CDKN2A in Melanoma: Recent Advances

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ABSTRACT

Melanoma is a skin cancer that accounts for 1% of total skin cancers, with a strikingly high mortality rate that accounts for 80% of deaths amongst skin cancer patients. Melanoma is a skin cancer driven by melanocyte mutations inducing uncontrolled cellular division. One specific gene, *CDKN2A*, is commonly associated with melanoma. *CDKN2A* codes for two proteins termed p14 and p16, each involved in their respective molecular pathways. Both, p14 and p16 affect the cell cycle, but in unique ways which can lead to the uncontrolled proliferation of mutated melanocytes and melanoma pathogenesis. Emerging therapeutic and molecular screening techniques have been used to detect *CDKN2A* mutations to evaluate potential genetic mechanisms driving melanoma pathology across patients. In this review, I present a brief history of melanoma, examine a select number of disease associated genetic mutations, and describe how these mutations affect downstream signaling pathways involving p14 and p16 leading to melanoma formation. I conclude with a discussion synthesizing historical and emergent biochemical signaling findings in mutant *CDKN2A* to evaluate future potential targeted therapeutic strategies.

Keywords: melanoma, *CDKN2A*, p14, p16, skin cancer, cell cycle signaling, pathology

INTRODUCTION

Background and brief history of melanoma

Melanoma is a cancer that originates from mutations in melanocytes, which are pigmented cells of the skin. In the US, melanomas account for 1% of skin cancer diagnoses with the majority of diagnoses arising squamous and basal cell carcinoma, which are skin cancers that develop from the epidermis layer of the skin (Ali et al., 2024; Hasan et al., 2023; Saginala et al., 2021). Despite accounting for a small percentage of skin cancer diagnoses, melanoma is responsible for approximately 80% of skin cancer-related deaths (Saginala et al., 2021). Given melanoma's high mortality rate and poor prognosis, it is of significant clinical importance to further investigate mechanisms underlying melanoma formation to develop effective strategies for diagnosis and therapeutic approaches.

Melanoma was first identified in 1804 by French physician Rene Laennac. Laennac recognized that melanoma is a distinct disease and coined the term *melanose*, which describes the abnormal cells deemed now as tumors presented on the skin. Melanoma is derived from the Greek terms *mela* and *oma*, meaning *dark* and *tumor*, respectively (Rebecca et al., 2012). In the mid-1800s, Dr. William Norris, an English physician, devised general principles for melanoma and found the connection between nevis (moles) and cancer (Norris, 1857). Dr. Norris' observations are the earliest pathological descriptions of melanoma, and his experience in treating patients helped to define fundamental principles and characteristics crucial to modern research of melanoma. Dr. Norris observed that melanoma had a high metastatic potential

which is the tendency for a tumor to form metastatic lesions, or new tumors and described the textures and colors of the tumor. Importantly, he noted that in some cases the risk of developing melanoma increased with a family history of the condition (Winnard et al., 2008). Phenotypically, melanoma is characterized by discoloration on the skin, often presenting as a change in the color of a preexisting mole. Melanoma is most commonly diagnosed in Caucasians and the median age of onset is 66 years old (Waseh & Lee, 2023). To this day, physicians and researchers continue to use these discoveries and descriptions for investigating and treating melanoma (Rebecca et al., 2012). More recently, subcellular genetic, molecular, and cellular aspects of melanoma have been described, including identification of the cell cycle as a principal component of melanoma pathogenesis. Identification of cell cycle processes driving melanoma pathology and mortality allows for probing subcellular and cellular mechanisms underlying disease, thereby further informing targeted therapeutic development and diagnostic methods.

Description of cell cycle and cancer formation

The cell cycle has a specific set of functions and checkpoints that a cell must go through in order to divide successfully. There are four distinct phases of the cell cycle cycle: gap 1 (G1), DNA synthesis (S), gap 2 (G2), and mitosis (M) (Liu et al., 2022). During the cell cycle, the cell will interact with cyclins and Cyclin-Dependent Kinases (CDK), which regulate the cell division (Mercadante & Kasi, 2025).

