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Overview of Skin Cancer and Risk Factors

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Abstract: Skin cancer is a complex and serious health condition with high metastatic abilities and comprises two types including melanoma, the most dangerous type, and non-melanoma skin cancer, such as basal cell carcinoma and squamous cell carcinoma. Skin cancer has a high prevalence ratio and millions of mortalities worldwide. Multiple risk factors account for the initiation, development, progression, and metastasis of skin cancer such as ultraviolet radiations, X-rays, immunocompromised situations, skin lesions, and alteration in genetic makeup. *CEP55, FOXM1b,* and *HELLS* genes play critical roles in the progression of the cell cycle, cell proliferation, cell division, DNA replication, and repair system. The overexpression of these genes involves complex molecular mechanisms and is linked with the development and progression of multiple cancers including skin cancer. This review article summarized the history and recent advancement of risk factors for skin tumorigenesis development and progression.

Keywords: Skin cancer; Overexpression; Risk factors; HELLS; CEP55; FOXM1b

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1. Introduction

Skin is the outer covering and largest organ of the human body. It is like a barrier that prevents the body from UV light and other toxic substances to balance the temperature of the human body. The skin consists of three layers dermis, epidermis, and hypodermis [1]. The outer layer of the skin is the epidermis, the dermis is the skin's inner layer and the deep layer of fat is the hypodermis. The skin protects organs from microbes and regulates the temperature of the body [2]. There are three layers of skin epidermis which is the outermost layer, beneath the epidermis the layer is dermis and the third layer is hypodermis. Mostly all of the human skin is coated with hair follicles while some can appear hairless. Generally, there are two kinds of skin, hairy and hairless. The epidermis is composed of three systems of cells which are keratinocytes and Langerhans, cells in the Malpighian layer, and melanocytes in the basal layer [3]. The function of the keratinocyte cells is to synthesize keratin, a thread-like protein with a very protective role. The variation in the layer's thickness depends on the region of the body. For example, the epidermis layer in the eyelid has a thinnest less than 0.1 mm whereas the thickest layer presents in the sole and palm of feet measuring up to 1.5 mm [4].

The dermis is the middle layer that is beneath the epidermis and is made up of collagen protein which is fibril in structure. The dermis layer is present on the subcutaneous tissue which consists of little projections of fat cells called

lipocytes. The dermis comprises three different cells: mast cells, macrophages, and fibroblasts [5]. Hypodermis lies beneath the dermis and is also called subcutaneous tissue. The purpose of its attachment to skin is to underline muscle and bone and supply through nerve and blood vessels. This layer consists of elastin and loose connective tissue. They consist of different cells adipocytes, fibroblasts, and macrophages. The hypodermis layer consists of about 50% of fats and fats serve as a protection and insulator for the body. A hormone produced by lipocytes called leptin regulates body weight [6].

Skin cancer was discovered by a French physician Theophile Hyacinhe Laennec (1781–1825), in the 1800s and he was also the inventor of the stethoscope. For the first time, he described autonomous diseases known as black tumors. An old woman was affected by "Cancer Anthracine" at the age of 52 years and a small black spot appeared which bigger with time. The patients later produced metastasis on the skin and due to the tumor, the women died. Like this, different special cases can be proved by English and German authors [7]. The cancer that arises from the skin is called skin cancer and it arises due to the invasion of abnormal cells to other regions of the body [8]. Non-melanoma are then categorized into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSC grows slowly and can destroy the tissues near it and cannot spread into another region. However, melanoma is the most invading and aggressive skin cancer. More than 90% of skin cancers are caused by UV light, as exposure to UV light increases the risk of skin cancer [9].

The incidence rate of skin cancer varies by age and histological type. The most common skin cancers are melanoma and non-melanoma consisting of basal cell carcinoma and squamous cell carcinoma. Melanoma is the 19th and non-melanoma is the 5th most common cancer in the world [10]. Skin cancer is more common in fair-skinned people and the occurrence of skin cancer is associated with skin color and geographical zone. In whites, melanoma is more common than in other ethnic people. The developing rate of melanoma is 2.4% in Caucasians, 0.5% in Hispanics, and 0.1% in blacks [11]. Melanoma is more common in males than in females. Malignant melanoma presents more in females as compared to males after age 50 but overall melanomas are more common in men. At the age of 15–29, melanomas are increasing faster in females than males [12]. The sum of all data showed a continuous increase in the incidence of skin cancer in Europe, Canada, and the USA during the last decades. In New Zealand, the highest incidence rate has been reported with 50 cases within 100,000 persons, 48 cases per 100,000 persons in Australia, followed by 48 cases per 100,000 in the US, and 13.2 cases per 100,000 in Europe [13–14]. In Asia, skin cancer is approximately 2 to 4 percent of all cancers. The frequency of skin cancer is very low in the Pakistani population as compared to the Western world. However non-melanoma skin cancer is increasing in the Asian population including Pakistan [15]. Skin cancer will double in the next 30 years in the Asian population. Among the 80,000 deaths that occurred in 2010 due to skin cancer, 49,000 were due to melanoma while 31,000 were due to non-melanoma skin cancer [16].

