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RESEARCH ARTICLE

Melanoma: A Therapeutic Revolution Happening Before Our Eyes

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ABSTRACT
Malignant melanoma (MM) is among the most common cancers in the world. Although incidence has been increasing worldwide, most of the cases have been reported to occur in the European continent. Risk factors for the development of MM have been clearly recognized; yet, the accepted theory is that the risk of melanoma is highly determined by the interplay between genetic factors and exposure to sunlight. Morphological characteristics classify melanoma into four subtypes: Superficial spreading melanoma (SSM); nodular melanoma (NM), Lentigo maligna (LM) and Acral lentiginous melanoma (ALM). SSM represents approximately 70% of the cases. Mitogen-activated protein kinase (MAPK) has been identified as a key regulatory element in most melanomas. MAPK is the most relevant signal pathway in the development of melanoma; while the microphthalmia-associated transcription factor (MITF) is a target of extracellular signal-related kinase (ERK) and controls the production of the pigment melanin, cell cycling and survival. Surgical resection is still considered the cornerstone of the treatment in the vast majority of patients with early-stage melanoma. However, treatment of metastatic or recurrent melanoma has significantly been improved with the advent of targeted immunotherapies. The greatest advantage has been observed with the use of checkpoint-inhibitor immunotherapy. But, Adoptive cell therapy (ACT) for the treatment of metastatic melanoma, in patients who have progressed to immunotherapy and/or targeted therapies without success, is currently under investigation with promising results.

Keywords: malignant melanoma, immunotherapy, targeted therapy, checkpoint-inhibitor immunotherapy

EPIDEMIOLOGY

Melanoma is the most aggressive neoplasm of the skin. It is derived from melanocytes, which come from the neural crest and specialize in the synthesis and production of melanin. With 324,635 new cases and 54,043 deaths reported in 2020, this neoplasm is among the most common cancers in the world. Incidence of malignant melanoma has been increasing worldwide. Accordingly, rates for men and women have risen from 2.3 and 2.2 / 100,000 people in 1990 to 3.1 and 2.8 / 100,000 people in 2008. [1,3] Though, most of the cases have been reported to occur in the European continent. This represents 46.4% of the total registered cases. Actually, in this continent, incidence has been increasing at an accelerated and constant rate. Cumulative data indicate 3 - 4 cases/100,000 inhabitants in the 70´s to 10 - 15 cases/100,000 inhabitants per year in the year 2000. In the United States, Melanoma represents approximately 100,000 new cases and 7,000 deaths each year. [1,2] This increase could be explained by improved surveillance protocols along with early diagnoses.[4]

Risk factors for the development of melanoma have been clearly recognized and include: skin type, personal history of melanoma, the presence of dysplastic nevi or multiple atypical moles. A family history of melanoma is present in 5% to 10% of the patients. And, inherited germline mutations in key regulators such as TERT, TERF21P, POT1 and ACD explain a much smaller percentage. Each one of them accounting for less than 1% of the cases.[5] Environmental factors such as exposure to sunlight, excessive sunbathing and artificial tanning are also linked to the development of this cancer. Though, the widely accepted theory is that the risk of melanoma is highly determined by the interplay between genetic factors and exposure to sunlight.[6]

CLASSIFICATION

Traditional classifications of melanoma consider the morphological characteristics of the lesion. Hence, cutaneous melanoma can be divided into four main subtypes: Superficial spreading melanoma (SSM); nodular melanoma (NM), Lentigo maligna (LM) and Acral lentiginous melanoma (ALM). Superficial spreading melanoma is considered the most common histological subtype of melanoma; representing approximately 70% of the cases. The vast majority of this type of neoplasms are diagnosed in early stages. They do not usually appear from a nevus; and most common presentation areas are the back and legs for women and the upper back for men. The lesion appears as a thin plate with irregular edges and uneven pigmentation.[7] Nodular melanoma represents 15 to 30% of the cases. This is the second most common type of melanoma. This lesion usually presents as dark nodules or papules, with symmetrical edges and either a uniform color or an amelanic aspect. Though, it is generally small in diameter. In most of the cases, it appears in the trunk, head and neck.[8] Lentigo maligna represents 4 to 15% of melanomas. This lesion usually appears on sites of greater UV exposure or sun-damaged skin. Therefore, it is the most common subtype of melanoma presenting in the head and neck of individuals. It usually occurs in older patients. This skin tumor arises either as a macula, or as a brown-color patch with asymmetric pigmentation or with multiple color tonalities. Additionally, it usually shows a gradual growth over the years.[9] Acral lentiginous melanoma is the least frequent subtype of melanoma; representing less than 1% of the cases. Nonetheless, this variant of melanoma is most frequently observed in patients with darker skin pigmentation. And, the most common sites of presentation are hairless areas. That is, the palms, the soles or under the nail beds. Morphological features of this neoplasm include an irregular brown to black macula, with either raised ulcerated or bleeding edges. [10]

