Review

Clin Ter 2023; 174 Suppl. 2 (6):29-36 doi: 10.7417/CT.2023.2469

Omics sciences and precision medicine in melanoma

M.C. Medori[1], K. Donato[2,3], K. Dhuli[1], P.E. Maltese[1], B. Tanzi[1], S. Tezzele[1], C. Mareso[2], J. Miertus[1], D. Generali[4], C.A. Donofrio[5,6], M. Cominetti[5], A. Fioravanti[5], L. Riccio[5], T. Beccari[7], M.R. Ceccarini[7], P. Gisondi[8], F. Bellinato[8], L. Stuppia[9,10], V. Gatta[9,10], S. Cecchin[1], G. Marceddu[2], M. Bertelli[1,2,3]

[1]MAGI'S LAB, Rovereto (TN), Italy; [2]MAGI EUREGIO, Bolzano, Italy; [3]MAGISNAT, Atlanta Tech Park, Peachtree Corners (GA), USA; [4]Department of Medicine, Surgery and Health Sciences, University of Trieste, Italy; Multidisciplinary Unit of Breast Pathology and Translational Research, Cremona Hospital, Italy; [5]Department of Neurosurgery, ASST Cremona, Italy; [6]Division of Biology and Genetics, Department of Molecular and Translational Medicine, University of Brescia, Italy; [7]Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy; [8]Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy; [9]Department of Psychological Health and Territorial Sciences, School of Medicine and Health Sciences, "G. d'Annunzio" University of Chieti-Pescara, Italy; [10]Unit of Molecular Genetics, Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, Italy

Abstract

Background. This article provides an overview of the application of omics sciences in melanoma research. The name omics sciences refers to the large-scale analysis of biological molecules like DNA, RNA, proteins, and metabolites.

Methods. In the course of this review, we have adopted a focused research strategy, meticulously selecting the most pertinent and emblematic articles related to the topic. Our methodology included a systematic examination of the scientific literature to guarantee a thorough and precise synthesis of the existing sources.

Results. With the advent of high-throughput technologies, omics have become an essential tool for understanding the complexity of melanoma. In this article, we discuss the different omics approaches used in melanoma research, including genomics, transcriptomics, proteomics, and metabolomics. We also highlight the major findings and insights gained from these studies, including the identification of new therapeutic targets and the development of biomarkers for diagnosis and prognosis. Finally, we discuss the challenges and future directions in omics-based melanoma research, including the integration of multiple omics data and the development of personalized medicine approaches.

Conclusions. Overall, this article emphasizes the importance of omics science in advancing our understanding of melanoma and its potential for improving patient outcomes. ***Clin Ter 2023; 174 Suppl. 2 (6):29-36 doi: 10.7417/CT.2023.2469***

Key words: *Melanoma, omics science, genomics, metabolomics, diagnosis, precision medicine, therapy*

Introduction

During the past few decades, the incidence of cutaneous melanoma (CM) has increased, thus turning this disease from a very uncommon condition into a malignancy of increasing medical significance. Australia and New Zealand reported the greatest incidence rates, with 30 to 60 cases per 100,000 inhabitants each year (1,2). In 2017, cuticle melanoma was the fifth most prevalent malignancy among men and the sixth most prevalent among women in the United States. Moreover, 72% of all skin cancer fatalities (excluding basal-cell and squamous-cell carcinoma of the epidermis) were attributed to cutaneous melanoma. In Europe, the 5-year age-standardized relative survival for cutaneous melanoma diagnosed in 2000-2007 ranged from 74% in Eastern Europe to 87% in Western Europe (1). The Central Malignant Melanoma Registry (CMMR) has recorded over 70,000 cases of CM in Germany. At age 80, the proportion of dense melanoma significantly increases, and reaches 20% in both sexes (2).

To date, it is widely acknowledged that an individual's melanoma risk is influenced by the interplay of genetic factors and UV exposure. Epidemiological studies have identified a history of sunburns and intermittent solar exposure as risk factors for melanoma. Interestingly, eighty percent of melanomas develop in regions with intermittent sun exposure. The role of sunlight in melanoma development has been a topic of debate for decades, as its impact on the etiology of melanoma is significantly less obvious compared to nonmelanoma skin cancer (2,3). The strongest evidence

Correspondence: Maria Chiara Medori, MAGI'S LAB, Rovereto (TN), Italy. Email: chiara.medori@assomagi.org

ISSN 1972-6007

linking UV exposure to melanoma comes from xeroderma pigmentosum, a natural genetic experiment (4).

Invasion and metastasis are the two defining characteristics of cancer, which serve as the foundation for pathologic diagnosis and staging of melanoma (4). Early detection of malignant melanoma is crucial for reducing the overall mortality associated with this disease. Large-scale screening programs, both in the United States and abroad, have proven useful in predicting high-risk patients (3).

