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Regulation of DNA Repair Process by the Pro-Inflammatory NF- κ B Pathway

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1. Introduction

Skin is the largest organ of the body. It is organized into three main layers, epidermis, dermis and subcutaneous layer. The epidermis, an outermost avascular layer, is formed by keratinocytes at the epidermal basal layer that differentiate into corneocytes at the outer layer of the epidermis. The dermis lies below the epidermis separated by a basement membrane and is composed mainly of fibroblasts. The primary function of skin is to constitute an efficient barrier to protect the organism both from water evaporation and from external aggressions. Skin is an excellent organ system to study DNA damage and repair since skin is routinely exposed to external and internal aggressors which can induce DNA damage. Sunlight is the primary environmental inducer of damage in the skin. In particular ultraviolet radiations (UVR) are known to induce damage on DNA bases by direct absorption of photons. Typical damages from the direct effect of UVR are the cyclobutane pyrimidine dimers (CPD) or the 6-4 photoproducts formation both created by dimerization of contiguous pyrimidines on the DNA [1]. Sunlight also induces significant damage to skin cells through the generation of Reactive Oxygen Species (ROS) which damage DNA nucleobases and the sugar phosphate backbone. Depending on the attacking ROS (singlet oxygen and hydroxyl radicals through the formation of superoxide radicals), different modifications are generated to DNA such as bulky (8-oxo- guanosine, as guanine is the most easily oxidized base, thymidine and cytosine glycol) and non bulky (cyclo purine and etheno adducts) base modifications, spontaneous hydrolysis of a normal or damaged nucleobase leading to an abasic site, (See review [2]). Finally ROS may also generate other forms of DNA damage such as single strand breaks (SSB) or double strand breaks (DSB) when the free radical attack is located on the poly- deoxy- ribose chain. Other external aggressors, such as cigarette smoke and pollu-

tion, may favor DNA damage onset by depleting intracellular anti-oxidant molecules such as glutathione and thus shifting the oxidative balance to favor oxidation by ROS. In addition to external aggression, cells are also subjected to internal aggression from ROS generated by oxidative metabolism or respiration as well as to the attack of genotoxic or photo-sensitizers coming from the diet.

DNA integrity being one of the key parameters to maintain a healthy organism, living cells have developed strategies not only to prevent DNA damage but also to efficiently repair any damaged DNA. In human cells, DNA is repaired by different mechanisms: Base Excision Repair (BER), Nucleotide Excision Repair (NER), Single and Double stranded Breaks Repair (SSBR and DSBR), Homologous Recombination (HR) and Mismatched repair. Basically, DNA alterations without strand breaks are repaired mainly by excision repair mechanisms where the damaged bases are removed from the DNA molecule by excision and then replaced with the right bases. In the case of the Nucleotide Excision Repair (NER) an oligonucleotide fragment of approximately 25-30 nucleotides is removed around the damaged DNA and the gap generated in the DNA duplex is filled by DNA synthesis using the opposite, normal DNA strand as a template. To complete the process of NER, the last nucleotide incorporated is covalently joined to the extent DNA by ligation [3]. BER consists of four to five steps in which specific enzymes play a role: excision of the damaged base by a glycosylase, incision of the resulting abasic site, processing of the generated termini at the strand break, DNA synthesis and ligation [4, 5]. A third mechanism called mismatched repair occurs when only one nucleotide mismatch appears in the DNA double chain. This mechanism is particularly effective for the repair of DNA error arising during replication due to the limited fidelity of the replicative machinery. Finally, DNA double strand breaks can be repaired by a specific process called homologous recombination and non homologous end joining [6].

