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Review Article

Skin cancer and DNA mutation due to ultraviolet radiation

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ABSTRACT

Ultraviolet (UV) radiation is emitted by the Sun as well as man-made sources such as tanning beds and welding torches. The process of energy being emitted from any source is known as radiation which can take many different forms, from extremely high-energy radiation like X-rays and gamma rays to extremely low-energy radiation like radio waves. UV photons are in the middle of the electromagnetic spectrum. They have higher energy than visible light but a lower energy than X-rays. It is divided into numerous groups based on the amount of energy they contain. Higher-energy UV photons are included in ionizing radiation, which means they have enough energy to ionize an atom or molecule. Ionizing radiation can cause cancer by damaging a cell's DNA; however, it doesn't have enough energy to penetrate deep into the body, thus it mainly effects the skin only. UV radiations are considered the most carcinogenic factors which leads to skin cancer. Over $50 million each year is estimated to treat the melanoma skin cancer, but the incidences kept rising each year. The tanning and pigmentation in the skin are the main factors to develop skin cancer that rise concerns about ozone depletion. Continuing research should contribute to an improved knowledge of the genetic and immune suppressive mechanisms involved in the role of the tumor suppressor. Research into skin cancer may help raise consciousness about the harmful effects of UV which leads to improved methods of prevention and treatment of skin cancer.

Keywords*:* Skin cancer, UV light, Ozone depletion, Melanin, Melanoma

INTRODUCTION

As dermatologist David Fisher of Massachusetts general hospital in Boston says *"This is an interesting, unexpected, and very important new mechanism of skin damage by UV radiation"*. Skin cancer, when caused by UV radiation, is called as mon-melanocytic skin cancer. UV radiations are the most harmful factors of the sunlight.[1] Most types of the cancer are inherited; they might be induced by lots of environmental factors, one of which is UV rays, that can end up with errors in DNA replication.[2] The persuasive evidence declares that UV radiation due to sun exposure does not cause skin cancer directly rather some indirect pathways take place in the body. Over the last few years, many cases of skin cancer have been reported worldwide. A report says that each year more than 1 million new patients of skin cancer appear and report the symptoms.[2]

UV radiations are considered as the carcinogenic factors that inhabit the sunlight and repeated exposure to the skin leads to skin cancer. However, the mortality rate due to non-melanoma skin cancer (NMSC) is rather low. Over $50 million each year is estimated to treat the non-melanoma skin cancer but the incidences kept rising each year.[2] It has been reported that the people who are sensitive to the sun rays are more prone to get infected by the radiation more likely because they have reduced capacity in their bodies to treat DNA damages induced by UV radiation.[3] This disturbs different pathways and cell cycles in the body.

Sun rays either cause tanning or thickening of the skin.[2] The tanning and pigmentation in the skin are the main factors to develop skin cancer that rise concerns about ozone depletion.[2]

The carcinogenic factors of the UV radiations both acts as non-specific damaging factors and mutagens and these properties help to initiate and promote the tumor in the body.[3] UV radiations have mixed effects on health-positive and negative. Positive effects by synthesizing vitamin D and endorphins and negative effects start with the excessive exposure and deteriorate health. A study was conducted by D' Orazio et al he reported that UV radiations were linked with 3 types of cancer-squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malign melanoma.[3]

TYPES OF SKIN CANCER

Many cleared pieces of evidence have been found indicating that there are three types of cancer caused by UV radiation. One is BCC, which occurs on the most exposed parts of the body under sunlight. It highly affects people with the fairer complexion. It grows slowly and most often doesn't show symptoms for years. BCC is the most common type of skin cancer. Second is SCC, it usually affects the part of the body and is tanned after exposure to the sun rays i.e., neck, chest, face, legs and arms. It also grows slow. And the last is, malignant melanoma, this type of skin cancer is caused by the melanocytes (pigments producing cells). All of the skin cancers are caused by excessive exposure of body parts in sunlight.[3] All of these together harm millions of Americans each year.[3] The rate of skin cancer among sun-sensitive and fairer people is higher, whether it is non-melanoma and melanoma, skin cancer is malignant among white people because their bodies correlate with the mechanism of polymorphism of melanocortin 1 receptor gene, which enhances the risk of cancer.[3,4] The chances for black and less-sensitive people to get affected by Sun rays are rather low. Potential risk increases when higher densities body parts exposed to the sunlight than low densities body parts. Depending on the indirect interaction, these 3 types of skin cancer affect individuals more commonly and occasionally, suggested by the studies on the animals.

