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Modern inside into Cutaneous Melanomagenesis

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ABSTRACT: Cutaneous Melanoma is a malignant, dangerous tumor that develops from melanocytes - the only cells that synthesize melanin and accumulate it in the skin, hair follicles, and retinal pigment epithelium. Melanin provides pigmentation to the skin, eyes, and hair. This substance also absorbs harmful UV rays (ultraviolet rays) and protects cell DNA from sun damage and possible further DNA sequencing mutations it may cause. Due to a combination of genetic and environmental factors, some melanocytes may undergo malfunction in their genetic apparatus, which leads to their uncontrolled division and proliferation, eventually turning into a malignant tumor. In cutaneous melanoma, mutations in the genes *BRAF* and *NRAS* most commonly predominate among other gene mutations found during melanomagenesis, accounting for 60 percent and 20 percent, respectively. This review aims to study melanomagenesis from the perspective of a wide range of internal and external factors, their impact on gene alteration, with a detailed examination of the mutated *BRAF*, *NRAS* genes, aberrant signaling pathways, and their roles in malignant tumor formation. Moreover, this review will discuss potential melanoma therapy by directly targeting mutated genes and propose some suggestions for further drug development.

KEYWORDS: Genetics and Molecular Biology of Disease, Cutaneous Melanomagenesis, *BRAF*/*NRAS* Genes, Signaling Pathways, Targeted Therapy.

Introduction

Cutaneous Melanoma is one of the most malignant forms of skin cancer that targets both men and women, but varies by age and different risk factors.[1] Cases of melanoma have significantly increased in recent decades and continue to represent one of the most life-threatening health conditions. The National Cancer Institute estimates the mortality rate will increase by 65% and the total number of skin cancer cases to surpass 2.3 million worldwide in 2040.[2]

Cutaneous Melanoma spreads from the epidermis, and when evolving, it penetrates the dermis and subcutaneous tissue. Thus, it grows through all layers of skin - epidermis, dermis, and hypodermis. Anatomically, these tissues are very well supplied with blood and lymphatic vessels, as well as nerves. This is why Cutaneous Melanoma is mostly characterized by aggressive, fulminant development and further rapid metastasis.

Melanomas are mainly caused by gene alterations, and most of them have potentially active mutations in genes such as *BRAF* and *NRAS*. *BRAF* gene mutations account for more than 60% of all cases of Cutaneous Melanoma,[3,4] when NRAS-mutated melanomas occur in up to 15-20 % of all recorded cases.[5] NRAS-mutated melanomas are more aggressive and associated with a poorer survival prognosis compared to melanomas without *NRAS* mutation.[5] The trigger for the occurrence of Cutaneous Melanoma is sporadic mutations in genes, in addition to genetic predisposition and known risk factors associated with it.

The combination of internal and external factors triggers the evolution of morphologically and phenotypically diverse clusters of mutated melanocytes that develop Cutaneous Melanoma. The two known signaling pathways involved in malignant formation play a crucial role in uncontrolled tumor cell division, proliferation, survival, and metastasis. The therapeutic approaches used today in melanoma management are focused on targeting mutated genes that operate dysregulated signaling pathways to stop tumor progression.

1. Melanoma:

1.1. Cutaneous Melanoma:

Cutaneous Melanoma is one of the deadliest forms of all types of skin cancer and accounts for 80% of the mortality rate among all of them.[2] There are four major morphological subtypes of Cutaneous Melanoma: Superficial spreading melanoma (SSM), Lentigo melanoma (LM), Nodular Melanoma (NM), and Acral Lentiginous Melanoma (ALM). [2,6] They differ by clinical appearance and histological features, along with diagnostic biomarkers, propensity for rapid metastasis, survival rates, and treatment approaches. The data shows the number of reported cases corresponding to SSM (70%), LM (4 –15%), NM (5%), and ALM(2–5%) of the reported cases. [2,7]

Cutaneous Melanoma results from mutations in melanocytes - pigment-producing cells that are present in the stratum basale of epidermis. It is a basic single row layer of skin cells called keratinocytes, which physiologically undergo continuous cell division and therefore promote skin cell renewal. The major function of melanocytes is the production of melanin, which, when consumed by keratinocytes, forms a shield above the cell's nucleus to protect its genetic material. During embryogenesis, these two types of cells present in the skin derive from two different embryonic origins. Keratinocytes origi-

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nate from the surface ectoderm, a superficial layer that builds epithelial tissues, whereas melanocytes are formed from a multipotent stem cell of the neural crest. This difference in embryonic origin gives melanocytes "special abilities" or inbuilt potential to express many signaling molecules and factors that promote rapid invasion, migration, and propensity to rapidly metastasize to other organs when not promptly addressed.[8] Gene mutations caused by alignment of many factors result in uncontrolled cellular proliferation, tumor formation, and fulminant metastasis after malignant transformation.

