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Mechanisms and prevention of UV-induced melanoma

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Summary

Melanoma is the deadliest form of skin cancer and its incidence is rising, creating a costly and significant clinical problem. Exposure to ultraviolet (UV) radiation, namely UVA (315–400 nm) and UVB (280–315 nm), is a major risk factor for melanoma development. Cumulative UV radiation exposure from sunlight or tanning beds contributes to UV-induced DNA damage, oxidative stress, and inflammation in the skin. A number of factors, including hair color, skin type, genetic background, location, and history of tanning, determine the skin's response to UV radiation. In melanocytes, dysregulation of this UV radiation response can lead to melanoma. Given the complex origins of melanoma, it is difficult to develop curative therapies and universally effective preventative strategies. Here, we describe and discuss the mechanisms of UV-induced skin damage responsible for inducing melanomagenesis, and explore options for therapeutic and preventative interventions.

Introduction

Skin cancer is the most common form of cancer, representing 40–50% of all cancers diagnosed in the US[1]. Approximately 3.5 million cases of skin cancer are diagnosed each year in the US alone, and that number is rising each year[1]. Skin cancers are broadly classified into two types: non-melanoma skin cancers (NMSCs) and melanoma. Of these, melanoma is the most aggressive and lethal form of skin cancer. Melanomas represent only 4% of all skin cancers, but they account for nearly half of all skin cancer deaths[2,3]. In 2017, it is expected that nearly 90,000 cases of melanoma will be diagnosed in the US, leading to nearly 10,000 melanoma-related deaths[4]. Recent advancements in targeted therapy (vemurafenib) and immunotherapy (pembrolizumab) for melanoma have offered improvements in survival to some patients, but most patients fail to have a sustained response[5].

An estimated 60–70% of cutaneous malignant melanomas are thought to be caused by ultraviolet (UV) radiation exposure[6]. Two types of UV radiation are primarily responsible for causing carcinogenic skin damage: UVA (315 nm-400 nm) and UVB (280 nm-315 nm). UVA is much more abundant than UVB in sunlight, accounting for 95% of solar UV radiation[7]. UVA is also the primary source of light used in indoor tanning beds, and tanning

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beds can reach UVA doses 12-times that of the sun[7]. UVA penetrates more deeply into the dermis than UVB[8], but is less genotoxic[9].

UVB causes direct DNA damage in the form of photoproducts, including cyclobutane pyrimidine dimers (CPDs) and 6−4 photoproducts (6-4PPs)[10]. CPDs and 6-4PPs can be recognized and repaired by the nucleotide excision repair (NER) pathway. In this pathway, DNA damage--sensing proteins, including XPC, DDB1, DDB2, and XPA, bind to sites of DNA damage, and recruit repair machinery to the site[10]. Dysregulation of NER is implicated in skin carcinogenesis and defects in NER cause Xeroderma pigmentosum, a disease which increases the risk of skin cancer more than 1000-fold[11].

UVA is thought to cause skin damage and ultimately tumorigenesis, primarily through oxidative stress-induced DNA damage[9]. UVA-induced oxidative DNA damage is recognized by 8-oxyguanine DNA glycosylase 1 (OGG1) and repaired by base excision repair (BER)[12] In this review, we will summarize the mechanisms by which UVA and UVB cause melanomagenesis and progression, and their implications for therapeutic and preventative strategies.

Mechanisms of UV-induced Melanoma

UV Radiation and Melanoma

Both UVB and UVA have been shown to induce melanoma in mice. UVB radiation has a well-established role in melanomagenesis, but UVA's contribution is controversial. In mouse models of childhood UV exposure, UVB induces melanoma formation[13,14]. In the same albino mouse model, perinatal UVA exposure is not sufficient to induce melanoma formation[13]. However, UVA was capable of inducing melanoma in pigmented C57BL/6 mice[14]. Furthermore, an increased risk of melanoma has also been linked to psoralen and UVA (PUVA) therapy [15]. The known effects of UVB are summarized in Figure 1 and the roles of UVA in melanoma are summarized in Figure 2.

