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Review

Molecular Profile of Skin Cancer

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Abstract: Neoplasia occurs as a result of genetic mutations. Research evaluating the association between gene mutations and skin cancer is limited and has produced inconsistent results. There are no established guidelines for screening skin cancer at molecular level. It should also be noted that the combinations of some mutations may play a role in skin tumors' biology and immune response. There are three major types of skin cancer, and the originality of this study comes from its approach of each of them.

Keywords: gene mutations; basal cell carcinoma; squamous cell carcinoma; melanoma

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1. Introduction

Skin cancer is the most common form of cancer worldwide, its incidence steadily increasing in recent years regardless of race [1].

It is already known that the neoplastic process occurs as a result of genetic mutations that alter cell proliferation, differentiation or death. These mutations affect three distinct categories of genes: proto-oncogenes, tumor suppressor genes and DNA repair genes. Any mutation in any of these three categories of genes can lead to the induction of a neoplastic process [2].

Tumor suppressor genes regulate the normal growth and differentiation of cells. The best known tumor suppressor gene involved in skin cancer pathology is gene p53. Changes at this level are directly related to the neoplastic process in approximately 50% of cancers. This gene is also known as the "guardian of the human genome" because of its role in regulating the cell cycle, conserving stability and preventing mutations. Moreover, the protein encoded by this gene can block the process of tumor angiogenesis occurring in response to DNA damage, DNA breaks, gene overexpression or activation of some oncogenes [3]. Interestingly, mutant p53 protein not only loses its tumor suppressor function but develops new functions: promotion of tumor cell proliferation, anti-apoptosis, angiogenesis, metastasis and metabolic changes [4,5].

2. UV Signature in Skin Cancer

The role of UV light in the pathogenesis of skin cancer has been recognized since 1894 and it is believed that this external factor induces important molecular changes, the alterations in p53 gene being even considered the "UV light signature" on human DNA (Figure 1). However, although exposure to UV type B was directly correlated with the induction of changes in p53 expression in the skin, these changes were correlated with clinical manifestations such as local erythema, a physiological defense reaction of the skin to this type of aggression [6].

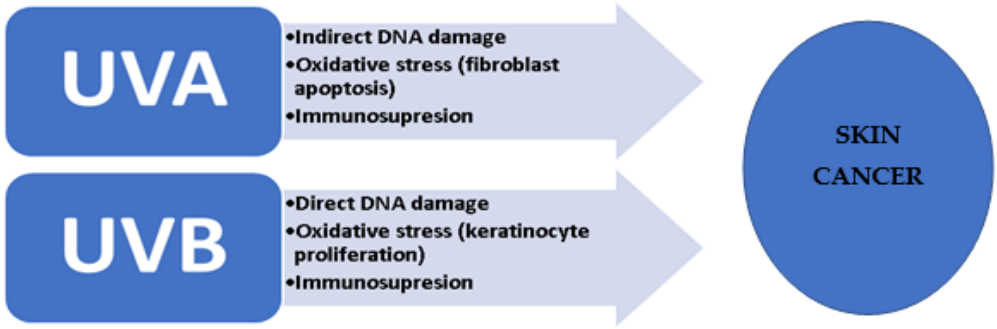

Figure 1. UV exposure and skin cancer.

In the case of melanoma, p53 gene mutations are considered late events associated with advanced stage disease, while in non-melanocytic skin cancers (NMSC), these mutations have been identified even in premalignant lesions such as actinic keratosis (AK), which is considered to be a form of in situ squamous cell carcinoma [7].

As for the incidence of these mutations, the opinions are divided; some authors believe that they are present in 92–100% of melanomas, while others argue they are present in only 7–27%. Mutations in this gene have been found in about 66% of AK cases [8,9].

The P16 gene is another tumor suppressor gene encoding the p16 protein, which is frequently inactivated in both melanocytic and non-melanocytic tumors [10].

Besides these two p53 and p16 genes, which have been studied for several years, other potential tumor suppressor genes were discovered very recently. A notable study conducted by van Kempen et al. revealed the unexpected function of the protein phosphatase 2A regulatory subunit PR70 that might act as a gonosomal melanoma tumor suppressor gene [11]. Another example could be the RASA2 gene that suffers recurrent inactivating mutations in melanoma. According to Arafeh et al. [12] RASA2, a tumor-suppressor gene that encodes a RasGAP, is mutated in 5% of melanomas. Recurrent mutations in this gene were found to increase RAS activation, melanoma cell growth and migration, while the loss of RASA2 expression was associated with reduced patient survival.