Most recently, the World Health Organization (WHO) reclassified melanocytic tumors into three main categories; based on chronic exposure to ultraviolet radiation / cumulative solar damage and nine evolutionary pathways. The tumors are conditioned by different genetic alterations; which lead to different subtypes of melanoma, as well as benign and intermediate melanocytic lesions. [11] In accordance with United Sates statistics, about 84% of melanomas are identified on early or localized stage; around 9% of the patients will present loco-regional disease at the time of diagnosis and nearly 4% of the lesions will debut with distant dissemination. The prognosis for malignant melanoma diagnosed in early stages is usually favorable. Five-year survival is achieved in 90% of the patients with early disease and in those whose primary tumor is 1.0 mm or less thick. In cases with localized melanomas greater than 1.0 mm thick, survival rates are significantly reduced to between 50% and 90%, depending on thickness, mitotic index and the presence or absence of ulceration. [12]

PATHOPHYSIOLOGY AND CURRENT TREATMENT ALTERNATIVES

Surgical resection is the cornerstone in the treatment of the vast majority of patients with early-stage melanoma and those with loco-regional involvement. Treatment under these circumstances is intended to be curative. However, this approach is modified in patients with advanced disease (metastatic stages); as well as in those with recurrence. Immunotherapy and targeted therapies play important roles in these settings.[13,14]

Accordingly, advances in the study of the biological activity of melanocytes and the pathogenesis of melanoma have allowed the development and implementation of targeted therapies. Therefore, substantially improving the care and prognosis of patients with advanced melanoma. The potential of these new therapies is still unlimited. Without a doubt, the therapeutic repertoire is growing at an accelerated pace. In the last decades, the most important advances in the field have been the discovery of the mitogen-activated protein kinase (MAPK) signal transduction pathway and the critical role of the microphthalmia-associated transcription factor (MITF) in the development of these neoplasms. MAPK is the most relevant signal pathway in the development of melanoma; while MITF is a target of extracellular signal-related kinase (ERK) and controls the production of the pigment melanin, cell cycling and survival.[13,14] As far as the pathogenic mechanisms involved in malignant degeneration of melanoma, two pathways have been identified. These pathways are closely related to ultraviolet radiation, the melanin-independent pathway and ultraviolet light DNA damage. Oxidative DNA damage within melanocytes has been shown to be strongly linked to an ultraviolet-mediated change in BRAF-induced melanogenesis through mutations in gene encoding for the TP53 protein.[15]

BIOMOLECULAR PATHWAYS OF MELANOMA DEVELOPMENT

The molecular mechanisms involved in the development of melanoma are still not completely clear. Though, some pathways have clearly been elucidated. As indicated earlier, mitogen-activated protein kinase (MAPK) has been identified as a key regulatory element in most melanomas. This pathway is activated by the binding of a growth factor to a receptor tyrosine kinase (RTK). This in turn leads to a protein phosphorylation cascade that favors both cell growth and perpetuity by the activation of NRAS; which serves as mediator in P13K and BRAF signal transduction pathways (Figure 1).[16] About 25% to 30% of melanomas have mutations at this point. BRAF acts on MEK-ERK leading to RSK and MNK1 activation and subsequent phosphorylation of MITF. The latter is a transcription factor not only for melanocyte melanogenic machinery such as PMEL, TRP1, tyrosinase and DCT; but also for antiapoptotic proteins such as BCL2 and BCL2A1 and cell cycle regulators like CDK2.[5] This means that any activating mutation that triggers a persistent stimulation of this serine/threonine kinases pathway will lead to cell cycle progression, cell transformation and increased survival. Additionally, mutations from LOF mutations in NF1 (a key negative regulator of NRAS) have similar effects. It has been shown that mutations in the NF1 gene are present in up to 14% of melanoma cases.[17,18] Another key regulator is the melamocortin-1 receptor (MCR1). It signals under the stimulating G protein-coupled receptor pathway by activation of AC/cAMP/PKA/CREB; which in turn acts on the MITF prompter to increase its transcription.[5] It has been shown that overactivation of either PKA/CREB or NRAS/ERK pathways drives melanoma development.

