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Review Article

UV INDUCED SKIN INFLAMMATION AND CANCER, WHERE IS THE LINK?

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A B S T R A C T

Skin cancer is one of the most common form of cancer in developed world. It is known that Ultra Violet radiation or UV is a causative agent of this disease. On the other hand, UV causes skin inflammation almost in a regular manner including sunburn. Chronic inflammation is well known to be associated with cancer promotion and progression. But, the link between the chronic inflammation induced by UV and skin cancer is a field of exploration. This review describes some of the underlying causes of the association between UV induced chronic inflammation and skin cancer.

INTRODUCTION

Skin cancer is one of the fatal types of cancer around the world. The number of new cases of skin cancer has been increasing steadily from last few decades and has become a serious concern today. The best-known way to control it is to prevent it. However, prevention of skin cancer is only possible if the etiology or the cause of the disease is thoroughly known. Now it has been accepted that solar radiation is one of the major cause of skin cancer. A part of solarradiation with a shorter wavelength (λ) than that of visible light, but longer than X-rays is known as ultraviolet radiation or UV. Overexposure to UV is known to be associated with many adverse health effects; different forms of skin cancer are some of the most severe among them, hence, it is a major public health concern.

The association of cancer development with chronic inflammation is a well-accepted idea. Several experimental tumor systems and epidemiological studies support this view [1-3]. Persistent expression of pro-inflammatory cytokines and other mediators including various growth factors at the site of tumor may help to increase in malignant cell survival and invasiveness. In this review authors have tried to focuses on the critical molecular link/s between UV exposure-induced skin inflammation and skin photo-carcinogenesis.

UV and skin cancer

Although low to moderate level of UV exposure and shorter exposure time are beneficial for us because it produce vitamin D in our skin, yet, overexposure to UV especially UVB radiation can cause inflammation of skin such as sunburn (a kind of acute inflammation) and other type of skin damages and some forms of skin cancer as well. Based on its effect on human health, UV radiation is popularly been subdivided into following classes: UV- A (long wave, 400 – 315 nm), UV-B (medium wave, 315 – 280 nm) and UV C (short wave, 280 – 100 nm) [ISO 21348:2007(E) Section 6.5.]. Of these, UV-C is the most detrimental with highest energy content and UV-A is least (lowest energy content). Earth's atmospheric ozone layer and diatomic oxygen together filter out solar UV-C and about 90% of UV-B. So the maximum UV radiation that reaches earth surface is UV-A, which is estimated about 95% of total UV radiation on earth surface, yet maximum health damage is caused by UV-B which accounts for only about 5 % of the solar UV radiation on earth surface.

UV is designated as group I type of carcinogen, means the most certainly it can cause cancer. All main types of skin cancers that is squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and melanoma can be caused by UV exposure especially in fairer-skinned radiation-sensitive people and incidences of non-melanoma skin cancer are much higher than that of melanoma under UV exposure. Studies found that ultraviolet B exposure increases the risk of non-melanoma skin cancer significantly which include SCCs and BCCs [1-4]. About 96% of skin cancers are either SCCs (80%) or BCCs (16%) [5, 6] and it was found that BCCs and SCCs occur mostly on sun exposed areas of body under chronic solar exposure indicating a clear connection between sun exposure and non-melanoma skin cancer formation [7]. Even, indoor UV tanners are more likely to develop skin cancer. Indoor UV

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exposure occurs from tanning beds, tanning booths, and sun lamps [8]. Avoiding longer exposure to sunrays or the indoor UV sources can lower the risk of UV induced skin cancer.