The importance of the DNA repair process and its relevance in skin aging and skin cancer has been highlighted by genetic disorders affecting genes responsible for DNA repair. For example the genetic diseases Xeroderma Pigmentosum (XP), Cockayne syndrome (CS) and Ataxia telangiectasia (AT) are rare autosomal recessive pathologies where different and specific enzymes of the NER and BER pathways are deficient due to inactivating mutation in their genes [7, 8]. These diseases are characterized at the level of the skin by extreme sensitivity to sunlight, resulting in sunburn, pigmentation changes, an early onset of the appearance of skin aging signs and a greatly elevated incidence of skin cancers in particular for XP disorder [9]. These changes can be explained by long lasting DNA damages that induces prolonged cellular inflammation through the activation of the NF- κ B pathway [10-13] and an acquired immune deficiency [14] as well as rapid accumulation of mutation leading to cell apoptosis, senescence and cell tumorigenesis [15, 16][17, 18].

2. Inflammation and DNA repair

During tissue damage and the subsequent inflammation, a number of mediators are released which have been shown to modulate DNA repair. The activation of the Melanocortin

Receptor 1 (MCR1) by either its natural ligand, the α -Melanocyte stimulating Hormone α MSH or synthetic analogs [17, 18] can enhance the DNA repair activity in cells. Also two interleukins (IL), IL12 and IL23, known to display anti-tumor activity [19-22], have been shown to accelerate the repair of UVB induced CPDs. Activation of detoxifying mechanisms such as the Nrf2 pathway may enhance also DNA repair [23]. Finally mono- and poly-ubiquitilation as well as sumoylation play an important role in the regulation of DNA repair (see review by [24]). Thus inflammatory mediators can directly affect the DNA repair process and therefore could be regulatory factors either enhancing or repressing DNA repair. Recent studies have identified that the NF- κ B pathway, which is a key regulator in the expression of inflammatory proteins, may be an important mediator in DNA damage and the subsequent repair.

3. NF- κ B signal transduction

NF- κ B was first described in 1986 as a nuclear factor essential for immunoglobulin κ light chain transcription in B cells [25]. Since that initial discovery, NF- κ B has been found to be a primary mediator involved in regulating immune responses, apoptosis and cellular growth, as well as being present in inflammatory diseases such as arthritis and asthma, [26]. The NF- κ B family of transcription factors shares a high-conserved sequence of amino acids within their *amino terminus*, which contains a nuclear localization sequence that is involved in the dimerization with sequence-specific DNA binding and with the inhibitory I κ B proteins.

In unstimulated cells, NF- κ B-family proteins exists as heterodimers or homodimers that are sequestered in the cytoplasm in an inactive form by virtue of their association with a member of the I κ B family of inhibitory proteins, most notably I κ B α , I κ B β and I κ B γ [27, 28]. About 200 extracellular signals can lead to activation through the dissociation of NF- κ B from the I κ B proteins. These activating signals include viral and bacterial products, oxidative stress, pro-inflammatory cytokines including IL-1 and TNF- α , and phorbol esters [29-33]. Ultraviolet (UV) radiation from sunlight induces IL-1 and TNF- α and creates reactive oxygen species that then leads to NF- κ B-mediated inflammation [34, 35]. The kinase activity of I κ K phosphorylates two serine residues (Ser32 and Ser36) on I κ B proteins, which results in the ubiquitination and degradation of I κ B by the proteasome. The degradation of I κ B reveals the nuclear localization sequence of NF- κ B [27, 28]. Free NF- κ B can then translocate to the nucleus and bind to a NF- κ B *consensus* sequence present within the promoter region of target genes, thereby upregulating the expression of hundreds of genes, including cytokines (Interleukin-1, -2, -6, etc.), TNF- α , immunoreceptors (immunoglobulin kappa light chain, MHC class I, etc.), cellular adhesion molecules (ICAM-1, VCAM-1, ELAM-1), and many others [33].

