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UV radiation effects on inducing skin cancer: perspective of prevention and new strategy for treatment

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ABSTRACT: Skin cancer is the most human malignancy. There are several risk factors which play important role in skin cancer development. UV radiation is one of these risk factors which induce different types of mutation in important genes such as tumor suppressor and protooncogene and DNA-repair genes. So prevention to exposure of UV radiation play critical role in Decreasing the skin cancer incidence. On the other hand, non-invasive treatments increase the skin cancer Patients' quality of life. Here we review the roles of the UV radiation in inducing the skin And its effects, its effects on gene mutation and the perspectives of prevention and treatment in this way. In the both fields of prevention and treatment nanotechnology plays a key role. Nanotechnology improves the photostability, skin retention, sun protection factor (SPF) and spectrum of protection of sunscreens. Nanotechnology has many advantages for skin cancer treatment which its selectivity is the most considerable one. There are also new methods for prevention and treatment of this disease including non-invasive ways, which have been reviewed in this article.

Keywords: *Prevention, Risk factors, Skin cancer, Treatment, UV radiation.*

INTRODUCTION

The highly heterogeneous group of diseases related to malignant cutaneous neoplasms [1]. Skin cancer is the most common type of cancer in the US with an increasing prevalence worldwide malignancy which is a diverse group of neoplasias derived from several different cell types that can have different outcomes [2, 3]. Skin cancer which is often classified as melanoma and non-melanoma cancers (NMSC) can affect individuals of all ages and races. NMSC's have a good prognosis and slim fatality, but due to disfigurement and medical costs there is a rather considerable morbidity. It rarely progress to metastasis; but, in an inappropriate diagnosis and management, they can extend to the skin, soft tissue, cartilage, and bone [4]. Nonmelanoma skin cancer (NMSC), largely encompassing basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) which basal cell carcinoma (BCC) is the most frequent among the neoplasms in white skin individuals, followed by squamous cell carcinoma (SCC) [5, 6]. NMSCs frequently found on commonly exposed body sites, such

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as ears, face, neck, and forearms [7-9]. BCC first proliferates slowly and associate with rare frequency of metastasis, whereas SCC can be highly invasive and metastatic. Patients with a history of SCC have a higher incidence of developing a second primary skin cancer within 5 years [10]. SCC comprises approximately 16% of skin cancer cases and Approximately 80٪ of all BCC occurs on the head and neck. Cumulative habitual sun exposure has a strong association with the incidence of SCC [6, 10]. Actinic keratosis (AKs) is believed to be precursor lesions to SCC [5]. Because most NMSCs originate from the epidermis, the upper layer of the skin, it is often detected at an early stage and can be treated locally [8, 11]. Skin cancer's outbreak is expected to increase even more, which emphasizes the importance of increased prevention and treatment efforts [11, 12]. Melanoma is severe than NMSC which three-fourths of all skin cancer-related deaths result from melanoma, [3]. Morbidity due to skin cancer is considerable, just as the mortality associate with this malignancy. Among the most cancer particularly melanoma occurs at younger ages. and it is the leading cause of cancer death in women aged 25 to 39 years old, in recent years the number of melanoma survivors has increased [13]. In this article, we intend to review the molecular mechanism behind UV- induced skin cancer. We also aim to discuss about new methods of skin cancer prevention and treatment including nanotechnology based methods.

Risk factors

There are several risk factors that have been described for NMSC and hypothesized to be responsible for increasing skin cancer including environmental and behavioral risk factors. Obesity and inflammation, obesity and the immune system, obesity and vitaminD, paler skin that burns easily, a personal or family history of skin cancer, and certain medical conditions that suppress the immune system are the most common constitutional factors, but ultraviolet radiation, specially UV-B, is the most critical one [14]. Keratinocyte carcinogenesis induced by UV radiation. Long time UV radiation, means several years or decades, can cause BCC or SCC development in exposed people. Thus, a history of excessive sun exposure, sunburns, and use of tanning booths increases the risk for skin cancer