Cell division is required during embryogenesis and is essential for postnatal growth and development. However, in development towards adulthood, the fraction of cells undergoing cell division significantly decreases as most become terminally differentiated. As such, for most tissues in the body the cells comprising them are in an arrested cell cycle state. Differentiated and cycle-arrested cells may acquire mutations that release the molecular “brake” on the cell cycle, causing the cell that acquired the mutation to begin the cell cycle anew and proliferate. Mutations in cell-cycle associated genes in melanocytes can induce abberrancies in the cellular cycle, including loss of cell cycle regulation, resulting in development of pathological tumor growth and ultimately death if left untreated. In this review, I focus on the synthesis of current literature to further elucidate how *CDKN2A* proteins affect the mutation of a cell during the G1/S stage and the G2/M stage and how this can give rise to melanoma.

To conclude, I describe recent observations and discoveries with respect to the pathological and molecular basis of melanoma, discuss recent advances in therapeutic applications, and conclude with a description of exciting new areas of scientific and clinical investigation.

MELANOMA AND SELECT GENES

Description of melanoma-associated genes

There are a variety of different genes associated with melanoma. Some of the earliest genes identified in relation to melanoma play roles in the cell cycle, cell growth, and genomic stability. These genes include *CDKN2A*, *BRAF*, *NRAS*, and *TERT* shown in **Table 1** (Toussi et al., 2020)**.** The *CDKN2A* gene, a tumor suppressor, is frequently mutated in melanoma and plays a crucial role in its development. *CDKN2A* was first identified as a cause of melanoma in 1994 (Kreuger

et al., 2023). Loss of function mutations in *CDKN2A* are found in up to 70% of melanoma cases as elaborated in **Table 2** (Kreuger et al., 2023). As a result of alternative exon 1 usage, *CDKN2A* can produce two distinct proteins, p14 and p16 as seen in **Figure 1**. The p14 protein facilitates the p53-mediated removal of damaged cells by sequestering HDM2, which binds and causes the degradation of p53. The p16 protein, however, inhibits the cell cycle by sequestering CDK4/6 and causing cell cycle arrest (Kreuger et al., 2023). The *CDKN2A* gene can cause melanomas to appear around 15 years earlier than the median age (Toussi et al., 2020). Excitingly, the identification of these genes in melanoma allow for the development of targeted therapeutic approaches.

Table 1. Genes associated with melanoma.

Gene	Gene Name	Phenotype	References
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A	Melanocytic nevi, melanoma, pancreatic, upper GI, and respiratory cancers; astrocytoma, neurofibromas and schwannomas (mutation affecting p14ARF)	(Toussi et al., 2020)
CDK4	Cyclin Dependent Kinase 4	Melanocytic nevi, melanoma, pancreatic cancer	(Toussi et al., 2020)
TERT	Telomerase Reverse Transcriptase	Melanoma, melanocytic nevi, other reported cancers (ovarian, renal cell, bladder, breast, and bronchial cancer)	(Toussi et al., 2020)
POT1	Protection of Telomeres 1	Melanoma, other reported cancers (glioma, chronic lymphocytic leukemia, colorectal, breast, and lung cancers)	(Toussi et al., 2020)
ACD	ACD shelterin complex subunit and telomerase recruitment factor	Melanoma, other reported cancers (breast, ovarian, cervical, uterine, thyroid, colon, lung, renal, urinary, prostate and esophageal cancers, lymphomas and leukemias)	(Toussi et al., 2020)
TERF21P	TERF2 interacting	Melanoma, other	(Toussi et al., 2020)

	protein	reported cancers (breast, ovarian, cervical, uterine, thyroid, colon, lung, renal, urinary, prostate and esophageal cancers, lymphomas and leukemias)	
MITF	Melanocyte inducing transcription factor	Melanoma, renal cell carcinoma, darker hair, fair skin, non-blue eye color	(Toussi et al., 2020)
MC1R	Melanocortin-1 receptor	Melanoma, red hair, freckling, light skin, and UV sensitivity (loss-of-function variants)	(Toussi et al., 2020)
BAP1	BRCA 1 associated protein	BAP1-inactivated nevi, uveal melanoma, cutaneous melanoma, mesothelioma, and renal cell carcinoma Other reported tumors (basal cell carcinoma, meningioma, cholangiocarcinoma, breast, lung, pancreatic, and thyroid cancer)	(Toussi et al., 2020)