Overview of inflammation and cancer

Inflammation is a kind of body's self-defensive response which is meant to evolve to eliminate the effect of harmful substances like irritants or pathogens and to help wound healing. Major role in this process is played by our innate immunity which is present in our body from birth. Inflammation can be classified as acute inflammation which upon exposure of any causative agents starts rapidly and becomes severe within a few while, and chronic inflammation, which can last for few weeks to several months. Some most common symptoms of inflammation include swelling, redness, pain and heat. These signs are even more relevant when the affected area is on skin however if it occurs in deeper parts of our body such as in internal organs it may only have few sign or no sign at all. This process can induce growth and activation of cells which are either directly parts of our immune system or associated with it. These cells can be found in almost all type of body tissues.

On the other hand, the disease caused by an uncontrolled cell division is commonly known as cancer and the process of cancer initiation and promotion is called carcinogenesis. Inflammation plays a specific role in carcinogenesis. Virchow indicated that cancer mostly form at the site of chronic inflammation, a long ago [1]. Epidemiological studies also support this finding. In many cases tumor microenvironment is found to be infiltrated by cells which are associated with innate or adaptive immune system of our body. These cells might enable tumors to mimic inflammatory conditions which might aid in tumor growth and such kind of inflammation is often designated as "tumor-associated inflammation". Development of cancer by tumor-associated inflammation can be exerted by a number of mediators, cytokines and chemokines are just few to name [9]. This mechanism can provide the tumor cells various growth factors and extra-cellular matrix modifying enzymes that also help in promoting invasion and metastasis of tumor cells [10, 11]. For instance, chronic inflammations at many forms can promote tumorigenesis such as particulate matters and other components of tobacco smoke trigger injury and chronic lung inflammation, thereby increasing the risk of lung cancer [12]. Obesity is also considered to be a risk factor for liver cancer development because obesity-associated inflammation may serve as a crucial driving force for liver cancer promotion [13].

It is firmly believed that UV can cause inflammation of skin too. The immune response of skin due to exposure of sun light is mostly caused by UVB. Low and moderate level of UV exposure cause skin tanning, but higher intensities of exposure may cause more serious dermatological problems such as solar dermatitis, more commonly known as sun rash which can be seen as small, reddish blisters or spots on skin that have been exposed to sunlight. It is caused due to inflammatory response of the body in skin [14]. So, this is worthy to investigate the critical link between UV induced skin inflammations in photocarcinogenesis of skin.

Mechanism of inflammation by UV

UV induced alteration of macromolecules and inflammation

UV radiation can alter functioning of a immune-cell via several mechanisms such as direct DNA damage (structural damage), generation of reactive free radicals including reactive oxygen species (ROS) and generation of prostaglandins, histamine and other pro-inflammatory mediators.

A recent study showed that DNA damage can directly initiates inflammatory response and p53 signaling network can be behind this mechanism. Injury to chromosomes can alter the expression of a family of proteins called Toll-like receptors (TLRs). These proteins play vital role by defending our body from infection. Once damaged, the TLRs interact with p53, a known tumor suppressor gene to regulate the intensity of inflammation. Although it is known way back that DNA damage induced by UV can alter the p53 signaling network and helps in initiation of UV induced skin cancer but the link between direct DNA damage and inflammatory responses is only recently been discovered [15].

Cellular functions can be changed upon UV exposure by indirect methods as well, for example by generation of reactive oxygen species intermediates within cells [16]. The reactive oxygen species, generated by exposure of UV in skin can also mediates damage to a plethora of cellular macromolecules like DNA, proteins and lipids. Such damages, at a much larger scale, can bring disrupted cell metabolism, harmful morphological changes, and can bring on the regulatory pathways that control survival, proliferation and apoptosis of skin cells. Oxygen radicals induce peroxidation of membrane lipids caused by irradiation may contribute to increased phospholipase activity which helps in prostaglandin formation which ultimately helps in mediating inflammatory response [17-19]. ROS is also associated with tissue damaging effects of inflammatory reactions [20]. ROS induced by UV radiation can cause inflammatory responses on skin and it eventually causes damage to the cellular matrix, which is one of the key reasons of UV induced aging effect [16, 21].