Another crucial feature that characterizes Cutaneous Melanoma is its heterogeneity due to the tumor transformation of melanocytes to form genetically divergent subpopulations of cells with different morphological and phenotypic profiles composing the tumor. These subpopulations are present in the form of a small fraction of cancer stem-like cells (CSCs), responsible for the promotion of melanoma progression, drug resistance, and recurrence, and many non-cancer stem-like cells (non-CSCs) that play supportive and regulatory roles in melanogenesis.[9]

1.2. Epidemiology of Cutaneous Melanoma:

According to the American Cancer Society, Melanoma has become the third most common type of skin cancer and the fifth among all types of cancer in the US. The same source predicts that 100,640 new cases of melanoma will be diagnosed in 2024 (58,8% of men and 41,2% of women), with the expected 8,290 deaths (65,5% and 34,5%, respectively).[10,11] Over the two decades, the observed rate of Melanoma has increased from 18,1 in 2000 to 23,8 (per 100,000 population) in 2021 (Figure 1), based on data published by the National Cancer Institute (USA). At the same time, it demonstrates the lowering of the death rate from 2,7 to 2,0, respectively.[10]

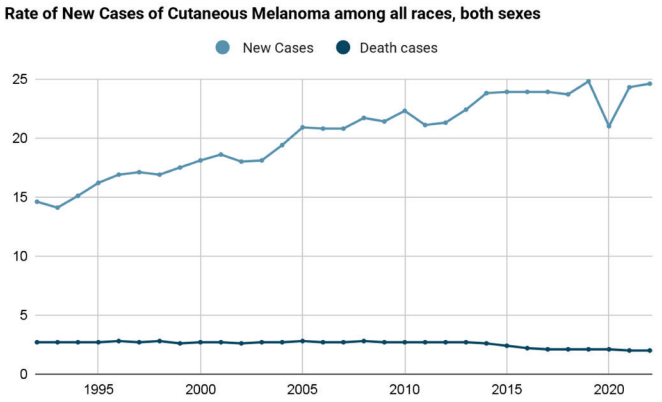
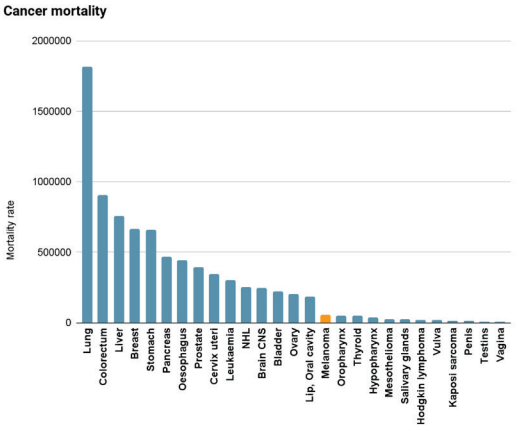
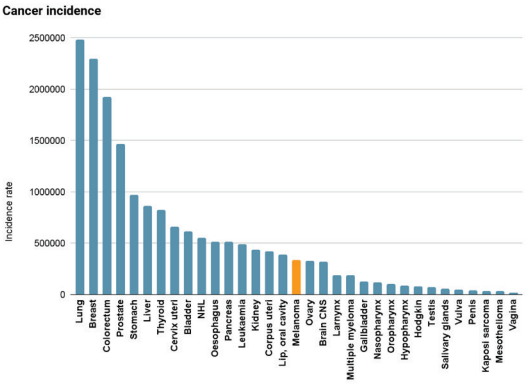


Figure 1: Rate of New Cases of Cutaneous Melanoma among all races, both sexes. The steady growth of new cases of Cutaneous Melanoma has been noted since the early 90s, while the death rate has stayed mainly unchanged. Data was acquired from the National Cancer Institute.[10]

From a global perspective, Cutaneous Melanoma has become a life-threatening condition for an increasing number of people. In 2022, it ranked in the top 20 of the most common types of cancer and caused 58667 deaths.

