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Book Chapter

Implication of Ultraviolet Irradiation in Photo-carcinogenesis

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Abstract

Human skin is exposed, on a daily basis, to various exogenous threats including ultra violet (UV) solar rays. Long-term UV exposure can lead to serious consequences such as photo ageing, freckles as well as formation of either malignant or benign skin tumors. Such exposure activates distinct signaling pathways and triggers the formation of lesions whose regulation and repair are

fine-tuned and can determine the cell's fate (survival, apoptosis or carcinogenesis).

UV Radiation, Skin Penetration and Resulting Damage

Solar UV radiation is sub-classified into UVA (320-400nm), UVB (280-320nm) and UVC (200-280nm). UVC is absorbed by the ozone layer rendering the UV spectrum reaching earth restricted to 95% UVA and 5% UVB. These two solar rays allow the induction of DNA lesions, thus playing a critical role in skin carcinogenesis. The more energetic UVB can be absorbed by the epidermis and superficial dermis; whereas the less energetic more penetrating UVA can reach deep into the dermis.

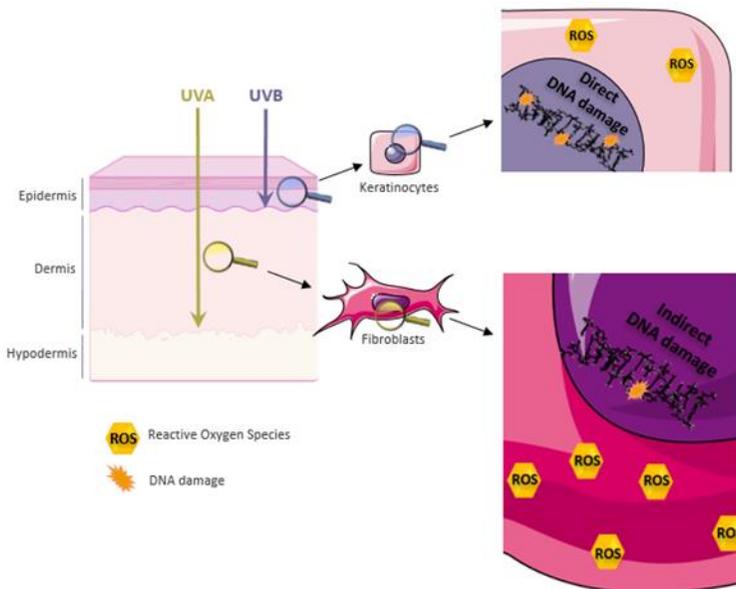


Figure 1: UV skin penetration and molecular outcomes.

Out of solar rays, UVA and UVB can penetrate the skin to reach deep into the dermis or be restricted to the epidermis respectively. UVB rays induce direct damages to the DNA and the formation of reactive oxygen species (ROS). UVA's damage to the DNA is indirect via photosensitization reactions by ROS produced at a high rate.

On one hand, UVB irradiation generates direct damages to the DNA in the form of dimeric pyrimidine photoproducts including Cyclobutane pyrimidine dimers (CPDs), 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs) and Dewar isomers [3]. The latter are formed between two adjacent pyrimidine sites TT, CT, TC or CC. The 6-4 PP are readily repaired in faster kinetics compared to CPDs where the TC and CC-CPD are the most mutagenic ones [4]. UVB also contributes to the generation of double-strand breaks via collapsing the replication forks at dimer sites and formation of reactive oxygen species (ROS) [5]. The generation of 8-hydroxy-2-deoxyguanosines (8-OHdG) was reported post UVB irradiation that leads to G→T transversion. The majority of UVB-induced mutations are C→T or CC→TT transitions designated as the UVB signature mutation [6]. On the other hand, UVA damage to the DNA is indirect via reactive oxygen species that are generated at bigger amounts than UVB-induced ROS. The most common UVA-induced lesion is 8-oxo guanine. CPDs' indirect formation post UVA are mediated by chemically generated excited electronic states [7]. In addition to DNA damage, ROS can also contribute to lipid peroxidation and protein oxidation (figure 1).

