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TGFβ signaling in photoaging and UV-induced skin cancer

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Abstract

Ultraviolet (UV) radiation is a major etiology for premature skin aging that leads to photoaging and UV-induced skin cancers. In skin, TGFβ signaling is a growth inhibitor for keratinocytes and a profibrotic factor in the dermis. It exerts context-dependent effects on tumor progression. Chronic UV exposure likely causes TGFβ1/Smad3 signaling activation and contributes to metalloproteinase-induced collagen degradation and photo-inflammation in photoaging. UV irradiation also causes gene mutations in key elements of the TGFβ pathway, including TGFβRI, TGFβRII, Smad2, and Smad4. These mutations enable tumor cells to escape from TGFβ-induced growth inhibition and induce genomic instability and cancer stem cells, leading to the initiation, progression, invasion, and metastasis of cutaneous squamous cell carcinoma (cSCC). Further, UV-induced mutations cause TGFβ overexpression in the tumor microenvironment (TME) of cSCC, basal cell carcinoma (BCC), and cutaneous melanoma, resulting in inflammation, angiogenesis, cancer-associated fibroblasts and immune inhibition, supporting cancer survival, immune evasion, and metastasis. The pleiotropic effects of TGFβ provide possible treatment options for photoaging and skin cancer. Given the high UV-induced mutational burden and immune repressive TME seen in cSCC, BCC and cutaneous melanoma, treatment with the combination of a TGFβ signaling inhibitor and immune checkpoint blockade could reverse immune evasion to reduce tumor growth.

Keywords

Skin aging; photoaging; ultraviolet; TGFβ signaling

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Conflict of interest

KY has no conflict of interests to declare. XJW is a founder and owns shares of Allander Biotechnologies, LLC, which has commercial interests in developing drugs related to regenerative medicine. Work related to the topic of this review was not supported by Allander Biotechnologies.

Introduction

Skin aging can be classified into two categories: chronologic and premature. Premature skin aging is primarily caused by environmental factors, such as ultraviolet (UV) irradiation (leading to photoaging) (Farage et al., 2008). In addition to the independent effect of UV radiation, skin changes during photoaging, such as deep wrinkles, can be accelerated by smoking, which may be attributed to the upregulated baseline level of matrix metalloproteinase 1 (MMP1) in skin (Durai et al., 2012, Lahmann et al., 2001). UV-induced skin cancer is another outcome of chronic UV exposure associated with 90% of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) cases, and 65% of cutaneous melanoma cases (Kim and He, 2014, Linos et al., 2009). In total, they account for 3.5 million new cancer cases, nearly 15,000 deaths, and over three billion dollars of medical costs annually in the United States, posing a major public health issue and economic burden (Rogers et al., 2015, Ruiz et al., 2019).

The major pathogenic effects of UV radiation on skin include the induction of reactive oxygen species (ROS) and genetic mutations. Within the spectrum of solar radiation, UVA often causes ROS to accumulate in the skin, altering gene and protein structures and functions, which results in decreased and fragmented collagen and elastic fibers in the dermis. This ultimately leads to deep wrinkles, skin laxity, and hyperpigmentation that characterize photoaged skin (Rittié and Fisher, 2002) (Figure 1). UVB can be directly absorbed by DNA molecules, generating photoproducts consisting of (6–4) pyrimidine and cyclobutane pyrimidine dimers (CPDs) (Mao et al., 2017). These photoproducts cause C>T and CC>TT UV-signature DNA mutations that represent at least 75% in cSCC and 25% in melanoma of total mutational events (Alexandrov et al., 2013, Pickering et al., 2014). These gene mutations in tumor-suppressive/oncogenic pathways result in genomic instability and signaling malfunctions, which either enable tumor cells to bypass growth inhibition and acquire increased proliferative and immune evasive properties, or contribute to a tumor microenvironment (TME) that benefits tumor growth and metastasis (Figure 1) (Ikehata and Ono, 2011). Progression of cSCC has been reported to be associated with loss-of-function mutations of TP53, NOTCH1, CASP8, CDKN2A, and is affected by oncogenic mutations involving RAS and PI3K signaling, cell cycle regulation, and squamous differentiation (Li et al., 2015). Similarly, UV-induced mutations cause Hedgehog signaling activation leading to the development of BCCs (Caro and Low, 2010).