Despite the identification of several markers and the development of algorithms for the rapid diagnosis of melanomas, tumors are often detected at an advanced stage, leading to a poor prognosis. It is widely recognized that the tumor microenvironment plays a crucial role in providing biomarkers for cancer. By analyzing markers such as lymphocyte cytosolic protein 2, autophagy, beclin 1, regulator 1, and loricrin, new insights into the role of the tumor microenvironment in melanoma progression have emerged. Furthermore, proteins like nicotinamide N-methyltransferase and TBC show promise as potential diagnostic markers for melanoma (5).

Variations in specific genes, influencing both the skin's protective response to UV light and the risk of melanoma, control how exposure to UV light affects us. Particularly, MITF amplification is more common in tumors with a poor prognosis and is connected to chemoresistant behavior. Mutant BRAF protein induces cell senescence in human melanocytes by increasing the expression of the cell-cycle inhibitor of kinase 4A (INK4A) (6).

In this article, we will discuss the epidemiology, genetic factors, and the use of omics sciences in refining diagnosis and treatment based on recent research and studies.

Genetics & Genomics

Having a family history of malignancy is linked to a higher risk of developing melanoma, as approximately 10% of melanoma cases have reported a relative with the disease. While most genetic changes related to melanoma development are somatic, the prevalence of heritable melanoma risk genes remains a critical factor in the occurrence of the disease (7-10).

High penetrance melanoma predisposition genes known to date include CDKN2A, CDK4, BAP1, POT1, ACD, TERF2IP, and TERT. Although these mutations are associated with approximately 50% of familial melanoma cases, the genetic basis for the remaining high-density melanoma families remains unidentified. The most extensively documented correlation is between CDKN2A germ line mutations and pancreatic cancer, whereas BAP1 germ line mutations have been linked to a cancer syndrome involving cutaneous melanoma, uveal melanoma, and mesothelioma. Other melanoma susceptibility genes with moderate to high penetrance have also been associated with renal cell carcinoma (MITF, BAP1) and glioma (POT1) (7,9-12).

Common gene mutations associated with melanoma

Numerous gene mutations have been linked to the development and progression of melanoma. These genes are involved in numerous signaling pathways, such as the receptor tyrosine kinase (RTK), phosphotidylinositol-3-kinase (PI(3)K), retinoblastoma (RB), p53, Wnt, and NFkB pathways (8,13).

BRAF, a serine-threonine kinase, is located in the MAP kinase signaling pathway downstream of RAS. BRAF mutations are found in approximately 60% of melanomas, and are particularly prevalent in melanomas that originate in locations with intermittent UV exposure. BRAF's oncogenic potential derives from its ability to phosphorylate MEK, which activates ERK and promotes cell proliferation. Due to their shared pathway membership, NRAS and BRAF mutations as well as NRAS and PTEN mutations are mutually exclusive in melanoma, whereas BRAF and PTEN mutations coexist in up to 20% of melanomas (8,11,13,14).

NRAS, a gene that encodes a member of the RAS family of small GTP-binding proteins, was among the first genes found to be specifically mutated in melanoma. The recurrence and high transforming potential of oncogenic NRAS mutations in human melanomas highlight the crucial role of this gene and its downstream effector mechanisms in melanoma development. NRAS mutations are the second most prevalent, affecting 20-30% of CM cases. The nodular subtype of melanoma is frequently associated with NRAS mutations that arise on the chronically UV-damaged skin of elderly patients. Additionally, NRAS-mutant melanomas tend to exhibit greater aggressiveness compared to BRAF-mutant melanomas, as evident from higher Breslow thickness and mitotic rate. (8,11,13,14).

MITF represents a novel category of lineage-survival oncogenes. Unlike oncogenic NRAS and BRAF, which gain novel and tumor-specific cellular functions through nucleotide mutations, MITF becomes oncogenic through deregulation, influencing survival mechanisms that are also present in the normal melanocyte lineage. It is widely accepted that wild-type MITF is crucial for lineage survival, and the absence (or loss) of melanocytes during development occurs in the absence of MITF (8,13).

Table 1. Common genetic mutations in melanoma.

Gene	Mutation	Frequency (%)
BRAF	V600E/K	40-50
NRAS	Q61R/K	15-20
NF1	Loss of function	10-15
KIT	L576P, K642E	2-3
TP53	Missense, truncating	1-2
CDKN2A	Loss of function	10-15
PTEN	Loss of function	5-10

Syndromes associated with melanoma

BAP1 tumor predisposition syndrome (BAP1-TPDS) is linked to an elevated risk for a particular cutaneous lesion and BAP1-inactivated melanocytic tumors. BAP1-TPDS is inherited autosomally and dominantly; currently, the majority of BAP1-TPDS patients have affected parents. First associated with BAP1-TPDS in 2011, CM is now recognized as the third most prevalent malignancy in BAP1-TPDS patients (15).