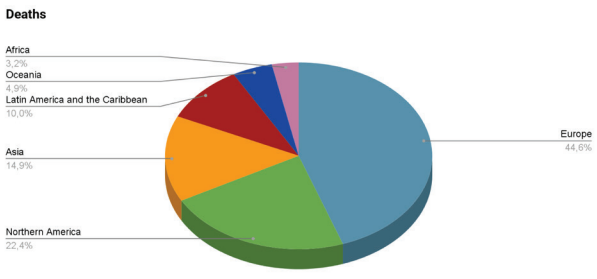


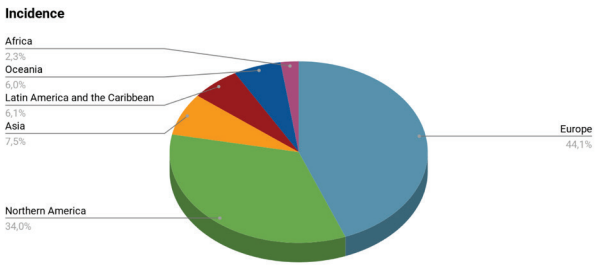


Cutaneous Melanoma	Incidence	Mortality
Rank	17	22
Statistics	331 722	58 667

Figure 2: Cancer incidence and Mortality statistics. Among other types of cancers in 2022, the incidence and mortality rates of Cutaneous Melanoma have the 17th and 22nd ranking, respectively. Data was acquired from the World Health Organization.[12]

Worldwide statistics for 2022 show the incidence rate of Melanoma varies depending on geographical location and ethnicity. When analyzing the diagrams below (Figure 3), it becomes evident that Melanoma is prevalent among populations of European and North American countries, where the Caucasian population dominates among other ethnic groups. Altogether, these two regions come up to 78,1% (259,128) of all cases of cutaneous melanoma determined in 2022. The mortality data show lower indices in the North American region, in contrast to the other regions. This fact may indicate good diagnostic procedures that allow early melanoma detection, population awareness, and/or accessibility to modern, effective treatment schemes.





Incidence for 2022	Number of cases
Europe	146 321
Northern America	112 807
Asia	25 003
Latin America and the Caribbean	20 291
Oceania	19 823
Africa	7 477

Mortality for 2022	Number of cases
Europe	26 180
Northern America	13 147
Asia	8 737
Latin America and the Caribbean	5 842
Oceania	2 859
Africa	1 902

Figure 3: Incidence and Mortality Statistics per Region. On the worldwide scale, Europe and North America demonstrate the highest incidence and mortality rates of Cutaneous Melanoma with 44.1% and 34.0% of new cases and 44,6% and 22,4% of deaths in 2022, respectively. Data was acquired from the World Health Organization.[12]

1.3. Risk factors:

For the manifestation of Melanoma, there are a few important risk factors that may play a crucial mutagenic role in its development. It is also important to emphasize that having risk factors in addition to genetic predisposition highly increases the possibility of developing any pathological condition, including melanomagenesis.

- UV radiation

The major risk factor associated with Cutaneous Melanoma is exposure to ultraviolet (UV) rays, such as solar and artificial UV radiation. Here, it is important to note that sunburn history (especially in childhood) has a much higher Relative Risk (RR) of 2,03 in comparison with Intermittent sun exposure (RR=1.61) and Sunbathing ('ever' intentional sun exposure; RR=1.44). It can be explained by the fact that children's skin is thin, has less protective melanin, and when it faces aggressive sunlight, sun-damaged cell DNA structures form permanent mutations due to immature DNA repair systems. Accumulating additional gene mutations over the lifetime, in addition to other external factors, significantly increases the risk of cutaneous melanoma development. [13-16]

- Phenotype

Caucasian ethnicity brings a higher risk of melanoma development, especially when this factor coincides with other ones. Therefore, people with lighter skin color, in addition to having red/blond hair, blue/green eyes, and skin that freckles and burns easily, are at increased risk. It is supported by the data from the WHO incidence rate above, which demonstrates 78% of all cases detected in 2022 in North American and European regions (Figure 2), with the ethnical prevalence of the caucasian population. It may be caused not only by the amount of melanin in the skin, but also by the type of melanin produced by melanocytes. It is known that there is a type difference in melanin presented in a darker or lighter skin - Eumelanin (dark pigment) and Pheomelanin (red/yellow pigment). It is also proven that Eumelanin has a higher UV protective potential in comparison to Pheomelanin.[16,19]

- Lifestyle habits

Consumption of liquors and spirits showed to be significantly correlated with melanoma, with the highest intake (>3.08 g/day) associated with a 47% increased melanoma risk compared with the lowest intake (0–0.13 g/day).[13] Drinking alcohol can make the skin more sensitive to sunlight, decrease skin immunity, increase the toxic burden of alcoholic metabolites and oxidative products, causing gene mutations that lead to elevated vulnerability to skin cancer.[17,19]