TGFβ signaling plays critical contextual-specific roles in numerous physiological and pathological events (Batlle and Massagué, 2019). TGFβ is a growth inhibitor for keratinocytes and a growth stimulator for dermal fibroblasts (Massagué et al., 2000). The growth inhibitory effect of TGFβ signaling makes it a potent tumor-suppressive factor at the early stage of cancer. TGFβ also regulates extracellular matrix (ECM) deposition (Massagué J., 2008). During photoaging in the skin, TGFβ is upregulated and activated, inducing excessive MMPs and pro-inflammatory cytokines; and prolonged infiltration of neutrophils, leading to progressive collagen degradation and aberrant elastic fibers that contribute to ECM destruction (Quan et al., 2009). UV radiation also induces loss-of-function mutations/deletions in TGFβ signaling components, including TGFβRI, TGFβRII and Smad4, that act as genetic drivers for initiation and progression of cSCC (Cammareri et al., 2016, Han G. et

al., 2005, Hoot et al., 2008, Hoot et al., 2010). Mutations and large deletions in TGFβ receptor or Smads genes in epithelial cells also trigger negative feedback to induce TGFβ expression (Cammareri et al., 2016, Han G. et al., 2005, Hoot et al., 2008, Hoot et al., 2010) that is secreted into the stroma to exert paracrine effects. The wide-ranging contributions of TGFβ signaling to UV-induced carcinogenesis make it a desirable treatment target for skin cancers. This review will focus on UV-induced alterations/mutations in TGFβ signaling components and their contributions to the pathogenesis of photoaging and UV-induced skin cancers. As a final point, emerging cancer therapies targeting aberrant TGFβ signaling with immune checkpoint blockade will be introduced in this review.

UV-induced TGFβ signaling alterations contribute to pathogenic changes in photoaging

TGFβ signaling has profound biological functions in regulating cell growth, differentiation, migration, immune/inflammatory responses, and angiogenesis (Batlle and Massagué, 2019). TGFβ1 is secreted in a latent form; active TGFβ1 is released when an N-terminal latent associated peptide (LAP) is cleaved from mature TGFβ1 by a number of mediators including MMP2/MMP9, ROS and integrins (Annes et al., 2003). In canonical TGFβ signaling, TGFβ binds to two types of serine/threonine kinase receptors, TGFβRI and TGFβRII, triggering intracellular signaling cascades (Massagué, 1998). When TGFβ binds to TGFβRII/TGFβRI complex, Smad2 and Smad3 phosphorylated by TGFβRI, followed by binding with Smad4 form a heteromeric complex and translocate to the nucleus, where they exert transcriptional regulation via Smad-binding elements (SBEs) (Massagué et al., 2005). Additionally, TGFβ signaling through non-canonical pathways includes ERK, p38/JNK, Rho/Rac, and PI3K/AKT (Zhang, 2017). Smad7 is induced by TGFβ signaling and functions as a TGFβ inhibitor through the prohibition of Smad2/3 phosphorylation and prevention of Smad2/3/4 complex formation (Itóh et al., 1998, Nakao et al., 1997)

A central function of TGFβ signaling in skin is to induce type I procollagen synthesis and secretion via SBE-targeted gene expression of connective tissue growth factor (CTGF) (Quan et al., 2010). Additionally, TGFβ inhibits MMP1-mediated collagen expression through the Smad3-dependent pathway (Yuan and Varga, 2001). In chronologic aging, aged dermal fibroblasts with reduced size/mechanical force downregulate TGFβRII, thus impairing the TGFβ/Smad signaling pathway (Fisher et al., 2016). TGFβ1 and Smad3 gene expression in aged skin fibroblasts are reduced (Purohit et al., 2016). Impaired TGFβ/Smad3 signaling results in a reduction of CTGF-dependent type I collagen synthesis but an increase in MMP1-induced type I collagen degradation, leading to dermal thinning in chronologic aging (Quan et al., 2010, Yuan and Varga, 2001).

