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Role of COX-2 and ROS in UV-B Induced Skin Carcinogenesis

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ABSTRACT

Non-melanoma skin tumors are among the cutaneous basal cell and squamous cell tumors (cSCCs), are the most predominant malignancies. While UV-stimulated p53 transformations give off an impression of being an early and essential occasion in the enhancement of skin tumors, another significant provider is the over-expression of cyclooxygenase-2 (COX-2). Oxidative pressures elevate with the moving inflammatory cells, are firmly related with cancer or malignant advancement, and have been demonstrated to be related with beginning, advancement, or movement measures during multistage carcinogenesis. UV generation of COX-2 illustration and Prostaglandin E_2 (PGE_2) creation is thought to advance skin carcinogenesis, as well as add up to even the most initial stages of UV-instigated skin damage. ROS (Reactive Oxygen Species) - intervened DNA injury assumes participation in the induction of carcinogenesis as well as in dangerous malignant alteration, and it might signify a significant donor in the pathogenesis of human carcinogenesis. The induction of COX-2 expression by acute UV exposure and constitutive up-regulation of COX-2 in UV-induced benign and malignant tumors leads to increased PGE_2 production. ROS present inside the cells which are intracellular signaling cascades perform a function such as secondary messengers where they induce and maintain the oncogenic phenotype of cancer cells; however, cellular senescence and apoptosis can also be induced by ROS, and hence they also, therefore, function as anti-tumorigenic species.

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INTRODUCTION

Skin is usually a soft layer, outer tissue which is flexible that covers the entire body of any animal. The main 3 functions of the skin are protection, regulation, and sensation. Skin plays a part in shielding the body against many pathogens. Their various other functions include insulation, body temperature maintenance, stimulation, and producing Vitamin D folates. Skin acts as a frontline defense from various exterior factors or exterior stress, which may include various environmental factors that may cause damage to the skin, genetic variations, and contagious substances that, may cause an unwanted impression on the integrity of the skin. Non-melanoma skin tumors are among the cutaneous basal cell and squamous cell tumors (cSCCs), are the most predominant malignancies. Danger factors for sCCSs incorporate high increasing UV exposure, hereditary inclination, persistent swelling, predecessor ionizing radiation, immunosuppression [1]. There is significant proof recommending the basic association of oxidative pressure in carcinogenesis. Subjection to bright ultraviolet (UV) light is the major etiologic factor prompting the improvement of the cutaneous squamous, furthermore basal

cell carcinomas and is likewise a dangerous factor for melanomas. Ultraviolet radiation-induced DNA injury causes a transient enhancement in p53 protein stable-state levels, which bring about the outflow of the cell cycle inhibitor p21 and impermanent development capture. If cells cannot fix the DNA harm, p53 stimulates apoptosis. As an alternative, if DNA harmed cells go through propagation, a consequence of lasting transformation can be seen. Repetitive UV contact leads to a collection of DNA harm and p53 transformations. While UV-stimulated p53 transformations give off an impression of being an early and essential occasion in the enhancement of skin tumors, another significant provider is the over-expression of cyclooxygenase-2 (COX-2) [2].

Oxidative pressure is an event caused by a difference between the manufacture and gathering of oxygen receptive species (ROS) in cells and tissues and the ability of a biological system to detoxify these responsive items. ROS production surpasses the cell's capacity to metabolize and detoxify them; a state of "oxidative stress" arises [3]. Normal ingestion of radical scavengers has been appeared to ensure against malignancy or cancer advancement in experimental animal models, as well as in epidemiological investigations in peoples. Oxidative pressure elevates with the moving inflammatory cells, is firmly related to cancer or malignant advancement. Oxidative pressure has been demonstrated to be related to beginning, advancement, or movement measures during multistage carcinogenesis [4]. Cancer growth progression is a multi-stage method categorized by the total activity of various changed cell measures including those of replication, angiogenesis, apoptosis, metastasis, etc. These incorporate synthetic chemical substances, x-radiation, ultraviolet radiation, singlet oxygen which are mediated by photosensitizers, and direct electron relocate that doesn't include the contribution of ROS [5].