4. NF- κ B and DNA damage

The NF- κ B pathway has been shown to be regulated by ionizing radiation at both the mRNA and protein levels by Brach et al., who demonstrated that NF- κ B transcripts were

transiently increased after irradiation, which was preceded by enhanced DNA binding activity of this transcription factor [36]. The causal role of NF- κ B in DNA damage has been hypothesized since suppression of the NF- κ B pathway by a pharmacological inhibitor resulted in a significant reduction in DNA damage as determined by T-T dimer formation in skin cells (Figure 1). Nuclear DNA double strand breaks (DSBs) are one of the most potent DNA damage signals to activate NF- κ B. This process can occur within 1–2 h after break induction through activation of the canonical inhibitor of κ B (I κ B) kinase (IKK) complex and I κ Ba degradation [12]. NF- κ B can be activated by Topoisomerase inhibitors (such as camptothecin) potentially via the generation of double strand breaks as well [13]. Furthermore activation of IKK following treatment with topoisomerase inhibitors was described to be dependent on the zinc finger domain in NF- κ B essential modulator (NEMO) [24]. DSBs can trigger two independent signaling cascades that eventually lead to the induction of NF- κ B via NEMO [35]. In one case, DSBs can activate ATM, which in turn can bind to and phosphorylate NEMO. In a parallel cascade, the p53-induced protein with a death domain (PIDD) translocates to the nucleus leading to the SUMOylation of NEMO. Consequently, the resulting activation of NF- κ B favors cell survival by turning on the transcription of several anti-apoptotic genes. In response to DSB, PIDD as well as ATM are capable of initiating cascades leading to pro- or antiapoptotic signals, NF- κ B presumably being a part of the pro-survival cascade [35]. Miyamoto et al., have summarized this model of NF- κ B activation by DNA damage as a ‘two signal’ model as it requires coincident NEMO SUMOylation and ATM activation by double strand breaks to permit robust NF- κ B activation [12]. Taken together these findings suggest that NF- κ B may have both causal and effector roles in the development of DNA damage.

5. NF- κ B and the DNA repair process

Although the mechanisms by which NF- κ B affects DNA damage are not fully established, one possibility is that NF- κ B may either directly or indirectly regulate DNA repair processes in cells. Protecting cells from apoptotic cell death following DNA damage is one of the major ways that NF- κ B activation regulates the DNA repair process. Wang et al., have demonstrated that NF- κ B functions as a positive modulator of cellular senescence, an intrinsic tumor suppression mechanism, by showing that human fibroblasts lacking NF- κ B activity prematurely exit from senescence [37]. Others have shown that skin cells devoid of NF- κ B activity exhibit deregulated growth correlating with impaired cell-cycle control [38, 39]. It has been proposed that the role of NF- κ B in cellular senescence could be cell type specific, differentially initiating senescence or acting further downstream in the DNA repair process to maintain the senescent state [37]. DNA damage caused by chemical genotoxic agents, such as camptothecin, has been described to activate the Ataxia Telangiectasia-Mutated (ATM) kinase and NEMO (I κ B kinase), leading to the inducing of NF- κ B p50/p65 heterodimer [40]. In a parallel signaling pathway, ROS can be generated by genotoxic agents in sufficient quantities to activate the NF- κ B pathway. ROS can also act as signaling molecules in immune responses, cell death and inflammation, where NF- κ B is involved [40]. Depend-

ing on the relative degree of DNA damage, multiple mechanisms of NF- κ B activation are engaged. Physical genotoxic agents such as UVA or hydrogen peroxide lead to extensive oxidative damage within the cytoplasm which can signal the activation of NF- κ B pathway in the absence of DNA damage.