- Immunosuppression

A decrease in immunity in general affects the state of the body and its ability to withstand external challenges, since immune surveillance of external and internal environmental factors is weakened. In this regard, the risk of cutaneous melanoma development and its resistance to immunotherapy also increases along with other pathological conditions.[18,19] Thus, immunodeficiency present in patients with HIV in Caucasians, Transplant recipients (renal), Non-Hodgkin's lymphoma, and Chronic lymphocytic leukemia correspond to the following rates of Cutaneous Melanoma: IR > 10-fold increased, RR: 3.6, RR: 2.4, and RR: 3.1, respectively.[13]

- Age

Based on the data presented by the National Cancer Institute (USA), the average age of the most frequently diagnosed skin melanoma among people is 65-74 (Figure 4), with the mean age of 66 years from 2017-2021.[10]

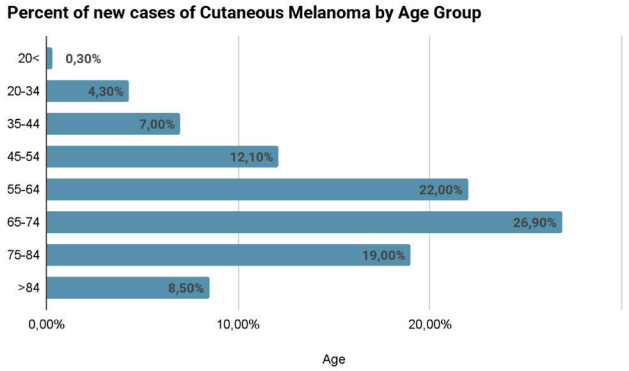


Figure 4: Percent of new cases of Cutaneous Melanoma. It is observed that the majority of new cases of Cutaneous Melanoma are mainly found in the age group of 65-74 years. Data was acquired from the National Cancer Institute.[10]

In addition, another source demonstrates a wider time period of 1992-2011 and proves the same melanoma manifestation rate of 55 years old 53%.[20] The undeniable correlation between

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older age and the occurrence of cutaneous melanoma development may account for the conclusion that melanomagenesis is a process of accumulating gene damage caused by many internal and external factors over a lifetime before turning normal melanocytes into malignant transformation.

- Sex/Gender

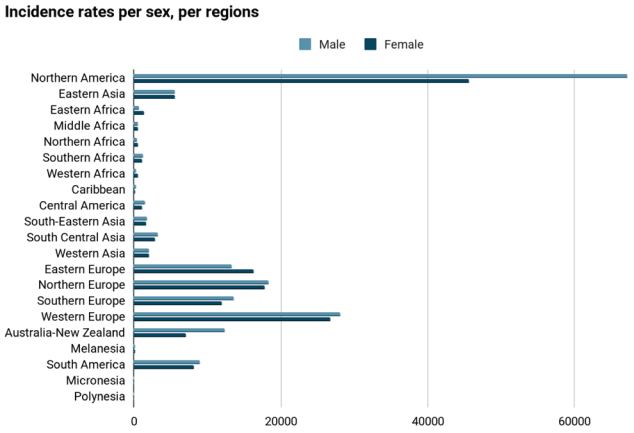

Figure 5: Incidence rates of Cutaneous Melanoma per sex, per region. It is demonstrated that on a worldwide scale, males in comparison with females are more prone to getting melanoma. Data was acquired from the World Health Organization. [12]

When studying global statistics from the perspective of sex/gender ratio, the data shows that males are more susceptible to Cutaneous Melanoma development. According to Global Cancer Observatory melanoma statistics, North America, along with Australia / New Zealand regions, demonstrates the biggest spread of incidence level between the two genders, where males are more often diagnosed with melanoma than females (Figure 5).[12] The possible conclusions that can be drawn from these statistics, excluding factors related to both sexes, are factors typical for men, such as risky sunbathing/sun exposure behavior, a higher level of alcohol intake, less awareness or melanoma alertness, and a lower conscious approach to health as a whole.

- Genetic Predisposition

Another crucial factor is genetic predisposition, which can be explained by the gene mutation shared between family members, as well as the common lifestyle habits and the same family phenotype. The risk of melanoma is higher if one or more of the first-degree relatives (parents, brothers, sisters, or children) have had melanoma or familial atypical multiple mole and melanoma (FAMMM) syndrome. Around 10% of people with melanoma have a family history of the disease.