UV and Genetic Alterations in Melanoma

Risk of melanoma is associated with both familial mutations and somatic mutations. Melanoma has one of the highest rates of mutation of any cancer[16]. Approximately 3–15% of melanomas arise due to familial genetic predisposition, in which UV-independent mutations play a significant role[17]. Germline mutations in *CDKN2A* (p16-INK4A-Arf), while rare, correlate significantly with the development of melanoma[18]. Other key somatic mutations in melanoma are UV-independent, including the $BRAF^{V600E}$ mutation found in 60% of melanomas and NRAS mutations found in 15–20% of melanomas[19]. While these mutations are not UV-signature mutations[20], they are more common in sun-exposed skin[20–23].

$BRAF^{V600E}$ mutation alone is often insufficient to drive malignant transformation of melanocytes[24]. Acquired mutations due to UV exposure can synergize with mutant BRAF to drive transformation. In mice with melanocyte-specific $BRAF^{V600E}$ mutations, UV exposure accelerates melanomagenesis[25]. 40% of the resulting tumors developed UV-signature p53 mutations, which further accelerated UV-induced melanomagenesis[25]. Similar UV-induced

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p53 mutations are seen in approximately 20% of human $BRAF^{V600E}$ mutant melanomas[25–27]. $BRAF^{V600E}$ mutation in melanocytes can also synergize with Arf deletion *in vivo* to accelerate UV-induced melanoma development[28].

Recent work indicates that UV-induced mutations accumulate as melanocytic nevi transform into melanoma, including driver mutations in CDKN2A, TP53, NF1, RAC1, and PTEN[25,29]. One study linked UV-induced DNA damage signatures to approximately 46% of driver mutations[30]. Melanomas from UV-exposed areas exhibited higher mutation load than melanomas developing in protected areas[27]. Whole-genome sequencing of melanoma patients has identified a number of additional mutations that are significant to melanoma development, many of which can be linked to UV-induced DNA damage. A detailed review of key mutations in melanoma has been summarized elsewhere[31].

Skin Color and Melanoma

Melanocytes produce two types of melanin: eumelanin and pheomelanin. Eumelanin is the most common type in dark skin and dark hair, and is synthesized upon binding of α-melanocyte-stimulating hormone (αMSH) to melanocortin-1 receptor (MC1R)[32]. In individuals with red hair and freckles, a loss-of-function mutation in MC1R prevents eumelanin production, leading to a higher proportion of pheomelanin[33]. Eumelanin reduces the accumulation of UV-induced photoproducts[34], while pheomelanin may actually contribute to UV-induced DNA damage by inducing free radical formation after UV[34]. Total melanin levels dictate UV response in melanocytes, independent of MC1R signaling. Higher melanin levels correlate with reduced UV-induced photoproduct formation, proliferation, and apoptosis independent of MC1R function in melanocytes[35,36].

Signaling through αMSH and MC1R suppresses melanomagenesis by modulating UV radiation response. αMSH treatment is sufficient to reduce UV-induced oxidative stress[37] and increase nucleotide excision repair (NER) in melanocytes with wild-type MC1R[38]. αMSH signaling activates NER by upregulating XPC and inducing the phosphorylation of DNA damage sensors Ataxia telangiectasia and Rad3-related protein (ATR) and ataxia telangiectasia mutated (ATM)[38]. Furthermore, αMSH signaling through MC1R increases the recruitment of XPA to UV-induced DNA damage sites by phosphorylating ATR, thus improving DNA repair[39,40]. Activation of NER by αMSH requires functional MC1R; mutant MC1R increases levels of UV-induced oxidative stress[36–38,41].