Of the proto-oncogenes, we mention RAS, the first oncogene described in association with melanoma by Albino et al. [13], with NRAS mutations present in about 15% of melanomas.

In recent decades, the attempts to identify skin cancer-associated antigens have resulted in varying conclusions, and the immunotherapy protocols are still in development. For example, vemurafenib approved by the FDA in 2011 under the name Zelboraf is a targeted therapy obtained by the study of gene mutations occurring in the process that leads to skin cancer [14].

UV radiation has long been recognized as a risk factor for skin cancer, through its multiple effects on the skin, effects that greatly contribute to the development of neoplasia by DNA damage, induction of immunosuppression or by promoting oxidative stress. Neoplasia on photoexposed areas (head, neck) is one of the most aggressive forms, with a local recurrence rate of up to about 47% [15].

UV radiation is divided into three wavelength ranges: UVA (320–400 nm), UVB (280–320 nm) and UVC (100–280 nm). UV-A radiation crosses the stratosphere, 90–95% of it

reaching the earth surface. These low-energy rays penetrate deep into the skin due to their long wavelength and lead to the occurrence of reactive oxygen species that distort the DNA; however, they are less carcinogenic than UV-B rays. The amount of UVB radiation that reaches the earth in 1–10%, but it is 100 times more mutagenic than UVA radiation. Because of its wavelength, UVB tends to damage the superficial epidermal layers, consisting of erythema, hyperpigmentation, sunburn, premature skin aging and, last but not least, carcinogenesis [16].

The process of carcinogenesis arises from oxidative stress and/or DNA damage or translational gene mutation type. Both UV-A and UV-B can cause local immunosuppression by reducing the antigen-presenting cells or by increasing the production of immunosuppressive cytokines. UV-C radiation fails to penetrate the ozone layer due to its short wavelength, so it does not reach the ground and is not involved in skin pathology [17].

The limited information about this disease and the low level of awareness of the population often make the patient not pay due attention to a change at the skin level. Even though 75% to 80% of NMSCs are located at the cephalic extremity, the physician often has no other option but to use palliative treatments in highly advanced cases, which are not candidates for curative treatment [18].

Clinical experience and the results of experimental studies have shown that skin cancer can be successfully treated by surgical removal of the lesion only in early disease stages when the prognosis is much better. On the other hand, when the patient is already in an advanced stage at diagnosis and local therapy is unfeasible, the physician turns to alternative solutions, such as inhibitors of mutant proteins [19].

It has already been proven that the expression of certain antigens varies during tumor progression; a deeper knowledge of these antigens could contribute to understanding the mechanisms of cancer progression with the main goal of developing therapeutic alternatives in the field of dermatologic oncology. All these things sped up modern medicine to move towards individualized therapy, seeking answers at the molecular level, and oncology is the field that can best exemplify this by using DNA testing in both therapeutic decisions and in evaluating patient prognosis.

3. Gene Mutations in Melanoma

BRAF is the most common mutant protein kinase found in human cancers (Table 1). The gene encoding this BRAF protein is located on the long arm of chromosome 7, at position 34 and is composed of 18 exons. BRAF gene encodes a protein belonging to the RAF family of serine/threonine protein kinases. The BRAF protein plays an important role in the RAS/MAPK signaling pathway by regulating the MAP kinase (mitogen-activated protein kinase), a protein involved in physiological processes such as cell division and growth, differentiation, secretion or even apoptosis [20].

The activation of a number of changes in cell phenotype requires several steps, by which the signal passes through a kinase cascade involved in the activation of various proteins. Kinases are enzymes involved in the transmission of different cellular signals, and therefore, any change in the RAS/MAPK signaling pathway may facilitate the neoplastic process and allow abnormal cells to divide uncontrollably.

Table 1. Gene mutations in melanoma.