Animals and UV Irradiation

Hairless SKH-1 mice of around 3±4 weeks old were bought and were utilized at 8 weeks old. Upon coming, the animals were housed in an environment-controlled quarter (22±1°C and at 50% humidity) with a 12 hr light and 12 hr dark cycle in yellow fluorescent lights. The mice were permitted free allowance to drinking water and standard feed regimen and were noticed every day during UV irradiation. The UV apparatus comprises 8 FS40 sunlamps, an IL- 1400 radiometer, and an attached UVB photometer. The spectral irradiance for the UV lamps was 280±400nm, 80% of which will be in the UVB region and the remaining 20% will be in the UVA region. The high intensity of the beam source was 297nm [Figure 1]. The effluence at 60cm from the dorsal side of the mice was 0.48± 0.50 mJ/cm^2/s. The animals were kept in a separate compartment in an open plastic enclosure on a revolving base to annul any distinctions impact across the UV lights.

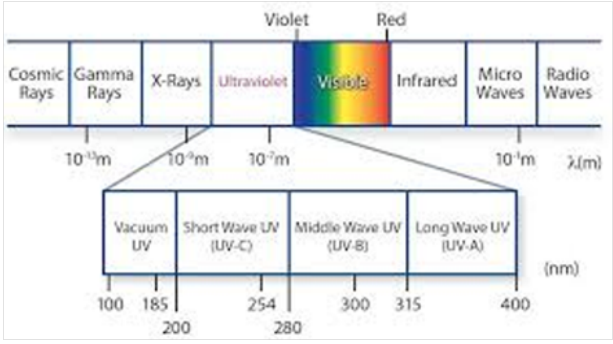

Figure 1: Ultraviolet A, B & C Wave length

The animals were provided with the controlled or investigational diets for 6 weeks when they were illuminated with UV radiation 3 times a week, with a starting dose of 90mJ/cm^2 which was enhanced by around 25% weekly, up to 220mJ/cm^2. During the tumor study, 30 hairless SKH-1 mice were put on control or medication-containing regime 1 week before the beginning of the UV illumination procedure. The animals were UV illuminated thrice a week by using the starting dose of 90mJ/cm^2 the beginning or 1st week, continued by a weekly elevation of 25% until 275mJ/cm^2 was attained. This procedure promotes skin tumors in hairless SKM-1 mice inside the period of 9 weeks. Every week tumor was tallied after the development of the first tumor and this procedure was continued up to the end of the experimentation period after 25 weeks. The tumor information is conveyed both as assortment (i.e., mean number of tumors per mouse). At the end of the trial period, the widths of the tumors were estimated and the tumors were allotted to either the 1 to 3mm size group or the > 3mm group, and the frequency of tumors in these groups was determined. Arbitrary tumors were then prepared for histological examination or utilized for the separation of RNA and protein [5].

UV and Skin Cancer

Chronic subjection of these animals to UVB illumination prompts the enhancement of the non-malignant epidermal tumors, the majority of which become Squamous cell tumors. Severe subjection of SKH-1 mice to the UVB prompts the manufacture of DNA injury in epidermal cells. Chronic or several UVB contacts leads to an enhancement in epidermal expansion and thickness and can also prompt p53 alteration and/ or allelic loss. This informa-

tion exhibit that UV-stimulated transformations and alterations in p53 manifestations are early occasions in UV-initiated skin carcinogenesis and are essential in cancer development [6].