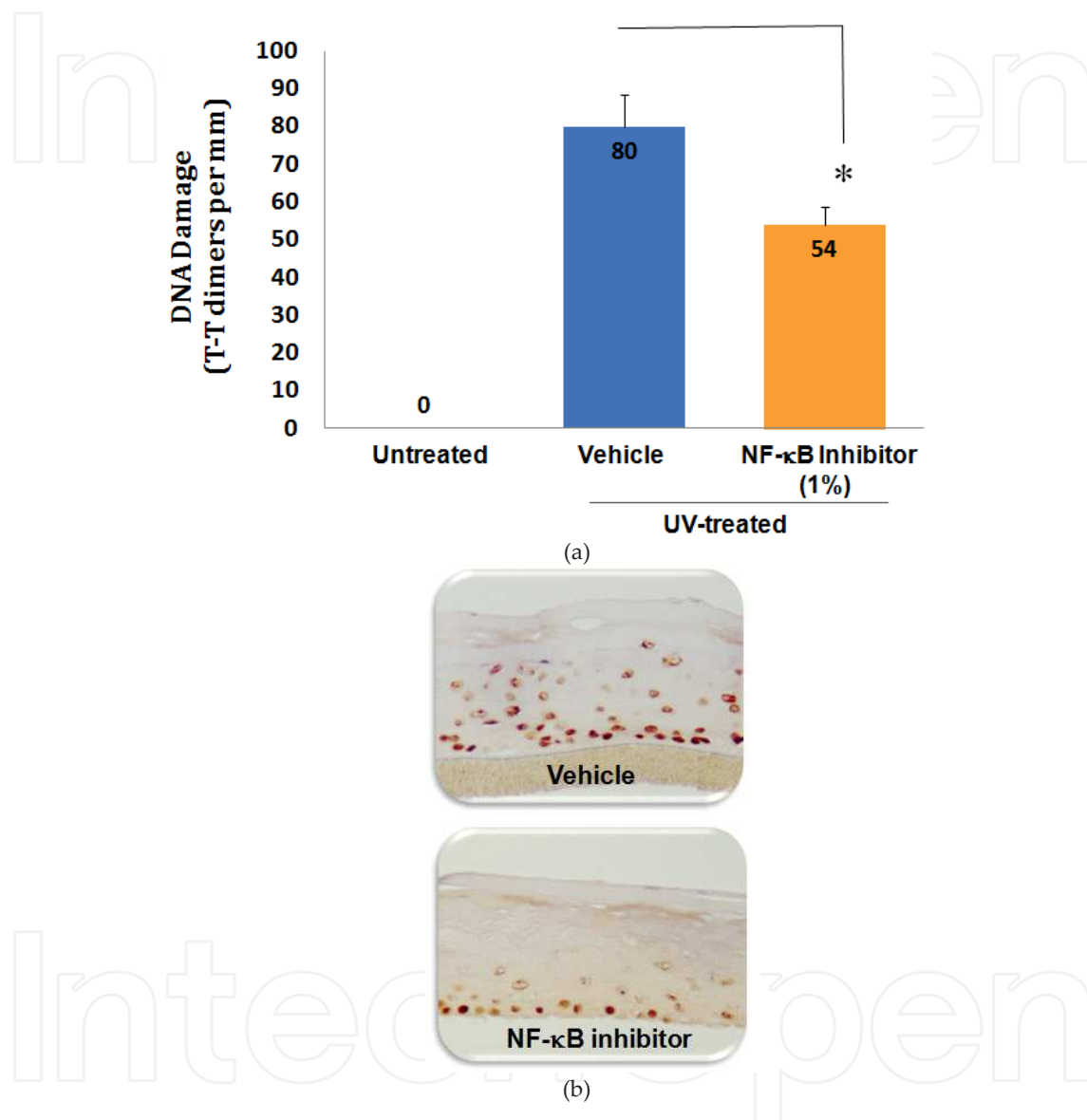


Figure 1. Topical pretreatment of skin equivalents with an NF- κ B inhibitor reduces UV-induced DNA damage
 Human epidermal skin equivalents were pre-treated with vehicle or NF- κ B inhibitor (4-hexyl-1,3-phenylenediol) for 2 hr prior to UV exposure, and DNA damage assessed by Thymine (T-T) dimer staining followed by blinded quantification. *P<0.05 using Student's t-test.