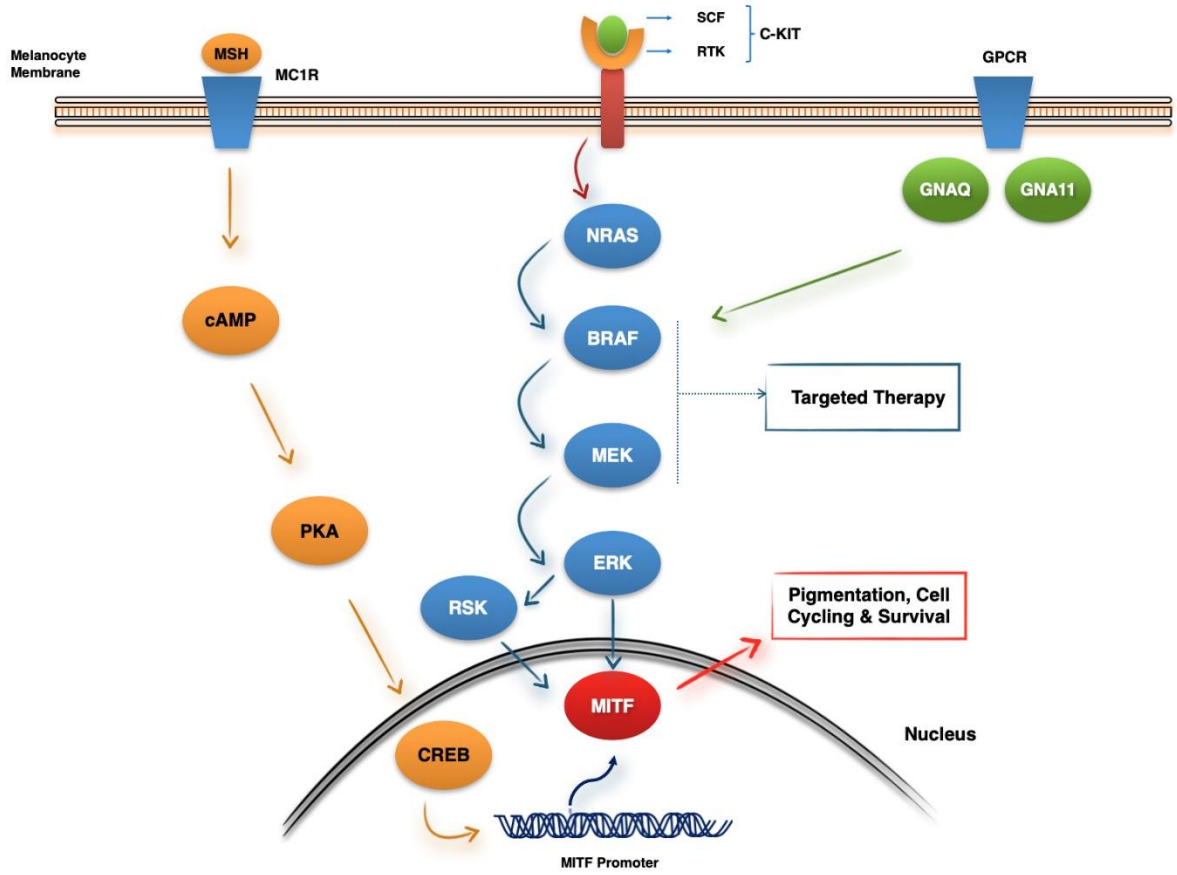

Figure 1. Biomolecular signaling pathways of melanoma development. Mitogen-activated protein kinase (MAPK) pathway is activated by the binding of a growth factor to a receptor tyrosine kinase (RTK) on melanocyte membrane. This in turn leads to a NRAS/BRAF/MEK/ERK cascade that targets microphthalmia-associated transcription factor (MITF); which serves as transcriptional regulator and drives melanoma formation. BRAF acts on MEK-ERK leading to RSK activation and subsequent phosphorylation of MITF. Stimulation of GPCR also triggers MAPK pathway through BRAF. Activated melanocortin-1 receptor (MC1R) leads to a CREB-mediated transcriptional activation of MITF. And, mutations in GNAQ/GNA11 are key elements in uveal melanoma. Adapted from: Teixido C, et al. Molecular markers and targets in melanoma. *Cells 2021;10(9):2320;* and Ostrowski SM, & Fisher D. Biology of Melanoma. *Hematol Oncol Clin North Am 2021;35(1):29-56*