Assimilation of UV beam by atoms in the cells brings about the production of reactive oxygen species (ROS), which can cause oxidative DNA injury. DNA damage brings about an elevation in the number of epidermal cells with wild-type p53 articulation. Employment of inflammatory cells into the dermis starts around 4 hrs after the UVB contact and neutrophil penetration stays high for a few days. UV initiation of COX-2 gene illustration seems, by all accounts, to be dangerously dependent on a cyclic AMP response element (CRE).UVB stimulates p38 mitogen-initiated protein kinase (MAPK) that prompts the phosphorylation of CRE binding protein (CREB) and initiating transcription factor-1, which then attach to the CRE site and transactivate the COX-2 gene promoter [7]. COX-2 is ordinarily not communicated in the majority of the tissues, yet it is extremely inducible by numerous stimuli, including cytokines, growth development factors, tumor supporters, and UV beam [8]. UV stimulation of COX-2 includes p53. DNA injury or ectopically conveyed wild-type p53 can produce COX-2 illustration via the up-guideline of the p53 target gene [Figure 2]. COX-2 and PGE2 have been appeared to have anti-apoptotic impacts and so the stimulation of COX-2 through the p53/Ras/Raf1/ERK pathway assists with neutralizing genotoxic stress-provoked apoptosis [9].

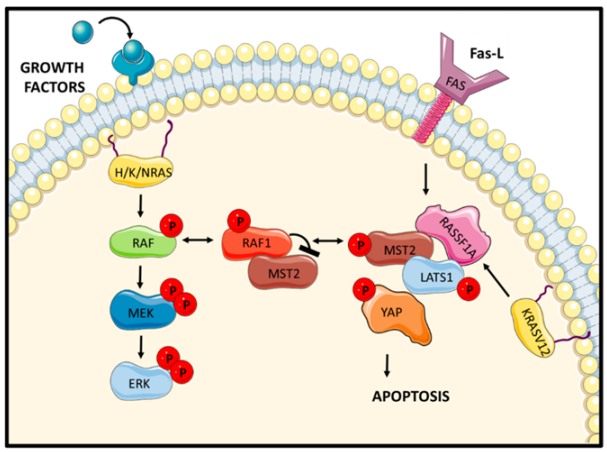

Figure 2: The RAF-MEK-ERK pathway

UV generation of COX-2 illustration and PGE_2 creation is thought to advance skin carcinogenesis, as well as add up to even the most initial stages of UV-instigated skin damage. COX-2 specific inhibitor, taken care of in the eating routine hindered UV. The utilization of COX-2 inhibitors to completely determine a part for CO- initiated keratinocyte propagation and elevated UV- initiated apoptosis, particularly in the multiplying basal layer [10]. Those COX-2 specific inhibitors have chemopreventive action against UV carcinogenesis just as UV-initiated inflammation and early skin injury COX-2 in carcinogenesis is dangerous in that these inhibitors have likewise been appeared to have COX-2-individual impacts. Genetic methodologies have also been utilized well to show particularly the function of Coxs in UV-initiated carcinogenesis [11]. COX-2 over expressing which is sturdily transfected human BCC cells concealed a greater amount of the proangiogenic factors, vascular endothelial development factor, and essential fibroblast development factor, stimulated endothelial cell tube development, and provoked more superior angiogenesis. The COX-2 over expressing BCC cells showed more prominent tumor development.

In addition to p53 modifications, other UV-incited measures are likewise measured as a critical step to the course of skin malignancy progression. COX-2 articulation has been demonstrated to be raised in SCCs, BCCs, and actinic keratoses. In the SKH-1 mouse model, COX-2 is overexpressed in benignant papillomas, hyperplastic skin, and in SCCs as a consequence caused due to the constant or continual exposure to UV radiation. Similar to p53 modifications, the COX-2 constitutive over-expression happens from the initial stage during UV-initiated carcinogenesis [12]. COX-2 /PGE_2 contains many anti-apoptotic properties in various cell types. Along with that, PGE_2 mediates various indications which are known to be involved in the induction of angiogenesis, inflammation, vascular permeability, and vasodilation. All of these various downstream properties of PGE_2 signaling and COX-2 over expression are known to encourage the development of UV-initiated skin carcinogenesis [Figure 3]. Despite the fact, that UVB frequencies are initially liable for UV-initiated DNA injury [13].