UV induced altered expression of cytokines and inflammation

The exact mechanism of skin inflammation induced by UV exposure is still partially known, but it is evident that pro-inflammatory cytokines and chemokines play a very crucial role in this process. It has been shown that the UVB radiation can cause production of inflammatory cytokines and chemokines from different skin cells. Keratinocytes and Langerhans cells of human skin are known to secret a number of cytokines such as transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), growth factors such as platelet-derived growth factor (PDGF), nerve growth factor (NGF), basic fibroblast growth factor (bFGF), colony-stimulating factor- 1 (CSF- I)etc and interleukins such as IL-1β, IL-6, IL-8, IL-10 and IL-12. UVB exposure can alter the secretion pattern of these cytokines and initiates the inflammatory response. Keratinocytes can be induced to produce cytokines by UVB irradiation and deregulation of this production has been described in several skin cancers [22]. UV stimulates keratinocyte cultures to secrete pro-inflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), IL-6, IL-8 and IL-10. The release of these cytokines can trigger a cutaneous inflammatory response that develops in skin

exposed to sunlight [23-25]. Cytokines such as TNFα, IL-1, and IL-6 can also promote macrophage migration and eventually inflammation at the site of exposure [18, 26, 27]. Long term exposure of skin under UV radiation can cause production of IL-1α interleukin and ultimately turns on skin-inflammation as well. In a study Magcwebeba et. al. showed recently that UVB can significantly induce production of IL-1α from keratinocyte (HaCaT) [28]. Proinflamatory cytokines such as IL8 is known to promote tumorigenic and metastatic properties in primary cutaneous melanoma after UV irradiation [29]. One study showed that inflammatory doses of UVB can induce IL-33 expression within the epidermal and dermal skin layers in vivo and ex vivo [30]. IL-33 is known to be involved in the process of angiogenesis [31].

Chemokines, a family of small cytokines, are also involved in UV induces skin inflammation. An interesting study at translational level revealed that CXCL5 mediated UVB induced pain at the site of inflammation [31, 32]. In non-melanoma, UV radiation induces production of CXCL8, a common chemokine, from keratinocytes and plays important role in proliferation and migration of SCCs, one of the most prevalent types of non-melanoma skin cancer. It suggests the potential role of CXCR1/CXCR2 axis in UV induced inflammation and progression of cancer. Chemokine CCL27 and its receptor CCR10 are found to be overexpressed in cutaneous SCCs [33]. TNFα and interleukin IL-1β upregulate CCL27 production from keratinocytes and hence promote skin inflammation [33, 34]. Other than this, it has been observed that after exposure to UV light, formation of prostaglandins and release of histamine are increased form skin cells. Vital role of prostaglandins in tumor development was further substantiated by demonstrating a reduced susceptibility of mice deficient for the prostaglandin E2 receptor to DMBA/TPA-induced tumor formation [35]. The Phospholipase activity also increases upon UV exposure that helps in prostaglandin formation by making more substrate available [36]. Cyclooxygenases (COX) are the enzymes which increase prostaglandin formation and these molecules are involved in UV induced acute or chronic skin inflammation. Consecutive expression of COX1 or COX2 (two isoforms of COX) are commonly found in skin inflammation caused by not only UV but also with chemical stimulants [37, 38].