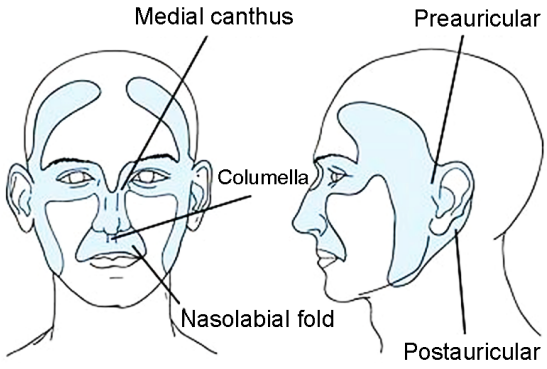

Fig. 1. Diagram of H zone. Especially problematic areas are the medial canthus, glabella, nasolabial folds, and periauricular region

[1, 2, 15, 16]. Also location, size and immunosuppression are important risk factors in recurrence and metastases, Recurrence and metastases are more likely to occur in some location of head and neck. "H" zone is the part of face that has been recognized as high risk locations for recurrence in this matter. Fig. 1 shows "H" zone. Nose, cheek, auricular area, periocular area, scalp, and forehead are common on recurrence. Also it is clearly proven that larger tumors have higher recurrence rates [17, 18]. At the end we have immunosuppression, many studies confirmed the higher risk of cancer, in patients with immunosuppression. SCC in patients with Immunosuppression is more aggressive, also the risk of metastases occurring in these patients is more than the others [19, 20].

Products induced by UV radiation

Mutagenic DNA photoproducts arise by ultraviolet light among adjacent pyrimidines in the form of dimers [21, 22]. Cyclobutane dimers between adjacent thymine or cytosine residues (CPDs), and pyrimidine (6-4) pyrimidine photoproducts [(6-4) PPs] between adjacent pyrimidine residues are main types of mutation which induced by UVB (280-320 nm) and UVC (200-280 nm) irradiation (Fig. 2), [12, 21, 23]. Also lower frequency of pyrimidine monoadducts, purine dimers and a photoproduct between adjacent A and T based arise with UV irradiation, [24]. CPDs are formed between the 5, 6 bonds of any two adjacent pyrimidines: 5'-TpT, 5'-TpC, 5'-CpT or 5'-CpC. (6-4) PPs are characterized by a stable bond between positions 6 and 4 of two adjacent pyrimidines, and are

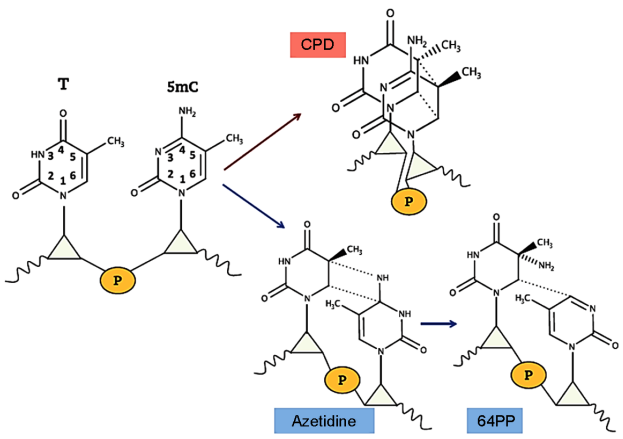

Fig. 2. Formation of cyclobutane pyrimidine dimers by UV radiation (Lara Martinez-Fernandez et al; 2017).

most commonly seen at 5'-TpC and 5'-CpC [22, 24]. In addition to UV mutagenic properties, it can disturb other important processes of cell cycle regulation. For example, Cyclobutane pyrimidine dimers on the transcribed strand block transcription strongly; as all complexes of transcriptions were blocked at the Cyclobutane pyrimidine dimers site. [25, 26]. Also T-T cyclobutane dimers are associated with inhibition of transcription factor binding in promoter sequences [27]. Sometimes UV acts as a promoter, such as DNA mutations arising from DNA polymerase incorporation errors, depurination, deamination of 5- methylcytosine, or oxidative damage which caused by free radicals. Mutations in genomic DNA can result in carcinogenesis by changing the function of genes which influence cell growth [12].