In melanoma patients, loss-of-function mutations in MC1R are linked to enhanced sensitivity to UV-induced cytotoxicity and increased incidence of melanoma, largely independent of skin type or hair color[42]. A recent meta-analysis of MC1R variants and melanoma risk showed that most variants increased risk and were associated with red hair and fair skin, but two were associated with melanoma risk independent of red hair or fair skin[34,43].

UVB radiation is capable of regulating MC1R signaling and pigmentation in melanocytes. UVB induces expression of a number of pigmentation-related genes in melanocytes[44], including αMSH and MC1R expression[32]. UVB activates expression of oxidative and ER stress response genes downstream of MC1R, although this is lost in cells expressing non-

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functional mutant MC1R[45]. UVB also induces the interaction of wild-type MC1R with PTEN, stabilizing PTEN and inhibiting PI3K/AKT signaling. In MC1R mutant cell lines, this interaction is lost and increased PI3K/AKT signaling drives transformation of $BRAF^{V600E}$ mutant melanoma cells[46]. *In vivo*, however, UVB exposure accelerates melanomagenesis independent of MC1R mutation status and pigmentation[47], suggesting that UVB-induced melanomagenesis does not require the pigmentation and MC1R signaling response. Conversely, UVA does not induce a pigmentation response[44], but may require pigmentation to induce melanomagenesis[14].

Downstream of MC1R, cAMP signaling activates transcription factor MITF[32]. MITF is a master regulator of melanocyte differentiation required for melanocyte survival[48–50]. MITF controls UVB-induced expression of pigmentation genes[32] and DNA repair and proliferation genes in melanoma cells[51,52]. Deletion of MITF in melanoma cells is sufficient to increase metastasis, concurrent with increases in mesenchymal markers[53] and ROCK-mediated invasion[54]. MITF overexpression promotes proliferation *in vitro*[48] and *in vivo*[53,55], in addition to reducing metastasis[53]. Amplification of MITF occurs in up to 20% of all melanomas, with a higher incidence in metastatic melanoma and in BRAF mutant melanomas[48]. MITF protein expression is suppressed by $BRAF^{V600E}$ in melanocytes and melanomas, however, which allows cell proliferation[48,56]. It is postulated that MITF amplification serves to maintain minimal MITF levels even in the presence of BRAF-mediated suppression for cells to survive the stresses of disease progression.

UV-Induced DNA Damage Repair in Melanoma

There is conflicting evidence regarding the ability of melanoma cells to respond to DNA damage compared to normal melanocytes. Some research has shown that melanoma cells exhibit reduced DNA damage repair[57] and that UVB exposure further lowered their XPC, DDB1, and DDB2 expression[57]. UVA similarly lowered XPC expression in melanoma cells, and they also show impaired repair of UVA-induced CPDs relative to normal melanocytes[58]. We have found that Sestrin2, a stress-inducible protein, is induced by UVB in melanoma cells and negatively regulates DNA damage repair[59]. Knockdown of Sestrin2 increased UVB-induced apoptosis and decreased tumor formation *in vivo*[60].

DNA repair is critical for suppressing melanomagenesis. Patients with xeroderma pigmentosum (XP), a disease caused by defective NER, have a 2,000-fold increased risk of melanoma[11]. In melanoma patients, low levels of XPC have been shown to correlate with poor survival[57]. In a genetically engineered mouse model of melanoma featuring deletion of Arf and expression of $BRAF^{V600E}$, UVB exposure accelerated melanomagenesis by inhibiting NER[28]. Further analysis concluded that Arf deletion induces XPC promoter hypermethylation and repression, as well as E2F4/DP1 inhibition in this model[28]. $BRAF^{V600E}$ mutation alone was also sufficient to repress UVB-induced XPC[28]. Melanocyte-specific deletion of Arf alone *in vivo* reduced repair of UVB-induced DNA damage[61]. Deletion of XPC alongside Arf knockout accelerated UVB-induced melanomagenesis *in vivo*[62].