The electromagnetic energy of UV radiation is consumed by particles inside the cell, and this energy is then moved to atomic oxygen-producing ROS [14]. COX-2 illustration can be stimulated by a p53-intervened initiation of the Ras / Raf /ERK pathway. Genotoxic stress, for example, UVB-initiated DNA injury, initiates p53 articulation, the antiapoptotic movement of COX-2 /PGE_2 is avoided to a limited extent the stimulation of apoptosis by DNA injury / p53, as treatment of cells with an inhibitor of COX-2 improved genotoxic stress-prompted apoptosis. Ultraviolet-A radiation (UVA), which relates to 90% of the sun radiation, can enter the skin in a dosage gathering manner, links with the impact of UVB, and encourages dermal collagen degener-

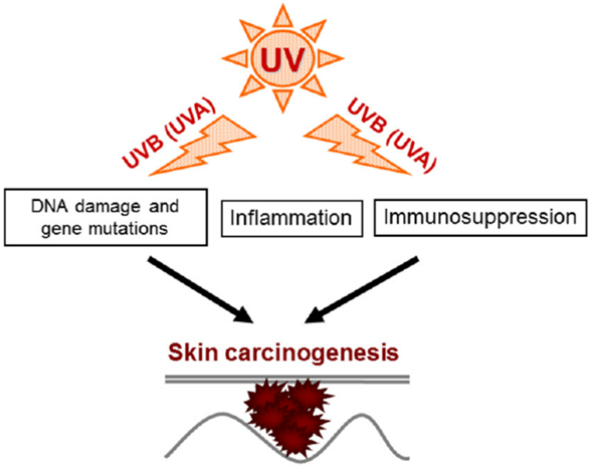

Figure 3: UV-induced carcinogenesis in the Skin

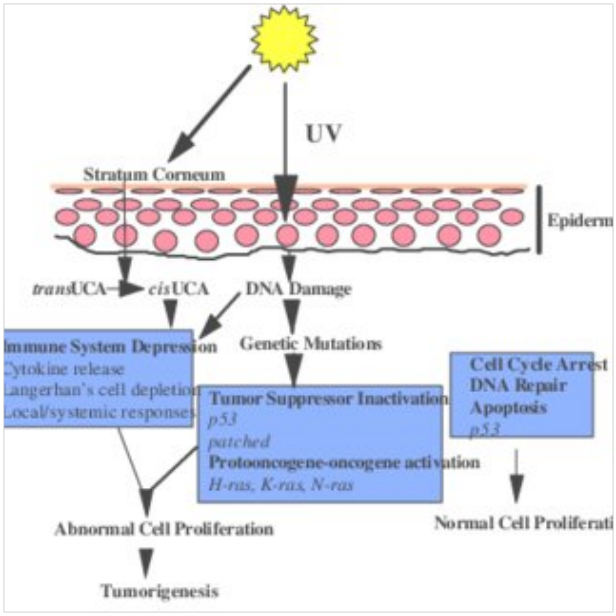

Figure 4: A model for induction of skin cancer by UV

ation, consequently causing skin irritation, inflammation, and untimely early maturing. UVA can influence different biological tasks including DNA replication, repairing, cell cycle control, and chromatin-modifying [15]. Every one of this evidence may add to the enhanced danger of skin malignancy related to UVA exposure.

Roles of Reactive Oxygen Species (ROS) in UV Carcinogenesis

ROS-intervened DNA injury assumes participation in the induction of carcinogenesis as well as in dangerous malignant alteration change and this manner; it might signify a significant donor in the pathogenesis of human carcinogenesis. UV-B prompts DNA injuries altered by ROS. UV-A additionally assumes a part in UV-incited carcinogenesis albeit just UV-B has been viewed as dependable. Skin tumors can be initiated by irradiating mice with UV-B. It has been set up that tumors are the outcomes that have come because of a collection of DNA injuries in critical genetic materials like oncogenes and additionally tumor-suppressing genetic material. UV illumination causes DNA alterations and accordingly is thought to be liable for sunlight prompted skin tumors [Figure 4].