P53 products, its mutations and cell cycle

The p53 gene effects cell cycle inhibition, transcription, DNA repair, regulation of differentiation, and apoptosis of cells which holding damaged DNA [28, 29]. The frequency of p53 gene mutations is 50% of all kinds of cancers and approximately in all skin cancers. The hotspots of C to T and CC to TT mutations are found at certain codons in skin cancers which are different from Hotspots that are observed in internal tumors. Two events depending on the different kind of mutation can occur to solve the problem, first stopping the cell cycle and second apoptosis. UV as an important carcinogen impresses characteristic fingerprints in p53 gene [12, 30]. P53 codes for a 53-kDa phosphoprotein "a DNA binding protein". mutations or loss of p53 plays a critical role in the procedure of carcinogenesis. Interactions between C-terminal regions of this protein produce the tetramers. The particular binding sites on target genes can be identified with these tetramers, so this process can stimulate their activation. In absence of UV damage, there is little p53 protein in the normal cell, but when cell is damaged by UV radiation, higher levels of p53 protein is produced to response to UV damage. In higher concentration of p53 the cellular repair pathway removes DNA lesions before DNA synthesis and mitosis or induces apoptosis. In certain specific types of cancer, p53 inactivation can be achieved through an epigenetic mechanism [24, 31- 33].

UV-induced skin cancers and P53 mutations

Three types of UV radiation, UVA, UVB and UVC, induce different kind of mutation in p53 gene. Different base changes in p53 gene have been seen in skin cancer, but C→T and CC→TT at dipyrimidine sequences are predominant which induce by UV radiation. In skin cancer about 32% of all p53 mutations, are C→T transition within two unique trinucleotide sequences, 5′TCG and 5′CCG. 5′CG (CpG) sequences in the human p53 gene are methylated to form 5mCG, by the same token a lot of skin cancer mutations involve pyrimidine dimers including 5-methylcytosine bases. In head and neck SCC, the frequency of GC→TA transversion is 20% and only a few transitions at CpG dinucleotides. This high frequency related to tobacco smoking [33, 22]. The CCTT tandem mutations which named UV "signature" mutations, detected in 60% of patients with XP tumors. Several studies demonstrated that XP patient, have been affected by BCC, SCC and sarcoma [34]. Another amazing finding about p53 mutation is that the p53 mutations were located on the non-transcribed strand [22]. It is necessary to say that p53 mutations arise well before skin cancer development [12].

The patched (ptc) gene is a tumor suppressor in humans

Genetic studies about Drosophila have been extremely successful in identifying molecular pathway which regulates tissue development and is conserved in vertebrates, including humans. This molecular pathway

named Hedgehog pathway. Genetic evidence suggested that the Hh protein could act as an intercellular signal [35, 36]. Hedgehog pathway is a master regulator of tissue differentiation, tissue polarity and cell proliferation [37-39]. In this review we do not want to express about this pathway in detail but speak about this pathway generally. Four components have key roles in Hedgehog signaling. These components are the Hedgehog ligand which named Hedgehog (Hh) itself refer to any of the three family members Sonic [Shh], Indian [Ihh] and Desert [Dhh], the Hedgehog ligand receptor that named Patched (PTCH), the cell surface signal transducer or Smoothened (SMO) with seven membrane-spanning domains similar to G protein–coupled receptor and finally the downstream effectors. These effectors include transcription factors of the Gli family [39]. Several proteins link SMO to Gli. These signal transducers include Fu, Su (Fu), Rab23 and protein kinase A (PKA) [37].