UV-Induced Apoptosis

Apoptosis is triggered in irradiated cells by three different mechanisms. UV-induced DNA damage favors the activation of ataxia telangiectasia and rad3 related (ATR), ataxia telangiectasia mutated (ATM) and DNA-PK kinases that ultimately activates p53 via checkpoint kinase ChK1/2 as part of the DNA damage response. p53 regulates the transcription of cell cycle protein p21 and several pro-apoptotic factors including APAF1, NOXA, PUMA, Bax and Bak. This contributes to the arrest of the cell cycle. If damage repair fails, P53 via downstream effectors the modulation of mitochondrial permeability to allow the release of cytochrome c. APAF1, procaspase 9 and cytochrome c favor the formation of the apoptosome leading to the activation of caspase 9 then caspase 3 [2]. Moreover, the production of reactive oxygen species post UV induces, in addition to DNA damage, lipid peroxidation, protein oxidation and the release of cytochrome c to mediate

another intrinsically triggered apoptotic pathway. One final mechanism of apoptosis is mediated via the extrinsic effect of UV in clustering death receptors, including the tumor necrosis factor (TNF) receptor superfamily members the CD95 (Fas/APO-1) or TRAIL, leading to the activation of a cascade of caspases from caspase 8 till caspase 3 [8] (figure 2).

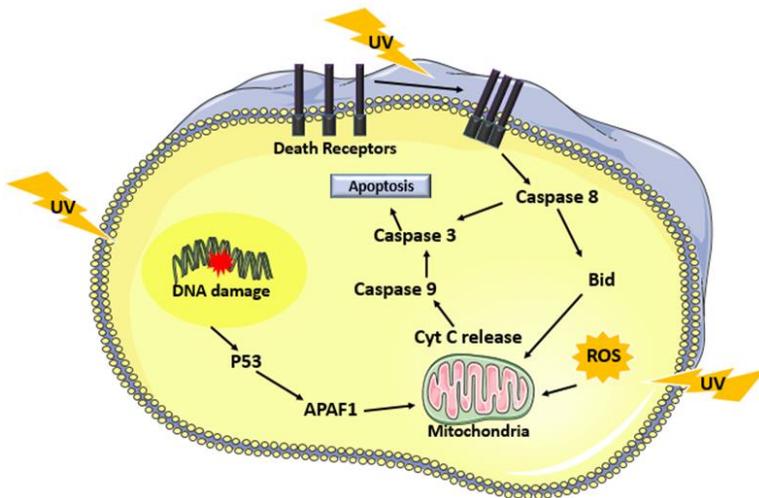


Figure 2: Mechanisms of UV induced apoptosis.

UV irradiation triggers cell apoptosis by three different mechanisms. The first is mediated by p53 activation due to DNA damage that ultimately leads to the activation of caspase 9 followed by caspase 3. Reactive oxygen species generated by UV also induce apoptosis by enabling the release of cytochrome c from the mitochondria. One final mechanism is via UV mediated clustering of death receptors leading to the activation of caspase 8.

UV-Induced Signal Transduction

AKT Pathway

The full kinase activity of Akt is achieved on one hand by its phosphorylation at two distinct sites, Thr308 phosphorylation via receptor tyrosine kinase activated PI3K and Ser473 by mTOR complex 2 (mTOR/Rictor; mTORC2) [9]. Its inhibition, on the other hand, is achieved by the tumor suppressor PTEN [10]. UV triggers tyrosine kinase receptors as well as the inhibition of PTEN to enable Akt activation post-irradiation [11]. This further

permits the activation of anti-apoptotic transcription factor NFκB [10] and p53 negative regulator MDM2 [12]. The latter together with Akt mediated inhibition of FOXO [13], pro-apoptotic forkhead transcription factor, and apoptotic proteins Bad and caspase 9 [14] infers an anti-apoptotic Akt mediated signal. Cell cycle progression is also achieved via the inhibition of nuclear translocation of cell cycle inhibitors p21 and p27 [15]. Akt also increases metabolic activity via the phosphorylation and thus inhibition of glycogen synthase kinase (GSK3) [16]. The outcome involves the modulation of protein synthesis and autophagy. The Akt-mediated inhibition of TSC2, tuberous sclerosis protein 2, leads to activation of mTOR/Raptor (mTORC1) that promotes translation via phosphorylation of eukaryotic initiation factor 4E (eIF-4E) binding protein-1 (4E-BP1) and p70/p85 S6 kinase (S6K) [17] (figure 3).