BCC occurs mostly on open regions of the body like the neck or face and it appears as a waxy bump, a brown or fleshed-colored scar-like lesion, and a bleeding sore that heals and reappears. SCC also occurs in sun-exposed areas and most likely in dark-skinned people. It may appear as a firm, red nodule and a flat lesion with a scaly, crusted surface. Melanoma can grow in any place on the body, in any case, typical skin or in a current mole that gets malignant [17]. Melanoma frequently shows up on the face of influenced men. In females, this sort of malignant growth frequently occurs on the lower legs. It may appear as a brownish spot with black dots, a mole that changes in color and size, a small lesion with an irregular border, a painful lesion that itches or burns, and dark lesions on palms, soles, fingertips, or toes [18].

2. Grades of skin cancer

Skin cancer is categorized into stages like other cancers. The World Health Organization (WHO) specified

the grading criteria for skin cancer and it is graded from I to IV [19]. Some of the main characteristics of these tumors are listed below in **Table 1.**

Table 1. Main characteristics of skin tumors (Grade I to IV)

Grade	Characteristics
I	They mostly look like normal cells/tissues and are considered low-graded tumors and are called well-differentiated.
II	These tumors have a slightly abnormal appearance and are called moderately differentiated.
III	These tissues look very abnormal and poorly differentiated. Grade 3 is considered a high grade.
IV	They look more abnormal than other cells and tissues. They are higher grades and spread faster than other lower grades.

3. Types of skin cancer

Skin cancer is grouped into malignant melanoma and nonmalignant skin cancers. Non-melanoma consists of basal cell carcinoma and squamous cell carcinoma. Research estimates have shown that BCC and SCC affect more than 3 million Americans a year [20]. Some of the common groups of skin cancer are shown in **Table 2**.

Table 2. Major types of skin cancer

Cancer types	Description	Appearance	Severity	Occurrence
Basal cell carcinoma	Develop in the basal cell of the skin epidermis	Non-lethal, open sour, small pink growth	Less severe than other types	Most widely occurred cancer
Squamous cell carcinoma	Develop in the squamous cells of the skin	Just like wart scaly patches, pen sores	More severe than the BCC	Less occur than BCC
Melanoma	Develop in the skin cell called melanocyte	Multi-colored, asymmetrical, size may reach 6mm	The most severe type termed a deadly skin cancer	It occurs rarely

BCC is the most common type of skin cancer and is also known as basal-cell cancer. BCC has a slow-growing rate and infects the tissue near it, but not spread to other areas. Globally, BCC represents 32% of all cancers and 80% of all skin cancers. It is considered that BCC originated from trichoblasts which are follicle-sebaceous-apocrine germ. On the other hand, one contention is that basal-cell carcinoma is trichoblastic carcinoma [21]. DNA damage due to exposure to the sun results in the formation of dimer. Most mutated regions are removed during the DNA repair mechanism but not all crosslink-caused mutation. More than 99% of people with BCC are White, and more than 95% are aged over 40 years old. Half of BCC patients are men [22].

The 2nd most common skin cancer is squamous cell carcinoma, which is also called cutaneous cell carcinoma and makes up about 20% of NMSC. SCC has more spreading ability than BCC to distinct regions. When limited to the peripheral layer of the skin, a precancerous or in situ type of SCC is known as Bowen's sickness [23]. They are created from the flat squamous cells that make up a lot of the epidermis, the peripheral layer of the skin. This sort of skin malignant growth is generally found on territories of the skin that have been exposed to the sun, for example, the neck, ears, face, or the back of the hand. However, they may be created in different regions, for example, in scars, skin ulcers, or the genital region. According to the 2015 GBD report about 2.2 million people have SCC and about 51,900 deaths occurred globally [24]. Melanoma is a type of skin cancer that develops from a pigment-containing cell known as melanocytes. Melanoma is also called malignant melanoma. They commonly occur on the legs in females and on the back in males. Approximately 25% of

melanoma develops from moles. Changes that occur in mole such as an increase in size, color changes, irregular edges, and itchiness indicate melanoma. Melanoma is caused by UV light exposure and low pigment levels [25].