Normally, Hedgehog signaling remains inactive in most adult tissues, but mutations may results in activation of this pathway and developmental abnormalities might be one of its consequences [39]. It is better to describe this pathway by speaking about Patched (PTCH) at first. Patched (PTCH) gene is a tumor suppressor gene. Patched (PTCH) is the transmembrane receptor for Hh protein. This receptor is a multipass membrane protein that has two vertebrate homologs, Ptc1 and Ptc2. Ptc1and Ptc2 play an important role in Hedgehog pathway. In contrast to Ptc1, which act like the Drosophila Ptc protein, Ptc2 function has remained unclear yet. We can describe the functions of Ptc generally. This receptor has several important roles in Hedgehog pathway which two of them play critical roles. The Ptc's first function depends on conditions, in other words its roles depend on presence and absence of Hedgehog ligand. In the absence of Hedgehog ligand, there is no interaction with Hedgehog ligand and PTCH, so the activation of a second downstream effector molecule which called Smoothened (Smo) signaling Is regulated negatively negatively by Hedgehog ligand. On the other hand, in the presence of Hedgehog ligand, PTCH bounds to Hedgehog protein. This interaction inactivate PTCH function which allows Smo to signal. Figs 3 and 4 show the cell signaling whit Hh and whiteout it.

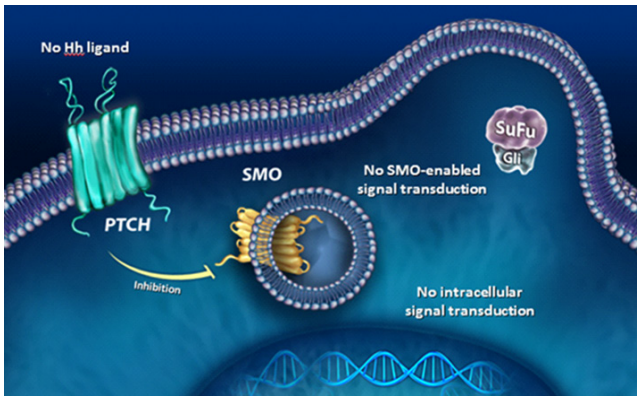

Fig. 3. In the absence of Hh ligand, PTCH inhibits SMO and the Hedgehog signaling pathway is suppressed

A second key role of PTCH is to limit the range of diffusion of Hedgehog proteins by binding and sequestering them. A second, unrelated protein called hedgehog-interacting protein (HIP) may also share this role in vertebrates [40]. If activation of Hedgehog pathway occurs on inappropriate time and condition, it can Result in OR several human cancer might be the consequences. several human cancers. There are different mechanisms which act in abnormal Hedgehog pathway signaling in different types of cancer. First mechanism (type I) is ligand-independent signaling driven by mutations. Mutations in key pathway regulators such as PTCH or SMO cause SMO to be in a constitutively active state, and second (type II) is autocrine ligand-dependent signaling which induce by overexpression of Hh ligand by tumor cells. First mechanism is observed in BCC and medulloblastoma while second mechanism Is observed in ovarian cancer, colorectal cancer and pancreatic cancer [38, 39].

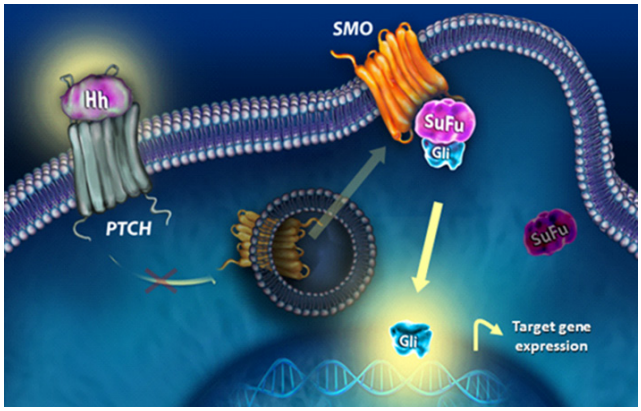

Fig. 4. Activation of the pathway is initiated by Hh ligand binding to PTCH, eventually resulting in target gene expression

Third mechanism (type III) is also ligand dependent but paracrine affects the other signals to develop the growth or surviving of the tumor. The other mechanism is secretion of Hh from stromal cells to receiving cells in a tumor which named 'reverse paracrine' signaling (type IIIb) [41]. BCC can rise in people with nevoid basal cell carcinoma syndrome (NBCCS) which is related to human PTCH gene mutation. On the other hand, mutation in PTCH or SMO Is directly related related to basal cell carcinoma (BCC) [41].