The most common somatic mutation in melanoma is a substitution of V600E in BRAF; which is an early event in the development of this neoplasia. This specific molecular anomaly is present in up to 40-50% of the melanoma patients. This leads to an uncontrolled clonal expansion and tumor progression. After triggering the signal pathway, there is an over-activation of MAPK/kinase signaling; which starts MEK and ERK phosphorylation. These downstream effects are known to be signals that favor growth and malignant transformation; which have been identified in the pathogenesis of various malignant neoplasms.[19] BRAF mutation is an independent event that enables malignant transformation, along with the intervention of other oncogenic stimuli. These mutations are present in up to 70 to 80% of dysplastic nevi, 40–50% of vertically growing melanomas and around 40–50% of patients with metastatic melanoma. Nonetheless, further research is needed to clarify the mechanisms of malignant transformation in BRAF-mutated melanomas.[20]

MODERN THERAPIES

Despite decades of pharmaceutical studies, surgical treatment with curative purposes still remains the cornerstone of treatment. It is the therapy of choice when melanoma is diagnosed in early stages. Since lymph nodes are at increased risk of recurrent and metastatic disease, therapeutic alternatives include surgical metastasectomy, chemotherapy, radiotherapy and, in recent years, immunotherapy. Actually, immunotherapy has changed the standard of care of metastatic melanoma.[21] Accordingly,

systemic chemotherapy has been widely utilized in patients who are not candidates to receive high-dose interleukin-2. Yet, this approach has not been demonstrated to have a direct impact on survival. Therefore, with newer approaches in immunotherapy and targeted therapy for BRAF-mutated tumors; chemotherapy has been limited to a second and third line of treatment in these settings.[14]

In recent years, melanoma treatment has significantly been improved with the advent of targeted immunotherapies. The progress in this field has been so noteworthy that 2018 Nobel Prize was awarded to James P. Allison and Tasuko Honjo from MD Anderson and Kyoto University, respectively; for the development of checkpoint-inhibitor immunotherapies in metastatic melanoma. The greatest advantage has been observed with the use of checkpoint-inhibitor immunotherapy; either targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4 -ipilimumab-) or programmed cell death receptor 1 (PD-1 -nivolumab-). Therapies have also been directed to mitogen-activated protein kinase (MAPK) pathway, with a combination of BRAF and MEK inhibitors (Figure 1). All these in patients with tumors carrying V600 mutation of the BRAF gene.[22] Interestingly enough, all of these therapeutic agents have been approved in the last 15 years. Without a doubt, we are living at a landmark stage in the development of inhibitor immunotherapies. The choice of treatment is based on different factors such as; functional status, comorbidities and whether the patient has previously been treated. The role of immunotherapy and targeted therapies are constantly evolving. Therefore, enrolment in clinical trials seems to be the best alternative whenever possible.

Selective BRAF inhibitors include vemurafenib, encorafenib and dabrafenib. Their mechanism of action is through down-regulation of extracellular response kinase levels in BRAF V600E-mutated tumors. This treatment has demonstrated an evident and well documented clinical response.[23] In order to avoid paradoxical stimulation of the RAS pathway, a MEK inhibitor is utilized; thereby blocking the activation of the mitogen-activated protein kinase pathway.[24] MEK is a post-activation mediator of RAS and RAF, in the mitogen-activated protein kinase pathway; which correlates with the presence of mutation in BRAF. Several MEK inhibitors have been developed, such as cobimetinib, trametinib, binimetinib and selumetinib, with a clinical role in metastatic melanoma. These inhibitors are usually prescribed in combination with BRAF inhibitors.[24]

CLINICAL IMPLICATIONS

Small molecule selective inhibitors that effectively target BRAF, MEK, and KIT mutations in melanoma patients have already been introduced in the clinical arena. And, mitogen-activated protein kinase (MAPK) inhibitors, regulated by extracellular signals (ERK), are currently being developed.[25] Adoptive cell therapy (ACT) for the treatment of metastatic melanoma, in patients who have progressed to immunotherapy and/or targeted therapies without success, is currently under investigation with promising results. This therapy involves tumor infiltrating lymphocytes (TIL), chimeric antigen receptor (CAR) T-cell therapy, and T-cell receptor (TCR) transduced T cells. The tumor-infiltrating lymphocyte (Lifileucel) therapy has demonstrated an objective response rate of 36%, at 18 month follow-up, in patients with metastatic melanoma resistant to immunotherapy.[26]

CONCLUSION

In the last decades, there has been a better understanding of the biomolecular pathways involved in the development of melanoma. And, mitogen-activated protein kinase (MAPK) has been identified as a key regulatory element in most melanomas. Although, surgical treatment with curative purposes still remains the cornerstone of treatment for melanomas diagnosed on early stages; targeted immunotherapies have significantly improved the management of either metastatic or recurrent melanomas. Moreover, adoptive cell therapy (ACT) is currently under investigation with promising results. This review summarizes the molecular pathways leading to melanoma development; as well as the current state of the art in checkpoint-inhibitor immunotherapy.