INTERACTION OF THE SKIN WITH UV RADIATION

The skin comprises one-sixth of the total body weight and is the largest organ of the body. It plays its role to protect the internal bodily environment from the external one-from UV rays as well. The skin possesses optical properties that carry out photobiological responses in the skin. The skin has 3 functional layers that scatter and absorb the optical light.[5]

UV rays are the cause of mutation and DNA damages

At 240-290 nm, DNA absorbs UV radiations.[2] However, the genetic material's integrity is highly protected via enzymatic repair mechanisms which reduce damages for the DNA. In human beings, UV rays produce pyrimidine dimers.[6] Due to UV irradiation, dimers in the DNA structure on any 2 pyrimidine bases can be formed. Thymine-thymine dimers in the DNA structure can easily and readily be formed than any other.[6] This way, UV rays produce mutagenic photoproducts in the genetic material.[2] These dimers in DNA are termed as cyclobutane dimers and pyrimidine-pyrimidone (6-4) photoproducts. Cyclobutane dimers are produced between adjacent nucleotide of C4 and C6 C-atoms in the structure. 4-membered ring is formed by saturating the double bonds.[2] In the same way, pyrimidine-pyrimidone (6-4) photoproducts are the lesions produced on two adjacent pyrimidines-3 prime 4 positioned carbon and 5 prime 6 positioned carbon.[20] The lesions are more commonly produced between cytocin-cytocin and cytocin-thymine nucleotides.[2] Both of the lesions are mutagenic, cyclobutane dimers are produced three times more than pyrimidine-pyrimidone (6-4) photoproducts. This is the reason why Cyclobutanes are the major contributor to the mutation while photoproducts could easily be repaired in many organisms.[2] This mutation escalates the UV rays' sensitivity in the body either by lowering the body's ability to respond to the DNA damage or by reducing the ability to tolerate.[6]

The mutation can also disturb various cell cycles that involve DNA integration, can damage transcription binding factors, and may block entire transcription and elongation processes, which may produce carcinogenic effects.[2] If the photodamage doesn't get responded and repaired instantly, it could become a permanent mutation.[6] This mutation in the genetic material may cause the insertion and deletion of many unwanted bases. After being severely exposed to the UV radiation, discontinuity in the first DNA replication has been observed; gaps are seen in the template strand opposite to the pyrimidine dimers.[6]

Mutation in DNA results in carcinogenesis

Skin cancer due to UV radiation has the highest incidences in the world. SCCs occur when the excessively exposed body parts exhibit UV damage.[7] It is one of the major etiological elements to produce cancer, however body tries to repair DNA damages trough nucleotide excision repair but the damages if go severe, may end up with mutations in many cells.[21] As UV radiation act as initiator and promoter of the tumor, they are characterized as complete carcinogens. After exposure, a mutation occurs and results in depurination, oxidative damage, error in the

functioning of the DNA polymerase and deamination. UV A rays (UVAs) are although less effective carcinogens as compared to UV B rays (UVBs). UVBs can function as a promoter of carcinogenesis in the skin. Mutation induced by UVB produces aggressive tumors in the skin which has low anti-tumor activity.[23] Both UVA and UVB are highly effective carcinogens together-studies on animals have suggested.[2] Studies further declare that UVA rays don not produce much impact on cell cycles as UVB rays do-they have carcinogenic properties. Cell growth due to mutation in the genetic material can also be influenced to upgrade carcinogenesis.[2] Non-melanoma skin cancer may arise out of stem cells; however, it is not known whether BCC or SCC gets initiated from stem cells.[7] Cancerous cells in SCC originate from keratinocytes and can move down to the dermis, the areas with SCC damages may show wrinkles and pigmentations.[7] Carcinogenesis due to mutation occurs in 3 stages-initiation, promotion, and progression. DNA mutation is one of the events takes place in the initiation stage and may get prolong for years until a promoting agent doesn't get introduced in the body. Promoters do not behave as tumor agent but get combined with the initiators to increase the severity. The 3-7 events take place to switch the normal cell into a carcinogenic cell.[2]