Unlike chronologic aging, photoaging is a cumulative process that depends on the intensity of UV radiation (Fisher et al., 2002). If the dose/intensity of exposure is too low to induce skin damage, UV irradiation activates AP1 and p53 that represses TGFβ expression and restrains integrin-dependent latent TGFβ activation (Mohammed et al., 2016, Yang et al., 2008). When UV radiation, such as narrowband UVB at 50% of the minimal erythema dose (MED), is used to treat psoriasis (Kleinpenning et al., 2009), expression and activation of

TGFβ in keratinocytes are repressed (Singh et al., 2010). Conversely, high dose UV irradiation stimulates photo-inflammation, promoting aging-related signal transduction, resulting in acute photodamage that is repaired through the wound healing process (Fisher and Voorhees, 1998, Quan et al., 2002).

Distinctive from chronologic skin aging, MMP induced collagen degradation and elastin degeneration are key mechanisms in photoaging(Quan et al., 2009). Interestingly, MMP1, 3, and 9, which are responsible for collagen degradation, are only induced in the epidermis of photoaged skin (Quan et al., 2009). It has been reported that Smad3 is increased in chronically sun-exposed skin and is predominantly located in the cell nucleus throughout the epidermis and dermis, indicating TGFβ/Smad3 signaling activation in both keratinocytes and fibroblasts (Han K. H. et al., 2005). It is likely that during photoaging, TGFβ1 levels increase and are activated by environmental MMPs and ROS (Abe et al., 2002). TGFβ/Smad3 signaling activation in keratinocytes induces production of MMPs and inflammatory cytokines, and the recruitment of neutrophils/macrophages (Caley et al., 2015). Supporting this notion, we observed that K5.TGFβ wildtype (wt) transgenic mice with TGFβ overexpression in basal keratinocytes developed Smad3-dependent chronic skin inflammation with upregulated MMP9 and MMP2, and infiltration of neutrophils (Li et al., 2004, Zhang et al., 2014). Moreover, daily UVB exposure for 28 days induces photoaging in the skin of Wistar rats; they had an increased level of TGFβ1 in exposed skin that correlated with levels of inflammatory cytokines IL6, IL1β, and TNFα and the severity of collagen destruction (Bora et al., 2019).

UV-induced mutations in TGFβ signaling components contribute to the initiation, progression, and metastasis of cSCC

TGFβ signaling acts as either a tumor suppressor or a tumor promoter in a context-dependent manner (Massagué J., 2008). The tumor repressive function of TGFβ signaling relies on Smad-dependent induction of cell-cycle arrest and apoptosis (Colak and Ten Dijke, 2017). The ability to circumvent TGFβ-induced tumor inhibition is a prerequisite to utilize TGFβ signaling for tumor promotion (Massagué Joan, 2008). In SCCs with intact TGFβ signaling, the tumor-suppressive function of TGFβ1 is maintained (Li et al., 2006). However, UV-induced TGFβ signaling suppression may have already mitigated its growth inhibitory effect on keratinocytes before mutations occur. This could explain the epidermal hyperplasia in precancerous lesions, such as actinic keratosis (AK) and seborrheic keratosis (SK) (Shao et al., 2012). However, given the low prevalence of carcinogenesis in cases of AK and SK, TGFβ signaling alterations alone are not sufficient for tumor malignancy (Shao et al., 2012). In addition to the induction of TGFβ signaling suppression, UV irradiation also causes a high number of gene mutations in TGFβ signaling components in both epidermal keratinocytes and stem cells (Kim and He, 2014). Sequence analysis of human primary cSCCs identified frequent UV-signature mutations in TGFβRI- and TGFβRII- encoded genes (Cammareri et al., 2016). Loss-of-function TGFβRI mutation has been identified as causative for multiple squamous epitheliomas in sun-exposed skin, indicating that compromised TGFβ signaling could enhance susceptibility to UV-induced skin cancer (Goudie et al., 2011). Although a large mutational burden after long-term exposure to UV