Among the various types of DNA damage, repairing double strand breaks can be particularly challenging to cells [41, 42], and may contribute to genomic instability associated with most cancers [42-45]. Wiesmuller et al., have shown that NF- κ B is involved in double strand removal and repair via a stimulatory action on homologous repair, involving the targets

ATM and the tumor suppressor gene BRCA2 [46]. NF- κ B is known to bind to the BRCA2 promoter and activate BRCA2 gene expression [47]. The role of NF- κ B in ATM function and DNA repair was demonstrated by Siervi et al., in T-cells where levels of ATM mRNA and protein were significantly reduced by NF- κ B blockade [48]. Activation of NF- κ B by ATM results in an anti-apoptotic signal in the cells. Wiesmuller et al. have also described that NF- κ B utilizes multiple mechanisms to enhance homologous recombination, including stimulation of the activity of CtIP-BRCA1 complexes to trigger DNA end processing, and upregulation of ATM and BRCA2 for strand transfer [46].

The nuclear factor p53 controls several physiological processes including DNA repair and cell cycle arrest. Cross-talk between NF- κ B and p53 has been established by multiple groups ([49, 50]; see review by [51]), including results that suggest NF- κ B may have both anti- and pro-apoptotic roles. Only a limited number of studies have investigated the role of NF- κ B in DNA damage and repair in skin cells (including: [38, 39, 52-55]). Evaluation of the p53-NF κ B cross-talk by Puszyński et al. in HaCat keratinocytes cells showed that inactivation of NF- κ B improved p53-mediated DNA repair and prevented arsenite-induced malignant transformation of HaCaT cells [54]. Marwaha et al. have shown that in primary skin cells, such as dermal fibroblasts and keratinocytes, treatment with T-oligos led to the up-regulation and activation of p53, coinciding with decreased NF- κ B DNA binding activity and inhibition of transcription from NF- κ B-driven promoter constructs [53]. Thyss et al. have demonstrated that the sequential activation of NF- κ B, Egr-1 and Gadd45 cascade induces UVB-mediated cell death in epidermal cells [55], a process that was crucial in order to eradicate the cells that bear the risk of becoming tumorigenic. In HaCat keratinocytes, hydroxytyrosol (main component of olive oil described as an inhibitor of NF- κ B), has been shown to significantly reduce the DNA strand breaks caused by UVB, and also attenuate the expression of p53 and NF- κ B in a concentration-dependent manner [52]. And finally, pharmacological inhibition of NF- κ B increased the DNA repair capacity of primary human keratinocytes suggesting a potential inhibitory role of the NF- κ B pathway on NER /BER in skin cells (Figure 2).

6. NF- κ B and the decrease in DNA repair capacity of dermal fibroblasts: A role in accelerating the skin aging process?

Aging of the dermal compartment of skin is generally associated with fibroblast aging. Indeed in skin biopsies of aged donors, a general decrease in collagen synthesis activity is observed as well as an accumulation of senescent cells that display a catabolic phenotype [56, 57]. We have recently shown that there is a general decrease in DNA repair capacity in aging dermal fibroblasts. Indeed, using two different types of DNA repair measurement that directly measure the activity on human dermal fibroblasts nuclear extracts on plasmid [58] and oligonucleotides [59, 60] bearing specific damages, we showed that the level of NER and BER are dramatically reduced in dermal fibroblasts from a group of female volunteers with age comprised between 40 and 50 years old compared to a results obtained in a younger group 20-30 years old for both chronically UV-exposed skin or non-exposed skin site [61, 62]. Sauvaigo et al. also demonstrat-

ed that SSB repair decreased with aging in dermal fibroblasts [60]. This suggests that the depression in the repair capacity of skin cells may contribute significantly to a lower resistance of aged tissue to DNA damage and thus accelerate the aging process of the skin tissue. The decreased DNA repair may also increase the occurrence of senescent cells as we have seen that on average subjects with the low DNA repair activity display more severe signs of skin aging such as wrinkle, overall photo-damage and firmness (Unpublished results).