Gene	Type	Incidence (%)	Type of Melanoma	Comments	Therapeutic Modalities
P53 (Benjamin et al., 2007; Xu et al., 2013)	tumor suppressor gene	92–100 or 7–27	Cutaneous	- associated with advanced-stage disease directly - correlated with the exposure to UV-type B	PRIMA-1
TP 53 (Oliver et al., 2010)	tumor suppressor gene	50	Cutaneous	- somatic mutations	PRIMA-1MET
P16 (Zhang et al., 2004; Borg et al., 2000)	tumor suppressor gene	10	Familial malignant melanoma	- loss of p16 protein expression was common event in melanoma	ABT-737 ABT-263 (oral administration) 3MR (novel suicide gene therapy)
Protein phosphatase 2A regulatory subunit PR70 (O'Connor et al., 2018)	tumor suppressor gene	1	Gonosomal melanoma	- PPP2R3B expression was lower in males than in females - independently correlated with poor clinical outcome.	SMAPs, Phenothyazines
RASA2 (Arafeh et al., 2015)	tumor suppressor gene	5	Cutaneous melanoma	- encodes a GTPase-activating protein (GAP)	MEK inhibitors
RAS (Albino et al., 1984)	proto-oncogene	15	Cutaneous melanoma	- activates the mitogen-activated protein kinases (MAPKs) and other signaling pathways involved in cell survival, proliferation and apoptosis	Salirasib
BRAF V600K (Kulkarni et al., 2017)	proto-oncogene	10	Melanoma in situ Lentigo maligna	- tumors appear over 50, in males, and the tumors often occur in the head and neck area (prone to sun damage)	Sorafenib Farnesyl-transferase inhibitors MEK inhibitors PLX4032 Vemurafenib and Dabrafenib
BRAFV600E (Kulkarni et al., 2017)	proto-oncogene	40	Cutaneous melanoma	- has been reported to be more frequent in benign than in dysplastic nevi or melanoma	
BCORL1 (Mologni et al., 2018)	tumor suppressor	10	Cutaneous melanoma	- correlated with resistance of the disease to previous effective drugs - represses E-cadherin expression via interaction with CtBP	immunosuppressive therapy Azacitidine Lenalidomide

Table 1. *Cont.*

Gene	Type	Incidence (%)	Type of Melanoma	Comments	Therapeutic Modalities
CTNNB1 (Cerami et al., 2012)	tumor-suppressor gene	23	Malignant melanoma	- is a central component of the Wnt (wingless) signal-transduction pathway	TTK inhibitors
GNA11 and GNAQ (Van Raamsdonk et al., 2010)	proto-oncogene	50–85	Uveal melanoma Non-epithelial melanocytic lesions cutaneous melanoma	- the reduction in melanoblast numbers - encode G-protein alpha subunit q and alpha subunit 11, respectively, and are paralogs	Selumetinib Sotrastaurin (AEB071)
C-KIT (Ponti et al., 2017)	proto-oncogene	11	Melanomas located in acral regions and mucosae	- resistance to anti-BRAF or anti-MEK targeted therapy	Imatinib Milotinib

BRAF gene mutations may be inherited or acquired. Inherited mutations can cause birth defects, and acquired (somatic) mutations occur later in life and are present only in certain cells. Somatic mutations cause the BRAF protein to be continuously active and to transmit messages to the nucleus even in the absence of chemical signals. Somatic mutations cause continuous activation of BRAF protein to transmit messages to the nucleus even in the absence of chemical signals. This increase in protein activity interrupts the regulation of signaling pathways. This misregulation can result in heart defects, growth problems, skeletal abnormalities and other features found in Noonan syndrome. At least four BRAF gene mutations were found in patients with Noonan syndrome [21].

Mutations in the BRAF V600 protein are found in approximately 50% of melanomas and it is estimated that approximately 8% of solid tumors contain this mutation. Of these, approximately 80–90% result from the substitution of glutamic acid for valine at position 600 (V600E) [22,23].

600K BRAF mutation occurs in about 20% of melanoma cases, and most frequently in melanoma in situ or lentigo maligna. V600E BRAF mutation is found in cancers such as hairy cell leukemia, colon cancer, papillary thyroid carcinoma, Langerhans cell histiocytoma and astrocytoma [24–26].

V600E BRAF mutations lead, by the hyperactivation of MAPK pathway, to a change in cell division rate and induce the proliferation of neoformation vessels by promoting the release of EGF (endothelial growth factor) or the overexpression of proinflammatory cytokines, such as IL-8 [27,28].