Multiple skin tumors—including cylindromas, spiradenomas, trichoepitheliomas, and (infrequently) membranous basal cell adenoma of the salivary gland—typically appear in the second or third decade in patients with CYLD cutaneous syndrome (CCS). Overall, women have more malignancies than men. Germline pathogenic variants of CYLD are autosomal dominantly inherited; the majority of people with CYLD cutaneous syndrome inherit it from their parents (16).

POT1 tumor predisposition (POT1-TPD), an autosomal dominant inheritance, is distinguished by an increased lifetime risk for multiple cutaneous melanomas, among other cancers. Currently, the majority of POT1-TPD patients have affected parents (17).

Multiple café au lait macules, intertriginous freckling, and multiple cutaneous neurofibromas characterize Neurofibromatosis 1 (NF1), a multisystem disorder. NF1 is an autosomal dominant inherited disorder, but approximately half of the affected individuals having NF1 due to *de novo* NF1 disease-causing variant. NF1-mutant tumours are aggressive and have a poor prognosis for survival; they are also prevalent in elderly patients with sun-exposed skin. NF1 mutations have been reported in roughly 14% of melanomas. Currently, there are no treatments on the market that target mutant NF1 cancers exclusively (14,18).

Proteomics, Metabolomics & Microbiomics

In the past decade, innovative molecular and proteomic analysis tools have revolutionized the discovery of cancer biomarkers. Proteomic strategies can be categorized into two groups: Those that characterize the entire protein complement of the cells or tissue of interest and those that analyze only the proteins present in specific specimens (typically blood, but also other fluids like saliva or urine) (19). More than 51,100 biomarkers have been identified and studied for melanoma. These biomarkers encompass tissue-based tumor cell and tumor microenvironment biomarkers, along with circulating tumor DNA (cf-DNA), mir-RNA, proteins, and metabolites. These biomarkers offer invaluable insights for diagnosing, prognosing, and predicting treatment response (20).

Biomarkers are used for screening (to determine who is more prone to developing multiple myeloma), diagnostics (to equip clinicians with the ability to accurately diagnose multiple myeloma), and staging (to determine the total melanoma burden present in a patient at any given time). In addition, they are used to provide information on mechanisms for combating metastatic disease and the development of novel treatments, as well as to predict and clarify the likelihood of disease progression and treatment response (20).

The comprehensive analysis of gene expression has significantly enhanced the understanding of tumorigenesis, invasion, and metastasis. Recently, gene expression assays have played a crucial role in guiding therapeutic decision-making. However, the current staging system for melanoma, which relies on Breslow thickness, ulceration, and mitotic count, proves inadequate. The varied progression rate and the presence of regional and distal metastases categorize patients into heterogeneous groups with diverse outcomes and therapeutic responses. Consequently, more aggressive surgical and adjuvant therapies are applied to large populations, leading to a diluted therapeutic effect and exposing more patients to potential toxicity (19).

Metabolite phenotyping facilitates the development of novel therapies and improves the understanding of complex metabolic diseases, such as melanoma (21,22). Single-cell omics methods have revolutionized biology by unraveling the heterogeneity that underlies population averages. One potential application is pharmaco-omics, wherein the genetic or functional makeup of diseased tissues is used to guide the implementation of personalized therapeutic strategies for patients. An example of this is Raman spectro-microscopy, which involves spatial mapping of metabolites within individual cells, aiming to identify druggable metabolic susceptibilities in a series of patient-derived melanoma cell lines (23).

Regardless of the genetic driver mutation, different ceramide and phosphatidylcholine species were observed among melanoma subtypes. Additionally, beta-alanine metabolism showed variations among melanoma subtypes and exhibited significantly higher levels in the plasma of mice with melanoma compared to healthy mice. Furthermore, beta-alanine, p-cresol sulfate, sarcosine, tiglylcarnitine, two dihexosylceramides, and phosphatidylcholine were identified as potential plasma biomarkers for melanoma (22).

Currently, immune checkpoint inhibitors (ICIs), especially antibodies targeting the cytotoxic T-lymphocyte-

Table 2. Syndromes associated with Melanoma.