Apoptosis and DNA repair against carcinogenesis

Tumor in the body is characterized by increased apoptosis. This is seen because skin possesses some protective mechanisms to save cells from tumor-one is DNA repair mechanism and the other is apoptosis (programmed cell death). If any of these pathways fails to occur, mutation may be transferred to the daughter cells after the cell cycles and contribute to carcinogenesis. DNA repair is the crucial mechanism that occurs first and is lacked by the UV rays' sensitive individuals and they ultimately end up with higher risks for skin cancers.[2]

UV rays are the potent inducers cause cell death. Plethora of factors along with UV induced mutation provoke DNA repair which is often followed by cascade of apoptotic pathway.[24]

Mutation in the DNA may completely block the other cell cycles which involve DNA itself. Various cell cycles may be blocked on the points before DNA replication and before chromosomes segregation. This disruption influences the genes, which are highly active in cell growth and the functional cycles. When the cycles are disrupted, the brain senses it and activates the factors that repair DNA. If the factors fail to repair DNA, then another pathway, which is programmed cell death, also called an apoptotic pathway initiate which endeavors to stop tumor. A report on the animal study suggested that excessive exposure of UVB induces the apoptotic pathway because the radiations are more severe.[2] The DNA repair and apoptotic pathway show the localization of p53 protein. It gives an indication that localization of this protein takes part in repairing DNA damage by UV radiations.

TUMOR SUPPRESSOR GENES

UV radiations when causing carcinogenesis, they inactivate some tumor- suppressing genes and this way, they over-activate the overgrowth of oncogenesis.[2] Dominant proto-oncogenesis occurs due to excessive UV radiation because it requires only one copy of the gene to produce its effects. Proto-oncogenesis controls differentiation and proliferation of the cell and divided into 3 groups-one is growth factors and receptors, second is signal transduction protein, and last is a nuclear factor. Mutagenic factors in UV radiation cause overexpression of altered genes which introduces carcinogenesis. Some tumor suppressor genes that get altered by UV irradiation are p53 tumor suppressor gene, patched gene and RAS oncogenes.[2]

P53 tumor suppressor genes

This gene, in skin cancer, gets altered nearly 50% and considered to the most altered one.[2] This gene and its products are the most complex molecules which by various ways take part in different cell cycles and functions.[8] Alteration in the p53 gene shows a direct relation in developing cancer. More than 50% of the cancers inside the body show alteration in the p53 gene.[8] However, oncogenic transformation is particularly seen in non-melanoma skin cancer, in which p53 mutation is more common. P53 genes essentially have codes for mutation and DNA binding protein. The loss of the p53 gene may result in carcinogenesis. In humans, p53 is located on the 17th chromosome and contains 20 kilobases and 11 exons.

Many studies have further revealed that the p53 gene plays a vital role in controlling the cell cycles, repairing DNA, carrying out multiple cellular processes, apoptosis, and senescence.[2] In humans, the mutation is rather common in the p53 suppressor gene; almost 90% is involved in SCCs.[9] Data of the studies have found the relationship between the UV radiations and actinic keratoses and earliest mutation is seen here.[9]

Effect of UV on tumor suppressor gene p53 on cell cycle

P53 tumor suppressor genes are practically involved in carrying many cellular functions.[9] However, the cell cycle is under the direct influence of cyclin-dependent kinase (Cdk). The cell cycle is controlled by the Cdk family and inactivates the negative regulators inside the cell. During the mutagenic stress, the

accumulation of p53 protein occurs, which arrests the cell cycle at the G1 phase. Repairing of the DNA damage is allowed before the S phase begins.[2] DNA damage due to genotoxic stress can also cause an irreversible arrest to the fibroblast mitosis. Accumulation of p53 protein may also result in the expression of the other useful proteins that regulate the cell cycle. For example, p21 protein breaks Cdk-cyclin and complex by forming other complexes, which release elongation factors and aid in DNA synthesis.[2]