UV-induced PTCH mutations play a role in BCC development

The first relationship between improper Hh signalling and cancer reported by Hahn et al and Johnson et al in 1996. They founded that Gorlin patients experience numerous basal cell carcinomas (BCCs) during their life; also they develop other kinds of cancer such as medulloblastoma and rhabdomyosarcoma tumour [42]. In many studies reported that in NBCCS patients with BCCs, BCC observed on sun exposed sites. Most PTCH mutations in NBCCS patients lead to a truncated protein. There is some evidence that confirm the role of UV radiation in Ptc mutations, for example a GCAT transition which characterize as UV-induced mutations, is a known mutation in a NBCCS patient with BCC. This UV-induced mutation produces a stop codon Which leads to premature termination of the protein. Also in some BCC cases without NBCCS UV signature mutations were observed. This evidence confirms that UV radiation has critical role in inducing mutations on Ptc gene [12].

Prevention

Always prevention is better than treatment; using sunscreen is common way to prevent. Nanotechnology plays important role in any field specially the pharmaceutical and health industry. Today, nanotechnology has a key role in overcoming traditional drawbacks associated with sunscreens by improving their photostability, skin retention, sun protection factor (SPF) and spectrum of protection. There are two different strategies for sunscreen formulations according to the nanotechnology application. In first strategy focuses on the nanoencapsulation of organic filters. The carriers of these nanoencapsulation are prepared with biodegradable materials. This nanoencapsulation of organic filters act as systems to control their release and delivery to the skin, and also block the UV radiation. The second is based on the using of nanosized filters into the sunscreens formulations; they are not nanocarriers of complex architecture but nanoparticles prepared directly by nanosizing the bulk material of the sunscreen [43]. One of the advantages of these sunscreens is, increasing the persistence of substances which applied on the skin. [44, 45]. So, nanotechnology performs an important role in skin cancer prevention by improving the formulation of sunscreen products. Some studies reported the topical treatment by using active photolyase which placed in lyposome. Photolyase is a monomeric DNA repair flavoenzyme. This enzyme reverses damage Which induced by UV radiation and produced by almost all living organisms that are exposed to sunlight, the only exceptions to this rule are mammals, such as humans [46]. Results of a study which has done by Helger Stege et al. in 2000 demonstrated that exogenous active photolyase to human skin is highly effective approach to protect human skin from harmfully UVB radiation-induced pyrimidine dimers. Also results of this study confirmed that exogenous application of photolyase is different from conventional photoprotection. Phatolyse is able to remove lesions that has already occurred. Also the other studies showed the same results which confirm a higher level of protection to the UVR-exposed human skin with photolyase-containing liposomes [47, 48]. Other important substance in prevention filed is a-tocopherol. Weixing Chen et al in 1997 showed that a-tocopherol acts as an effective sunscreen in vivo which preventing premutagenic DNA lesions formation in effective genes which involve in skin carcinogenesis. So, protection of the p53 gene and the other genes which play important role in carcinogenesis, against photodamage can help to skin cancer prevention by topical tocopherol [49, 50].

Treatment

In the field of cancer, treatment has significant role. So, choosing a suitable treatment strategy is very important and highly effective on patients' quality of life with any types of cancer. Treatment of melanoma depends on the depth of the primary tumor and the

stage of the disease at the presentation time The distance between the upper layers of the epidermis and the deepest point of tumor penetration named Breslow thickness which is measured in millimeters. The Breslow thickness is one of the most important prognostic indicators of the primary lesion. This measurement is used to categorize a lesion as thin (51 mm), intermediate (1.01–4 mm), or thick (>4 mm) [51, 10]. Local surgical excision is a treatment for the primary melanoma. The best margin for surgical excision which reported in studies is 0.5 cm to 1cm for melanoma in situ. The recommended margin for melanomas with 1 mm thick or less is 1 cm, and margins of 2 cm are recommended for lesions with thickness of 1 mm to 4 mm. Systemic therapy may also be used in treatment of advanced melanoma, there are various treatment methods for patients with advanced melanoma, including interleukin 2, vemurafenib, ipilimumab, dacarbazine, temozolomide, imatinib (C-KIT mutated tumors only), paclitaxel, and combination therapy. Local surgical excision method is an invasive treatment for melanoma skin cancer.