Syndrome	Gene	Inheritance	Associated Cancers	Other Clinical Features
BAP1 Tumor Predisposition Syndrome	BAP1	Autosomal dominant	Uveal melanoma, cutaneous melanoma, mesothelioma, renal cell carcinoma	Atypical melanocytic lesions, ocular melanocytosis
CYLD Cutaneous Syndrome	CYLD	Autosomal dominant	Cylindromas, spiradenomas, trichoepitheliomas	Brooke-Spiegler syndrome
POT1 Tumor Predisposition	POT1	Autosomal dominant	Cutaneous melanoma, glioma, chronic lymphocytic leukemia	Familial melanoma
Neurofibromatosis 1	NF1	Autosomal dominant	Neurofibromas, optic pathway gliomas, malignant peripheral nerve sheath tumors	Café-au-lait spots, Lisch nodules, neurofibromas

associated protein 4 (CTLA-4) or the programmed death 1 (PD1) immune checkpoints, are considered the mainstay of melanoma immunotherapy. However, approximately 50% of patients do not respond to treatment (24, 25). Immunotherapies often face primary resistance, and despite initial remarkable responses to MAPK signaling inhibitors, acquired drug resistance eventually develops (26). Adoptive cell transfer (ACT) of tumor-infiltrating lymphocytes (TILs) is an alternative immunotherapeutic approach that demonstrates high efficacy in melanoma treatment (25).

Those involved in melanoma treatment are in desperate need of improved prognostic and predictive markers, but so far, these markers have remained elusive. Several tissue markers, such as S100, MART-1, and gp100/HMB45, are utilized to differentiate melanoma from other types of malignancies. Lactate dehydrogenase (LDH), which correlates with advanced-stage tumor development, stands as the most robust independent prognostic factor in stage IV melanoma and serves as the strongest prognostic serum biomarker (19).

Despite the widespread use of immunohistochemical markers, S-100 remains the most sensitive marker for melanocytic lesions, while markers like HMB-45, MART-1/Melan-A, tyrosinase, and MITF demonstrate relatively excellent specificity but not as high sensitivity as S-100. Ki67 remains the most effective adjunct for distinguishing benign melanocytic tumors from malignant ones (27).

Microbiome & Melanoma

Increasing evidence suggests that the gut microbiome is intimately associated with a variety of pathophysiological processes and plays crucial roles in antitumor immunotherapy by shaping the systemic immune response (24,28,29). Short chain fatty acids (SCFAs) and other microbiome-derived metabolites are currently recognized as mediators of tumor pathogenesis and immunotherapy. Icariside I, a novel anticancer agent isolated from *Epimedium*, inhibited B16F10 melanoma growth in vivo by modulating gastrointestinal microbiota and host immunity. Icariside I exhibited potent immunological anti-tumor activity, as indicated by the upregulation of multiple lymphocyte subsets, including CD4+ and CD8+ T cells as well as NK and NKT cells, in the peripheral blood of mice with tumors (24).

The studies presented evidence of fungi being present intratumorally and often spatially associated with cancer cells and macrophages. Comparison of intratumoral fungal communities with corresponding bacteriomes and immunomes revealed co-occurring bi-domain ecologies, frequently characterized by permissive rather than competitive microenvironments and distinct immune responses. Clinically focused evaluations suggested prognostic and diagnostic potential of tissue and plasma mycobiomes even in stage I malignancies, along with synergistic predictive performance when combined with bacteriomes (30).

Lipids & Melanoma

Among the most notable features of metabolic reprogramming is the heightened rate of lipid synthesis, which has emerged as a mediator influencing both traditional oncogenic signaling pathways and the progression of melanoma. Various alterations in fatty acid metabolism have been reported to contribute to the aggressiveness of melanoma cells. Notably, a high level of the lipogenic enzyme fatty acid synthase is associated with tumor cell invasion and poor prognosis. Fatty acid assimilation from the surrounding microenvironment, fatty acid oxidation, and fatty acid storage all appear to play a crucial role in tumor cell migration (31-33).

Pharmacogenomics

Genetic variation influences an individual's response to pharmacological treatments. Understanding this variation has the potential to improve the safety and efficacy of therapy by guiding the selection and administration of medications for a specific patient. In the context of cancer, tumours may contain mutations that define the disease, but a patient's germline genetic variation also influences drug response (both efficacy and toxicity) (34,35). In developed countries, adverse drug reactions (ADRs) are among the top 10 main causes of mortality and illness. ADRs exhibit distinct characteristics based on genotype, age, gender, race, pathology, drug class, route of administration, and drug-drug interactions. Pharmacogenomics (PGx) provides the physician with useful information for optimizing

Table 3. Melanoma Treatment and Biomarkers.

Melanoma Treatment and Prognostic Markers	Summary
Mainstay of melanoma immunotherapy	Immune checkpoint inhibitors (ICIs), particularly targeting CTLA-4 and PD-1
Treatment response	Approximately 50% of patients do not respond to ICIs
Alternative immunotherapeutic approach	Adoptive cell transfer (ACT) of tumor-infiltrating lymphocytes (TILs)
Resistance to treatment	Primary resistance to immunotherapies is common; acquired drug resistance can develop with MAPK signaling inhibitors
Prognostic markers	Lactate dehydrogenase (LDH) is the strongest independent prognostic factor in stage IV melanoma; S100 is the most sensitive marker for melanocytic lesions
Additional tissue markers	MART-1, gp100/HMB45, HMB-45, tyrosinase, and MITF have high specificity, but lower sensitivity than S-100
Effective adjunct for distinguishing benign from malignant melanocytic tumors	Ki67

drug efficacy and safety in the treatment of serious medical conditions (36,37).