UVB-initiated H_2O_2 creation advances the phosphorylation of ERK1/2, JNK, and p38. ERK1/2 initiates development factors and starts the tumor development procedure; phosphorylated JNK activates activator protein-1, engaged with methods like stimulus of tumor aggravation, invasion, metastasis, and angiogenesis; while p38-ERK is engaged with the instruction of NF-αB. Surely, in vivo considers have discovered that contact with UVB triggers NF-αB/p65 and its movement to the nucleus, in this manner initiating genetic material engaged with various procedures, for example, irritation, inflammation (COX-2 also, iNOS), or the cell cycle [16].

The cancer-causing nature of oxidative pressure is credited to the genotoxicity of ROS in different cell measures. ROS collection is just like an ordinary occurrence in numerous malignancy cells. Such collection can cause direct DNA injury or harm by enhancing a cell's alteration or mutation rate [17]. ROS-provoked DNA injuries along with an incapable DNA restoration method are well-recognized injuries similar to human malignancies, for example, on account of breast tumor cell lines and human breast tumor tissue [18]. Oxidative pressure is initiated by an irregularity between the creation of reactive oxygen and a biological order's capacity to promptly detoxify the reactive intermediates or effectively fix the resultant injury.

DNA injury assumes a part in the improvement of carcinogenesis [Figure 5]. Activities of ROS should be significant, probably their impacts on p53, cell multiplication, invasive property and even, metastasis. Persistent inflammation inclines to melanoma injury; in any case, the task of ROS in this is probably going to be complicated for the reason that ROS can some of the time produce action as an anti-inflammatory mediator [19].

Hereditary modifications, immune inhibition, and malignant alteration are observable facts associated with the source of disease. Malignancy is generally assumed to emerge from a solo cell that has become "instigated" by mutation of a couple of vital genetic materials, brought about by irregular mistakes in DNA replication or a response of the

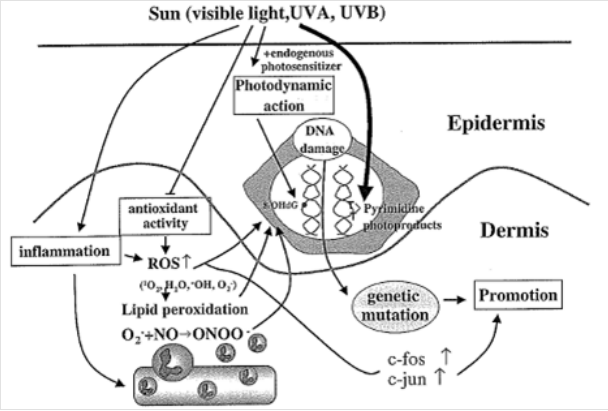

Figure 5: Mechanisms of UV-induced skin carcinogenesis

DNA with free radicals or other chemical substance species. UVB enhances ROS in epidermal cells, and triggers signaling pathways associated with modifying cell development, discrimination, and multiplication and accordingly encouraging the clonal development of tumor cells. Reactive oxygen species are produced through a mixture of occasions and pathways and are known to respond with all segments of the DNA fragment: harming both the purine and pyrimidine bases [20]. Lasting alteration of hereditary material which results due to these "oxidative injury" events addresses the initial step implicated with mutagenesis, carcinogenesis, and maturing in different malignancy tissues free-radical mediated DNA injury. ROS-initiated DNA injury includes single-or double-stranded DNA breakage, purine, pyrimidine, or deoxyribose changes, and DNA cross-joins. DNA harm can result in capture or enlistment of record, replication mistakes, and genomic precariousness, which are all related to carcinogenesis [21].