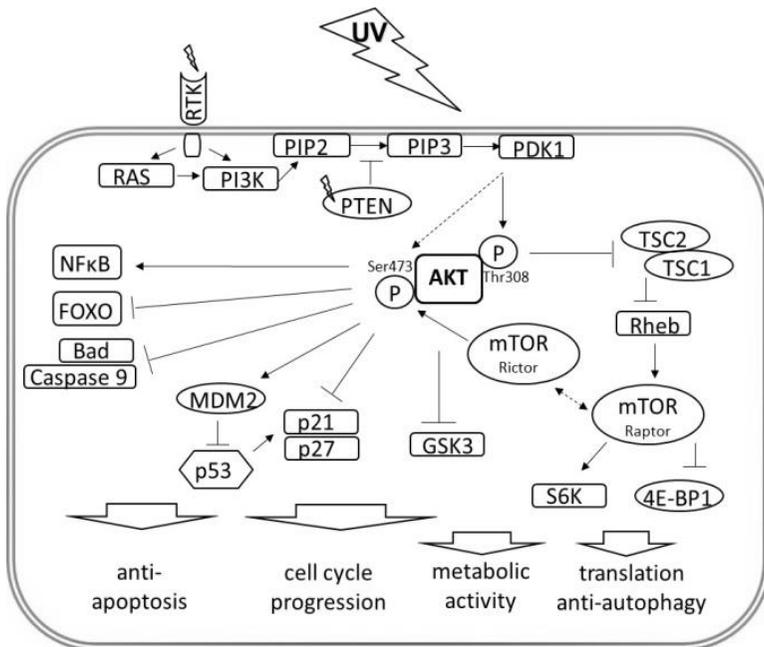


Figure 3: Physiological functions triggered by UV induced Akt signaling. UV induced Akt activation can induce the activation of several downstream cellular functions including inhibition of apoptosis, cell cycle progression, metabolic activity inductions and translation. Detailed description available in the text [2].

MAPK Pathway

Another UV-activated pathway is the mitogen-activated protein kinase (MAPK) pathway with final effectors including the c-JUN NH2 terminal kinases (JNKs), the extracellular signal-regulated kinases (ERKs) and p38 kinases that regulate the activity of transcription factors NF κ B and AP-1. The different forms of UV irradiation (UVA, UVB, UVC) explicit different modes of MAPK activation that is dose-dependent.

UVA induced MAPK signaling

UVA induces the activation of epidermal growth factor receptor (EGFR) that then leads to the phosphorylation of the 40S ribosomal protein S6 by p70^{S6K} (70-kD ribosomal S6 kinase) and p90^{RSK} (90-Kd ribosomal S6 kinase, also known as MAPKAP-K1) [18,19]. The activation of p70^{S6K}, on one hand, is achieved by different MAPK pathways phosphorylating four distinct sites.

PI3K activation induces the phosphorylation at Ser411, Thr421 and Ser424 while mTOR phosphorylates the Thr389 site. These four sites are phosphorylated by ERK1/2. P38 phosphorylates Thr389 and JNK added phosphate groups on both Ser411 and Thr389 [20]. On the other hand, ERK and JNK but not p38 enable the phosphorylation/activation of p90RSK at Ser381 [21]. It should be noted that the inhibition of EGFR abrogated the UV induced phosphorylation of ERK but not p38 and JNK implying that EGFR mediated signaling to p90RSK and p70S6K is ERK [22] and PI3K dependent. These ribosomal kinases regulate various cellular functions like proliferation and differentiation. Moreover, UVA irradiation can direct cellular decision towards apoptosis triggered by p53 and JNK [23]. The latter being activated by sphingomyelinase (SMase) and thus ceramide hydrolysis [24] (figure 4).