Inherited *BRAF* and *NRAS* somatic gene mutations are characterized by incomplete penetrance, predisposing to melanoma formation, meaning that more elements need to accumulate to bring the disease to manifestation. Mutations in the *CDKN2A* gene are rare in sporadic cases but have been implicated in up to 30% of hereditary melanomas.[21] Since melanomagenesis is a multifactorial process, it requires specific genetic, epigenetic, and additional risk factors to coincide and be accumulated in one organism. The increased risk of melanomagenesis may include a shared family lifestyle of frequent sun exposure, a family tendency to have lighter skin tone, certain gene changes (mutations) that run in a family, or a combination of these factors.[12]

- Moles (Nevi)

Moles, or nevi, are benign growths of melanocytes considered to have both direct precursors and markers of increased risk for melanoma. People with >100 moles are at a seven-fold increased risk of developing melanoma in comparison to those with <15.[22] Guidelines suggest these moles should be constantly surveyed based on the ABCDE criteria (asymmetry, border irregularity, color variation, diameter >6 mm, and evolution), and if suspected, surgically removed with margins of at least 2 mm.[23]

2. Gene mutations:

2.1. Melanomagenesis:

Melanoma is a tumor composed of cells with different morphological and phenotypic profiles that form the basis for the phenomenon known as tumor heterogeneity. All these morphologically and phenotypically diverse cells are derived from normal melanocytes that have been pathologically transformed during melanomagenesis.

The genetically divergent subpopulations of tumor cells are represented by a small fraction of **CSCs** and many **non-CSCs**. These two malignant cell types differ by their stemness abilities, proliferative potential, differentiation, plasticity, metastatic activity, as well as treatment response. Other cells that are usually contributed to the normal skin morphology, such as keratinocytes, fibroblasts, endothelial and different immune cells, also play a vital role in tumor formation by releasing signaling molecules, growth factors, and cytokines that enable tumor formation and metastatic activity.

Melanoma tumor CSCs, also called Melanoma stem-like cells (MSC), are characterized by stemness properties-dependent protein markers - unique surface proteins associated with aberrant signaling pathways employed during tumor progression, drug resistance, and relapse. As a result of their origin, these cells have evolved genetically to evade drug toxicity and to promote tumor progression and metastasis. This feature may also explain why most available therapeutic approaches targeting MSCs tend to fail, and melanoma continues to proliferate and expand by spreading metastasis to nearby lymph nodes and other parts of the body.[24,25]

Many functional genes, such as ***BRAF***, *CDKN2A*, ***NRAS***, TP53, and NF1, are significantly altered by different mutations and associated with melanoma.

Among them, the most common are *BRAF* and *NRAS*, with ***BRAF^{V600E}*** alteration found in 50% of all melanoma cases.[9]

Since Melanoma is a tumor with heterogeneity, it demonstrates high levels of biological complexity during Melanogenesis. Consequently, melanoma cells undergo genetic, epigenetic, and/or phenotypic modification to survive in the human body.

Epigenetic alterations may play a crucial role in melanomagenesis, as these modifications in the cell genome without

changing its DNA sequence may regulate gene activity through DNA methylation, histone modification, non-coding microRNA activity, or chromatin remodeling. As a result of this, certain DNA sequences, encoding certain proteins, can be turned on/off, altering their functional task.

Therefore, in order to understand Melanoma development, possible pathway activations, and its response to the applied drug treatment procedures, gene mutations should be examined carefully.

2.2. BRAF mutation:

BRAF is one of the most important genes related to melanoma formation, as more than 60% of all cutaneous melanoma cases have been proven to have mutations in this specific gene. *BRAF* is a member of the *RAF* kinase family, which plays a significant role in the regulation of essential physiological cell functions. The *BRAF* gene is located on chromosome 7 (7q34) and encodes the BRAF protein, a 94 kDa intracellular enzyme of 766 amino acids. It is involved in the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) signaling pathway. The MAPK/ERK pathway consists of a chain of intracellular proteins that regulates normal cell growth, differentiation, proliferation, and apoptosis.[26,27]

In other words, the final goals of this signaling pathway in physiological conditions are the control of cell cycle progression and the regulation of their life cycle through apoptosis.[28]

Single-point mutations can turn *BRAF* into an oncogene that is found predominantly in cutaneous melanoma.[29] Among of all cases of Cutaneous Melanoma caused by *BRAF* gene mutations, more than 90 % are taking place at codon 600.[3,4] At this point, single nucleotide mutation (*BRAF*V600E: nucleotide 1799 T > A; codon GTG > GAG changes aminoacid encoding from **valine (V) to glutamic acid (E)**, and results in a **480-fold** increase in BRAF protein kinase activity compared with its native form.[26,30]