Cancer subtypes may be driven by somatic mutations, or somatic mutations may merely be bystanders. When identifying somatic mutations in DNA-sequencing studies, tumour samples are a mixture of cancerous and normal cells, which must be accounted for. When investigating somatic mutations to identify a suitable targeted therapy, it is essential to consider the relevant pathways (35).

2-Hydroxyoleic acid-inserted liposomes

The inclusion of 2OHOA in liposomes notably enhanced the concentration of hydrophobic model pharmaceuticals like mitoxantrone, paclitaxel, and all-trans retinoic acid (ATRA). In vitro, the anticancer activity of liposomes incorporating ATRA and 2OHOA was significantly superior to that of conventional liposomes containing ATRA alone. In a syngeneic mouse model of B16-F10 melanoma, mice treated with ATRA-incorporated/2OHOA-inserted liposomes exhibited a significantly slower tumor growth rate compared to the control group. Immunohistochemical analyses suggested that the increased antitumor activity of ATRA-incorporated/2OHOA-inserted liposomes was at least partially due to an increase in apoptosis induction (38).

Vemurafenib

Considering the involvement of polymorphic enzymes and drug transporters in vemurafenib pharmacokinetics, genotype-based administration could prove to be an effective approach for reducing interpatient variation and optimizing patient care. The study results indicate that patients carrying variants in ABCB1 (3435C>T) or CYP3A4*22 have an elevated risk of experiencing severe vemurafenib-related toxicities. The functional effects of these polymorphisms suggest that increased systemic exposure to vemurafenib may be responsible for the observed toxicities (39).

Polyphenols

Both cancer cells and healthy cells are substantially impacted by anticancer medications. Numerous polyphenolic extracts, when taken in conjunction with standard anti-tumor medications, can contribute to the anti-proliferative effect of the drugs and substantially reduce the adverse effects. Studies have shown the protective effects of polyphenols from *Vaccinium*, *Citrus*, *Olea*, and *Cynara* against the adverse effects of four well-known chemotherapy agents, which are Cisplatin, Doxorubicin, Tamoxifen, and Paclitaxel (40).

Inhibitors

Melanoma development was inhibited by signal inhibitor to phospholipase, protein kinase C, Ca2+ release, calmodulin, and mitogen-activated protein kinase kinase 1/2. However, once melanoma had developed, only the inhibitor to mitogen-activated protein kinase kinase 1/2 significantly inhibited the proliferation of melanoma, with partial inhibition by inhibitors to protein kinase C and phospholipase C. The expression of phosphorylated extracellular signal-regulated kinase 1/2 and Ki-67 was highly correlated with the inhibition of melanoma proliferation. These findings indicate that activation of each mGluR1 signaling pathway is required for melanoma development. However, the extracellular signal-regulated kinase pathway is essential for melanoma proliferation (41).

Sodium dichloroacetate (DCA)

In recent decades, metabolism has become a defining characteristic of malignancy. It was specifically linked to immunotherapy resistance in melanoma. High glucose utilization and lactate production are shared characteristics of melanoma. Lactate significantly contributes to the acidification of the tumor microenvironment (TME) and imparts an immunosuppressive TME, which inhibits immunotherapy responses. Sodium dichloroacetate (DCA) redirects the precursor of lactate to mitochondrial metabolism, thereby preventing excessive lactate production (42). The use of oral sodium dichloroacetate (DCA) in patients with metastatic melanoma results in tumor reduction and long-term disease stability. It has been demonstrated in vitro and in vivo that DCA can serve as a cytostatic agent, without inducing apoptosis (43).

It is essential to recognize that the implementation of DCA as a standard in melanoma therapy faces numerous obstacles. Among these obstacles is the unmet need for instruments and markers to monitor and predict the response of melanoma metabolism to DCA, and to ascertain how patient-specific metabolic phenotypes influence this response (42).

Diagnosis, Treatment & Personalized Medicine

In the past decade, the field of melanoma has witnessed an unprecedented number of clinical advancements. Modern therapeutic strategies based on disease mechanisms have facilitated the transformation of disease management. Targeted approaches that predominantly inhibit the BRAF oncoprotein pathway have a high predictability of efficacy, but less than optimal response depth or duration. Immunotherapy is predominantly founded on the inhibition of one or two immune checkpoints and has a reduced predictability of response, but a higher proportion of long-lasting remissions (44-47).

The Human Genome Project and Human Proteome Project initiatives have substantially improved our comprehension of human health and disease, playing a crucial role in the ongoing move toward personalized medicine. These advancements are attributed to improved screening methods, novel therapeutic strategies, and a deeper understanding of the underlying biology of cancer. Nevertheless, cancer remains a complex and heterogeneous disease, subject to

modulation over time by various factors, including genetic, molecular, cellular, tissue, population, environmental, and socioeconomic influences (48).