Notes: Table modified from (Toussi et al., 2020)

Table 2. Select Mutations in *CDKN2A* associated with melanoma

CDKN2A Protein Mutation	Effect on p14 or p16	Reference(s)
p.A4_10Edel7	P16	(Danishevich et al., 2023)
p.M1_S8dup	P16	(Danishevich et al., 2023)
p.20T_21Adup	P16	(Danishevich et al., 2023)
p.G23D	P16	(Danishevich et al., 2023)
p.R24P	P16	(Burgstaller-Muehlbacher et al., 2015) (Danishevich et al., 2023)
p.L32P	P16	(Danishevich et al., 2023)
p.G35E	P16	(Danishevich et al., 2023)
p.G35A	P16	(Danishevich et al., 2023)
p.A36RfsX17	P16	(Danishevich et al., 2023)
p.P38R	P16	(Danishevich et al., 2023)
p.Q85H	P14	(Burgstaller-Muehlbacher et al., 2015)
p.R115Q	P14	(Burgstaller-Muehlbacher et al., 2015)
p.A121T	P14	(Burgstaller-Muehlbacher et al., 2015)
p.F23F	P14	(Burgstaller-Muehlbacher et al., 2015)

Notes: Portions modified from (Danishevich et al, Table 2).

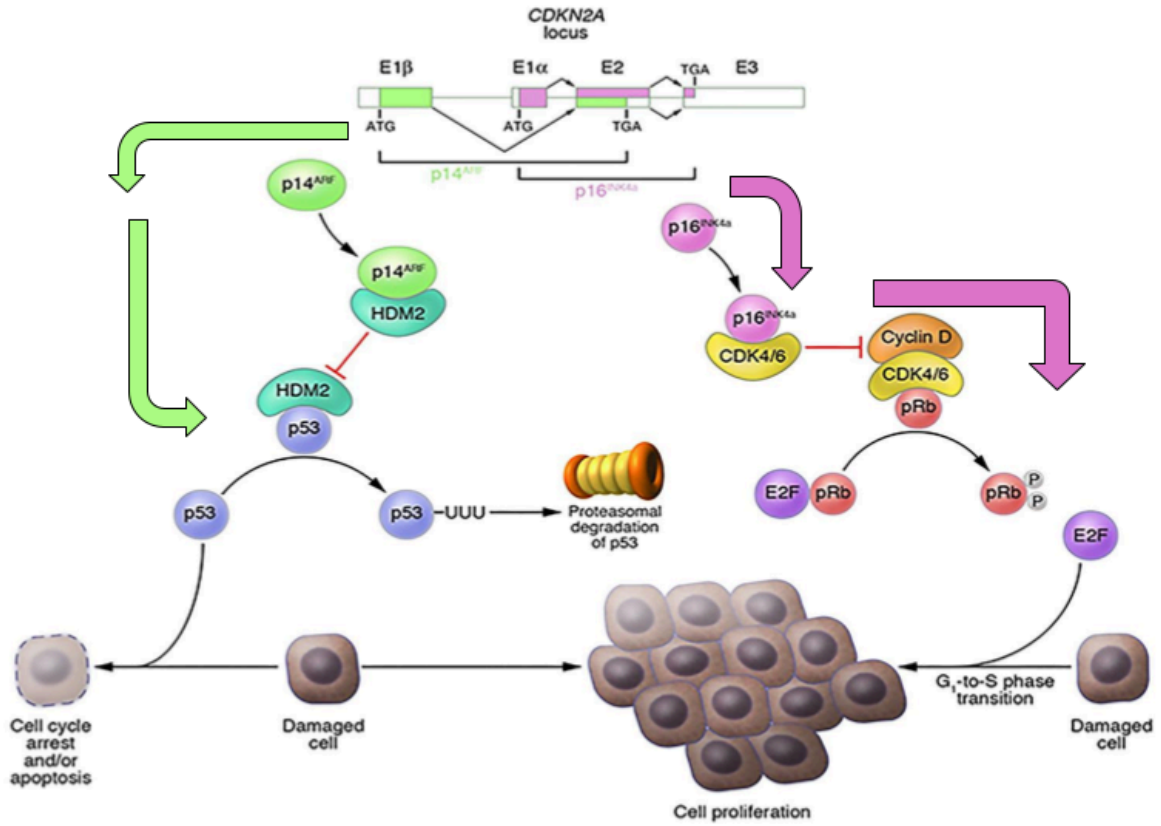

Figure 1. Adapted from Chudnovsky et al, 2005 Figure 2. The pathways affected by mutations in the *CDKN2A* locus. *CDKN2A* is found on human chromosome 9p21 and encodes two different tumor suppressors, $p16^{INK4a}$ and $p14^{ARF}$. P14 is translated from reading exon 1B, 2 and 3, while p16 is translated from reading exon 1A, 2, and 3. P16 regulates the sequestering of CDK4 and CDK6, binding to cyclin D and inducing phosphorylation of Retinoblastoma protein (Rb). The absence of p16 causes CDK4 and CDK6 to bind to cyclin D and phosphorylate Rb, releasing the E2F transcription factor. This causes the movement from the G1 stage of the cell cycle to the S phase, causing a damaged cell to proliferate. P14 sequesters HDM2, a p53-specific ubiquitin ligase. The absence of p14 causes HDM2 to target p53 for ubiquitination and causes damaged cells to not arrest, causing them to proliferate (Chudnovsky et al., 2005).