UV induced signal transduction modification and inflammation

Many specific signal transduction pathways and transcription factors have been identified to be responsible for the inflammatory effect of UV on human skin. Studies suggest that mitogen activated protein kinase or MAPkinase pathways and Ataxia telangiectasia mutated kinase or ATM kinases are most common pathways among many that become active under UV exposure and play an important role in UV-induced inflammation and photoaging [38, 39]. Particularly it has been found that the UV induced activation of transcription factors such as nuclear factor kappa B (NF-κB) and members of the activator protein-1 (AP-1) complex can be modulated as downstream effectors molecules of Mitogen activated protein kinases (MAPKinases), signal transducers and activators transcription 3 (STAT3) and also phosphatidylinositol-3-kinase (PI3K)-Akt signaling networks [38-41]. In fact, some reports suggest that MAPK activation is the central cellular response upon UV exposure. Normal human keratinocytes are found to have higher degree of ERK and JNK MAPkinases activity after UV exposure [41-43].UVB induced activation of p38 MAPK and Akt help in survival of keratinocytes and resists apoptosis and thereby provide a chance to accumulate more DNA damage, which might lead to cancer [44]. UV radiation induces PI3K pathway for cell survival and inflammation and this could be achieved as a downstream signaling of epithelial growth factor receptor or EGFR [45].

Transcription factor 'nuclear factor-kappa B' or NF-κB is known to have a pivotal role in chronic inflammatory diseases [46]. In a study, Abeyama *et. al.* showed induced sunburn reactions in mice under laboratory condition could be prevented by blocking UV-induced, NF-κB–dependent gene expression with oligodeoxynucleotides (ODNs) containing the NF-κB *cis* element (NF-κB decoy ODNs) suggesting vital role of NF-kB in regulation of gene transcription in sunburn [47]. It has been shown UVB induced DNA damage is necessary and sufficient to mediate NF-κB activation. But Simon *et. al.* showed that UVB can also directly activate this transcription factor independently from chromosomal DNA damage [48]. Other evidences suggest that NF-κB activity can be altered due to UVB exposure in HaCaT cells which can bring changes in the normal signaling [49]. Consecutive activation of this protein is linked with expression of proinflammatory cytokines and progression of SCC in murine model [50]. Hyperactivity of NF-κB in SCCs is also linked with a-catenin [51] which plays a crucial role in cellular differentiation. Chronic UVB exposure can increase the activity of NF-κB indirectly. UVB can reduce the expression of inhibitor of nuclear factor κB kinase-α (IKKα) in mice model. NF-kB and IKKα play a very important role in retaining homeostasis of skin. Interestingly expression of IKKα was also found to be down-regulated in skin squamous cell carcinomas emphasizing the importance of this signaling pathway [52]. The study by Xia et. al. suggests, reduction in the expression of inhibitor of nuclear factor-κB kinase alpha (IKKα) can promote UVB induced chronic inflammation and the process of carcinogenesis in mice model [52]. The importance of this molecule was also admitted recently by another study where the authors showed deletion of IKKα can induce VEGFR signaling which may be responsible for the tumor growth by regulating transcription factor AP-1 [53]. Interestingly, IKKα also have a role in SCC promotion [54].

According to another study, Endothelin-1 (ET-1), a vasoconstrictor peptide and one of the melanogens that contributes to UVB-induced tanning, was found to promote inflammation in various pathological processes, at least in part, indicating the role of UV in inducing inflammatory responses. Blocking of ET-1 receptors (ETA) was found to decrease cutaneous inflammation following UV irradiation [55]. UV can also modulate the expression of ICAM-I or intercellular adhesion molecule-1, a glycoprotein that can binds with integrin molecules [56] which are involved in regulation of cell cycle and cell motility. It has been shown that up-regulation of ICAM-I by UVA is mediated by activation of transcription factor AP-2 [57]. Studies have also found that exposure to UV light induces clustering and internalization of cell surface receptors for epidermal growth factor (EGF), tumor necrosis factor (TNF), and interleukin-1 (IL-1). The study founds whereas activation of each receptor alone resulted in modest activation of JNK MAPkinase, co-administration of EGF, TNF, and IL-1 resulted in a robust

synergistic response equal to that caused by exposure of UV light. Hence the study suggests, physical stresses may perturb the cell surface or alter receptor conformation, and hence altering the signaling pathways normally used by growth factors and cytokines [58].

All these reports suggest that inflammatory response is a fundamental process when skin cells are exposed under UV light and this mechanism is linked with a diverse group downstream signaling molecules with various functioning.