Another most common mutation at codon 600 is *BRAF^{V600K}*, substituting **valine (V)** for **lysine (K)**, 10-20 % (GTG > AAG).[31] Other rare two-nucleotide variation of the predominant mutation are *BRAF^{V600R}* (GTG > AGG) (<5%), *BRAF V600 'E2' (GTG > GAA)* (<1%), and *BRAF^{V600D} (GTG > GAT)* (<5%), *V600M* (<1%) and *V600G* (<1%).[26, 32-36] It is important to emphasize that both single and two-nucleotide mutations significantly affect the kinase functionality, causing cell mutagenic activity to drastically increase. The prevalence of *BRAF^{V600K}* has been reported as being higher in some populations. Thus, *V600K* activating mutations were more common than previously reported and occurred at a rate of 20% in the Australian population that has chronic UV exposure. [35,37]

Exposure to ultraviolet light is a major causative factor in melanoma, although the relationship between risk and exposure is complex. For example, in light-skinned people, the group that is predominantly affected by melanoma, tumors are most common on areas that are intermittently exposed to the sun, such as the trunk, arms, and legs, rather than on areas that are chronically exposed to the sun, such as the face. In melanoma, tumors arising in non-sun-exposed areas and intermittently exposed to ultraviolet radiation (UVR) skin demonstrate mainly *BRAF* and *NRAS* mutations. Melanomas on chronically sun-damaged skin exhibit multiple gene mutations, where the frequency of the *BRAF* mutation declines and becomes rare.[38-40] *BRAF* mutations in cutaneous melanoma are most common on the trunk (affecting the head and neck less frequently), on skin without marked solar elastosis, and at a younger age, thus suggesting a pathophysiology role for intermittent UV exposure in early life rather than chronic sun damage.[26, 41] BRAF-mutated melanomas arise early in life at low cumulative UV doses, whereas melanomas without *BRAF* mutations require accumulation of high UV doses over time. *BRAF* mutations in cutaneous melanoma are independently associated with age, anatomic site of the primary tumor, and the degree of solar elastosis at the primary tumor site.[41]

2.3. NRAS mutation:

NRAS mutations are found in 15%–20% of melanomas. The *NRAS* gene mutation was the first oncogene identified in melanoma in 1986.

The *NRAS* gene is located on chromosome 1 (1p13.2) and encodes the protein *NRAS* that acts as a GTPase and plays the role of a molecular switch between active and inactive states. Commonly, *NRAS* mutations are found at codons 12, 61, or, less frequently, 13, and represent single-nucleotide mutations.[42,50]

Whereas a mutant *NRAS(Q61)* gene disrupts the GTPase activity of RAS, locking it in its active conformation, leading to continuous activation of the MAPK/ERK pathway. *NRAS(G12)* and *NRAS(G13)* mutations contribute to the structural changes in the protein, thus decreasing its sensitivity to GTPase-accelerating proteins and also resulting in sustained activation of the MAPK/ERK pathway, although to a lesser degree. PI3K/AKT (phosphoinositide 3-kinase) is another pathway that can be altered by the *NRAS* gene mutation.[43, 44]

Typical patients harboring the *NRAS* mutation tend to be older (over 55) and have a history of chronic ultraviolet (UV) exposure.[45-47] The lesions are usually located at the extremities and have greater levels of mitosis than BRAF-mutant melanomas. Moreover, *NRAS* mutations are associated with lower rates of ulceration and thicker primary tumors. Histologically, mutant *NRAS* tumors are more aggressive than other subtypes, have elevated mitotic activity, and have higher rates of lymph node metastasis.[48-50]

2.4. Signaling pathways:

Signaling pathways play an important role in the regulation of many biological processes. Studying and a deep understanding of their perplexing mechanisms, alterations that eventually replace normal physiological conditions due to the malfunction of mutated genes, offers a way to develop efficient targeted therapeutic approaches to the treatment of cutaneous melanoma.

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MAPK/ERK pathway:

A special role in the process of melanogenesis is played by the mitogen-activated protein kinase (MAPK) pathway, which regulates cell survival, proliferation, differentiation, apoptosis, and cell response to different stress factors.

The MAPK signaling pathway is a complex network of signaling cascades, including several branches with different functional characteristics and biological consequences.