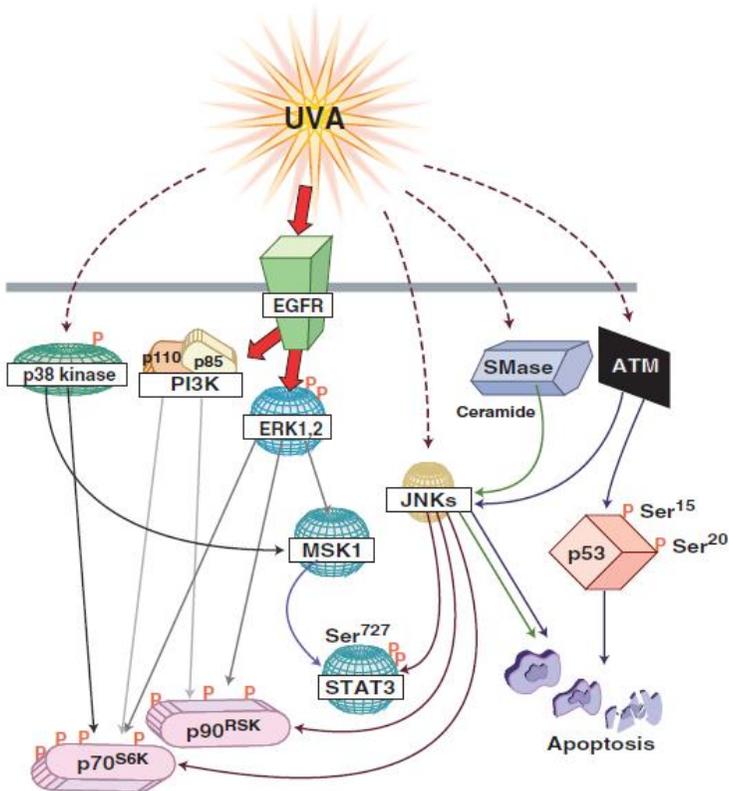


Figure 4: UVA induced MAPK signaling.

UVA activates EGFR that leads to the phosphorylation/activation of several downstream effectors including p70^{S6K} and p90^{RSK}. UVA mediated apoptosis is mediated by the activation of JNK, ATM, or SMase [1].

UVB induced MAPK signaling

MAPK mediated UVB induced activation of AP-1 via PKC

UVB-induced activation of AP-1 implicates protein kinase C (PKC) that favors activation of JNK and ERK [25]. ERK further on mediates activation of AP-1 [26]. P38, however, was shown to be activated in EGFR dependent mechanism post UVB and that it further on led to apoptosis [27] (figure 5A).

MAPK-mediated UVB Induced Apoptosis

UVB-induced p53 dependent apoptosis is mediated via the phosphorylation of the latter at Ser20 by JNK [28]. Nonetheless, p38 and ERK phosphorylate p53 at Ser15 [29] (figure 5B). Apoptosis is also mediated by the activation of the pro-apoptotic protein BAD. The phosphorylation of BAD is carried out by several kinases including JNK1, ERK downstream kinases RSK1 and MSK1 and by p38 kinase allowing BAD's dissociation from the anti-apoptotic Bcl-XL [30] (figure 5C).

MAPK mediated UVB Induced Chromatin Remodeling

The phosphorylation of nucleosome structural protein histone H3 regulates its role in enabling gene expression and chromatin remodeling. Two phosphorylation sites are present on histone H3 which are the Ser10 and Ser28. Ser10 phosphorylation is mediated via ERK and p38 [29] whereas Ser28's phosphorylation is mediated by JNK, ERK and p38 kinases together with ERK and p38 downstream kinase MSK1 [31,32] (figure 5D).

MAPK mediated UVB Induced Growth Control

Growth control regulation can be mediated at either the transcriptional level via ribosomal kinases or at the translational level by translation initiation factors. UVB activates PI3K pathway triggering the phosphorylation of several downstream effectors like Akt and p70S6K [33]. Akt UVB-induced activation is mediated via MSK1 [34] (figure 5E). Moreover, the p38 kinase through its downstream effector MSK1 phosphorylates eukaryotic initiation factor 4E (eIF-4E)-binding protein (4E-BP1) allowing its dissociation from eIF-4F, relieving the translational block and allowing cap-dependent translation initiation [35] (figure 5F).

