 49
miR-30d-5p	The magnitude of the phenomenon increases directly proportional to the level of development of the stage.	The categorization of patients into high-risk and low-risk groups.	50
miR-320a-3p	A reduction was observed in the number of patients with stage 0 melanoma, compared to healthy individuals.	A potential diagnostic biomarker	51
miR-34a-5p	A decrease in miR expression has been observed in melanoma compared to benign nevi. This decrease becomes more significant as the TNM stage increases. The overexpression of this gene inhibits cell proliferation and migration in vivo, significantly inhibiting tumor growth and reducing ZEB1 expression.	A tumor suppressor; a potential prognostic biomarker.	52
miR-374a-5p	A decrease in miR expression was observed in patients with stages I-IV compared to the healthy control group.	A potential diagnostic biomarker	22, 53
miR-382	The reduced expression is associated with suppression of in vivo invasion and metastasis in vitro in aggressive primary melanomas compared to non-aggressive melanomas.	A potential prognostic biomarker	54
miR-424	The increased expression in the blood and tissues of patients with melanoma correlates with the thickness of the tumor, the presence of metastases, and the cancer stage.	A potential prognostic biomarker	55
miR-425	The risk of melanoma progression increases as the disease develops.	The classification of patients into high- and low-risk groups.	56
miR-514a-3p	It regulates the function of the NF1 transcription factor and modifies the response to targeted BRAF therapy.	A potential prognostic biomarker	57
miR-516b	The reduced expression is associated with suppression of in vivo invasion and metastasis in vitro in aggressive primary melanoma compared to non-aggressive melanoma.	A potential prognostic biomarker	58
miR-550a-3p	The level of miR expression is increased in patients with stages I-IV compared to healthy individuals.	potential prognostic biomarker	59
miR-627-5p	The level of miR expression is increased in patients with stages I-IV compared to healthy individuals.	A potential diagnostic biomarker	60
miR-629-5p	The level of miR expression is increased in patients with stages I-IV compared to healthy individuals.	A potential diagnostic biomarker	61
miR-675-3p	The level of miRNA expression is significantly increased in both melanoma tissue and peripheral blood.	A potential diagnostic biomarker	98
miR-720	The expression level of miR is increased in patients with stages I-IV compared to healthy individuals, and it shows different expression patterns in metastatic melanoma.	A potential diagnostic and prognostic biomarker	62

mRNA levels for SOX, leading to increased migration and invasion of melanoma cells. Conversely, inhibition of TUG and increase of miR-145-5p leads to a decrease in COX mRNA levels and a reduction in melanocyte "stemness" [29].

The expression levels of several miRNAs, including miR-126-5p, miR-211-5p and miR-22, as well as miR424, 425 and 514a-3, miR516b and miR550a, miR627-5 and miR629-5, and miR720 have been found to be significantly increased in melanoma patients stages I-IV compared to healthy individuals. This suggests that these miRNAs may serve as biomarkers for early detection and monitoring of melanoma skin [22, 23].

In patients with stage 0 melanoma, there was a decrease in the expression of several microRNAs. These microRNAs include miR-134-5p, miR-16, miR-182-5p, miR-197-3p, miR-200c-3p, miR-204-5p, miR-205-5p, miR-206, miR-211-5p, miR-28-5p and miR-301a-3p [25, 28-37]. These microRNAs may be potential diagnostic biomarkers as they are also reduced in healthy individuals compared to melanoma patients [24]. Additionally, the levels of miR-204-5 and miR-30d-5p expression have been linked to tumor size and depth of invasion according to Breslow's classification, indicating their potential role in tumor progression prediction [39, 47].

It has been well established that the effect on mitogen-activated protein kinase (MAPK) signaling pathways is crucial in determining the course of tumor development. In this regard, miR-129a-5p has potential to regulate expression of critical signaling molecules, offering promise for improved therapeutic outcomes in melanoma patients resistant to *BRAF*i treatment [25, 31].A potential indicator of invasive growth in this type of tumor is the appearance of regional and distant metastases. According to the literature, the expression of certain microRNAs (miRNAs) is different in metastatic melanoma tissues compared to non-metastatic tumors. Specifically, the levels of miR-146a-5p, miR-150-5p, miR-15b, miR-27a-3p, miR-301a-3p, miR-382, miR-424, miR-516b, and miR-720 are altered in metastatic melanoma cells [30, 32, 33, 38, 46-61]. These microRNAs have been identified and can be used as markers to indicate an increased risk of recurrence [25].