Therapeutic targeting of CDKN2A in melanoma

While the roles of p14 and p16 and their associated molecular pathways in melanoma are well described, the clinical implications remain a robust area of investigation. Treatments for melanoma have historically included chemotherapy and surgical removal (Davis et al., 2019). Researchers have incorporated molecular level techniques to diagnose patients. These include genetic sequencing and matching and digital droplet polymerase chain reaction (ddPCR) to help diagnose patients with melanoma (Connell et al., 2024; McFadden et al., 2023). Precision medicine has been a promising therapy for melanoma patients as it incorporates the patient's own endotypes at the genomic and cellular levels,into their treatment (Leachman et al., 2017). Recent studies have expanded the qualifications for genetic screening for melanoma and other cancers in hopes of applying this same improved treatment to a wider array of patients (Leachman et al., 2017). Current clinical trials for melanoma treatment include combinations of antibody based treatments (nivolumab and ipilimumab), molecular target and match therapies, and many others (*A Phase II/III Trial of Nivolumab, Ipilimumab, and GM-CSF in Patients with Advanced Melanoma*, 2016, *Clinical Trial: NCT02645149 - My Cancer Genome*, n.d.). In addition, the use of PD-1 inhibitors has been found to help treat melanoma patients with multiple melanomas occurring throughout their lifespan (Helgadottir et al., 2020). Overall, there are an increasing number of trials dedicated to ameliorating the impact of *CDKN2A* loss in melanomas that can hopefully help those affected by this disease.