Furthermore, genetic analysis is now playing an increasingly significant role in guiding patient care. As new genes are discovered and key molecular pathways in melanoma progression are elucidated, therapeutic interventions targeting these pathways are becoming accessible (49, 50). The advent of next-generation sequencing (NGS) technologies has made it possible to sequence multiple cancer-driving genes in a single assay, with enhanced sensitivity for mutation detection (51).

Mass spectrometry remains the principal platform for proteomics analysis, with shotgun proteomics or bottom-up being the most frequently used approach. Recently, chromatographic methods have gained widespread recognition as methodologies worthy of consideration due to their distinct advantages, particularly in sample manipulation, recovery, and automation. Multidimensional purification has been found to be particularly effective, resulting in high purification factors and reducing sample complexity before MS analysis, thus facilitating a more comprehensive exploration of the proteome (48).

The existing therapeutic approaches for melanoma include surgical resection, chemotherapy, photodynamic therapy, immunotherapy, biochemotherapy, and targeted therapy. Depending on the patient's health and tumor characteristics, treatment strategies may involve single agents or combinations of therapies. However, the effectiveness of these treatments may be reduced due to the emergence of various resistance mechanisms. Studies focusing on the genetic profile of melanocytes and the identification of molecular factors involved in the development of malignant transformation have revealed novel therapeutic targets (52,53).

Caution should be exercised when administering radiation therapy, as the combination of BRAF inhibitors and radiation therapy has been linked to increased toxicity. Patients with stage 4 melanoma, whether untreated or treated with BRAF inhibitors and MEK inhibitors, exhibit a median overall survival of 22 to 25 months, with a 3 to 5-year overall survival rate reaching 40 percent. Favorable prognostic factors include normal lactate dehydrogenase concentrations, fewer than three metastatic sites, and satisfactory Eastern Cooperative Oncology Group performance. However, a significant drawback of targeted therapy is the development of resistance during treatment (1,54).

In the context of treating metastatic melanoma, numerous novel medications have been developed in the last decade, substantially improving the prognosis for patients with this condition. However, the majority of patients do not demonstrate a long-lasting response to these treatments. As a result, new biomarkers and drug targets are needed to enhance the diagnostic and therapeutic accuracy of melanoma (55).

Conclusion

In conclusion, "omics" science has emerged as a powerful tool in the study of melanoma. The integration of genomics, proteomics, and metabolomics has allowed for a more comprehensive understanding of the molecular mechanisms involved in the development and progression of this deadly disease. "Omics" approaches have identified numerous potential biomarkers for early detection, prognosis, and treatment response, which could greatly improve patient outcomes. However, further research is needed to validate these biomarkers and translate them into clinical practice. The application of "omics" technologies in melanoma research is a promising path for the development of personalized and targeted therapies, ultimately leading to better outcomes for patients.

Acknowledgements

This research was funded by the Provincia Autonoma di Bolzano in the framework of LP 14/2006.

Conflicts of interest statement

Authors declare no conflict of interest.

References

1. Schadendorf D, van Akkooi ACJ, Berking C et al. Melanoma. Lancet. 2018 Sep; 392(10151):971-984
2. Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol. 2009 Jan-Feb; 27(1):3-9
3. O'Neill CH, Scoggins CR. Melanoma. J Surg Oncol. 2019 Oct;120(5):873-881
4. Houghton AN, Polsky D. Focus on melanoma. Cancer Cell. 2002 Oct;2(4):275-8
5. Georgescu SR, Mitran CI, Mitran MI et al. Apprising Diagnostic and Prognostic Biomarkers in Cutaneous Melanoma-Persistent Updating. J Pers Med. 2022 Sep;12(9):1506
6. Miller AJ, Mihm MC Jr. Melanoma. N Engl J Med. 2006 Jul 6;355(1):51-65
7. Read J, Wadt KA, Hayward NK. Melanoma genetics. J Med Genet. 2016 Jan;53(1):1-14
8. Berger MF, Garraway LA. Applications of genomics in melanoma oncogene discovery. Hematol Oncol Clin North Am. 2009 Jun;23(3):397-414, vii.
9. Artomov M, Stratigos AJ, Kim I, et al. Rare Variant, Gene-Based Association Study of Hereditary Melanoma Using Whole-Exome Sequencing. J Natl Cancer Inst. 2017 Dec;109(12):djx083
10. Soura E, Eliades PJ, Shannon K, et al. Hereditary melanoma: Update on syndromes and management: Genetics of familial atypical multiple mole melanoma syndrome. J Am Acad Dermatol. 2016 Mar;74(3):395-407; quiz 408-10
11. Newton-Bishop J, Bishop DT, Harland M. Melanoma Genomics. Acta Derm Venereol. 2020 Jun;100(11):adv00138
12. Landi MT, Bishop DT, MacGregor S, et al. Genome-wide association meta-analyses combining multiple risk phenotypes provide insights into the genetic architecture of cutaneous melanoma susceptibility. Nat Genet. 2020 May; 52(5):494-504
13. Pimiento JM, Larkin EM, Smalley KS, et al. Melanoma genotypes and phenotypes get personal. Lab Invest. 2013 Aug; 93(8):858-67
14. Guhan S, Klebanov N, Tsao H. Melanoma genomics: a state-of-the-art review of practical clinical applications. Br J Dermatol. 2021 Aug; 185(2):272-281
15. Pilarski R, LGC M, Carlo MI, et al. BAP1 Tumor Predisposition Syndrome Synonyms: BAP1 Cancer Syndrome;