Mechanism of UV induced skin carcinogenesis

UV induced alteration of macromolecules and cancer

The mechanism of UV induced skin carcinogenesis is a multifaceted process that includes three different stages; initiation, promotion and progression. Overall the process of photocarcinogenesis includes direct DNA damage in skin cells, production of reactive chemical species within cell and activation/deactivation of different cellular pathways. In the initiation stage DNA mutations occur in genes such as in p53 tumor suppressor gene. At promotion stage by alterations in signal transduction pathways in the affected cells are found more commonly and forms premalignant lesions [59]. In the progression stage tumor the premalignant lesion becomes malignant and metastatic by multiple complex mechanisms. UV, especially UVB induce direct damages not only to DNA [the formation of cyclobutane-pyrimidine dimers (CDPs) and pyrimidine-pyrimidone (6-4) photoproducts ((6-4)-PP)] but also to proteins.

UV induced DNA damage can give rise to mutations and eventually activation of oncogenic tumor suppresser genes [60]. In a majority of human non-melanoma skin cancers, p53 protein is found to be involved [59, 61]. p53 gene mutations are the one of the best-studied phenomenon in UV induced skin cancers. p53 mutations, such as C to T transitions or double base changes such as CC to TT, are often found in all type of skin cancer and hence known as UVB signature [62]. Mutation of p53 genes have been detected in approximately 30–50% of the cases in BCCs and in a greater percentage in SCCs. There are evidences suggesting that UV induced DNA damage/or mutation can help in initiation of SCCs [63, 64]. Both UVA and UVB irradiation can act in mouse skin models as a complete carcinogen, which means that these wavelengths of light can function as initiation, promotion and progression factors. Studies have also showed that many other proteins involved with p53 signaling also play important role in UV induced skin cancer initiation and/or promotion. Few such proteins are p16, cyclin D1 and h TERT. All these proteins are involved in cell cycle regulation. Altered p53 function can change the rate of cell proliferation that leads to carcinogenesis. Improper functioning of DNA damage response mechanism/s (protective mechanisms) and DNA repair mechanism in UV exposed/damaged cells may often linked with photocarcinogenesis of skin. For example, in normal condition after DNA damage, p53 can inhibit transcription of CDKs (cycline Kinases) by activating p21, and arrest the cell cycle. This also helps in DNA repair. But UV induced mutation on this gene can reverse the scenario and hence helps in development of tumors [65].

Apart from p53, few other genes are often been identified that can be effected directly by UV induced mutation and cancer development. Ras oncogene is involved in development of different type of cancer and the role of ras oncogenes in UV induced skin cancer has also been studied. The ras family includes H-ras, K-ras, and N-ras. Ras proteins participate in signal transduction by binding to GTP. Ras is involved in growth control and upon activation can induce cell proliferation [66, 67]. It has been found that Ras mutation is involved in non-melanoma skin cancers [68, 69]. Studies suggest that UV exposure is involved in the development of BCCs by inducing Patched or ptc mutations. This protein can negatively regulate Hedgehog signaling which is one of the very important pathways in embryonic development and also found to be involved in cancer promotion. Genomic ptc mutations generally forms a truncated protein [70].

Findings from genetic and molecular studies for last few years have identified that INK4a/ARF locus acts as the “gatekeeper” melanoma suppressor. This locus encodes two very important tumor suppressor proteins in human, p16INK4a and p14ARF. Studies have identified the components of the p16INK4a/Rb pathway as the principal and rate-limiting targets of UV radiation actions in melanoma formation [71].