4. Risk factors

Multiple factors are responsible for skin cancer such as UV exposure, hereditary factors, and environmental risk factors. Skin cancer is also caused due to genetic polymorphisms. Skin cancer is more common in older than young people. Mostly non-melanoma skin cancer appears after 50 years of age. In recent years, skin cancer dramatically increased in people after 65 years of age. After 70 years of age, Merkel cell cancer is most common. Skin cancer also develops in younger people, when they have fair skin [26]. In humans, the most exposed organ to ultraviolet radiation (UVR) is the skin. DNA damage, a mutation that occurs in genes, and other factors that play a role in the photoaging of skin are affected by ultraviolet radiation [27–28]. UVR reaching the surface of the earth is influenced by several factors like altitude, latitude, weather conditions, and UV light elevation. There are two main types of ultraviolet rays UVA and UVB. Rays that are passed into the skin deeper are UVA than UVB such as elastosis. There is indirect damage from UVA rays to DNA, mediating the formation of free radicals and damage to cellular membranes. Erythema or sunburn is caused due to UVB rays [29]. DNA damage will occur even on low exposure to UVA/UVB. Before the age of 20, most skin damage was from UV light, but the effects will only appear many years later. People who work outdoors have a higher risk of developing skin cancer because of more exposure to the sun. UV rays directly affect the p53 suppressor gene, which is found mutated in melanoma [30]. The incidence of melanoma correlates with the annual average amount of UV radiation. The intensity of UV will be greater on and near the equator. Latitude shows a direct relationship with the incidence of melanoma. Melanoma will be greater in those individuals who are living in high-altitude regions due to greater UV influences [31]. In women, melanoma is found frequently on the legs and commonly on the back of men due to UV exposure. People living in the high UV radiation of Australia have a higher risk of melanoma than those who are living in Northern Europe and migrated there at 10 years of age or older [32].

Every stage of carcinogenesis is affected by UV exposure so it is a complete carcinogen. After high exposure to UV, apoptosis of keratinocytes led by the pathway p53/p21/bax/BCL-2 followed by a hyperproliferative phase, resulting in epidermal hyperplasia. Exposure to solar radiation which is nonionizing specifically UVB and UVA is an important risk factor in the pathogenesis of BCC [33]. UV radiation of keratinocytes increases the production of the gene proopiomelanocortin (POMC) and α-melanocyte-stimulating hormone (αMSH), which is highly involved in pigmentation of skin whether skin produces red-yellow pigment (pheomelanin) or brown-black pigment (eumelanin) [34]. UV radiation not only damages the DNA directly but also indirectly by producing UV-induced immunosuppression and free radicals. UV radiation affects Langerhans cells (LCs) which result in the loss of dendritic network form in the epidermis [35]. LCs are damaged by UV which induces regulatory T cells (Tregs) to produce IL-10, an immune-suppressive cytokine. Dermal fibroblasts and keratinocytes produced IL-33 which is why mast cells (MCs) in the skin increase response to UV radiation [36]. Proteoglycan (PGs) are formed from GAG strains and protein scaffolds. PGs take part in the structuring of collagen fiber, and it affects the formation and separation of extracellular matrix. Heparan sulfate proteoglycans (HSPG) play a role in the extracellular matrix [37]. Proteoglycan strain cleaves by heparanase which increases the tumor cell growth, resulting in the formation of oligosaccharides that enhance angiogenesis and growth factors production, causing inflammation and cell proliferation [38]. Therefore, heparanase is involved in the formation of BCC and SCC. Discontinued UV exposure might be associated with melanoma and BCC appearance and continuous UV exposure is related to SCC. UV exposure affects the expression of p53 which changes in both SCC and AKs [39].