Cutaneous/Ocular Melanoma, Atypical Melanocytic Proliferations, and Other Internal Neoplasms (COMMON Syndrome). (Accessed on 28/08/2023 at https://www.ncbi.nlm.nih.gov/books/NBK390611/)
16. Dubois A, Rajan N. CYLD Cutaneous Syndrome Synonyms: Brooke-Spiegler Syndrome (BSS), Familial Cylindromatosis (FC), Multiple Familial Trichoepithelioma (MFT). (Accessed on 28/08/2023 at https://www.ncbi.nlm.nih.gov/books/NBK555820/)
17. Henry ML, Osborne J, Else T. POT1 Tumor Predisposition. 2020 Oct 29 [updated 2022 Mar 10]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023
18. Friedman JM. Neurofibromatosis 1 synonyms: NF1, von Recklinghausen disease, von Recklinghausen's neurofibromatosis. GeneReviews®. University of Washington, Seattle; 1993-2021. (Accessed on 28/08/2023 at https://www.ncbi.nlm.nih.gov/books/NBK1109/)
19. Sabel MS, Liu Y, Lubman DM. Proteomics in melanoma biomarker discovery: great potential, many obstacles. Int J Proteomics. 2011;2011:181890
20. Donnelly D 3rd, Aung PP, Jour G. The "-OMICS" facet of melanoma: Heterogeneity of genomic, proteomic and metabolomic biomarkers. Semin Cancer Biol. 2019 Dec;59:165-174
21. Taylor NJ, Gaynanova I, Eschrich SA, et al. Metabolomics of primary cutaneous melanoma and matched adjacent extratumoral microenvironment. PLoS One. 2020 Oct;15(10):e0240849
22. Weber DD, Thapa M, Aminzadeh-Gohari S, et al. Targeted Metabolomics Identifies Plasma Biomarkers in Mice with Metabolically Heterogeneous Melanoma Xenografts. Cancers (Basel). 2021 Jan;13(3):434
23. Du J, Su Y, Qian C, et al. Raman-guided subcellular pharmaco-metabolomics for metastatic melanoma cells. Nat Commun. 2020 Sep;11(1):4830
24. Chen G, Cao Z, Shi Z et al. Microbiome analysis combined with targeted metabolomics reveal immunological anti-tumor activity of icariside I in a melanoma mouse model. Biomed Pharmacother. 2021 Aug;140:111542
25. Harel M, Ortenberg R, Varanasi SK et al. Proteomics of Melanoma Response to Immunotherapy Reveals Mitochondrial Dependence. Cell. 2019 Sep;179(1):236-250.e18
26. Azimi A, Pernemalm M, Frostvik Stolt M et al. Proteomics analysis of melanoma metastases: association between S100A13 expression and chemotherapy resistance. Br J Cancer. 2014 May;110(10):2489-95
27. Ohsie SJ, Sarantopoulos GP, Cochran AJ, Binder SW. Immunohistochemical characteristics of melanoma. J Cutan Pathol. 2008 May; 35(5):433-44
28. Mekadim C, Skalnikova HK, Cizkova J, et al. Dysbiosis of skin microbiome and gut microbiome in melanoma progression. BMC Microbiol. 2022 Feb;22(1):63
29. Makaranka S, Scutt F, Frixou M, Wensley KE, Sharma R, Greenhowe J. The gut microbiome and melanoma: A review. Exp Dermatol. 2022 Sep;31(9):1292-1301.
30. Narunsky-Haziza L, Sepich-Poore GD, Livyatan I, et al. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. Cell. 2022 Sep;185(20):3789-3806.e17
31. Pellerin L, Carrié L, Dufau C, et al. Lipid metabolic Reprogramming: Role in Melanoma Progression and Therapeutic Perspectives. Cancers (Basel). 2020 Oct;12(11):3147
32. Feng J, Isern NG, Burton SD, et al. Studies of Secondary Melanoma on C57BL/6J Mouse Liver Using 1H NMR Metabolomics. Metabolites. 2013 Oct;3(4):1011-35
33. Abaffy T, Möller MG, Riemer DD, et al. Comparative analysis of volatile metabolomics signals from melanoma and benign skin: a pilot study. Metabolomics. 2013;9(5):998-1008
34. Kang H, Li J, Wu M, et al. Building a Pharmacogenomics Knowledge Model Toward Precision Medicine: Case Study in Melanoma. JMIR Med Inform. 2020 Oct; 8(10):e20291