The current gold standard for detecting BRAF mutation remains direct sequencing of tumor DNA, and polymerase chain reaction is a more efficient additional method that is used successfully in such cases. In Table 2, we present the modern methods for BRAF detection; the major disadvantage is the high cost, which makes the method less accessible (Table 2).

Table 2. Modern methods for BRAF detection.

Author, Year	BRAF Detection Method	Results and Conclusion
Kiniwa et al., 2021	• Circulating tumor cells (CTCs) were isolated from peripheral blood using a high-density dielectrophoretic microwell array, followed by labeling with melanoma-specific markers (MART-1 and/or gp100) and a leukocyte marker (CD45).	• CTCs are present even in the early stage of melanoma, and the number of CTCs seems to reflect patients' responses to BRAF/MEK inhibitor treatment. • Genetic heterogeneity of BRAF may contribute to resistance to BRAF/MEK inhibitors. • The usefulness of CTC analysis for monitoring responses to targeted therapies in melanoma patients, and for understanding the mechanism of drug resistance.
Marsavela et al., 2020	• Predictive value of circulating tumour DNA (ctDNA) Droplet digital polymerase chain reaction assays were designed for ctDNA detection. • Whole exome sequencing of ctDNA was also conducted in 9 patients commencing anti-PD-1 therapy to derive tumour mutational burden (TMB) and neoepitope load measurements.	• Trend of high TMB and neoepitope load in responders compared to non-responders. • Changes in ctDNA can serve as an early indicator of outcomes in metastatic melanoma patients treated with systemic therapies and, therefore, may serve as a tool to guide treatment decisions.

Table 2. *Cont.*

Author, Year	BRAF Detection Method	Results and Conclusion
Marczynski et al., 2020	• To standardize a liquid biopsy platform to identify hotspot mutations in BRAF, NRAS and TERT in plasma samples from advanced melanoma patients and investigate whether it was associated to clinical outcome. • Digital polymerase chain reaction using tumor cell lines for validation and determination of limit of detection (LOD) of each assay and screened plasma samples from healthy individuals to determine the limit of blank (LOB).	• We established a specific and sensitive methodology with a LOD ranging from 0.13 to 0.37%, and LOB ranging from of 0 to 5.201 copies/reaction. • Somatic mutations occurred in 17/19 (89%) patients, of whom seven (41%) had ctDNA detectable their paired plasma. ctDNA detection was associated with shorter progression free survival ($p = 0.01$). • Data support the use of ctDNA as prognosis biomarker, suggesting that patients with detectable levels have an unfavorable outcome.
Zocco et al., 2020	• We investigated whether extracellular vesicle (EV)-associated DNA (EV-DNA) has value as an alternative source of circulating BRAFV600E. • Clinical practice-compatible protocol for the isolation of EV-DNA and assessed BRAF gene status on plasma samples from metastatic melanoma patients at the beginning and during BRAFi therapy.	• The protocol improves the detection of BRAFV600E gene copies in comparison to the reference protocol for ctDNA isolation. • EVs are a promising source of mutant DNA and should be considered for the development of next-generation liquid biopsy approaches.
Colombino et al., 2020	• To compare BRAF mutational testing performed by conventional nucleotide sequencing approaches with either real-time polymerase chain reaction (rtPCR) or next-generation sequencing (NGS) assays in a real-life, hospital-based series of advanced MM patients.	• Our study evidenced that rtPCR and NGS were able to detect additional BRAF mutant cases in comparison with conventional sequencing methods. • Therefore, we argue for the preferential utilization of the aforementioned assays (NGS and rtPCR) in clinical practice, to eradicate false-negative cases and improve the accuracy of BRAF detection.
Herbreteau et al., 2020	• The purpose of this study was to determine whether the detection of ctDNA, based on the identification of BRAF and NRAS mutations before systemic treatment initiation, was associated with the prognosis of metastatic melanoma. • Tested for the presence of BRAF and NRAS mutations in circulating DNA before treatment initiation, using the Cobas BRAF/NRAS Mutation Test (Roche).	• The expected mutation was detected in the plasma of 34/68 patients (50% sensitivity). • ctDNA detection was associated with AJCC stage, along with the number and nature of metastases. • ctDNA was less frequently detected in NRAS-mutated than in BRAF-mutated melanoma (36% and 66%, respectively).