P53 suppressor gene and apoptosis

Prompt expression by p53 induces apoptosis and stable growth arrest.[10] Two independent pathways are involved for p53 to induce programmed cell death, apoptosis. One pathway depends on p53 and causes up and downregulation of several proteins in the cell while the second pathway depends on p53 protein but on its transcriptional property. In the second pathway, p53 binds with the protein in the process of synthesis and repairing of the DNA, which later leads to apoptosis.[2]

Inactivation of p53 gene

During the mutation, the transactivation activity of DNA can be lost due to the overproduction of the protein. However, due to some of the mutations, p53 becomes unable to induce apoptosis but can induce cell arrest.[15] Due to three genetic alterations, the p53 gene gets inactivated. First, due to the total or partial deletion of the gene. Second is when the oncogenic potential is acquired by mutants of p53. For example, 175His p53 lacks tumor suppressor function and third, some mutation can also produce a negative effect to suppress p53 function by inhibiting the binding activity of DNA.[2]

Various functions in biological cells attribute to p53 to introduce programmed cell death apoptosis. It gets cleared from the evidence that apoptotic activity plays a crucial role in tumor suppression.[11]

P53 suppressor gene mutation in early skin cancer

In the skin cancer, in the human and mice both, p53 genes have been found mutated highly.[25] Most of the damages induce damages by mutating the critical functioning of the p53 gene. In human SSCs, more than 90% of the mutation occurs in p53 genes and in BCC, 53% of p53 gets mutated, which decreases the sunburn cells' appearance.[26] However, the sun starts deteriorating skin by producing apoptotic keratinocytes underneath due to excessive exposure.[12]

Some prior studies have revealed that in human skin cancer, at pyrimidine sites, UV mutation frequently substitutes CT and CCTT bases. This mutation has been seen in other internal cancers neither in humans nor in mice which induce carcinogenesis. This CCTT transition in skin cancer is rather unique due to which, it is identified as the "signature of mutation". Most of the mutations at the p53 gene were found at non-transcribed strands.[2] Skin cancer in mouse contains several p53 mutant alleles-all with single base change. Progression of skin cancer from benign to malignancy covers the same stages as colon cancer. The stages are helpful for the determination of the time taken by the mutation of the p53 gene. For instance, p53 mutation in colon cancer occurs late while, it takes place quite earlier in skin cancer, where UV radiations are the etiological agent. PCR and ligase chain reaction techniques have detected the mutation on the P53 gene at codon 245 and 247/248 in skin cancer. However, most of the studies have declared the correlation between the frequencies of mutation at codon 247/248 and the risk of BCC skin cancer. Other studies have found 60% of the mutation in examined actinic keratoses (AK) samples, while 89% of this mutation in AK samples was caused by UV radiation.[13] However, the frequency of mutation is low in less-exposed skin, while, on over-exposed skin, patches of mutated p53 cells were found which either raised from hair follicles or from epidermal-dermal junction. Recent studies have revealed that sun-exposed skin contain immune-positive colonial patches that predominantly have mutations by UV radiation.[14]

PATCH GENE IS THE TUMOR SUPPRESSOR GENE

Recent experimentations and observation have revealed that patched gene works as the tumor suppressor in BCC.[27] It is due to patch gene controls its own transcription by inactivating mutation. When this gene is mutated, it may lose its control on regulation and lead to overexpression of PTCH mRNA.[2]

PTCH gene is conserved in vertebrates and drosophila

Patched gene was cloned in drosophila and results have predicted that the protein has more than 1280 amino acids and the weight of the gene is 143 kilodalton. It serves as the segment polarity gene in drosophila which controls growth and differentiation of the cells at the level of the embryo. It plays its part in the development of each segment.[2]

PTCH gene regulates the activity of other genes involved in cell differentiation and growth. The activity of the PTCH gene is attained by opposing the activity of the hedgehog (Hh) gene, which induces cell growth at an embryonic level.[28] Cells when receive the signals from hedgehog, start transcription of many genes that carry out process of growth. Hh gene also induces the transcription of PTCH gene. The patched gene then responds to the hedgehog signals and blocks

the transcription and growth of the cells when it is required.[16] There is always a balance between opposing activities of the patched gene and hedgehog gene. When signals from the hh gene remain unchecked, it may lead to overgrowth of the cell.[17]