In the process of analyzing the spectrum of miRNAs related to melanoma development, particular attention is paid to miR-21. This miRNA's level is elevated in metastatic melanoma tissues. It is known that miR-21 affects the expression of FBXO11 by RNA interference. FBXO, the protein product of the FBXO gene, is involved in promoting proliferation, migration, and blocking apoptosis of A375 melanoma cells. Other important targets include SPRY, PDCD and PTEN. miR-2 also activates signaling pathways through ERK/NF-κB, which are associated with inflammatory responses [42]. A comprehensive review on the significance of microRNA expression in skin melanoma tissue has been conducted. In Table 2, we have summarized the results of studies on the use of specific microRNAs as biomarkers for the diagnosis and prediction of diseases, as well as the study of the effect of microRNAs on the melanogenesis process.

It reveals that miR-146a-5p, miR-203, miR-211, miR-378, miR-524, miR-542, miR-106, miR-675, miR-125, miR -183, miR -214, and miR -302 are all significantly increased in melanoma cells compared to healthy adjacent skin, while miR-93 is significantly decreased [62-109]. Furthermore, miR-204-5p, miR-125b, miR-128-3p, and miR-138-5p are classified as oncogenic miRNAs. These miRNAs have a clear correlation with the progression of the disease [5, 23]. A correlation was found between changes in the levels of miR-203, miR-106b-5p, miR-548b, miR-10a-5p, miR-137, miR-181a/b, miR-200a-5p, miR-25, miR-377, miR-493, and miR-7-5P in tumors and patient overall survival. Additionally, the abundance of miR-1180-3p, miR-152-5p, miR-155-5p, miR-185, miR-18a-5p, miR-302a-3p, miR-485-5p, miR-510, miR-513c, and miR-633, as well as miR-942-5p was associated with signs of invasive tumor growth and Breslow thickness [62-98]. The underlying mechanism of this process is likely due to the stimulation of melanoma cell proliferation and growth, which can be caused by a *BRAF* mutation [25]. The correlation between the progression of regional metastases and the high expression of miR-1246 has been established [22].

Among the most significant mechanisms of tumor progression, the toll-like receptor (TLR), the nuclear factor κB (NF-κB), and the epidermal growth factor receptor (EGFR) pathways are of particular interest. A total of thirty-eight target genes have been identified for miR-146-5p, and the *NRAS* gene is one of them. It is one of the most frequently mutated genes in melanoma, has been identified as a target for anti-cancer therapy [25]. Another microRNA with the potential to cause cancer is miR-211. When absent, it inhibits the proliferation and invasion of tumor cells, leading to disruption of the tricarboxylic acid cycle and oxidative phosphorylation pathways that are essential for cell growth and survival [22-24]. miR-211 is a microRNA that is specifically expressed in melanocytes and acts as a potent inhibitor of melastatin-1 (TRPM1), which codes for a transient receptor potential cation channel belonging to the M subfamily and member 1 [106]. With regard to miR-378, which is overexpressed in tumorous tissues, the *FOXP3* gene has been shown to be a target of this microRNA. This interaction can activate the Wnt/catenin signaling pathway, promoting the proliferation and migration of melanoma cells [25].

A multifaceted impact on signaling has been demonstrated for miR-524-5p, miR-106b-5p, and miR-17-5p. These microRNAs are linked to the modulation of mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathways, as well as phosphoinositide 3-kinase (PI3K) and AKT signaling cascades, including in melanoma cell lines that are resistant to *BRAF* inhibitors. Activation of transforming growth factor beta (TGF-β)/SMAD and hypoxia-inducible factor 1 (*HIF-1*) signaling is correlated with the influence exerted by miR-675 [25]. The influence of miR-548b on tumorigenesis is mediated through the regulation of the expression of the *HMGB1* gene, which leads to suppression of the proliferation, migration, and invasion of melanoma cells into neighboring tissues [25].