Different studies have shown that X-rays also affect the pathogenesis of NMSC. A study reported that the skin cancer risk is increased due to therapeutic ionizing radiations (IRs), like X-rays. It has been reported that radiation therapy for acne can increase the risk of new BCC [40]. Those who received radiation therapy at an early age have a higher risk of NMSC [16]. The dormancy period between the development of NMSC and first exposure is at least 20 years, although the dormancy effect differs based on treatment age and therapy types received [41]. Production of radicals or bond-breaking is due to the ionizing radiation absorption that leads to damage in cellular molecules. Double (DSBs) or single bond breaks are produced due to IR exposure. Cell death is caused by double-stranded breaks [42]. After DSBs, H2AX histone is converted to a γ-H2AX phosphorylated form in the involved region to repair the damage. Different studies have shown that cellular mass could be increased after cellular damage due to P53 accumulation. Apoptosis, DNA repair, or arrest of the cell cycle results in P53 accumulation [43].

Gamma, beta, and alpha are different types of cutaneous human papillomavirus (HPV). In immunosuppressed patients, beta-HPV plays a role as a cofactor in SCC. Different studies have shown that in SCC lesions DNA is detected in multiple beta-HPV types [15]. Beta-papilloma virus plays a role in tumorigeneses of SCC, changing cell cycle progression, repairing DNA, and surveillance of the immune system resulting in the expansion of keratinocytes [44]. Different studies have shown that some alpha-HPV is identified in SCC. HPV77 is detected in cutaneous lesions of immunosuppressed patients. However, in SCC, the exact role of HPV remains unclear because, in normal skin samples of SCC patients, the DNA of HPV has also been found [45]. In the rise of skin cancer, the involvement of HPV infection was described by Lutz and Lewandowsky based on Epidermodysplasia verruciformis (EV) for the first time. EV is a heritable disease characterized by specific types of HPV, called EV-HPV types, which are now termed β-HPV types [46]. The risk of causing SCC is likewise expanded by exposure to cancer-causing chemicals, overall arsenic. In vitro arsenic exposure results in an increase in the expression of many proteins, such as keratin 7 and keratin 9. On the other hand, the involucrin production is reduced. Inflammatory pathways were associated with these proteins which affect the growth of skin neoplastic, such as nuclear factor (NF)-κB and tumor necrosis factor (TNF)-α [47]. Previous studies have shown that a member of the transmembrane 4 superfamily CD151, increases the carcinogenesis of skin and induces SCC development. Therefore, it has been concluded that inflammation causes an increase in carcinogenesis by testing animal models with chemicals [48].

In carcinogenesis, immunosuppression plays the main role in NMSC development. Earlier studies have shown in immunosuppressed patients, that many class I and II of (human leukocyte antigen) HLA allele groups were related to SCC. However, many studies have not proved this association. A study has observed that there is no association between SCC and HLA-A*11 [49]. It has been reported that there is no association found between SCC and HLA-DRB1/01 in immunosuppressed patients, opposite to the association found positive in immunosuppressed patients [50]. It has been reported that in SCC, the heterogeneous expression of protein class I HLA may also explain why immunosuppression raises the risk of BCC to 10-fold, but SCC up to 65-fold. Indeed the pathogenesis of SCC may be better controlled by immune surveillance because of the partial expression of protein I HLA, in comparison to BCC, wherein BCC the protein class I HLA is completely absent [51]. Therefore, this lost insusceptible observation shows that immunosuppression would influence SCC pathogenesis more than that of BCC. In this way, research suggested that the unusual expression of the HLA-G protein on the outside of SCC malignant growth cells in immunosuppressed patients was taken into consideration. The immunomodulatory impacts of HLA-G under ordinary physiological conditions are very much reported [52]. HLA-G in early-stage tissues, grown-up resistant special organs, and hematopoietic cells give inhibitory signs to natural killer cells (NKC) and T cells. Subsequently, HLA-G articulation on SCC tumors

could permit tumoral cells to contrarily manage NK and T lymphocyte-interceded obliteration. Moreover, it has been accounted for that HLA-G articulation was available in different malignant growths (melanoma, colon, breast, lung, and renal), and that melanoma cell lines communicating HLA-G isoforms had repressed cytotoxic reactions from NK and T-cells [53]. Besides, UV radiation has suppressive effects on skin immunity. It has been reported that lesions such as cyclobutane pyrimidine dimers (CPDs) are immune-suppressive and are induced by UV radiation [54]. Furthermore, other molecules are stimulated by UV radiation with immunosuppressive characters like prostaglandins, platelet-activating factors, reactive species of oxygen (ROS), and IL-10. Moreover, memory T cells, cytotoxic T cells, and mast cells are inhibited by UV radiation and activated by the natural killer cells, T lymphocytes, and regulatory B lymphocytes. All these findings highlight sharply the clear relationship between UV radiation and immunosuppression [55–56].