CDKN2A AND MELANOMA

The p14 and p16 proteins are generated by alternative exon 1 usage

The proteins encoded by the *CDKN2A* gene (p14 and p16) regulate different stages of the cell cycle but have the same effect (*i.e.*, cause arrest of the cell cycle required in fully differentiated tissues). The p14 ($p14^{ARF}$) and p16 ($p16^{INKDA}$) proteins are generated via the reading of alternative exon 1 regions, termed 1α and 1β found on human chromosome 9 at locus 21 as seen in figure 1 of Kreuger et al study published in 2023 (Kreuger et al., 2023). Researchers have found gene variants (*CDKN2A* and *CDKN2B*) located in 9p21 that can predispose individuals to melanoma, particularly a specific type of melanoma known as Cutaneous Malignant Melanoma (CMM) (Laud et al., 2006). While p16 affects the G1/S stage, p14 affects the G2/M stage. Studies on the $p14^{ARF}$ protein have had conflicting results, thus the role of p14 remains to be elucidated as results have not demonstrated a stage specific role as definitively as p16 (Laud et al., 2006). Mutations resulting in the inactivation of the p16 protein are found in 67.5% of melanomas studied, whereas the alteration and subsequent inactivation of the p14 protein was only found in 27.4% of melanomas studied (Kreuger et al., 2023).

Role of p14 in the cell cycle

The p14 protein (or $P14^{ARF}$) is generated by reading exon 1β of the *CDKN2A* genes along with the second and third exons (Fig. 1, Laud et al. 2006). While both p14 and p16 are encoded from overlapping regions in the genome, they share no amino acids, as p14 is translated from an alternative reading frame (ARF) than p16. Thus, mutations within p14 can additionally induce downstream mutations in p16 and degradation of cell cycle signaling feedback loops as demonstrated in **Figure 1.** Multitudes of mutations including but not limited to frameshift mutations, splice site variation, and mutations within exon 1β resulting in aberrant amino acid

formation all drive changes in protein structure and function (Eckerle Mize et al., 2009). The p14 pathway involves interacting with the Murine Double Minute 2 Protein (MDM2), which prevents the degradation of the p53 protein (Palmieri et al., 2015). Inhibition of p53 by p14 induces arrest of the G2/M stage of the cell cycle, causing apoptosis to occur, thereby preventing the damaged cell from replicating and spreading (Laud et al., 2006). Mutations which reactivate the cell cycle in differentiated melanocytes in an arrested state, results in melanoma due to unregulated and increased cell division.

Role of p16 in the cell cycle

The p16 protein is generated by incorporating exon 1α of the *CDKN2A* gene. It is read from the first 3 exons and the alpha section of exon 1 (Laud et al., 2006). The binding of p16 to CDK4 and CDK6 creates a complex that can interact with cyclin D. This interaction causes the cell to receive a cue for cell cycle activation moving from G0 to G1. Cyclin D complexes with both CDK4 and CDK6 and induces kinase activity, causing the phosphorylation of the Retinoblastoma protein (Rb) (Williams et al., 2014). This process then leads to the cell cycle arrest at G1/S stage (Kreuger et al. 2023). In damaged cells lacking functional p16, downstream signaling pathway inhibition results in depression of the cell cycle and the transition to the S phase, which replicates DNA with mutations that subsequently cause uncontrolled cell division processes (Eckerle Mize et al., 2009). In turn, at the cellular level, melanocytes form and multiply, leading to melanoma pathogenesis (Chudnovsky et al., 2005).