REFERENCES

1. International Agency for Reserch on Cancer. Melanoma of skin ASR. Glob Cancer Obs [Internet]. 2020;1–2. Available at: http://globocan.iarc.fr/old/bar_sex_site.asp?selection=16120&title=Melanoma+of+skin&statistic=2&populations=6&window=1&grid=1&color1=5&color1e=&color2=4&color2e=&submit=Execute (Last visited Abril 30th, 2022)
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin 2018;68(6):394–424*
3. Karimkhani C, Green AC, Nijsten T, Weinstock MA, Dellavalle RP, Naghavi M, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol 2017;177(1):134–40*
4. Garbe C, Leiter U. Melanoma epidemiology and trends. *Clin Dermatol 2009;27(1):3–9*
5. Ostrowski SM, & Fisher D. Biology of Melanoma. *Hematology/Oncology Clinics Of North America 2021;35(1):29-56*
6. Zanetti R, Rosso S, Martinez C, Nieto A, Miranda A, Mercier M, et al. Comparison of risk patterns in carcinoma and melanoma of the skin in men: A multi-centre case-case-control study. *Br J Cancer 2006;94(5):743–51*
7. Lasithiotakis KG, Leiter U, Gorkievicz R, Eigentler T, Breuninger H, Metzler G, et al. The incidence and mortality of cutaneous melanoma in Southern Germany: Trends by anatomic site and pathologic characteristics, 1976 to 2003. *Cancer 2006;107(6):1331–9*
8. Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States: Beware of the nodular subtype. *Arch Dermatol 2005;141(6):745–50*
9. Swetter SM, Boldrick JC, Jung SY, Egbert BM, Harvell JD. Increasing incidence of lentigo maligna melanoma subtypes: Northern California and national trends 1990-2000. *J Invest Dermatol 2005;125(4):685–91*
10. Coleman WP 3rd, Loria PR, Reed RJ, Krementz ET. Acral lentiginous melanoma. *Arch Dermatol 1980;116(7):773-6*
11. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. *Arch Pathol Lab Med 2020;144(4):500–22*
12. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol 2009;27(36):6199–206*
13. Teixido C, Castillo P, Martinez-Vila C, Arance A, Alos L. Molecular markers and targets in melanoma. *Cells 2021;10(9):2320*
14. Smalley KSM, Sondak VK. Melanoma — An Unlikely Poster Child for Personalized Cancer Therapy. *N Engl J Med 2010;363(9):876–8*
15. Noonan FP, Zaidi MR, Wolnicka-Glubisz A, Anver MR, Bahn J, Wielgus A, et al. Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. *Nat Commun 2012;3:884*
16. Omholt K, Platz A, Kanter L, Ringborg U, Hansson J. NRAS and BRAF Mutations Arise Early during Melanoma Pathogenesis and Are Preserved throughout Tumor Progression. *Clin Cancer Res 2003;9(17):6483–8*
17. Akbani R, Akdemir KC, Aksoy BA, Albert M, Ally A, Amin SB, et al. Genomic Classification of Cutaneous Melanoma. *Cell 2015;161(7):1681–96*
18. Krauthammer M, Kong Y, Bacchiocchi A, Evans P, Pornputtapong N, Wu C, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. *Nat Genet 2015;47(9):996–1002*
19. Beeram M, Patnaik A, Rowinsky EK. Raf: A strategic target for therapeutic development against cancer. *J Clin Oncol 2005;23(27):6771–90*
20. Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, et al. High frequency of BRAF mutations in nevi. *Nat Genet 2003;33(1):19–20*
21. Wellbrock C, Hurlstone A. BRAF as therapeutic target in melanoma. *Biochem Pharmacol 2010;80(5):561–7*

22. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. *N Engl J Med 2011;364(26):2507–16*
23. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature 2010;467(7315):596–9*
24. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature 2010;464(7287):427–30*
25. Solit DB, Garraway LA, Pratilas CA, Sawai A, Getz G, Basso A, et al. BRAF mutation predicts sensitivity to MEK inhibition. *Nature 2006;439(7074):358–62*
26. Sarnaik AA, Hamid O, Khushalani NI, Lewis KD, Medina T, Kluger HM, et al. Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma. *J Clin Oncol 2021;39(24):2656–66*