Changes occur in DNA that affect gene expression through acetylation, methylation, and phosphorylation. These changes play an important role in apoptosis, cell division, cell proliferation, growth, and tumorigenesis [57]. There are several epigenetic risk factors for skin cancer. Changes occur in some genes increasing the risk of skin cancer. Cyclin Dependent Kinase Inhibitor 2A (CDKN2A) also called P16 is the best-known gene that associates the higher risk of melanoma. There are other genes like MC1R, MITF, and TERT genes that are associated with a higher risk of skin cancer [58]. About 5%–10% of skin cancer cases are inherited. There are 50/50 chances of skin cancer if the patient has a defined genetic mutation. One type of melanoma caused by hereditary are called familial atypical mole-melanoma syndrome (FAM-M syndrome), caused by an alteration in the CDKN2A gene on chromosome 9. Mutations in p16 result in unregulated cell growth and have an increased lifetime risk of developing melanoma [59–60].

5. Role of CEP55, FOXM1b, and HELLS genes in skin cancer

Centrosomal protein 55 (*CEP55) is a gene that encodes the protein CEP55* and plays an important role in cytokinesis. The upregulation or downregulation of *CEP55* has resulted in cytokinesis problems and increasing multinucleated cells. The growth of cancer cells has been increased due to overexpression of *CEP55* [61]. The *CEP55* gene is located on chromosome 10q23.33, extents 32.5kb of genetics distance, and forms 70-kDa proteins comprising 464 amino acids which are translated by 9 exons. As for the cytogenetic location of *CEP55*, it is a member of the centrosome and mid-body associated protein family, and it takes part in the cytokinesis process. Much evidence has shown that *CEP55* was overexpressed in multiple tumors [62]. Overexpression of *CEP55* may increase the migration, invasion, and proliferation of tumor cells. In different oncogenic processes the main role played by the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway, includes apoptosis, differentiation, cell proliferation, invasion, epithelial-mesenchymal transition (EMT), and migration [63]. Different studies have shown that there is an interaction of other molecules to signal the PI3K/Akt pathway that may regulate the biological behavior of cancerous cells. Previous research demonstrated that in ESCC, *CEP55* is overexpressed. They showed that *CEP55 increases the proliferation of cells* in-vivo and in vitro, regulates migration and invasion of cells, and induces ESCC cells to undergo EMT via the PI3K/Akt pathway [64]. The knockdown of *CEP55* can significantly inhibit viability and tumor cell proliferation and result in tumor cell death. It has been determined that EP55 is an antigen related to tumors as well as a cancer-testis antigen. Testis-specific proteins that are typically expressed mostly in the testes but become additionally expressed in malignancy are known as cancer-testis antigens [65]. According to some current studies, CEP55 influences the PI3K/AKT signaling pathway and promotes cancer. An increasing body of research shows a link between CEP55 overexpression and the onset and spread of several malignant tumors, such as lung,

stomach, and breast cancers. When CEP55 is knocked down, tumor cells may experience severe viability and proliferation inhibition or possibly die. It has been shown that liver patients with overexpression of CEP55 may have a poor prognosis [66].

Forkhead box M1b (*FOXM1b*) gene is present on chromosome 12p13.13 and is made up of 10 exons. Due to the splicing of Exon Va and VIIa, *FOXM1* gives rise to 3 isoforms which are *FOXM1a, FOXM1b, and FOXM1c. FOXM1a* contains both Va and VIIa which is why *FOXM1a lacks* transactivational ac tivity [67]. Both *FOXM1b* (which lacks either exon) and *FOXM1c* are transcriptionally active. It has been suggested that *FOXM1b* is present in cancer cells and has a high transforming potential. *FOXM1b* is involved in transcriptional activation and is expressed in the testes and skin. The expression of *FoxM1* in primary breast cancer, basal cell carcinomas, and hepatocellular carcinoma is up-regulated [68–70].