The modulation of melanoma cell sensitivity to pro-apoptotic stimuli may be regulated through the involvement of microRNAs. In particular, miR-125a-5p and miR-214 have been shown to inhibit pro-apoptosis proteins MLK3 and BAK, allowing tumors to evade apoptosis and contribute to the pathogenesis of melanoma with a *BRAF*V600E mutation. These microRNAs may facilitate the growth and resistance of tumors to apoptosis [25].

Another mechanism of action associated with microRNAs involves altering the expression of transcription factors. In particular, miR-137 and miR-4458 influence the activity of transcriptional regulators by directly targeting TBX3, EZH2, c-Met, and YB1. This process effectively inhibits the ability of melanoma cells to invade and migrate [24, 25].

The modification of the tumor microenvironment may play a role in the mechanisms of microRNA action. An increase in miR-17-5p expression has been shown to modulate the level of PD-L1 mRNA in melanoma cells resistant to *BRAF* inhibitors. High levels of PD-L1 have been linked to melanoma invasiveness and aggressiveness [25]. Meanwhile, miR-183 targets MITF and has the ability to influence the rate of melanin synthesis and regulate cell proliferation. The effect of miR-200a-5p is linked to the upregulation of TSP1 protein expression, which is associated with *HLA-1* expression in melanoma cell cultures [20]. miR-222 specifically targets the p27Kip1 gene, which is a regulator of the cell cycle in mammalian cells, in the Me1402/R melanoma cell line [109]. miR-302a-3p inhibits the expression of *METTL3*, a catalytic subunit of the N6-adenosine-methyltransferase complex. This suppresses tumor growth and prevents metastasis [20, 109]. Other notable mechanisms include regulation of the *PTPN11* gene by miR-3065-5p, and regulation of NF-κB by miR-7 and miR-377 [89]. It has been shown that miR-493 suppresses proliferation by regulating the expression of the IRS-4 gene [109]. miR-93-5p has been shown to play a role in tumor development by regulating the expression of UBC, a potential target for melanoma treatment [20].

We have identified a list of microRNAs (miRNAs) that can be used for both tumor diagnosis and predicting the prognosis of the disease. These include miR-134, miR-146, miR- 16, miR -182, miR-93, miR-200, miR-4, miR 5, miR --27, miR-3, miR-22, miR-32, and miR-72. miRNAs associated with invasive growth and metastasis

Table 2. The Analysis of microRNA Expression Patterns in Tumor Tissue from Individuals with Melanoma