irradiation is typical in cSCCs, only a few mutated genes, including loss of heterozygosity or loss-of-function mutations in genes encoding Smad4, TGFβRII and TGFβRI, have been identified as driver mutations for cSCC (Cammareri et al., 2016, Han G. et al., 2005). These mutations alone or facilitated by additional oncogenic mutations, such as RAS or TP53 mutations, allow tumor cells to escape from TGFβ-indued tumor suppression, driving tumor initiation, and progression (Massagué Joan, 2008).

We determined that loss of heterozygosity at the Smad4 locus was detected in 57% of human skin SCC samples (Hoot et al., 2008). Consistently, Smad4 protein loss occurs in up to 70% of cSCC, and downregulation of Smad4 expression is frequent in AK lesions (Han G. et al., 2005). Mice with keratinocyte-specific Smad4 deletion develop spontaneous SCCs and have a higher susceptibility to UV carcinogenesis, revealing that loss of Smad4 is a driver mutation in cSCC (Mitra et al., 2013). In addition to abrogation of TGFβ-induced growth inhibition, Smad4 loss in cutaneous keratinocytes causes a reduction in Snail expression that compromises Ercc1-mediated Snail-dependent DNA repair resulting in increased susceptibility of epidermal keratinocytes to UV-induced skin carcinogenesis (Mitra et al., 2013).

Inactivation of TGFβRII is another frequent loss of function mutation in cSCC (Han G. et al., 2005). UVB radiation causes a quick decline of TGFβRII expression in the epidermis, suggesting that TGFβRII mutation could be an early event in UV-induced TGFβ signaling alteration. In support of this, a recent study identified a mutated TGFβRII gene to be a UV-signature mutation in cSCC (Cammareri et al., 2016). At the protein level, expression of TGFβRII is decreased in 55.9% of cSCC cases (Han G. et al., 2005). Transgenic mice with keratinocyte-specific deletion of TGFβRII subjected to 2-stage chemical carcinogenesis that triggers HRAS (transforming protein p21) mutations similar to those induced by UV exposure experience accelerated benign papilloma formation, malignant conversion, and metastasis of cSCC, demonstrating a tumor-repressive role of TGFβRII in cSCC. Moreover, loss of functional TGFβRII in tumor epithelia selectively blocks the molecular and pathological alterations required for TGFβ1–mediated epithelial-mesenchymal transition (EMT) but acts cooperatively with TGFβ1 for tumor invasion in a paracrine manner (Han G. et al., 2005).

In addition, we found that skin $K15^+$ stem cells within the hair follicle bulge are also subjected to UV-induced mutations (White et al., 2013). Transgenic mice with KrasG12D mutation and Smad4 deletion in $K15^+$ stem cells generate cancer stem cells (CSCs). These CSCs give rise to skin SCCs, BCCs and induce EMT and lung metastasis through microRNA9 (White et al., 2013). Similarly, in murine skin, targeted activation of the RAS/RAF/MAPK pathway by RAS mutation or TP53 mutation/inactivation, coupled with deletion of TGFβRI in $LGR5^+$ stem cells promotes rapid development of cSCCs (Cammareri et al., 2016). Therefore, TGFβ signaling components with UV-induced mutations in epidermal keratinocytes and stem cells facilitate the ability of tumor cells to bypass growth inhibition and acquire the capacity to proliferate and evade the immune system, leading to cSCC initiation, progression, and metastasis.