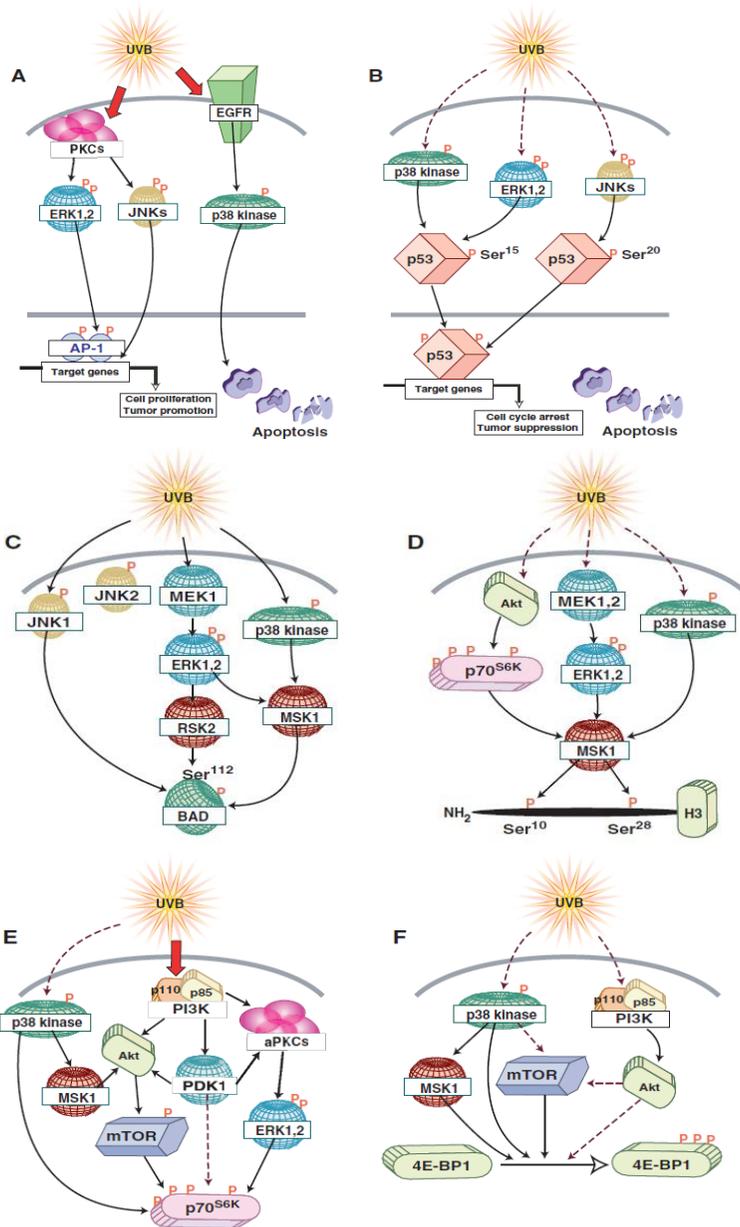


Figure 5: UVB induced MAPK signaling.

UVB can trigger different cellular functions via the activation of the diverse cellular effectors. (A) UVB can, on one hand, activate PKC leading to the activation of AP-1 and, on the other hand, mediate the activation of p38 via EGFR that leads to apoptosis. (B) P53 phosphorylation is achieved by both

ERK and p38 at Ser15 and by JNK on Ser15. (C) BAD phosphorylation at Ser112 is facilitated by JNK1, RSK2 and MSK1. (D) Histone H3 is phosphorylated at two sites: Ser10 by ERK and p38 kinase and at Ser28 by ERK, p38 and JNK. MSK1, a downstream effector of ERK and p38, also favors the phosphorylation at Ser28. (E) UVB mediated activation of Akt is PI3K dependent and MSK1 can also be involved in such activation. (F) 4EBP1 phosphorylation by the p38 kinase to MSK1 pathway favors its activation and dissociation from eIF-4E [1].

UV-Induced Mutations and Carcinogenesis

p53

p53 plays a critical role in the cell cycle arrest post-stress induction. It activates cell cycle checkpoints halting cycle progression allowing enough time for DNA damage repair. If the repair was unsuccessful, p53 aids in the commitment of the cell to apoptosis by the expression of several pro-apoptotic proteins. UV-induced activation of p53 is mainly mediated via (ATR) that phosphorylates checkpoint kinases (chk1/2) ultimately leading to p53 phosphorylation at Ser15 and Ser20 [36]. Mutations in p53 can be mainly detected in squamous cell carcinoma and less in basal cell carcinoma. Such mutations carry the UV fingerprint C → T transition [37]. Such mutations hinder the pro-apoptotic activity of p53 resulting in amplification of DNA damage accumulating cells. That combined with UVR-induced upregulation of heat shock proteins poses a combined effect on carcinogenesis evident via their co-localization with mutant p53 in squamous cell carcinoma [38].