UV exposure also forms free radicals and induces a significant decrease in skin antioxidants, weakening the skin’s ability to protect itself against the free radicals generated after sunlight exposure. Singlet oxygen, superoxide anion and hydrogen peroxide are the major player which are produced due to high energy of UV and can oxidize a large number of intracellular molecules including DNA. This alteration in intracellular oxidizing environment exerts different phenotypic effects [72, 73]. Oxidative DNA damage is known to be involved in the process of skin carcinogenesis upon UV exposure [74]. On the other hand overflow of ROS formed due to UV exposure can exerts its biological effects by alteration of different signaling pathways including NF-κB and activator protein-1 (AP-1). In general this transcription factors are activated by ROS induced hyperactivity of MAPkinase signal cascade [75, 76]. UV induced intracellular ROS production can also activate EGFR signaling by inactivating phosphatases. Active EGFR can upregulate AP-1 transcription rapidly which is necessary for proliferation of epidermal cells [77].

UV induced modulation of signalling cascades and Cancer

Many studies have shown that UV light also involves the activation of different signaling cascades and transcription factors by multiple ways. These altered signaling cascades are mostly found in the promotion and progression stages of skin cancer. In particular, transcription factor NF-κB had been found to be involved in development of SCCs. The exact mechanism of NF-κB activation by UV radiation is still unclear, but evidence suggests the involvement of reactive-oxygen species, inhibition of the IkB negative regulator, and induction of TNF receptor 1/TNF receptor-associated factor-2 signaling could be the major mechanisms behind this [78, 79]. Mitogen-Activated Protein Kinase pathway is another key pathway that is activated by UV exposure in skin cells. This pathway includes three sub-branches, ERK, JNK and P38 MAPkinases. ERK is mainly activated by extracellular stimuli leading to cell growth and proliferation. UV induced sustained activation of ERKs mediates cell cycle progression through G1- and S-phase entry by regulating the expression of cyclin D. Other two MAPkinase pathways can also help in carcinogenesis and can be activated by UV induced oxidative stress [41, 78, 79]]. A recent study shows that activation of p38

MAPkinase pathway is a critical step in developing UV induced skin cancer [80].

UVA can also activate MAPKinase pathways and can regulate activator protein-1 (AP-1) mediated transcription and cyclooxygenase-2 (COX-2) expression. A study proposes that UVA-mediated increases in AP-1 and COX-2 may play a role in tumor promotion through increases in interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) [81]. COX2 is a very important target gene for UVB-light-mediated signal transduction resulting in immune-modulation and carcinogenesis. In almost all type of skin cancer including non melanoma COX2 is found to be expressed constitutively. COX2 is a very important molecule in prostaglandin (PG) signaling as well. Studies have shown that PG signaling is involved in different non melanoma skin cancer. UV exposure can upregulate COX2 and thus can increase the rate of biosynthesis of some form of PGs. PGs can help in survival of cells by activating different pathways including protein kinases (PK) A, PKB (or AKT), and PKC as well as Ca2+ dependent signaling [37, 82-84]. Interestingly TGF-b, which plays a crucial role in the inflammatory process can up-regulate prostaglandin generation and COX-1 and -2 expressions in mast cells and might significantly contribute in skin carcinogenesis.

Transcription factor AP-1 is activated in UV irradiated cells and reported to be involved in UV induced promotion of skin carcinogenesis. Activation of AP1 can increase higher rate of transcription of c-FOS gene through cyclic-AMP-response-element-binding protein (CREB). This protein thus helps in cell proliferation. In vivo studies suggest that inhibition of this molecule inhibits the ability of tumor formation of SCC cells in mice model. c-FOS is a component of AP1 protein which is a heterodimer. UV has been known to increase c-FOS level in cell. This can be achieved by induction of upstream signaling pathways such as p38 and ERK MAPkinases in human keratinocytes [85].Inhibition of these pathways can hinder UV induced proliferation of human keratinocytes. Mechanism of upregulation of COX2 by UVB can mediated through CREB. Upon activating the PI3K pathway in cells UV can decrease the phosphorylation of CREB (ser 129) which in turn help binding of this protein on the promoters of c-FOS and COX2 genes and increase their expression [86].