COX-1 and COX-2 Play Important Roles in PGE_2 Synthesis

UVB light is a recognized etiologic factor in the growth of Squamous cell carcinoma (SCC). The growth of UVB-initiated SCC happens because of changes at both hereditary and epigenetic levels. Hereditarily, UVB-initiated DNA injury is a serious occurrence at the beginning of SCC [22]. Interestingly skin tumor progress and development are frequently reliant upon changes in genetic illustration due to epigenetic occasions. Contact of skin to UV irradiation induces COX-2 illustration, which plays a part in an increase in PGE_2 levels. PGE_2 signaling utilizing its receptors plays a part in UV-initiated inflammation, edema, and keratinocyte propagation and responds to UV-initiated apoptosis. The oxidative nature of the COX enzymatic action may lead to the creation of reactive oxygen species, which in combination with the discharge of reactive oxygen species through the inflammatory cell can also play a role in oxidative DNA injury [23]. Chronic inflammation and a pro-oxidant state, together they are joined to COX-2 expression, mutually with UV-initiated p53 alterations are possibly the driving forces following the enhancement of UV-initiated non-melanoma skin tumor. COX inhibitors are efficient in reducing tumor proliferation and occurrence. In usual UV-initiated skin, COX-1 and COX-2 play important roles in PGE_2 synthesis [Figure 6]. The initiation of COX-2 illustration by acute UV contact and constitutive up-guideline of COX-2 in UV initiated benign and malignant cancers lead to enhanced PGE_2 creation and initiation of EP receptor signaling as a consequence in enhanced epidermal proliferation, initiation of inflammation, angiogenesis, and vascular permeability [24]. All these effects of COX-2 up-guidelines along with UV-initiated p53 mutations are probably the driving forces following the carcinogenic procedure induced and elevated by chronic UV exposures.

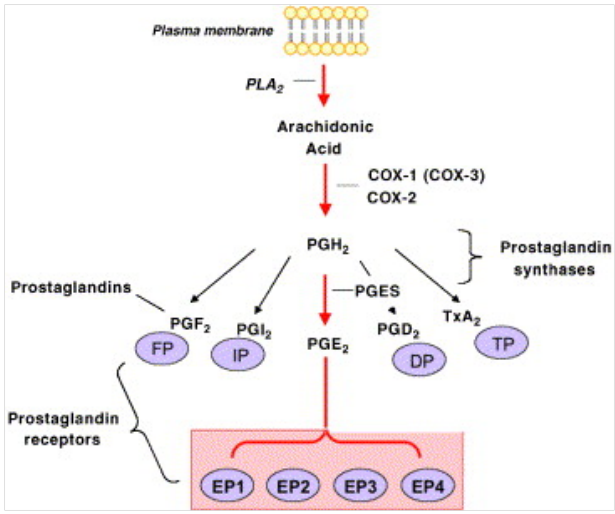

Figure 6: COX-1 and COX-2 play important roles in PGE_2 synthesis

It has been recognized that oxidative stress plays a significant role in UV-initiated skin carcinogenesis. Inflammatory procedures may initiate DNA alterations in cells utilizing oxidative stress. ROS inside cells behaves as secondary messengers in intracellular signaling cascades which instigates and maintains the oncogenic phenotype of tumor cells. The function of oxidants in the instigation of genetic alterations, it is obvious that ROS provoked cell-signaling pathways those involved in cell development regulatory pathways and hence they are instrumental in the progression of carcinogenesis [25]. The commencement of transcription factors includes both MAP-kinase/AP-1 and NF-αB pathways that have a straight effect on cell propaga-

tion and apoptosis. Thus DNA injury, genetic alterations, and changed genetic illustration, all act as a key player in the progression of carcinogenesis. Cancer is a relatively complex, multi-factorial, and multistage disease with several molecular modifications involved in every phase (which are namely initiation, promotion, and progression) of its enhancement. Oxidative stress has long been known to play a significant role in the human carcinogenesis process.

CONCLUSION

In UV-induced skin carcinogenesis, the agent nature of pyrimidine photoproducts does have been planned. These days it's been cam upon that inhibition performs a vital role in UV-induced skin carcinogenesis. The global reports are going to be essential to see even if there are any target genes for ROS in different several of carcinogenesis.

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Conflict of Interest

The authors declare no Conflict of interest, financial or otherwise.

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