Familial mutations in CDKN2A

Melanoma has hereditary components as around 7-15% of occurrences are diagnosed in patients with a family history (Toussi et al., 2020). Out of familial cases, 22% of these are found to have been caused by mutations in the *CDKN2A* gene (Toussi et al., 2020). First described in the 1960s, Familial Atypical Multiple Mole and Melanoma Syndrome (FAMMM) is a genodermatosis (genetic skin disorder) affecting those with multiple melanocytic nevi (moles) (Eckerle Mize et al., 2009). FAMMM was historically found to be linked to the gene *CDKN2A* in 1992 in research conducted by Dr. Lynch, who along with Dr. Krush in 1968 discovered a connection between pancreatic cancer and melanoma (Eckerle Mize et al., 2009). The diagnosis for FAMMM syndrome includes clinical observation of multiple nevi and a familial history of the disease (Eckerle Mize et al., 2009). Physicians use the “ABCDE” mnemonic device which includes the following characteristics: Asymmetry, Border irregularity, Color change, Diameter over 6 millimeters, Evolution (changes in the growth of the spot) to initially identify if the discolored lesion has the possibility of being diagnosed as melanoma (Ward et al., 2017). Genetic testing has been used to screen patients for mutations in the *CDKN2A* gene. Germline mutations in *CDKN2A* can increase the chance of melanoma pathogenesis by over 65-fold, additionally increasing the penetrance of melanoma from 60-90% (Helgadottir et al., 2016). *CDKN2A* carriers were found to have poor prognosis and low survival rates for both melanoma and nonmelanoma cancers, as this gene affects fundamental cell cycle regulation underlying mechanisms of pathogenesis of a multitude of cancers, not solely melanoma (Helgadottir et al., 2016).

THERAPEUTIC APPROACHES TO TREATING MELANOMA

In order to prevent the oncogenic effects of the inactivation of one of the *CDKN2A* pathways, current research aims to alleviate the negative consequences of melanoma-causing mutations in p14 and p16. These therapies include restoring CDK4/6 inhibition, targeting cell cycle controls including (BRAF/MEK as an example, using subcellular molecular-level screening tools outlined in **Table 3** (Kreuger et al., 2023; Connell et al. 2024; McFadden et al. 2023).

Table 3. Select therapies used to treat mutations within *CDKN2A* loss. Portions adapted from (Kreuger et al. 2023) Supplementary Materials.

Therapeutic Approaches	Mechanism of Action
Palbociclib (CDK4/6 Inhibitor)	Inhibits proliferation of melanoma cells
Ribociclib (CDK4/6 Inhibitor)	Disrupt melanoma growth in preclinical models
Abemaciclib (CDK4/6 Inhibitor)	Disrupt melanoma growth in preclinical models
Inhibition of CHK1 and MK2 Kinases	Inhibits the progression of the cell cycle
Inhibition of AURKA and AURKB	Reduce cell proliferation and increase apoptosis
Inhibit WEE1 and CHK1	Induces melanoma cell death
Elevating ROS levels	Repress cell growth
DNA or Histone Methylation	Restore *CDKN2A*

Therapies targeting the p16 pathway

Since mutation of the p16 pathway causes melanocytes to divide, many researchers focus on restoring function of this pathway through targeting portions of the complex interacting with p16 like CDK4 and CDK6 (Kreuger et al., 2023). To date, three different FDA-approved CDK4/6 inhibitors have been employed for breast cancer treatment. In addition, studies have shown that *in vivo* and *in vitro* melanoma cells are affected by these inhibitors (Kreuger et al., 2023). Melanoma cells treated with pharmaceutical targeted therapeutics include palbociclib, ribociclib, and abemaciclib, which are shown to decrease the phosphorylation of Rb, resulting in inhibition of melanocyte cell division (Kreuger et al., 2023).

Coordinating p16 pathway therapies with BRAF/MEK inhibitors

Clinical trials Using the aforementioned CDK4/CDK6 inhibitors in conjunction with BRAF/MEK inhibitors increases clinical benefits from polypharmaceutical combined treatment (Kreuger et al., 2023). Clinical success across trials provides the impetus to further probe the utility of these therapeutics for melanoma patients with mutations in *CDKN2A* in the hopes of developing a promising treatment for these patients with poor prognosis and high mortality rates *(Kreuger et al., 2023)*. Other therapies used to target the cell cycle include inhibition of the CHK1 and MK2 checkpoint kinases, which would prevent cellular entry into mitosis (Kreuger et al., 2023). Another form of cell cycle targeted therapies includes inhibiting the AURKA and AURKB (Aurora Kinase A and B) kinases which both regulate the G2/M stage of the cell cycle and the spindle assembly checkpoints (Kreuger et al., 2023). Combined with BRAF inhibitors or DNA damaging agents results in increased apoptosis *in vitro* of melanoma cells, demonstrating potential to be

evaluated in the context of treating melanomas (Kreuger et al., 2023). Therefore, further clinical trials investigating the effect of AURKA/B inhibitors on CDK2NA deficient tumors are required to determine efficacy in the clinic (Kreuger et al., 2023).