There are several methods for nonmelanoma skin cancer treatment, electrodessication and curettage, cryotherapy and laser ablation, excisional and Mohs surgery, topical therapy with fluorouracil; topical imiquimod therapy and radiation therapy are common modalities. Choosing the best and more appropriate treatment strategy needs to carefully consider possible recurrence requires careful consideration of possible recurrence or metastasis, functional outcome, cosmetic outcome, and the patients' preference [50, 52]. In electrodessication and curettage for removing tumor, a sharp curette is used to destruct the base of the lesion with electrodessication. For small and well-defined tumors, between the ablative techniques, electrodessication and curettage is common [11]. As some properties of this method, for instance, there are no histologically controlled borders, and electrodessication and curettage should not be used in high-risk lesions or some areas, such as face and hair-bearing areas because tumor cells can develop on hair follicles, and leads to inappropriate removal [52]. Cure rate of this method is high; in 97% to 98% of recurrence subjects have been reported (Kimel et al, 2002). Effective method for many primary NMSCs is Standard excision surgery, but after surgery, postoperative pathologic evaluation is necessary to confirm the complete removal of tumor. Wolf and colleagues reported that in SCC and BCC with less than 2cm in diameter margins, use of a 4-mm border results for complete removal is necessary. Other technique is cryotherapy which uses liquid nitrogen. Cryotherapy cure rates are low so it is rarely used for SCC and BCC. In this method SCC and BCC recurrence in more likely to occur and also postprocedure scarring and pigmentary changes might be its consequences. Topical therapies are another common method for skin cancer treatment. Topical therapies perform by topical 5-fluorouracil and imiquimod cream. Although there are some advantages for this method, some studies have reported disadvantages for it too for example in some study no increasing in number of apoptosis in treated cells with imiquimod reported [9, 52, 53]. In addition to mentioned methods, photodynamic technique; treatment, based on kinase inhibitors and applying nanotechnology are effective methods for skin cancer treatment.

Photodynamic technique has been introduced to clinical practice, both for diagnostic and therapeutic purposes. As we know early detection and diagnosis plays a critical role in treatment quality. Today scientists and physicians have tried to use combination of light and photo sensitizers in order to diagnose and treat carcinomas and malignant lesions. Photodynamic diagnosis (PDD) or Fluorescent diagnosis (FD) utilizes fluorescent drugs that accumulate in tumors and other hyper-proliferative tissues. Todays, among substances applied in the photodynamic approach, particular attention is focused on 5-aminolevulinic acid (5-ALA), methyl-5-aminolevulinic acid (MAL, Metvix) which its presence, represents a physiological requirement for heme production in cells. In fact MAL-induced red fluorescence is useful to evaluate surgical margins and to determine the extension of a skin cancer [54].

Photodynamic therapy (PDT) is a novel method for skin cancer treatment which implicates the injection of a photosensitizing drug and its activation by light to produce activated oxygen derivatives which selectively annihilate target cells [53, 37, 55]. As mentioned earlier it's based on photosensitizer power, also PDT requires the presence of light, and oxygen. PDT