There are three major domains of *FOXM1b*, consisting of the N-terminal repressor domain (NRD), FKH domain, and Transactivation domain (TAD). FKH plays a role in the activity of DNA binding whereas NRD helps in FOXM1b auto-regulatory activity. The structure of FKH domain of *FOXM1b* containing three α-strands (S1, S2, S3), three β-helices (H1, H2, H3), and two loops or wings (W1, W2) and arranged them in H1–S1–H2–turn–H3–S2–W1–S3–W2 order. In three alternatively spliced exons, FKH consists of two spliced exons. The absence or presences of these exons affect the specificity of DNA binding [71]. In humans, FOXM1a, b, and c are the variants. *FOXM1b* (also known as HFH-11B, FKHL16, Trident, Win, MPP2, MPM2) contains no additional exons. *FOXM1b* is transcriptionally active. The binding affinity of DNA in *FOXM1b* is higher than other variants [72]. The only isoform that was found showing cell cycle-dependent mRNA expression pattern in two different human cell lines is *FOXM1b*. It is expressed in B and T lymphoid, erythroid cell lines, myeloid cell lines, and different carcinoma cell lines. The function of *FOXM1b* is to regulate the expression of genes in the cell cycle. *FOXM1b* is expressed during the G1 phase and keeps an invariant transcript and level of protein during the G2, S, and M phases [73]. Cell proliferation is controlled by *FOXM1b* through inhibiting factors that repress the entry of phases M and S, like cyclin-dependent kinase inhibitors (CKI), p21 CIP1/WAF1 and p27Kip and by cyclin-dependent kinases (CDK) activators, like cyclin A/CDK2 for S-phase entry [74]. In addition, it also plays a crucial role in executing mitosis properly as evident from the development of pleiotropic mitotic defects such as aneuploidy and polyploidy, chromosome segregation anomalies, and defects in mitotic spindle formation in *FOXM1 deficient cells* [75].

According to a significant amount of evidence, FOXM1 is a transcription element related to proliferation. The thymus, testis, small intestine, and colon of adult mice exhibited elevated levels of *FOXM1*, while in vivo expression experiments in mouse embryos revealed significant levels of expression in all organs [72]. However, since the ovary, spleen, and lung have fewer dividing cells than other organs, the levels were noticeably lower there. Additionally, it has been discovered that *FOXM1* is expressed in erythroid, myeloid, and B and T lymphoid cell lines as well as several cancer cell lines; however, it lacks expression in inactive or terminally differentiated cells [76]. The main role of *FOXM1* is to control how cell cycle genes are expressed. It expresses itself in the G1 phase and continues to be represented at the same transcript and protein level in the S, G2, and M phases. *FOXM1* primarily regulates cell proliferation in mammalian cells by stimulating cyclins or cyclin-dependent kinases (CDK) activators, such as cyclin A/CDK2, for S-phase entrance, and by preventing elements that suppress S and M-phase entrance, such as cyclin-dependent kinase inhibitors (CKI), p21 CIP1/WAF1, and p27Kip [77]. The specificity subunits of the Skp1-Cullin1-F-box (SCF), Skp2, and Cks1, whose transcription has been linked to *FOXM1* regulation, are crucial for controlling CDKI degradation during the G1/S transition. Furthermore, as demonstrated by the emergence of pleiotropic mitotic problems in *FOXM1* defective cells, including aneuploidy and polyploidy, chromosomal segregation abnormalities, and difficulties in mitotic spindle

growth, it is essential for the efficient execution of mitosis [78]. Microarray, chromatin immunoprecipitation (ChIP), and, more recently, ChIP-seq studies have demonstrated that *FOXM1* regulates the expression of G2 phase genes, which include crucial mitotic regulators such as CCNB1 (Cyclin B1), Cyclin A, AURKB, Survivin, Plk1, Cdc25B (cell cycle progression and mitotic entry); CENPA, CENPB, CENPF (essential for mitotic spindle checkpoint integrity), and MYC (c-Myc) studies. Genes controlled by *FOXM1* control the cell cycle and other biological processes [79]. Additionally, FOXM1 prevents early cellular death. The characteristics of FOXM1 deficient MEFs and FOXM1 knockout MEFs showed early senescence. Through overexpression research, the traits were reversed by raising the expression of *FOXM1*, and a similar outcome was obtained using c-Myc to induce the polycomb protein Bmi-1 [80].