TGFβ overexpression in the TME of SCC, BCC, and melanoma

Overexpression of TGFβ has been observed in cSCC, BCC, and cutaneous melanoma, which may be attributed to UV-induced mutations in TP53 that abrogate the p53-mediated transcriptional inhibition of TGFβ (Elston and Inman, 2012). To support this, mutational inactivation of TP53 is present in cSCCs and frequently detected in lesions of AK and UV-irradiated skin (Xu et al., 2013). In keratinocytes, we have found that mutated TGFβ signaling components, such as loss of Smad2 and Smad4, and TGFβRII depletion increase expression of TGFβ1 secreted in both the epithelial and stroma (Han K. H. et al., 2005, Hoot et al., 2008, Hoot et al., 2010).

In a previous study, we found upregulation of TGFβ1 expression in 52.9% of human skin SCC samples and their adjacent epidermis, indicating TGFβ upregulation is an early event in cSCC (Han G. et al., 2005). Similarly, TGFβ is abundantly expressed in the intercellular spaces of hyperplastic epidermis overlying BCCs, and 86.2% of BCCs showed increased extracellular TGFβ in the desmoplastic stroma (Stamp et al., 1993). Increased TGFβ isoforms have also been reported in various stages of melanomas correlated with tumor progression (Berking et al., 2001).

To understand the role of TGFβ overexpression during the early stage of skin cancer, we generated K5.TGFβ1 wt mice with keratin 5 promoter-driven TGFβ overexpression in basal and hair follicle keratinocytes (Li et al., 2004). We observed severe skin inflammation in K5.TGFβ1wt mice characterized by highly expressed MMP2 and MMP9, elevated levels of proinflammatory cytokines such as IL1, IL6, IL8, and tumor necrosis factor (TNF), and angiogenesis through upregulated ALK1/pSmad1/5/8 signaling on endothelial cells (Li et al., 2004). TGFβ-induced inflammation and angiogenesis were also found in high-grade human melanomas (Wiguna and Walden, 2015). Interestingly, although K5.TGFβ1 keratinocytes maintain growth inhibitory properties, the epidermis of K5.TGFβ1 skin was hyperproliferative *in vivo*. Consistently, in a tumor-graft model on immunocompromised mice, TGFβ-expressing melanomas lack large necrotic areas and have fewer apoptotic cells compared to tumors without TGFβ expression (Berking et al., 2001). These data demonstrate that TGFβ induces inflammation and angiogenesis in the TME, enabling tumor cells to acquire mitogens and override TGFβ1-mediated growth arrest even during the early stage of tumor growth.

In addition to the induction of inflammation and angiogenesis, TGFβ also plays an essential role in modulating the tumor ECM primarily by stimulating cancer-associated fibroblasts (CAFs) (Chen and Song, 2019). CAFs produce cell-adhesion proteins including integrins, collagen, and fibronectin to structurally modify tumor ECM (Kalluri, 2016). A recent report indicated that TGFβ is associated with peritumoral fibronectin deposition by CAFs and plays a key role in tumor transition from a low-risk nodular BCC to a high-risk infiltrative phenotype (Kuonen et al., 2018). CAFs also produce matrix proteases that cause tumor matrix remodeling, leading to conditions permissive for cancer cell invasion (Zeltz et al., 2020). MMPs produced by CAFs provide a scaffold for the invasion of melanoma cells in skin (Javelaud et al., 2008). In a murine model of cutaneous melanoma, TGFβ-induced activation of CAFs was required for CTGF-induced tumor neovascularization

(Hutchenreuther et al., 2018). Moreover, as the most abundant cells in the TME, CAFs become an additional source of TGFβ ligands, resulting in an amplifying feedback loop that propagates TGFβ-induced tumor promotive effects in the TME.

Furthermore, TGFβ is a potent suppressor of T-cell-mediated immune surveillance and a key cause of resistance to checkpoint inhibitors. In SCC, TGFβ inhibits $CD8^+$ cytotoxic T cells, $CD4^+$ T cells, macrophages, dendritic cells, and NK cells, induces myeloid-derived suppressor cells, and stimulates the generation of regulatory T cells and Th17 cells (Dodagatta-Marri et al., 2019). Taken together, TGFβ effects on the TME provide a permissive environment for tumor progression, invasion, and metastasis.