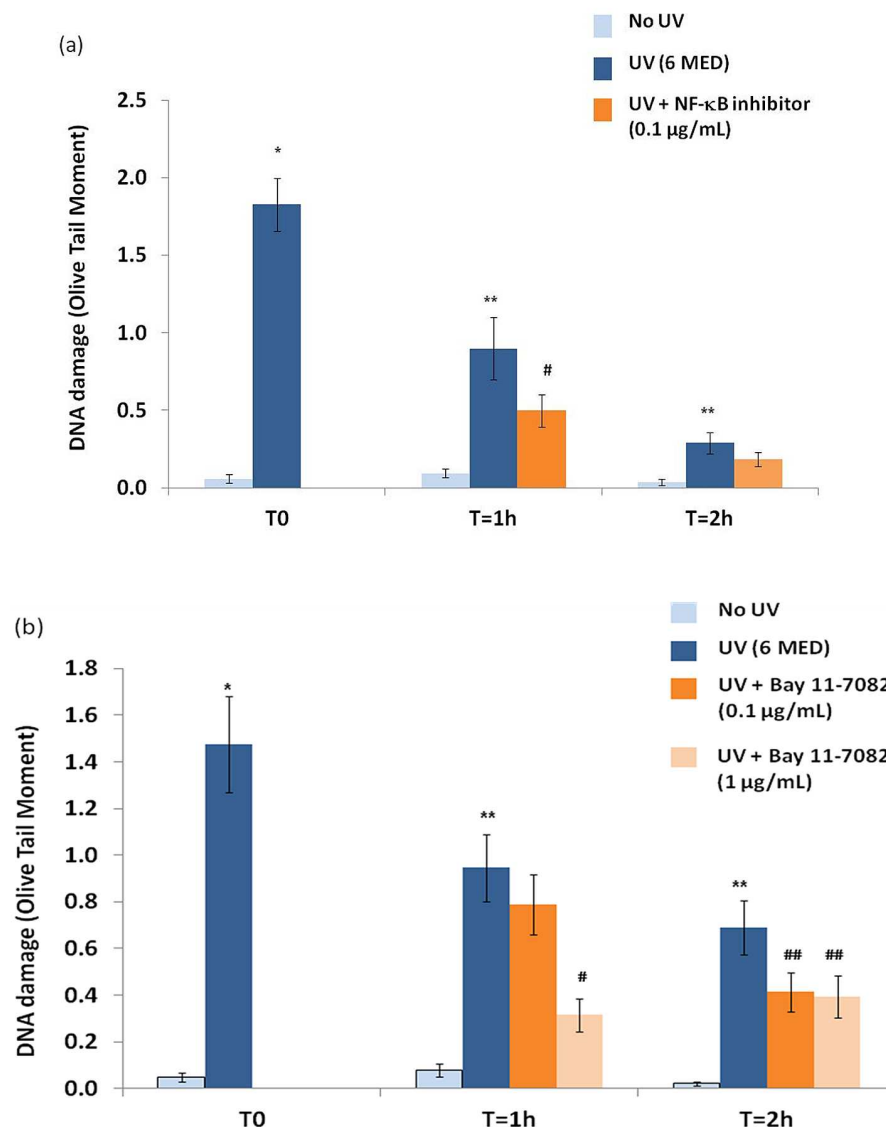


Figure 2. Treatment of primary human keratinocytes with NF- κ B inhibitors increased repair of UV-induced DNA damage. Primary human keratinocytes were exposed to UV, followed by immediate treatment with the NF- κ B inhibitors 4-hexyl-1,3-phenylenediol (Figure 2A) or BAY11-7082 (Figure 2B). DNA damage was assessed by Comet assay at T= 0, 1 and 2 hours after treatment with NF- κ B inhibitors