light sources are laser and non-laser, in other words using both of them is available. Mechanisms of PDT perform in six stage; first the photosensitizers accumulate in tumor and surrounding normal tissue, in second step, Appropriate wavelength light which matches with photosensitizer absorption wavelength is used, in third step photosensitizer absorb the wavelength light; at fourth light absorption leads to transfer energy to molecular oxygen, in fifth stage reactive singlet oxygen is produced and at the end step direct cellular killing, vascular shutdown and local damage by inflammatory and immune mediators occurs [56, 34]. PDT has many advantages among other methods for skin cancer treatment. In addition to being non-invasive; PDT is well tolerated by patients and it can be used in patients with anticoagulant therapy. PDT is the best choice for group of the patients with contraindications for multifactorial health risks that prohibit surgical intervention or patients who refuse surgery. There is no accumulation of toxic material even if it is repeated several times. Also this technique can be used in cases with large lesions and for areas that are related to the beauty for example facial areas. PDT takes short times for patient healing. One other important advantage of PDT includes the simultaneous treatment of multiple tumors. This method is cost effective; but apparently finding the better and non-invasive methods which increase patients' quality of life is necessary. Unlike photodynamic therapy (PDT), photothermal therapy dose not require reactive singlet oxygen to achieve cancer cell lethality. In PTT, appropriate wavelength light will be absorbed by a specific photosensitizer; and consequently it'll become exited and releases vibrational energy which rise cell temperature and cause cell death. Researchers found out that synthesizing particular kinds of photosensitizers which are capable to specifically target cancer cells, could help to improve the treatment outcomes.

Folate receptor is overexpressed in some certain cancer cells thus; it might be a great candidate for target therapy. Many studies performed PDT by Folate targeting strategy, synthesized Folate-conjugated gold nanorods(F-GNR) as targeted photothermal therapy agent. After treatment of KB cells with combined plasmonic photothermal therapy of 20 μM F-GNRs with seven pulses of laser light and 6-h incubation periods 56% cell lethality was observed [57]. In another study Ghaznavi et al, conjugated folic acid with Polyethylene glycol (PEG) coated gold @ iron oxide core shell nanoparticle which has appropriate wavelength absorption in near infrered region (NIR). Then the cytotoxicity potential of synthesized nanocomplex was assessed on KB cell with high level of Folat reception expression and MCF-7 cells with low expression level of Folate receptor. Cell lethality for KB cells and MCF-7 was reported respectively 62% and 33% after photothermal treatment [58]. According to Mirahimi et al study Folate-conjugated Fe_2O_3@Au nanocomplex, upon administration of NIR laser, can induce higher level of apoptosis in KB cells rather than non-targeted nanocomplex [59]. There are variety of studies which have used non-targeted noncomplex to perform PTT; for instance Eyvazade et al synthesized the novel nanocomplex, Au@IONPs, which could significantly kill cancer cells following treatment with laser beam (λ = 808 nm, 6.3 W/cm^2, 5 min) [60].

In addition to the above, way, which suggests focusing on tumor suppressor and protooncogene reactivation, there is a very interesting method with highly efficiency for treatment. This method is based on using of kinase inhibitors. Generally a lot of kinases are not oncogenes but they can act effectively in in cell signaling processes which control key properties of cells such as cell proliferation and survival. Here just we want to mention this method of cancer treatment. Normal signal transduction systems are very important in cell cycle so, any malfunction in these systems can affect development and triggers tumors progression. According to this, inhibition of kinases is a good option for different types of cancer treatment including skin cancer. The drug which are based on kinase inhibitors in compression with conventional drug has provided opportunities for very rapid development of cancer treatment. One problem in this way is to select patient populations and combination partners to use with these new drugs [61-63].

One important option for skin cancer treatment is nanotechnology. Nanotechnology is an area devoted to the manipulation of atoms and molecules leading to the construct structures in the nanometer scale size range, which retain unique properties. The search for new advanced materials is an important section of con-

temporary researches in numerous disciplines of science and the development of many new technologies [64]. During the past two decades, we saw the rapid developments in nanotechnology in multiple therapeutic, sensing, and targeting agents into nanoparticles, for detection, prevention, and treatment of oncologic diseases. The most advantage of this method is its selectivity. Many studies reported using nanotechnology with different material and methods for skin cancer treatment. Nanotechnology has the powerful ability for treatment of skin cancer [65]. Also PDT, treatment based on kinase inhibitors, topical therapies and cryotherapy are good candidates for noninvasive skin cancer treatment but UV radiation and its role in creating the mutations in the p53 gene and Ptch substrate as the key factors in the cell cycle regulation, which can induce the skin cancer is clear, so reactivation of these mutant genes or killing the cells with mutant P53 and Ptch pathway genes appears as a logical target for skin cancer treatment.