Targeting TGFβ signaling in photoaging and UV-induced skin cancer

The critical pathogenic roles of aberrant TGFβ signaling caused by UV irradiation make it a desirable target for the treatment of photoaging and UV-induced skin cancer. Although not usually considered a typical pathogenic event, photoaging affects facial appearance, skin function and increases the risk of skin carcinogenesis. It is important to prevent photoaging by avoiding long-term sun exposure and tanning and using sunscreen regularly. Because of their importance in the regulation of photoaging, TGFβ signaling components, and targets, such as phosphorylated Smad protein and collagen products, often serve as biomarkers to evaluate the photoprotective efficacy of potential prevention or treatments, such as sunscreen and Nicotinamide (Snaidr et al., 2019, Young et al., 2017).

Due to its broad impact and context-dependent effects, TGFβ inhibition may lead to harmful off-target effects. This is why utilizing TGFβ inhibitors in cancer therapy remains a significant challenge. However, when used in combination with other cancer therapies, particularly immunotherapy, it could be possible to reduce both dosing issues and off-target effects of TGFβ inhibitors (Lan et al., 2018). For example, UV-induced skin cancer, such as cSCC, BCC, and melanoma have a high mutational burden within the TGFβ-induced immune repressive TME, suggesting that using a TGFβ signaling inhibitor in concert with immune checkpoint blockade could be an important avenue to reverse immune evasion. To support this, TGFβ signaling inhibitor, LY2152799, along with anti-CTLA4 antibody synergistically suppressed both primary tumor growth and metastasis in a murine model of melanoma (Hanks et al., 2014). Knowing the pleiotropic effects of TGFβ, it is crucially important to predict response to therapy to allow selection of patients who will benefit from treatment with TGFβ inhibitors. Biomarkers such as TGFβ signaling component mutations, immunohistochemical staining for pSmad2, and TGFβ target gene expression could be used for patient screening to minimize unwanted on-target side effects.

During chronological aging, reduced expression of TGFβRII leads to TGFβ signaling suppression in aged dermal fibroblasts (Quan et al., 2002); in contrast, levels of TGFβ ligands in precancerous lesions and SCCs are increased (Han et al., 2005). Given that BCC and cSCC often arise from sun-exposed skin, utilizing an intermittent dosing schedule of TGFβRI kinase inhibitors to target enhanced TGFβ signaling activity may result in attenuated TGFβ signaling in tumors with activated TGFβ while sparing photoaged skin with low TGFβ signaling (Colak and Ten Dijke, 2017). This notion was explored in a

BRAFV600E melanoma mouse model, in which TEW-7197 (EW-7197), a TGFβRI kinase inhibitor, blocked TGFβ-induced MMP9 from stromal fibroblasts that augment treatment efficacy of anti-PD1 therapy (Zhao et al., 2018).

Summary and perspectives

The TGFβ signaling pathway plays a central role in the pathogenesis of photoaging and UV-induced skin cancers. Chronic UV exposure induces enhanced TGFβ production in keratinocytes. Increased TGFβ ligands cause photo-inflammation by releasing MMP2 and MMP9 to the dermis, and recruiting neutrophils that contribute to damaged and disorganized collagen fibrils, and solar elastosis. Meanwhile, fibroblasts in the photoaged dermis are expressing Smad3. Activation of TGFβ/Smad3 signaling in the dermis may induce a fibrotic response that could be connected to premature collagen production in photoaged skin (Figure 2, panel a). In the TME of UV-induced skin cancers, increased levels of TGFβ activate keratinocytes and endothelial cells, promoting the generation of CAFs, and repressing immune cell functions. Together, these effects contribute to an inflammatory, angiogenic, and immune inhibitory TME that supports tumor growth, invasion, immune evasion, and metastasis (Figure 2, panel b). The pleiotropic effects of TGFβ provide insight into the potential treatment of photoaging and skin cancer. Specifically, for skin cancers with a heavy UV-induced mutational burden and abnormal TGFβ signaling, immune checkpoint blockade combined with TGFβ blockade could be an important treatment strategy to inhibit tumor growth and reverse immune evasion in cSCC, BCC, and cutaneous melanoma.