One of the powerful activators of MAPK signaling pathways is epidermal growth factor (EGF).[57] It activates the MAPK cascade, starting with phosphorylation and activation of kinases at the top of the cascade, such as RAF, MEK, and ERK. This process leads to signal transduction from cell surface receptors to target sites inside the cell, initiating various cellular responses such as growth, proliferation, differentiation, and survival.

Phosphorylation and dephosphorylation determine their functional activity inside the cell, playing a key role in regulating the activity of MAPK kinases.

Dephosphorylation of MAPK kinases ensures the shutdown of the signaling cascade and the return of the cell to the baseline level of activity. This process can be carried out by various enzymes (phosphatases), which remove phosphate groups, thereby reducing the kinase activity of MAPK. Like phosphorylation, dephosphorylation is a key mechanism for regulating cellular signaling pathways. Dephosphorylation allows the cell to precisely control its responses to external signals and maintain homeostasis within the cellular environment. This balance between phosphorylation and dephosphorylation significantly affects cellular functions and the general condition of the organism. Understanding these mechanisms is important for the development of new treatments and diagnostics for many diseases associated with dysfunction of cell signaling.[58]

Mutations in the *BRAS* and *NRAS* genes turn on the ligand-independent activation of MEK or Mitogen-Activated Protein Kinase Kinase, also known as MAP2K, bypassing prior binding of epidermal growth factor (EGF) to its receptor (EGFR) on the cell membrane that normally leads to the activation of MEK. The whole MAPK/ERK pathway represents a cascade of biochemical reactions during which several key proteins are being activated in a sequence: RAS-RAF-MEK-ERK. The last one translocates signals to the cell nucleus, promoting cell proliferation, differentiation, and survival. Dysregulated of gene mutation MAP/ERK pathway results in uncontrolled cell growth and the formation of tumors, as well as the inhibition of apoptosis.[51]

PI3K/AKT/mTOR pathway:

Another crucial pathway employed in melanomagenesis is PI3K/AKT/mTOR. It plays an important role in cell growth, survival, and metabolism. Like the MAPK signaling pathway, the PI3K/Akt/mTOR pathway is activated in response to extracellular signals, such as growth factors and cytokines, through the activation of tyrosine kinase receptors (RTKs) and other cell surface receptors. Activated PI3K/AKT/mTOR pathway through a series of biochemical reactions leads to the activation of mTORC1 that promotes protein synthesis, cell growth, and survival.

However, when dysregulated, this pathway is often observed in melanoma due to genetic alterations, such as mutations and amplifications in pathway components.[51,52]

This pathway, along with cell growth and survival, confers resistance to applied therapies.

The two pathways - **MAPK/ERK** and **PI3K/AKT/mTOR** (Figure 6) often interact and may be simultaneously activated. It can contribute to more aggressive tumor cell proliferation, development, and treatment resistance.[51]

The scheme presented in Figure 6 demonstrates the key components of both pathways that are initiated at the same site and through the alternative biochemical reactions lead to the same biological response.

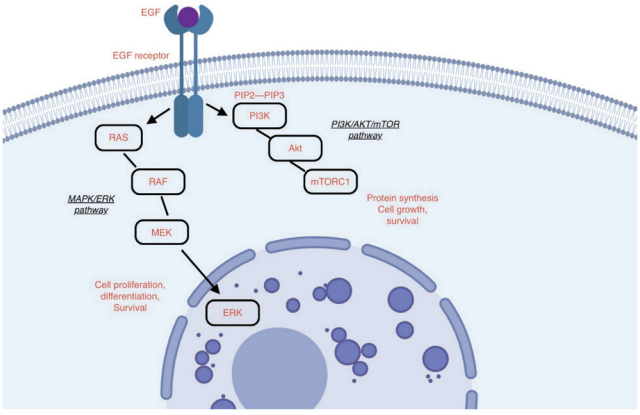

Figure 6: Signaling pathways involved in *BRAF* and *NRAS* gene mutations. The main role in melanomagenesis is played by two pathways- MAPK/ERK and PI3K/ERK, which often can interact and may be simultaneously activated, leading to more aggressive tumor cell proliferation and treatment resistance. (made in https://www.biorender.com/)

3. Therapies:

The earlier applied therapeutic methods in addressing melanoma were limited to Surgical Resection, Chemotherapy, Radiation therapy, and Immunotherapy. Nowadays, the traditional approach to melanoma treatment is being extensively developed in the direction of Targeted Therapy. It is focused on reaching the dysregulated pathways of genes involved in cell growth, their differentiation, and functionality. Melanomagenesis and its further development are mediated by genetic and epigenetic alterations amplified by the variety of risk factors that make changes to the multiple signaling pathways, including MAPK/ERK, PI3K/AKT/mTOR, and other ones not mentioned in this paper (JNK and Jak/STAT pathways).[9,53,54]

However, the biggest challenge and main issue in targeted therapy presented by inhibition of mutated *BRAF* and *NRAS* genes turned out to be Drug resistance and Melanoma recurrence.