Another limitation of this screening method is the existence of melanomas that do not contain canonical BRAF-mutations. One good example could be the study conducted by Nikolaev et al. regarding a patient with two metastases that were the hallmark of sample-specific mutations was absent. Mutations in MAP2K1 and MAP2K2 genes (MEK1 and MEK2, respectively) were found, resulting in higher resistance to MEK inhibitors because of the constitutive ERK phosphorylation [29]. Because these mutations can occur in 8% of melanomas, with negative consequences on the therapy (resistance to conventional chemotherapy), they must be taken into account.

Given the cancer-related dysregulation of different signaling pathways, for satisfactory clinical outcomes, the ideal therapy should be a combination therapy targeting different sites of several signaling pathways. This is supported by the fact that dacarbazine is effective only in 15–20% of patients with melanoma [30].

Besides the extensive studies regarding the BRAF mutations, researchers recently found other gene mutations that might be involved in the pathophysiology of melanoma and NMSC. An example could be the ER (estrogen related receptor) gene, studies of which have just begun, following the results of studies that showed a lower incidence of MM in women than in men. However, only few articles are available on this topic, the effects of ER gene in the modulation of metabolism and cancer being still intensively studied [31].

Tp 53 is another somatic mutation found in about 50% of cutaneous melanoma. Moreover, the combination of germline TP 53 and BRCA 1 (chromosome 7)/2 (chromosome 13) mutation may have played a role in melanoma formation [32]. There are also other genes that were found to suffer mutations that could lead to the appearance of skin cancer. According to Berger et al. [33], NRAS, ROS1, NTRK and ALK are only a few examples of genes that might be used as targets of the therapy in the near future. Moreover, alterations in some genes such as neurofibromin 1 or RAC 1 gene have been detected, their clinical relevance still to be revealed.

Recently, one study showed the possibility of the implication of another gene mutation in the pathology of skin cancer, especially when it comes to vemurafenib-resistant melanoma. Mologni et al. [34] discovered during their research activity the importance of the BCORL1 gene mutation. Found on the short arm of the X chromosome, in position 26, BCORL1 acts as a transcriptional corepressor, which may specifically inhibit gene expression when recruited to promoter regions by sequence-specific DNA-binding proteins such as BCL6. This repressive function may be mediated at least in part by histone deacetylase activities. The gene seems to be very important in the therapy of skin cancer, its mutations being correlated with resistance of the disease to previous effective drugs. A possible intervention for this class of mutants might be the association of vemurafenib with sorafenib, a pan-RAF inhibitor that seems not to be affected by the usual BRAF and BCORL1 mutations.

Another mutation found especially in melanoma is the alteration of CTNNB1 gene, known as the gene that encodes the protein catenin beta-1 (β-catenin). Somatic mutations have been found in up to 23% of the malignant melanoma cell lines [35], while other studies show that these mutations are rare in uveal melanomas [36]. Moreover, genes such as GNA11 and GNAQ can be mutated in up to 50% of melanomas, especially in uveal melanomas, which are related more to ophthalmology than to dermatology [37].

When it comes to mutations in DNA repair genes, studies are still at the very beginning. A study by Chae et al. [38] illustrates a long list of possible genes such as MLL3, POLQ, SLX4 and many more that might be altered and that could determine the apparition of different types of cancers. However, strong evidence found from pieces obtained after biopsy that were afterwards immunohistochemically analyzed are still to come in the near future.

In terms of UV exposure, TYRP1 (tyrosinase-related protein 1) and miR-204-5p (a member of the miRNA family; it is down-regulated and functions as a tumor suppressor in various types of human tumors) were highly expressed in patients with cutaneous melanoma living at higher altitudes [39].

Finally, we must not forget the C-KIT gene mutation that is retrieved in 11% of patients with melanoma. Frequently, C-KIT-mutated melanomas are located in acral regions and mucosae [40]. It is important to mention that these are distinctive clinico-pathological entities that require special therapy and have a different prognosis.