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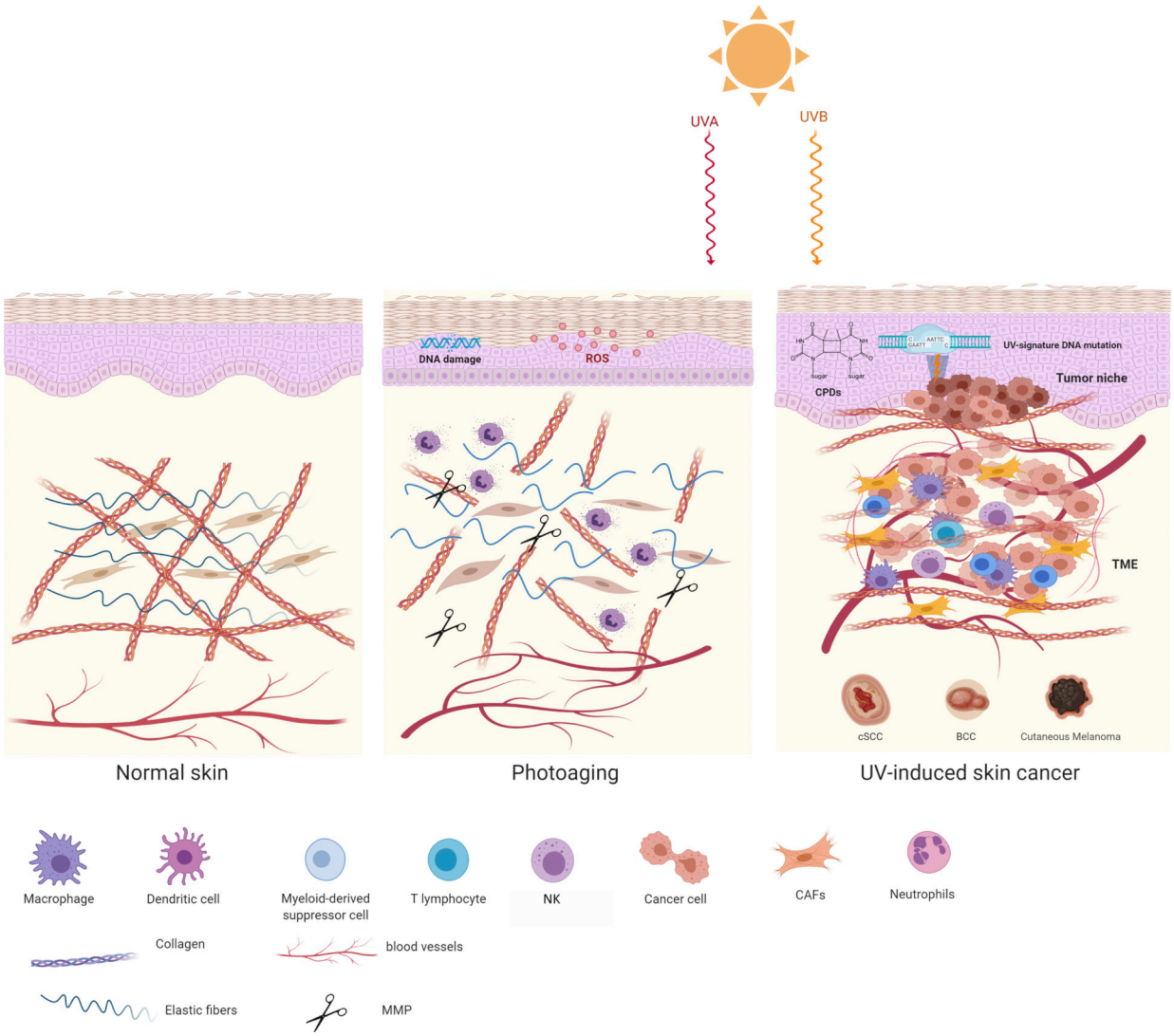

Figure 1. Skin morphology changes in UV-induced premature aging and UV-induced skin cancer.