PTEN

Phosphate tensin homolog is a known inhibitor of the PI3K/Akt leading to the deregulation of cell proliferation and induction of apoptosis. Besides, PTEN also has a role in the regulation of DNA damage repair of NER and DSB. In the course of NER, Ming et al. showed that downregulation of PTEN expression in the epidermis of mice predisposes them to skin tumorigenesis upon UV irradiation [39]. One hypothesis involves the reduction of xeroderma pigmentosum C (XPC) expression upon PTEN downregulation via the Akt/p38 pathway. XPC is a DNA damage recognition protein in the nucleotide excision repair

pathway required for the identification of the UV induced DNA damages. The decrease of XPC thus allows the accumulation of CPDs and 6-4PPs. In DSB, PTEN downregulation leads to decreased Rad51 expression [40].

PTCH

PTCH gene encodes for a membrane receptor in the sonic hedgehog (Shh) pathway. The later plays an important role in regeneration and re-differentiation of adult tissue. The canonical signaling in the Shh pathway starts with the binding of the Shh ligand to the transmembrane receptor Patched (PTCH) inactivating it. This will relieve the PTCH-mediated inhibition of smoothened (SMO). SMO will further on activate the downstream signaling to result in the translocation of the Glioma zinc finger transcription factors (Gli) to the nucleus to initiate transcription [41]. Some of the downstream expressed genes are involved in tumorigenesis and they include BCL2 for apoptosis resistance, SNAIL for epithelial-mesenchymal transition, Wnt2 for cell stemness, and TGF β for immune suppression among others [42]. PTCH mutations bear the UV signature C \rightarrow T or CC \rightarrow TT transitions. The latter allows the inactivation of PTCH and its role in the inhibition of smoothened (SMO) expression. Therefore, SMO can then mediate the activation of Gli1 transcriptional factor resulting in tumor formation [43]. Such deficiency was recorded in 85% of BCC [44]. Gorlin syndrome is characterized with an increased predisposition to basal cells carcinomas due to a mutation in PTCH1 tumor suppressor gene. Charazac et al. reported that fibroblasts from Gorlin patients exhibit high radio-sensitivity. These cells appeared to manifest low expression and activity of base excision repair pathway proteins thus linking Gorlin clinical manifestations to possible defects in DNA damage response or repair capacity [45].

NRAS and BRAF

NRAS and BRAF play a major role in the mitogen-activated protein kinase (MAPK) pathway. The binding of growth factor to their respective tyrosine kinase receptor activates this pathway. RAS GTPase then conveys the intracellular signaling.

Active Ras bound to GTP allows the recruitment of effectors including the RAF family of serine/threonine kinases that regulate cell proliferation. RAF further on activates MAP kinase kinase (MEK1/2) and then MAP kinase (ERK1/2). The latter promotes cell proliferation [46]. Activating mutations in these genes are mainly found in melanoma. Only a single mutation in either gene can exist at a time [47]. Mutations in either are of the activating type enhancing the MAPK signaling. BRAF most frequent mutation is a T→A transversion.[48]. NRAS most frequent mutation is either a C→A transversion or A→G transitions in sun-exposed areas [49]. These mutations are not exactly a C→T UV signature mutation, however, their comparison with the mutagenic profile in bacteria reveals that they may be derived from UVA mediated oxidative DNA damage [50].

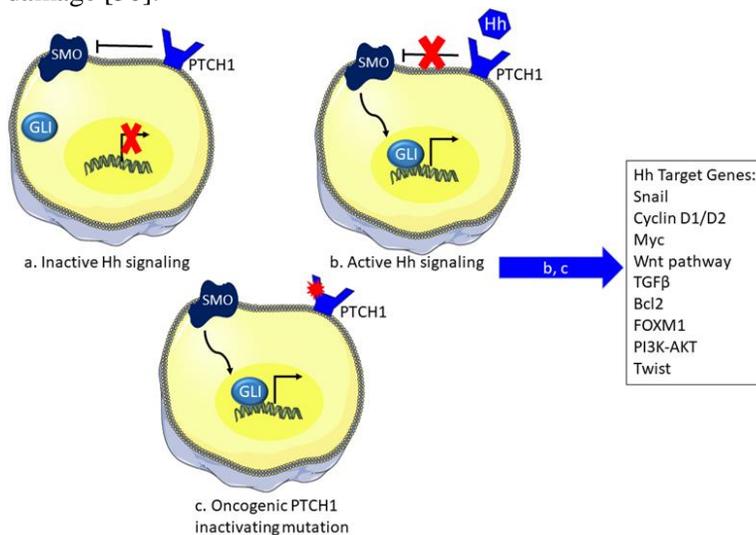


Figure 6: The sonic hedgehog pathway and the effect of UV irradiation.