In the late 1980s wild-type p53 gene was transfected into variety of human tumor cells. The results of this transfection led to induce apoptosis and growth inhibition [66]. In the field of P53 anticancer therapy, three classes of methods successfully have been developed which include targeting p53 itself, targeting p53 Regulators and targeting other p53 Family Members. The first class which target p53 itself, includes four branches: Targeting wt p53 — To Activate, Targeting wt p53 — To Inhibit, Targeting Mutant p53 – To Rescue and Targeting Mutant p53 – To Kill. Targeting p53 Regulators has three subcategories which are Mdm-2 (Murine Double Minute-2, Hdm2 in Human), Small Molecules that Disrupt Mdm2-p53 Interaction and SirT1/SirT2. Gene Therapy, Small Peptides and Small Molecules are three subclass of the targeting other p53 Family Members class. Each subcategory of the targeting p53 itself, targeting p53 Regulators and targeting other p53 Family Members, also divided in to the different methods [66].

There are several specific methods of gene therapy which tested by researchers in the field of head and neck cancer. One of these methods is gene addition therapy, in this approach P53 gene transfer was done in patients by injecting an adenoviral vector expressing wild type p53 into primary tumor. Another one is antisense RNA therapy which this method which can inhibit can inhibit expression of the mutant P53 gene by using RNA which is matched to the strand of DNA expressing gene. Third method is Cytoreductive gene therapy that involves the introduction of gene into a cell that enables a prodrug to be activated into active cytotoxic drug [67].

As we said above, Small Peptides and Small Molecules is the subclasses of P53 based cancer therapy, for example CP-31398 is one of these molecules [68]. Rao et al reported that CP-31398 can inhibit the growth of xenograft tumors in bothe immunodeficient and immunocompetent mice; also this molecule reduced UV-induced skin cancers [69, 70]. David et al in their publication on 2016 claimed gene therapy that using wild-type p53 which delivered by adenovirus vectors, is now in widespread use in China [66, 71]. The other amazing result about this molecule is which CP-31398 not only treats but also prevents UV light–induced squamous cell cancers in mice [70].

All of these results suggest gene therapy which targeting cells with mutant P53 can be very effective for head and neck cancer specially CP-31398 for skin cancers which reduced UV-induced skin cancers. Controlling HH signaling is a target for the treatment of cancers. In 2006 Lee et al published a review article which was titled “Targeting the Hedgehog pathway in cancer”. In this review Lee et al focused on HH pathway, which is abnormally activated in most basal cell carcinomas (BCC). They concluded that inhibition of Hedgehog pathway with the same small molecules used to target tumors where the pathway is mutated and blocking antibodies or other soluble receptor fragments directed at the ligands themselves can have therapeutic effects on skin cancer treatment [42].

Sachin Gupta et al in 2010 reported that understanding the mechanism of Hh proteins in cancer development is important for different types of cancers treatment including BCC and medulloblastoma [67]. They reported that most of BCC tumors either had inactivating mutations in PTCH (85%) or activating mutations in SMO (10%). In that review Sachin Gupta et al mentioned the Hedgehog pathway inhibitors such as cyclopamine and synthetic SMO inhibitor, are effective in BCC treatment. According to these results, better understanding of Hedgehog pathway mechanism

and the role of proteins involve in this pathway may be effective in in different types of skin cancer treatment., but it is important to notice that understanding and clearing the role of Hedgehog pathway in each of specific types of skin cancer is necessary to achieve this goal.

In conclusion, skin cancer is the most common human malignancy and UV radiation is most important risk factor for this malignancy, so using the sunscreens with new formulations that mentioned in this article plays an important role in skin cancer prevention. On the other hand, we see that the non-invasive treatments for skin cancer are developing rapidly these days. UV radiation cause specific mutation in P53 and Hedgehog pathway genes, so it seems that targeting these mutant genes has a high capacity to skin cancer treatment.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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