While the mechanisms contributing to the decreased DNA repair in aged skin are not known, in parallel we have observed that in aging dermal fibroblasts there was an increased

activation of the NF- κ B pathways which directly induced a transcriptional repression of the collagen gene expression [63]. Taken together, it could be hypothesized that the elevation of NF- κ B transcriptional activity may contribute to the decrease in DNA repair capacity of skin cells and thereby lead to accelerated skin aging. Since NF- κ B is activated by DNA damage, there is a potential for a vicious circle to take place as more NF- κ B may decrease the capacity of the cell to repair damages and lead to a longer persistence of the DNA damages.

7. NF- κ B and the development of resistance to alkylating agent-based chemotherapy

In addition to the putative role of NF- κ B and the decreased DNA repair capacity of skin cells leading to skin aging, NF- κ B regulation of DNA repair may also contribute to chemoresistance. Studies of chemotherapeutic resistance have shown a significant correlation exists between NF- κ B activation and the decreased effectiveness of some chemotherapeutic agents. Agents such as taxol and irradiation treatments upregulate the transcription factor NF- κ B which leads to promoting survival and chemoresistance in solid tumor cancers [64]. The mechanism for this chemoresistance is through the activation NF- κ B which can subsequently mediate cell survival, proliferation, invasion, and metastasis [65].

Sphingosine kinase may be of therapeutic interest in the context of inflammatory disease and drug resistant cancers. Sphingolipid metabolism has been shown to be aberrant in breast cancer tumor samples, resulting from an increase of sphingosine kinase expression [66]. The sphingosine kinase cascade pathway was first linked to the NF- κ B pathway in 1998 via demonstration that TNF induced adhesion was mediated through sphingosine kinase signaling, which links to downstream NF- κ B activation [67]. Using a novel selective Sphk2 inhibitor, ABC294640, Antoon et al. demonstrated inhibition of NF- κ B activation via inhibition of Sphk2 [68]. In vivo testing in a well-established immunocompromised xenograft model for tumor growth, demonstrated that this inhibitor showed lower proliferation of cancerous cells, and no tumor growth when compared to control. This establishes the underlying pathways including the inhibition of NF- κ B activation, as viable target for otherwise chemoresistant tumors [68].

Curcumin, a natural phenol that is present in turmeric has been shown to sensitize tumor cells to several anti-cancer drugs via modulation of NF- κ B and histone deacetylase. Curcumin suppresses activation of NF- κ B through I κ B kinase (IKK) activity inhibition [69]. In a xenograft model, curcumin plus paclitaxel significantly suppressed the incidence of breast cancer metastasis in lung tissue, and also demonstrated in these lung tissues was the reduction of the p65 subunit of NF- κ B [70]. By combining compounds which can either directly or indirectly inhibit the NF- κ B signaling pathway concomitant with chemotherapy, the resulting synergistic treatment may allow lower doses of the toxic chemotherapeutic agents to be used, improving patient responses [71]. These data help to demonstrate that down regulation of the NF- κ B pathway could lead to the tumor cells