It has been stated that melanoma progression and treatment failures are attributed to tumor heterogeneity due to genetically divergent subpopulations – CSCs and non-CSCs. The stemness property of CSCs (MSCs) leads to increased drug metabolism, enhanced repair capacity of damaged DNA, reactivation of drug targets, overactivation of growth and survival signaling pathways, amplifications, and impaired activity of apoptosis/autophagy-dependent pathways.[55,56]

Both signaling pathways studied in this review paper, MAPK/ERK and PI3K/AKT/mTOR, are interconnected at multiple points, and inhibition of one of them may not only fail to stop the development of the disease but also provoke its active growth by the activation of the other signaling cascade.

Improved clinical outcomes and treatment efficiency might be reasonably developed by the intersection of MAPK/ERK and PI3K/AKT/mTOR pathways simultaneously.[9]

The table below presents the major treatment procedures applied to the cutaneous melanoma provoked by *BRAF* and *NRAS* mutations:[59-61]

Table 1: Targeted therapies are applied for BRAF and NRAS driver mutations.

Driver mutation	*Targeted Therapeutics / Immunotherapy*	*International Nonproprietary name / INN*	*Efficacy*
BRAF V600K/E	BRAF inhibition	Vemurafenib Dabrafenib Ecorafenib	Combination of BRAF and MEK inhibitors has shown better results and contributed to the remarkable improvement in overall survival of patients with BRAF V600E advanced melanoma
	MEK inhibition	Cobimetinib Trametinib Binimetinib	
	Immune Checkpoint Inhibition ICIs	Ipilimumab Nivolumab Pembrolizumab	Effective in activating tumor-infiltrating lymphocytes (TILs) to rebuild immune response in patients with advanced or metastatic melanoma Combination of BRAF/MEK/ICIs improved with 5.7 months progression-free survival
NRAS-mut	B/C-RAF	Naporafenib	Directly targeted RAS protein drugs are not developed due to their high affinity to bind GTP and the lack of druggable pockets. Combination of several inhibitors and therapeutic approaches are proven to be effective
	MEK inhibition	Binimetinib Pimasertib FCN-159 Tunlametinib (HL-085)	
	Oncolytic viral therapy	Talimogene laherparepvec T-VEC	
	Immune Checkpoint Inhibition ICIs	Anti-PD-1	
	ERK inhibition	Ulixertinib (BVD-523)	
	CDK4/6 inhibition	Ribociclib (LEE011)	

Conclusion

Melanoma is a malignant tumor composed of genetically divergent subpopulations of cells, presented by a small fraction of CSCs and many non-CSCs. Due to tumor heterogeneity and special properties of CSCs cells, Melanoma is prone to rapid development and metastasis in different organs of the human body, which affects treatment outcomes and life prognosis. The data presented in this review paper demonstrate that different risk factors such as UV radiation, Phenotype, Age/ Gender, Lifestyle behavior, Family disease history, and Health condition, along with genetic mutations, play a crucial role in the development of Cutaneous Melanoma.

Mutations in the genes *BRAF* (60%) and *NRAS* (20%) most commonly dominate among other gene mutations found during melanomagenesis and cause dysregulation in MAPK/ERK and PI3K/AKT/mTOR signaling pathways responsible for cell growth, differentiation, and functional activities. Interconnectedness between the two major signaling pathways results in the targeted treatment failure and disease recurrence when singly addressed.

Over the past few decades, treatment options for cutaneous melanoma have advanced significantly, improving survival rates in patients with *BRAF* and *NRAS* mutations. However, not all the driver mutations are effectively targeted, especially in *NRAS* mutations.

There is a big need for new treatment procedures to address all known pathways through targeted therapy. The fact that these pathways are interconnected with each other and when one is blocked, the path can continue by an alternative route, should be taken into consideration by future researchers. Due to the limitations in available scientific data on a wider spectrum of additional signaling pathways activated during melanogenesis, further research studies for potentially effective novel therapies targeting points of pathway intersections are needed in the field of Cutaneous melanoma treatment.

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