A growing body of proof indicates that *FOXM1* plays a critical role in maintaining genomic integrity and responding to DNA damage. This idea was supported by the abnormalities that *FOXM1*-deficient MEFs showed, including polyploidy, aneuploidy, cytokinesis problems, chromosome missegregation, and a high frequency of DNA breaks [76]. When osteosarcoma cells were given a FOXM1 knockdown, similar outcomes were observed. According to research reports, FOXM1 overexpression reduces the buildup of double-strand DNA breaks in MCF-7 cells, indicating that it primarily plays an essential function in homologous recombination. Five HR genes are among the most significant FOXM1 target genes (brca2, xrcc2, exo1, rad51, brip1). In response to genotoxic stress, FOXM1 also promotes the expression of the DNA repair genes XRCC1 (X-ray cross-completing group 1) and BRCA2 (breast cancer-associated gene 2). It was recently discovered that NBS1, an essential part of the DNA damage repair complex, is also a *FOXM1* target gene [74]. Their research showed that *FOXM1* overexpression increases ATM phosphorylation and NBS1 expression by adjusting MRN (MRE11/RAD50/NBS1) complex phases, which activates DNA damage healing signaling. Additionally, it was discovered that *FOXM1* interacted with NFκβ in breast cancer cells subjected to doxorubicin to control the activity of DNA repair genes such as EXO1, RFC4, POLE2, and PLK4, thereby shielding the cancer cells from double-strand breaks caused by doxorubicin [81]. The balance between cell division, proliferation, and apoptosis is maintained by *FOXM1* signaling, and numerous human malignancies are characterized by aberrant *FOXM1* gene transcription. Several tumors, including head and neck squamous cell carcinomas, pancreatic cancer, lung cancer, stomach cancers, and cervical squamous cell carcinomas, have been linked to the development of the 12p13 chromosomal band encoding the *FOXM1* gene [82]. Furthermore, one of the most frequently elevated genes in human solid tumors is *FOXM1*, according to gene expression profiling of malignancies. This finding confirms the connection between *FOXM1* dysregulation and the advancement of cancer. The primary mechanism by which *FOXM1* exhibits oncogenic capability is through transcriptional activation of genes implicated in many aspects of cancer formation. There have been reports of many oncogenic signaling pathways interacting with the *FOXM1* pathway. It has been discovered that the hedgehog signaling pathway increases the expression of the *FOXM1* gene in lung, basal cell, skin cancer, and pancreatic cancers. This signaling pathway's constituent parts are connected to *FOXM1*. For example, it has been noted that Gli1 overexpression occurs in NSCLC, and this is known to activate the transcription of *FOXM1* in basal cell carcinoma [67]. Moreover, it has been demonstrated that Gli2 is primarily involved in basal cell and hepatocellular carcinoma. Additionally, notch signaling is essential for the continued existence of prostate cancer cells. It achieves this by downregulating Akt and *FOXM1*, which inhibits cell proliferation and induces death [83].

The existence of *FOXM1* interaction motifs in the Caveolin-1 (Cav1) promoter, which is known to be essential for the advancement of pancreatic cancer, and EMT significantly elucidates the involvement of *FOXM1* in the development and severity of pancreatic cancer. Additional research on the *FOXM1*-Cav1 signaling pathway in developing more effective therapeutic strategies to manage this fatal cancer [84]. Similar to

FOXM1, COX-2 is also overexpressed in a variety of tumors and has been linked to other illnesses. Lung cancer is caused by the binding and stimulation of COX2 promoter expression by the *FOXM1*-responsive component present in the COX2 promoter [85]. *FOXM1* has been linked to tumor angiogenesis, invasion, and metastasis, and it is involved in the initiation and advancement of numerous malignancies. According to the latest findings, downregulating *FOXM1* prevents breast cancer cells from growing, migrating, and invading other cancers such as pancreatic, hepatic, and stomach cancers [86]. By preventing the expression of several molecules, including uPA, uPAR, MMP-2, MMP9, and VEGF (vascular endothelial growth factor), which are involved in the breakdown of extracellular matrix and angiogenesis. Along with other genes known to accelerate tumor growth, *FOXM1* is also included in the cluster of genes associated with breast tumor development. Research has demonstrated that *FOXM1* regulates ERα expression in breast cancer cells biologically. In addition to promoting carcinogenesis and hormone insensitivity in breast tumors, ERα regulates *FOXM1* [69]. Further data indicates that *FOXM1* expression is negatively regulated by ERα, which in turn plays an anti-proliferative effect in the progression of breast cancer. A HER2-resistant breast tumor may benefit from targeting *FOXM1* as a novel therapeutic target, as indicated by a different study that likewise revealed a favorable association between *FOXM1* expression and HER2 status. Overexpression of *FOXM1* was found to stimulate the promoter of Slug, an EMT-related gene, hence promoting EMT in breast cancer [67].