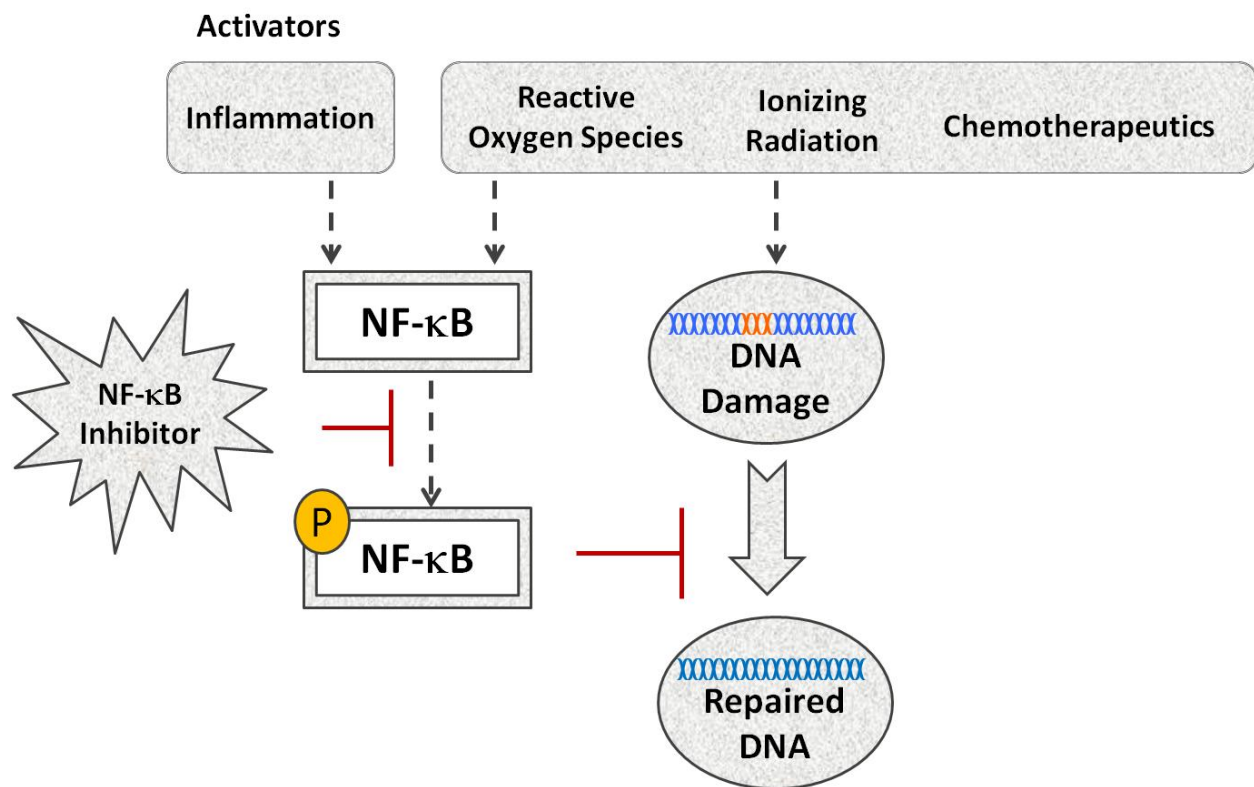


Figure 3. Model showing the effects of NF- κ B on DNA damage and repair

becoming more susceptible to current chemotherapies, and allow for lower doses of these therapies, leading to better patient outcomes.

8. Summary: The regulation of DNA damage and DNA repair by NF- κ B

Skin is under continuous assault from a variety of damaging environmental factors including ultraviolet irradiation and atmospheric pollutants. Extrinsic factors, particularly sunlight, have been demonstrated to accelerate the intrinsic aging process by increasing free radical production and decreasing antioxidant protections which can result in DNA damage and can affect the repair of damaged DNA. The age-related accumulation of somatic damage is worsened by sun exposure, leading to an increased incidence of skin disorders, skin cancer and potentially skin aging. New findings on the molecular mechanisms involved in the regulation of DNA damage and the subsequent repair of damaged DNA in the skin can help identify new targets to modulate DNA repair activity and thereby have a significant effect on skin physiology. The NF- κ B pathway is a key regulator of inflammatory mediators in skin cells and has been reported to be the final common pathway for the conversion of environmental insults into inflammation in the skin. Through the ability to regulate processes that result in increased DNA damage and decrease the repair of damaged DNA, the NF- κ B pathway may be a primary pathway linking inflammation and DNA damage.

Pharmacological inhibition of NF- κ B therefore may provide protection to skin from the numerous external aggressions encountered daily and reduce the DNA damage to oxidatively challenged and aging skin by increasing endogenous DNA repair processes.

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