microRNA	Expression	Functions	Source
miR-146a-5p	The expression of miRNAs has been found to be higher in melanoma cells than in healthy adjacent skin cells.	A potential diagnostic biomarker	62, 104
miR-106b-5p	The level of miR expression was significantly higher in melanoma tissues compared to epidermal melanocytes. Additionally, an increase in miR expression correlates with a poorer five-year overall prognosis.	A potential prognostic biomarker; a putative factor that may influence the cell cycle.	63
miR-10a-5p	The downregulation of miR was associated with improved overall survival.	A potential prognostic biomarker	64
miR-1180-3p	The reduced expression of miR is associated with an increased likelihood of invasion.	A tumor suppressor; apotential prognostic biomarker	65
miR-1246	The expression of miR correlates with the development of metastatic melanoma.	A potential prognostic biomarker	66
miR-125a-5a	The upregulation of microRNA (miR) expression inhibits the activity of the pro-apoptotic proteins MLK3 and BAK, allowing the tumor to avoid apoptosis.	It promotes the development of cancer, associated with melanoma resistance due to the BRAFV600 mutation.	67
miR-125b	The upregulation of miR expression was linked to the inhibition of cell invasion and migration.	A tumor suppressor; a potential prognostic biomarker	68
miR-128-3p	The upregulation of miR inhibits the proliferation, invasion, and migration of melanoma cells.	A tumor suppressor; a potential prognostic biomarker	69
miR-137	miR is able to suppress the invasion and migration of melanoma cells by specifically targeting certain genes, such as TBX3, EZH2, c-Met and YB1 transcription factors. A decrease in expression of these genes is linked to a worse prognosis for melanoma patients.	A tumor suppressor; a potential prognostic biomarker	70
miR-138-5p	The upregulation of miR leads to the suppression of cell proliferation in the G0/G1 phase.	A tumor suppressor; a potential prognostic biomarker	71
miR-152-5p	The expression of miR is significantly increased in cell lines resistant to brain metastasis, which promotes the invasion of melanoma by blocking the action of the metastasis suppressor gene, TXNIP.	The inhibition of miR-152-5p could potentially delay the development of resistance to BRAFi.	72
miR-155-5p	miR is involved in the process of metastasis formation.	A potential prognostic biomarker	73
miR-17-5p	The upregulation of miR-mediated PD-L1 mRNA was observed in BRAFi-resistant melanoma cells, and a strong correlation was found between high levels of PD-L1 and melanoma invasiveness and aggressiveness.	A potential prognostic biomarker	74
miR-181a/b	The upregulation of miR is positively associated with a higher patient survival rate.	A potential prognostic biomarker	75
miR-183	The upregulation of miR results in a reduction of MITF expression, which leads to a decrease in melanin production and cell proliferation rate.	A tumor suppressor	76
miR-185	The expression of miR is associated with metastatic melanoma.	A potential prognostic biomarker	77
miR-18a-5p	miR is involved in the process of metastasis formation.	A tumor suppressor; a potential prognostic biomarker	78
miR-200a-5p	The miR level is positively correlated with the survival rate in metastatic melanoma. miR has been shown to decrease the amount of TAP1 protein, which in turn leads to a reduction in the surface expression of HLA-1 in melanoma cell lines.	A potential prognostic biomarker	79
miR-203	The downregulation of miR was linked to poor overall survival in patients. Increased proliferation and growth of melanoma cells were accompanied by an increase in BRAF expression.	A potential prognostic biomarker	105
miR-204-5p	A decrease in miR expression has been linked to a faster cancer progression.	An oncogene suppressor.	81, 106, 109
miR-214	The overexpression of miR results in an increase in cell proliferation and affects sensitivity to BRAFi.	A potential therapeutic target	83
miR-222	The miR specifically directs its action towards the mammalian cell cycle regulator p27Kip1 in the melanoma cell line Me1402/R.	A potential prognostic biomarker	84
miR-25	The expression of miR is inversely correlated with prognosis.	A potential prognostic biomarker	85
miR-302a-3p	The upregulation of miRNA leads to the suppression of METTL3 expression, which in turn reduces tumor growth and metastatic potential.	A tumor suppressor; a potential prognostic biomarker	86
miR-3065-5p	The miR is upregulated and the PTPN11 gene is controlled.	A potential prognostic biomarker	87
miR-377	The downregulation of miR has been linked to aggressive proliferation and metastasis. It acts as a negative regulator of NF-κB.	A potential prognostic biomarker	88
miR-378	The miR is abundantly expressed and exerts an inhibitory influence on the FOX3 target gene, which in turn stimulates the proliferation and migration of melanoma cells through the Wnt/catenin signaling pathway in tissue samples.	A potential prognostic biomarker; a potential factor controlling the cell cycle	89
miR-4458	The miR overexpression induces apoptosis.	An oncogene suppressor.	90
miR-485-5p	The overexpression of miR reduces the proliferative capacity and inhibits the invasive characteristics of melanoma cells.	A tumor suppressor; a potential prognostic biomarker	91