Diagnostic approaches to supplement therapeutic strategies

As a supplement to the therapeutic strategies targeting pathways that induce cell division, molecular tools have also been developed to help address the limitations of forward genetic screening approaches to correlation of gene mutations to disease pathogenesis mechanistically thereby underscoring the imperative to identify relevant gene mutations to screen for when diagnosing melanoma. Recently, investigators have used cutting-edge molecular tools to determine methods to diagnose and assess effective therapeutic regimens and treatment approaches. These approaches include Molecular Match Target Therapy (MMTT) and digital droplet Polymerase Chain Reaction (ddPCR) to stratify patients across endotypes based on aforementioned aberrant mutations, and, in doing so, determine effective therapeutic approach to use when considering treatment of patients with melanoma a (Connell et al. 2024; McFadden et al. 2023).

MMTT offers personalized medicine strategies for patients with melanoma driven by genetic and cell cycle signaling alterations using personalized medicine based on the patient's own genome to reduce potential off-target impacts. This approach has become promising in medical sciences as technology emerges allowing for probing of molecular components to target to refine treatment based on efficacy for patient cohorts stratified by genetic drivers of pathology. The molecular match target therapy study found that around 60% of patients reached a stable state for 6 months, demonstrating higher efficacy than the current treatments (Connell et al. 2024). Diagnostic approaches involving ddPCR are used to detect copy number variations in a cost-efficient way. This method is able to detect genome structure changes that result in loss of *CDKN2A* expression within the tumor, providing additional diagnostic metrics while providing invaluable insights on potential structural related molecules for targeted therapeutic development for precision medicine (McFadden et al. 2023). When employed in clinical trials this method had high success rates, providing a basis for researchers to provide access to a large number of patients (McFadden et al. 2023). These recent advances have proven to be highly successful in identifying the tumor's genetic mutations and improving diagnosis (McFadden et al. 2023). The aim is to further determine mechanisms underlying therapeutic success in ameliorate disease phenotypes. Results from these studies can be built upon in future research to further investigate abberrancies in genome architecture and composition related to cell cycle dysfunction, which can be applied to a broad range of related disorders, benefitting a greater number of patients,

There have been many advancements in targeting genes for therapeutic intervention in melanoma patients, however, emergent technologies and research findings continue to provide future avenues through which to further target genes to develop personalized effective therapies. Nevertheless, some technologies including sequencing and ddPCR, have demonstrative results in increasing diagnosis accuracy and treatment selection based on diagnosis, and furthermore have been shown to cure patients with melanoma (Connell et al. 2024; McFadden et al. 2023). Further research is needed to understand familial inheritance of the mutation and the complete effect this alteration has on the development of melanoma.

SUMMARY

Melanoma skin cancer affects many people worldwide. Despite its incidence in comparison to other skin cancers, it remains the leading cause of death compared to other common skin cancers. Melanoma pathology is driven by mutations of genes involved in cell cycle processes in melanocytes. Genes discussed in this review include *CDKN2A, BRAF, NRAS, and TERT,* and are commonly associated with melanoma. This review focuses on *CDKN2A*, the most prevalent gene mutated and correlated with disease in melanoma patients. *CDKN2A* encodes two proteins reviewed here, p16 and p14. Mutations in *CDKN2A* can cause melanoma to form due to the indispensable role in regulation of the cell cycle. This review concludes with a summary of historical and emergent perspectives and therapeutic approaches to treat skin cancer to investigate potential opportunities using novel methods and materials to treat melanoma in addition to further understanding fundamental mechanisms of cell cycle dysfunction providing utility for other diseases in which cell cycle dysfunction drives pathology.

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