The genes of human and mouse are 96% similar and genes of human and drosophila are 40% similar.[2] Hedgehog gene and its analogs both can induce PTCH transcription in the vertebrates.[16] Hh with high affinity can bind with PTCH and the complex is formed, these stages of the event are important invertebrate to elucidate PTCH signaling pathway in human.[2]

Mutation in PTCH gene and nevoid BCC syndrome

Mutation in the PTCH gene is linked with nevoid basal carcinoma syndrome [NBCCS], also called Gorlin syndrome.[29] This disorder is characterized by a number of BCC, which may appear at a younger age along with other abnormalities such as face and head alteration, cysts in jaws and skin, which may cause a number of tumors. Patients with NBCCS, show mutation in the PTCH gene, this mutation is the reason for developing tumors.[18] The mutation and interruption in the PTCH signaling pathway is one of the key features of developing BCC.[2] UV radiation causes mutation which induces inactivation of the PTCH gene and expected to overexpress patched mutants. Mutation in PTCH can also cause overexpression of hedgehog activity; this may have a role in tumorigenesis.[2]

Patched mutation due to UV radiation develops BCC

Patients with nevoid BCC syndrome can develop many BCC on the sun-exposed sites. The onset of the skin tumors depends on the skin pigmentation and sun exposure. BCC is developed in patients who are susceptible to mutation of the patched gene. Most of the mutation is seen in the PTCH gene which shortens the protein.[18] In NBCCS patients, fibroblasts are also sensitive to UVB radiation. This shows a link between sensitivity to U VB, a mutation in a patched gene, and development of sporadic BCC in the patient with NBCCS.[22]

THE ROLE OF RAS ONCOGENES IN SKIN CANCER

Ras's gene is the family of proteins, which are expressed nearly in all animal cells. The family, in actual, relates to the GTPase class which takes part in cell signaling. The ras family encodes 21 kilodalton protein. Ras family with all of its members is located in the inner wall of the animal cells and binds to the GTP to carry out signal transduction.[30] This helps activator to bind with the cell surface and transfer to the nucleus, the signals may involve in the control of the cell and any mutation in the ras gene may cause continuous activation of the pathway of signal transduction.[19] Ras's gene gets activated in the cell, when bind with GTP, but mutation induced by UV radiation may reduce the hydrolysis of GTP to GDP, and this way, it increases the activation.[2] This mutation in human skin cancer occurs less about 10-40% of skin cancers in humans. However, the frequency of mutation in the p53 gene is rather high in contrast. But, the frequency of RAS mutation is higher in XP diseased patients.[2]

Due to UV radiation, the most affected are p53 and patched genes; however, the RAS genes are not much affected.[22]

CONCLUSION

With the depletion of the ozone layer, UV rays get highly carcinogenic. They more affect sun-sensitive and fairer people than those are less-sensitive and black because they don't have much capacity to treat DNA damages. On the other hand, extensive count of melanocytes lay beneath the skin that provide ultimate protection to the cells from the damages of UV rays. However, evidence shows that UV rays damage skin cells via indirect pathways. Mutagenic factors inhabit in UV rays induce carcinogenesis either by inactivating or altering the functions of important gatekeeper genes-p53, patched, and RAS genes. These genes are responsible to carry out certain crucial pathways in the cells. They play an important role in cell growth, cell differentiation, protection, and transcription. These genes are also responsible to stop cell growth as well. UV rays, especially UVB, when continuously target organs, their mutagens invade in the skin and then in the cells and induce possible destructions. They produce dimers in the DNA structures and damage the ability of the DNA to recover. This damage induces apoptosis. Skin cancer has three types-BCC, SCC, and Melanoma, of which, BCC is the most common one and easily affect people. For skin cancer, excessive sensitivity to UV radiation is a significant risk factor. Continuing research should contribute to an improved knowledge of the genetic and immune suppressive mechanisms involved in the role of the tumor suppressor and the already identified oncogenes and genes not yet detected. Research into skin cancer may help raise consciousness about the harmful effects of UV exposure and lead to improved methods of prevention and treatment of skin cancer.

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