Table 2. Continued

microRNA	Expression	Functions	Source
miR-493	The downregulation of miRNA has been linked to poor prognosis in melanoma patients. miR inhibits proliferation by targeting IRS4 mRNA, which is involved in cell growth and survival.	A tumor suppressor	92
miR-510	miR expression was negatively correlated with prognosis; a correlation was found between T stage and Breslow depth value	A potential prognostic biomarker	93
miR-513c	The expression of miR is inversely correlated with prognosis, and a relationship is observed between the T stage and the Breslow depth value.	A potential prognostic biomarker	94
miR-524-5p	The miR level in normal skin was higher than in melanoma, and the level of this substance in nervous tissue was even higher. This substance inhibits the MAPK/ERK signaling pathway and partially blocks the PI3K/AKT cascade.	A potential biomarker for response to BRAFi therapy and metastasis.	95, 108
miR-548b	A decrease in the expression of miR-548b compared to adjacent tissues was observed, and overexpression of miR-548 was associated with improved overall survival in melanoma patients.	A potential prognostic biomarker	96
miR-633	The upregulation of miRNA expression was inversely correlated with tumor cell proliferation and migration.	A potential prognostic biomarker	97
miR-675-3p	miR has been found to be overexpressed in various melanoma cell lines, tissues, and blood samples. There are reports of correlations between miR-675-3p and the TGF-β/SMAD and HIF-1 pathways.	A potential prognostic biomarker	98
miR-7-5p	The downregulation of miR is associated with a poor prognosis for melanoma patients, as it inhibits the growth and metastasis of melanoma cells by targeting RelA/NF-κB directly.	A tumor suppressor; a potential prognostic biomarker	99
miR-93-5p	miR is implicated in the process of metastasis.	A potential prognostic biomarker; a potential therapeutic target	100
miR-942-5p	The upregulation of miR results in a decrease in apoptosis and an increase in cell proliferation, as well as in the processes of invasion and migration.	A potential prognostic biomarker	101
miR-99a	The expression of miR is significantly increased in invasive cell lines.	A potential prognostic biomarker	102
miR-let-7c	The level of miRNA is increased in proliferative cells.	A tumor suppressor; a potential prognostic biomarker	102, 103

of skin melanoma include let-7c, miR-1180-3p, miR-1246-5, miR-128-5p, miR-137-3p, miR146a-3, miR-5-3, and miR-152A-5. These miRNAs have been shown to be involved in the development of melanomas, suggesting that they may serve as diagnostic markers and potential targets for therapy. It has also been established that individual miRNA can regulate multiple genes, while the transcriptional activity of one gene can be controlled by multiple miRNAs. miR-93A-5 has been identified as a key regulator of tumorigenesis through its modulation of UBC expression, making it a promising therapeutic target.

Furthermore, the impact on the initiation and progression of cancer can be assessed by both an increase and decrease in the concentration of endogenous miRNAs within a cellular environment [2]. The direst prognosis for melanoma of the skin is associated with mutations in critical genes that are part of the MAP-kinase signaling pathway. Among these critical genes, *BRAF* stands out as particularly important, followed by genes from the RAS family, including HRAS, KRAS and *NRAS* [3]. According to scientific literature, somatic mutations in the *BRAF* or *NRAS* genes within the *RAS/BRAF/MEK* signaling cascade are linked to an aggressive course of disease, poor prognosis and low survival rates among patients with skin melanoma. Therefore, exploring the role of miRNAs in regulating the activity of signaling genes in melanocytes is a crucial area of research in experimental biology and oncology today.

In conclusion, the advancement of multidimensional omics technologies holds immense promise for the future of medical treatment, particularly in addressing a wide range of human illnesses. Melanoma has mutations that are tightly intertwined with the biological behavior of tumors, significantly influencing the course and outcome of the disease. Specifically, a subset of these mutations has been identified as mutually exclusive, involving specific signaling molecules and signaling cascades.

Simultaneously, it has now been well established that inactivation of one component can activate alternative signaling pathways, ultimately leading to a more pronounced intensification of carcinogenesis. Consequently, this study not only reveals the impact of transcription factors and growth factors on carcinogenesis, but also emphasizes the importance of non-coding RNA, which constitute a unique set of biomarkers that determine the biological and molecular characteristics of tumors.

Author Contribution Statement

The corresponding author(s) is responsible for providing the contributions of all authors at submission. All authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time. LVS and VAB: Conceptualization, Investigation, Writing-original draft, Writing-review & editing. OLN, SYC and EAS: Conceptualization, Investigation, Writing-original draft, Writing-review & editing. ABZ and AAB: Validation, Writing-review & editing, Supervision. All authors read and approved the submitted version.

Acknowledgements

Abbreviations

BRAF: mutant cRAF protein

*BRAF*i; *BRAF* inhibitor

EGFR: epidermal growth factor receptor

ERK: extracellular signal-regulated kinase

HIF-1: hypoxia-inducible factor 1

MAPK: mitogen-activated protein kinase

miRNA: microRNA

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

PI3K: Phosphoinositide-3-kinase

TLR: toll-like receptor

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the YYY (Ethics Committee name and the reference number if any).

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