Chronic UV exposure induces DNA damage and ROS accumulation in the skin. These detrimental factors cause decreased and fragmented collagen and elastic fibers in the dermis that lead to photoaging. Meanwhile, UV radiation generates photoproduct CPDs that cause UV-signature DNA mutations in keratinocytes and epidermal stem cells. These mutations result in cancer initiation and contribute to an inflammatory, angiogenic, and immune inhibitive tumor microenvironment (TME) that supports the progression, invasion, and metastasis of cSCC, BCC, and cutaneous melanoma. ROS, reactive oxygen species; CPDs, cyclobutane pyrimidine dimers; cSCC, cutaneous squamous cell carcinoma; BCC, basal cell carcinoma.

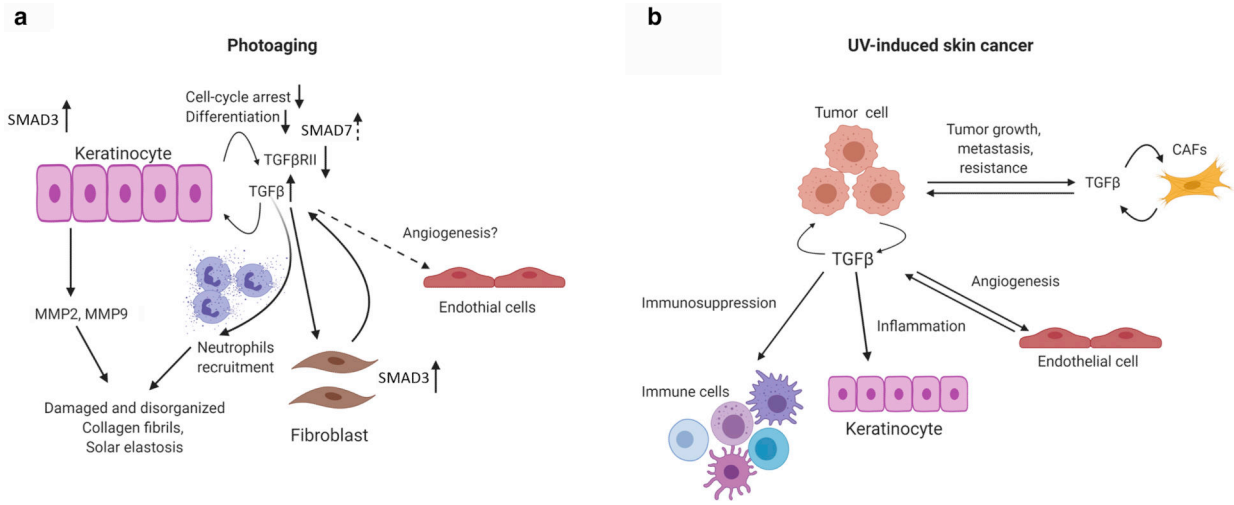

Figure 2. The role of TGFβ signaling in the pathogenesis of photoaging and UV-induced skin cancer.

During photoaging, keratinocyte-derived TGFβ production induces photo-inflammation by MMP2, MMP9, and the recruitment of neutrophils, Meanwhile, fibroblasts in the dermis activate TGFβ/Smad3 signaling to induce a fibrotic response. These effects cause damage to collagen fibrils and formation of solar elastosis. In UV-induced skin cancer, TGFβ in the TME activates keratinocytes and endothelial cells, and promotes the generation of CAFs and represses immune cell functions, leading to a TME that favors tumor growth, invasion, and metastasis.