4. Gene Mutations in NMSC

Besides melanoma, there is also the heterogeneous group of NMSC, where two main entities are found: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Each has its own genetic and epigenetic pathway of development. While the PTCH1 gene mutation is thought to be the most common cause of the genesis of BCC by inadequately activating the Hedgehog pathway, in SCC, the pathophysiology is still not clearly explained. Activation of RAS is pretty common in human SCC, but mutations in other genes such as XPC are also acknowledged [40–45]. According to de Feraudy et al. [40], the loss of expression through deletions in the 3p chromosome region and mutations of the XPC gene may happen early during skin carcinogenesis. However, their exact mechanism of action in the tumorigenic process remains unclear.

In contrast to melanoma, in NMSC, other potential oncogenic gene mutations were found. For example, an analysis conducted by Tagliabue et al. [41] came to the conclusion that there is a strong correlation between MC1R variants and the development of NMSC. More precisely, V60L, D84E, V92M, R151C, R160W, R163Q and D294H variants of MC1R play a role in the promotion and the sustaining of NMSC development (Table 3) [42–55].

Because of the abnormal sonic hedgehog signaling in BCC, which is caused by the PTCH1 mutation, up-regulation of other molecules such as GLI1 and GLI2 is often observed. The predominance of either GLI1 or GLI2 in relation to the development of BCC is still unclear; however, there seems to be a positive feedback loop in which GLI2 directly activates the expression of GLI1. Moreover, there is a small number of sporadic BCCs where SMO mutations are found, also resulting in the up-regulation of this pathway [42,56–61].

Not only the classical pathways are meant to be targeted in skin cancer therapy. Nowadays, due to the increasing resistance of tumor cells to conventional chemotherapy, single-target inhibitors are no longer the ideal mean of treatment. This is why multi-target inhibitors could be an attractive alternative, having shown efficacy. One example is the novel therapy implemented by Singh et al. [43] that consists of the combination of doxorubicin and celecoxib that inhibits both the protein kinase B (AKT) and the cyclooxygenase-2 (COX-2) pathway.

Finally, we analyzed the articles published in 2021–2020 on BRAF detection, and we found a tendency of new methods to detect BRAF mutation in circulating tumor DNA, which is a more feasible method than isolating it from FFPE samples of melanoma patients. The methods mentioned in Table 3 (e.g., droplet PCR, COBAS RT PCR) have the advantage of being clinically standardized and validated, making it possible to compare results obtained from different medical centers and countries, as was possible for HPV detection [44,62]. With these new molecular approaches, we hope for optimal detection of melanoma patients with BRAF mutation who are eligible for targeted therapy.

Table 3. Gene mutations in non-melanoma skin cancer.

Gene/Gene Product	Type	Incidence (%)	Type of Skin Cancer	Comments	Therapeutic Modality
P53 (Loureiro et al., 2020)	tumor suppressor gene	66, 50	Actinic keratosis SCC	- identified even in premalignant lesios - encodes p53 proteine, a well-known tumor suppressor - causes the cell cycle to stop in the presence of DNA damage	Analogous to melanoma therapy
P16 (Zhang et al., 2004)	tumor suppressor gene	41 non-metastatic and 30 metastatic tumours squamous cell carcinoma	SCC	- frequently inactivated in human cancers, consists of two overlapping genes that encode two unrelated proteins, p16INK4a and p14ARF, functioning as cell cycle inhibitors	Analogous to melanoma therapy
PTCH1 (Noubisi et al., 2014; Hasanovic et al., 2018)	tumor suppressor gene	mutations PTCH in 90 sporadic BCC	BCC	- overexpressed in BCC - induces GL 1 promotor-driven luciferase activation in keratinocytes	PTCH1 drug efflux antagonist
RAS (de Feraudy et al., 2010)	proto-oncogene	33	SCC Keratoacanthoma	- the molecular mechanism is consistent with the paradoxical activation of MAPK signaling and leads to accelerated growth of these lesions	Anti-EGFR agents
XPC (Dupuy et al., 2013)	DNA repair gene	10–90 (more prevalent in Africa)	Xeroderma pigmentosum	- early during skin carcinogenesis	Meganucleases, zinc-finger nucleases or TALE nucleases
MC1R (Tagliabue et al., 2015)	DNA repair gene	24–67 (66–67 for European origin)	BCC SCC	- important role in normal pigmentation	BMS-470539