Later on, it has also been found that UV especially UVB helps in progression of SCCs by some other mechanisms such as by upregulating survival pathways related to EGFR signaling which is controlled by mitogen-activated protein kinases (MAPKs) and phosphatidylinositol 3-kinase (PI3K). UV-induced activation of EGFR has been shown to activate Akt through a PI3K dependent mechanism [45, 86]. Evidence also exists for an EGFR-dependent MEK/p38 MAPK/PI3K-mediated stimulation of COX-2 in response to UV irradiation [87]. According to some reports UVB can upregulate the activity of AP-1 in keratinocytes as a downstream molecule of ERK or p38 MAPK pathways, which might help in tumor cell proliferation and survival [88].

UV can also activate TNFα signaling in skin cells. According to a study, low dose of UVB can induce significant amount of TNFα production in skin and this molecule has been reported to be involved in tumorigenic activity [89]. MAPK and NF-kB are again found to be involved in TNFα production and in carcinogenesis [90].

A recent study showed that UV irradiation can directly activates cannabinoid receptors 1 and 2 (CB1/2). These receptors also exert their effect on cells via of mitogen-activated protein kinases and nuclear factor-kB pathways [91]. Chronic exposure of skin to UVB radiation induces cancer by two major and distinct mechanisms, by inducing somatic mutations and by deactivating immune response or immune surveillance. Chronic UV exposure can significantly decrease the expression of the Fas receptor and its ligand in the skin epidermal cells which in turn makes the cell apoptosis resistant and this could accumulate more mutations leading to increased chance of cancer formation [92].

In BCCs, apart from higher rate of p53 mutations, aberrant sonic hedgehog (SHH) pathway has been found. In skin, this pathway has been involved in growth and morphogenesis of hair follicles. In the absence of SHH, patched1inhibits smoothened (SMO), which is a G-protein-coupled-like receptor. SMO is released upon binding of SHH to patched1and can initiate a signal transduction cascade that causes activation of the transcription factor Gli. Thus, deregulation of this pathway by either loss of PTCH or forced expression of SMO results in elevated levels of the transcription factor Gli1 and as a consequence induces hair follicle tumors [93-96]. UV exposure can induce specific mutations in human patched gene and helps in basal cell carcinoma formation [97].

Similarities between UV induced inflammatory and photocarcinogenic mechanisms

Inflammation and/or immune activation is known to cause progression of cancer in different organs [98]. It is a fact that cancer can be promoted by inflammation specifically chronic inflammation which harbors a tumor-supporting microenvironment. Active inflammatory cells are often found to be present in tumor microenvironment. Cells which are most commonly found are tumor-associated macrophages (TAM), mast cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils and lymphocytes. These cells produce a variety of mediators such as reactive oxygen species, tumor necrosis factor α (TNFα), interleukins (eg IL-1, IL-6, IL-8) and enzymes such as COX-2 which activate or are activated by transcription factors such as NF-κB and STAT-3 [98, 99]. These transcription factors are also known to stimulate and maintain uncontrolled cell proliferation which ultimately develops cancer at different organs including SCCs [100]. The pro-inflammatory cytokines are often found to be involved in skin tumor initiation and promotion. For example, transgenic over-expression of the inflammatory cytokine IL-1α in basal keratinocytes also resulted in enhanced carcinoma formation [101]. The tumor promoting effect of inflammatory cytokines was also validated by some studies where it was found that IL-6, G-CSF and GM-CSF are responsible for the enhanced tumor growth of HaCaT cells and human BCCs [102-104]. Thus, involvement of some specific cytokines/chemokines to the tumor-promoting effect of inflammation is massively significant.