Variation in the expression of genes may result in cancer development. The first proof of *FOXM1b* connected to epigenetic regulation was the knowing of *HELLS*, a chromatin redesigning/DNA helicase, as a downstream target of *FOXM1* in head and neck squamous cell carcinomas (HNSCC) [67]. Atypical upregulation of *FOXM1b* was found to reprogram the normal cells by altering its methylation towards those found in malignancy cells, through the enrollment of *HELLS* and two DNA methyltransferases *DNMT1* and *DNMT3B*. Evidence from previous studies has also shown that expression of *FOXM1* with *HELLS* and *CEP55* is a biomarker for early cancer detection. In many cancers, overexpression of *FOXM1b* was detected and it was associated with instability of chromosomes. During mitosis, Phosphorylation of *FOXM1b* occurs and is initiated by Cyclin–Cdk complexes, such as Cdk1, Cdk2, and mitogen-activated protein kinase (*MAPK)* in G1 and continued through the G2 and M-phases of the cell cycle [88]. Activation of *FOXM1* may inhibit tumor suppressor proteins P53 and other inhibiting factors such as p21 and p27. This means that over-expression of *FOXM1* is associated with an increase in cancer cells [89].

Lymphoid-specific helicase (*HELLS*) gene encodes an enzyme called Lymphoid-specific helicase in humans. The function of helicase included DNA strand separation, replication, repair, recombination, and transcription. *HELLS* are involved in cellular proliferation and play a role in leukemogenesis [90]. If downregulation occurs in *HELLS*, then genetic instability increases, and additional effects on DNA methylation could contribute to tumorigenesis. *CEP55* accompanied by other molecules (*FOXM1* and *HELLS*) could be used as a biomarker set for early diagnosis of head and neck squamous cell carcinoma [91]. The *HELLS* gene is located on chromosome 10q23.33, and forms 97-kDa proteins comprising 838 amino acids which are translated by 26 exons. *HELLS* protein consists of helicase C-terminal and helicase ATP binding. It also contains a nuclear localization signal [92]. *HELLS* is a member of the SNF2 family of chromatin remodeling proteins that use ATP to change the structure of chromatin. These changes together with altering in other epigenetic mechanisms like methylation of DNA, and histone modification change the cellular processes such as mitosis, transcription, DNA repair, and meiosis. *HELLS* is also important for gene control of stem cells, meiosis, DNA repair, and packaging of repetitive DNA [93–94]. *HELLS* play an important role in cellular proliferation and mammalian development through methylation of DNA and chromatin-remodeling. Removing of *HELLS* gene caused cellular senescence, premature aging, developmental retardation, gene modification, or upregulation of *HELLS*

causing various cancers including skin cancer [95]. In the embryonic stem cell, expression of *HELLS* was identified recently as one of the consent genes. *HELLS* is involved in the control of expression of the p16 tumor suppressor gene through repression, and decreasing *HELLS* caused increasing in the expression of p16 in small lung cancer [96]. P16 is also suppressed by *FOXM1b* [97]. A study additionally recommended that *HELLS* could control the expression of stem cell genes to induce the proliferation of stem cells and keep up self-renewal by interfacing with two transcriptional factors, E2F3 and MYC. In CRC, *HELLS* incites the expression of TET2 and TET3, which essentially impair metastasis, while in most revealed cases, *HELLS* is considered a positive controller of metastasis [98]. It can be hypothesized that the *HELLS* gene's role in DNA repair has potential involvement in skin cancer, particularly considering the role of UV radiation in inducing DNA damage.

6. Conclusion and future dimensions

The intricate interplay between genetic predisposition and environmental factors in the pathogenesis of skin cancer is a complex and multifaceted area of research. While the focus of this review has been on the roles of *CEP55, FOXM1b*, and *HELLS* genes, it is imperative to acknowledge the broader spectrum of genetic and environmental risk factors contributing to skin cancer development. Established risk factors such as excessive sun exposure, fair skin type, and immunosuppression undoubtedly play pivotal roles. However, the identification of additional genetic markers and their interactions with environmental stimuli holds the potential to revolutionize the understanding of disease etiology and prevention. Future research should delve deeper into the complex interplay between these genes and other established risk factors. Large-scale population-based studies incorporating both genetic and environmental data are essential to elucidate gene-environment interactions and identify high-risk populations. Furthermore, functional studies aimed at elucidating the precise mechanisms by which these genes contribute to skin cancer pathogenesis are warranted. Ultimately, a comprehensive understanding of the genetic and environmental landscape of skin cancer will enable the development of personalized prevention strategies, early detection methods, and targeted therapeutic interventions. By unraveling the intricate web of factors contributing to skin cancer, researchers can strive towards improving patient outcomes and reducing the global burden of this disease.

Disclosure statement

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Author contribution

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