35. Wheeler HE, Maitland ML, Dolan ME, et al. Cancer pharmacogenomics: strategies and challenges. Nat Rev Genet. 2013 Jan;14(1):23-34
36. Cacabelos R, Naidoo V, Corzo L, et al. Genophenotypic Factors and Pharmacogenomics in Adverse Drug Reactions. Int J Mol Sci. 2021 Dec; 22(24):13302
37. Schweitzer J, Maibach H. Pharmacogenomics in dermatology: Taking patient treatment to the next level. J Dermatolog Treat. 2015 Feb; 26(1):94-6
38. Jang EJ, Choi WR, Kim SY, et al. 2-Hydroxyoleic acid-inserted liposomes as a multifunctional carrier of anticancer drugs. Drug Deliv. 2017 Nov; 24(1):1587-1597
39. Goey AK, With M, Agema BC, et al. Effects of pharmacogenetic variants on vemurafenib-related toxicities in patients with melanoma. Pharmacogenomics. 2019 Dec; 20(18):1283-1290
40. Maiuolo J, Musolino V, Gliozzi M, et al. The Employment of Genera Vaccinium, Citrus, Olea, and Cynara Polyphenols for the Reduction of Selected Anti-Cancer Drug Side Effects. Nutrients. 2022 Apr;14(8):1574
41. Abdel-Daim M, Funasaka Y, Komoto M, et al. Pharmacogenomics of metabotropic glutamate receptor subtype 1 and in vivo malignant melanoma formation. J Dermatol. 2010 Jul;37(7):635-46
42. Repurposing an old drug: Dichloroacetate's potential to reduce acidification of the tumour microenvironment in melanoma. (Accessed on 28/08/2023 at https://umcgresearch.org/w/repurposing-an-old-drug-dichloroacetate-s-potential-to-reduce-acidification-of-the-tumour-microenvironment-in-melanoma)
43. Khan A, Andrews D, Shainhouse J, et al. Long-term stabilization of metastatic melanoma with sodium dichloroacetate. World J Clin Oncol. 2017 Aug; 8(4):371-377
44. Jenkins RW, Fisher DE. Treatment of Advanced Melanoma in 2020 and Beyond. J Invest Dermatol. 2021 Jan; 141(1):23-31
45. Tarhini A, Kudchadkar RR. Predictive and on-treatment monitoring biomarkers in advanced melanoma: Moving toward personalized medicine. Cancer Treat Rev. 2018 Dec; 71:8-18
46. Helgadottir H, Rocha Trocoli Drakensjö I, Girnita A. Personalized Medicine in Malignant Melanoma: Towards Patient Tailored Treatment. Front Oncol. 2018 Jun;8:202
47. Chakraborty R, Wieland CN, Comfere NI. Molecular targeted therapies in metastatic melanoma. Pharmgenomics Pers Med. 2013 Jun;6:49-56
48. Su M, Zhang Z, Zhou L, Han C, Huang C, Nice EC. Proteomics, Personalized Medicine and Cancer. Cancers (Basel). 2021 May;13(11):2512
49. Griewank KG, Scolyer RA, Thompson JF, Flaherty KT, Schadendorf D, Murali R. Genetic alterations and personalized medicine in melanoma: progress and future prospects. J Natl Cancer Inst. 2014 Feb;106(2):djt435
50. Valenti F, Falcone I, Ungania S, et al. Precision Medicine

and Melanoma: Multi-Omics Approaches to Monitoring the Immunotherapy Response. Int J Mol Sci. 2021 Apr;22(8):3837
51. de Unamuno Bustos B, Murria Estal R, Pérez Simó G, et al. Towards Personalized Medicine in Melanoma: Implementation of a Clinical Next-Generation Sequencing Panel. Sci Rep. 2017 Mar;7(1):495
52. Domingues B, Lopes JM, Soares P, et al. Melanoma treatment in review. Immunotargets Ther. 2018 Jun; 7:35-49
53. Bhatia S, Tykodi SS, Thompson JA. Treatment of metastatic melanoma: an overview. Oncology (Williston Park). 2009 May;23(6):488-96.
54. Luke JJ, Flaherty KT, Ribas A, et al. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat Rev Clin Oncol. 2017 Aug;14(8):463-482
55. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. Cancer Biol Ther. 2019; 20(11):1366-1379