Chronic inflammation caused by UV exposure can provide a perfect microenvironment to promote tumor development by influencing higher rate of cell proliferation and inducing DNA damage [105]. One of the most important components that link chronic inflammation and cancer promotion is the cytokine which is produced by activated innate immune cells and

eventually support tumor progression [105, 106]. Inflammatory cells such as macrophages can generate high level of ROS which causes induced cell proliferation. Nitric oxide and oxygen radicals can also promote mutation in those proliferating epithelial or stromal cells that may eventually develop cancer later [107]. Macrophages and lymphocytes can also secrete TNFα which is able to induce oncogenic mutations in tumor suppressor genes like p53 and inhibits its tumor suppressor activity [108]. Cytokine signaling in general can contribute to tumor progression by either increasing cell proliferation rate or by inhibiting apoptosis of damaged cells. Macrophages can secrete cytokines which help in tumor progression and metastasis [109]. Different growth promoting cytokines like TGFβ, VEGF may help in suppression of immune-surveillance [110]. Again inflammatory cytokines are found to be more commonly associated with tumor formation [111]. Pro-inflammatory cytokine TNF-a, which plays an essential role during skin inflammation, is associated with tumor promotion during carcinogenesis. Reports are available that suggest TNFα can be produces by SCCs itself which helps in the maintenance of the tumor [112].Many of these cytokines including TNFα exerts their effect by activating the transcription factor NF-kB which also shows anti-apoptotic effect and helps in survival and proliferation of cancer cells [113, 114]. Other group has shown that TNF-a signal transduction ultimately resulted in the activation of AP-1 responsive genes, such as GM-CSF or MMP-9 which promote inflammation and angiogenesis. It can even stimulate proliferation and invasion of skin tumor and keratinocytes [115, 116]. Some reports suggest that chemokines are involved in cancer promotion similarly [117]. Under UV exposed condition all these factors can help in development of skin cancer.

Accumulating data suggest that COX-2, a key player in the inflammatory response, is highly upregulated during carcinogenesis [118]. Evidence suggests that high levels of COX-2 expression and prostaglandin PGE2 production enhance tumor formation in skin [119, 120]. Overexpression of this enzyme sensitizes mouse skin for carcinogenesis [134]. COX-2 expression is also dependent on inflammatory cytokines such as IL-1 and TNFα and on growth factors like EGF [121]. IL-1 and TNFα are specific contributor of UV induces skin cancer.

It is very interesting to observe that AP-1, STAT-3 and NF-kB are the most important transcription factors involved in COX-2 expression. UVB activates AP-1 and NF-kB through the MAPKs and PI-3K/Akt pathways [41, 122] and both of them are involved in UV induced skin inflammation and carcinogenesis. Network of signaling molecules associated with AP-1 and NF-kB transcription factors are found to be common for both UV induced skin cancer and skin inflammation. These findings suggest a strong connection of these two mechanisms in the development and maintenance of skin cancer. In this process the role of MAPkinases as central signaling cascade, is commendable to mention [123]. In fact, the effect of anti-inflammatory drugs in chemoprevention of epithelial skin tumors has been studied extensively as the link seems to be undeniable and non-steroidal anti-inflammatory drugs (NSAIDs), e.g. inhibitors of COX-2, have been highly successful in preventing skin tumors in the mouse model.

CONCLUDING REMARKS

Inflammation and cancer both are complex processes that are mediated by a number of signaling networks. Although evidences for involvement of inflammatory mechanism in cancer is yet to explore but overall this review provides a handful of information in support of a strong connection between UV radiations induced skin inflammation and skin cancer. Inflammatory response of skin in presence of solar radiation could be considered as an important sign for cancer initiation and promotion. Various cytokines as a response of inflammations are the initiator of the carcinogenic process. The role of ROS in this context is mention worthy. Cytokines can also block the apoptosis of UV induced DNA damage cells and helps in accumulation of mutations that lead to cancer. Activated molecules such as NF-kB and TNFα may play an essential role in controlling the whole process. Hence the anti-inflammatory treatment might play a vital role in controlling the ever increasing rate of UV induced skin cancer. Especially anti-inflammatory drugs that target NF-kB or AP1 signaling could be effective against the disease.

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