Table 3. *Cont.*

Gene/Gene Product	Type	Incidence (%)	Type of Skin Cancer	Comments	Therapeutic Modality
GLI1 and GLI2 (Pellegrini et al., 2017)	transcription factor	17	BCC Melanoma	- frequently overexpressed - increased expression following mutations at any level of the HH signaling pathway (PTCH1, SMO, SUFU) - GLI transcription factors regulate angiogenesis - GLI 1 activity is positively influenced by KRAS, TGF, AKT and negatively by p53,PKA, PKC	TAK-441
TP53 (Pellegriniet al., 2017)	tumor suppressor gene	50	BCC, CSC	- TP 53 inactivation is detected in 50% of human cancers, including all skin cancers - inactivation of TP 53 gene is the second most common event associated with BCC pathogenesis	APR-246 COTI-2
SMO (Yao et al., 2020)	proto-oncogene	10–20	BCC	- coupling to G protein Gαi in the regulation of Hedgehog	SMO inhibitors: LDE225, LEQ506, BMS833923
MYCN (Wu et al., 2021)	proto-oncogene	30	CSC, Melanoma	- member of the MYC family of transcriptional activators, downstream effector of the HH pathway - identified in 30% of BCC - influences cell growth, proliferation, differentiation and apoptosis	DFMO (2-(difluoromethyl)ornithine), an ODC inhibitor (ornithine decarboxylase)

Table 3. *Cont.*

Gene/Gene Product	Type	Incidence (%)	Type of Skin Cancer	Comments	Therapeutic Modality
CRD-BP (Noubisis et al., 2014)	multifunctional RNA binding protein, anti-apoptotic,	10–15	BCC, CSC Melanoma	- correlates with the activation of both WnT and Hh signaling pathways - induces abnormal cell proloferations and suppression of apoptosis - controls the activity of other genes involved in proliferation, invasion and inhibition of apoptosis (TrCP1,c-myc)	Dacarbazine VBN, TMZ
MCP-1 CCL2 (Wells et al., 2003)	chemokine with potent monocyte chemotactic activity	30–40	Melanoma	- member of C-C family of chemokines - involved in the chemotaxis of monocytes, T lymphocytes and skin dendritic cells - expressed and secreted by keratinocytes - MCP-1 expression may be induced by TNF or INF treatment	MCP-1-blocking antibodies CCR-2B antagonists
PPP6C (Pellegriniet al., 2017)	tumor suppressor	15	CBC	- mutations were detected in 15% of BCC - regulates cell cycle progression in humans cells by controlling cyclin D1, inactivating RB1 - participates in the activation LATS1	DMBA/TPA (12-Otetradecanoylphorbol 13-acetate)
Jak3 (Wells et al., 2003)	cytoplasmic non-receptor tyrosine kinases.	18–21	CSC of the head and neck Melanoma	- differential hybridization showed induction of tyrosine kinase 3 (Jak3) in BCC compared to normal skin - associated with keratinocyte differentiation	JAK inhibitors (Tofacitinib)

Table 3. *Cont.*

Gene/Gene Product	Type	Incidence (%)	Type of Skin Cancer	Comments	Therapeutic Modality
E2F5 (Heller et al., 2013)	tumor suppressor. transcription factor	10	CBC	- recent evidence shows that E2F5 contributes to tumorigenesis - has a stable role by inhibiting MYC	Paclitaxel
DAPK1 (Heller et al., 2013)	tumor suppressor	60	Head and neck cancers	- a tumor suppressor with increased expression in BCC - inhibits ERK - affects the Ras-MAPK and TGF-β pathways	Decitibane, gliotoxin and paclitaxel
TERT (Jager et al., 2016; Pellegrini et al., 2017)	ribonucleoprotein polymerase	39, 22	Basal cell carcinomas, cutaneous melanomas squamous cell carcinoma (tongue and skin)	- TERT promotor mutations are found at a high frequency in many cancers (melanoma, non-melanoma skin cancer, bladder cancer, glioma) - associated with UV exposure	oncolytic virotherapy

5. Conclusions

The continuous study of the molecular pathophysiology of skin cancer could lead to a better understanding of the mechanisms underlying the neoplastic process, with the translation of possible benefits in the therapeutical field of this disease. The studies conducted so far offer a limited insight into the complexity of the oncogenic mechanisms involved in skin cancer; this field remains open for further investigations and new targeted therapeutic strategies.

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