The SHH pathway controls the expression of several downstream effectors. a) In the inactive state, PTCH receptor inhibits SMO and thus preventing the translocation of Gli to the nucleus blocking transcription of underlying genes. b) However, in the presence of the Hh ligand the PTCH receptor becomes inactive losing its inhibitory effect on SMO favoring the activity of Gli in transcription. c) Inactivating mutation of PTCH induced by UV irradiation relieve SMO inhibition and activates the pathway to express downstream genes via Gli. SHH: sonic hedgehog, PTCH: patched receptor, SMO: smoothened, Gli: glioma transcription factor

RAC1 and PREX2

PREX2 is a GTP/GDP exchange factor that can promote tumorigenesis via the inhibition of PTEN, a known regulator of the PI3K signaling pathway [51]. PREX2 also mediates the activation of the GTPase RAC involved in cell migration [52]. Large scale cancer genomic profiling revealed the involvement of mutations in these two genes with the melanoma oncogenesis [53, 54]. These genes interact to promote the PI3K/Akt [52, 55]. Mutations in the RAC1 gene possess the typical UV signature C→T transition mutation in sun-exposed areas that allows the activation of RAC1 and the underlying signaling pathways [56]. PREX2 mutations are also mainly found in sun-exposed areas [54] where it inhibits PTEN annulling its effect in the inhibition of the PI3K pathway.

Although other genes have been recorded to be involved in skin carcinogenesis, they do not possess a UV signature mutation profile signifying a different origin other than UV as their carcinogenesis initiator. The latter includes mutations in the cell cycle genes found in both basal and squamous cell carcinoma [57]. In addition, loss of p16INK4A was also identified in melanoma leading to the enhancement of CDK4 activity promoting proliferation [58].

UV-Irradiation Induced Immunosuppression

Genetic mutations alone do not represent the only initiators of skin tumorigenesis. An intricate signaling network interplays with such mutations leading ultimately to tumor generation one of which is the UV irradiation-induced immune suppression. The first form of suppression is mediated via the defective antigen presentation activity of Langerhans cells. UVR leads to the elevation of IL6, IL10 and TNF α levels thus inhibiting the skin immune response by downregulating Langerhans cells activity [59]. Moreover, UV irradiation was found to have a negative effect on the number of natural killer cells in a UV dose-dependent manner. The latter cells are implicated in anti-tumor and anti-viral infection [60]. UVB exposure also increases the expression of cyclooxygenase (COX-2) enzyme that catalyzes

the first step for the conversion of arachidonic acid to active prostaglandin involved in the inflammatory response. COX-2 is implicated in the development of several types of tumors [61]. Finally, one last activator of immune suppression is urocanic acid (UCA), a histamine deamination product highly available in the skin [62]. The inhibition of UCA with an antibody against it enabled the delay of tumor formation in irradiated skin [63].

Conclusion

Despite the filtration of the harmful UVC radiation by the ozone layer, the two remaining solar ultraviolet rays reaching the earth's surface are proving to be hazardous. UVB radiation can directly damage the DNA of exposed cells while UVA can indirectly create such damage via the generation of reactive oxygen species. After such induced stress, the cells that fail to repair the damage can either be committed to apoptosis or persist where their damaged DNA progresses to the UV signature C→T transition. These mutations have been identified in several genes correlated with skin carcinogenesis signifying a link between UV exposure and tumorigenesis. Moreover, UV irradiation activates several downstream signaling pathways including the Akt and MAPK pathways implicated in the regulation of cell proliferation, apoptosis and tumor promotion among many others. Finally, an additional instigator of tumor formation can be the UV-induced immune suppression where the inhibition of the action of some immune cells allows the cells' harboring damage and tumors escape from the surveillance of the body. For that, possessing an active repair system is essential to eliminate such dangerous UV-induced lesions where any defect will give rise to diseases like Xeroderma Pigmentosum and others with increased risks of skin cancers and neurodegeneration.

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