However, other studies suggest that there are no differences in repair of UV-induced DNA damage between melanocytes and melanoma cell lines[63]. While several studies found an

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association between DNA damage response gene upregulation and melanoma progression, the upregulated genes did not include NER genes[64,65]. Arf-deficient mice with XPA deletion were sensitive to UVB-induced nevus formation, but developed fewer melanomas than mice with Arf deletion alone[66]. This work suggests that UVB-driven progression from nevus to melanoma may depend on specific NER pathways in some genetic backgrounds. Similarly, loss of cell cycle regulator RhoA led to defective repair of UV-induced DNA damage, which decreased proliferation and reduced survival of melanoma cells[67].

Oxidative modification of DNA is an important mechanism of UVA-induced skin damage and carcinogenesis. Melanocytes have diminished repair of UVA-induced oxidative damage, as melanin acts as a photosensitizer to UVA[68]. Dysplastic nevi have increased ROS levels relative to normal melanocytes, supporting a role for ROS accumulation in melanomagenesis[69]. Several potential mechanisms of ROS accumulation in melanomas have been suggested. Loss-of-heterozygosity mutations in hOGG1, an enzyme that repairs oxidative DNA damage, have been demonstrated in a small number of melanomas[70,71]. Additionally, we have found that UVA induces Sestrin2 in melanocytes and melanoma cells, which in turn suppresses antioxidant response factor Nrf2 and increases ROS production[59]. Deletion of p16 could also contribute to UV-induced ROS accumulation and oxidative DNA damage in melanocytes[72]. However, one study has found that OGG1 is overexpressed in some metastatic melanomas[73].

ROS and reactive nitrogen species (RNS) generated in melanocytes in response to UVA radiation lead to the production of “dark CPDs” hours after UVA exposure[74]. The accumulation of oxidatively modified DNA only in pigmented, and not albino, mice with UVA-induced melanoma [14] suggests that melanin could play a role in UVA-induced oxidative stress. Loss of MC1R reduced repair of UV-induced CPDs in melanocytes, leading to increased UV-induced apoptosis[36]. Accordingly, melanin content was inversely correlated with UV-induced apoptosis and CPD formation[36]. Melanomas featuring disruptive mutations in MC1R are associated with a 42% increase in UV-signature mutations over those in MC1R wild-type melanomas[75].

The effect of antioxidants on melanomagenesis has been explored in mouse models. The antioxidant N-Acetylcysteine (NAC) has been found to delay the onset of UV-induced melanoma *in vivo*[76]. In a mouse model with $BRAF^{V600E}$ mutation and PTEN deletion, NAC increased metastasis, but had no effect on primary tumors[77]. NAC treatment also increased migration and invasion of melanoma cell lines *in vitro* by activating RhoA[77].

UV and Autophagy in Melanoma

Autophagy has been shown to play a context-dependent role in tumorigenesis. Autophagy can suppress tumor growth by clearing oncogenic proteins and organelles damaged by oxidative or genotoxic stress. Alternatively, autophagy can provide the macromolecule building blocks needed by highly proliferative cells and allow cells to survive a range of stress conditions. In melanoma, autophagy likely has different functions at each stage of tumor progression.

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Recent work suggests that malignant melanomas have increased autophagic flux relative to benign nevi[78–80]. Furthermore, high levels of autophagy in melanoma correlates with metastasis[80], poor response to chemotherapy, and shorter overall survival[78,80]. Induction of autophagy has been suggested to be a pro-survival mechanism for melanoma cells[79,81,82]. Autohagy is also associated with proliferation, invasion, and metastasis[79], as well as promoting ROS accumulation[82].

$BRAF^{V600E}$ mutant melanomas exhibit enhanced autophagy due to chronic ER stress[83] and mTOR inhibition[84]. Increased autophagy has been shown to increase cell survival in $BRAF^{V600E}$ mutant melanomas[85–87]. In models of $BRAF^{V600E}$ mutant melanoma with PTEN-deficiency, autophagy is required for tumorigenesis[86]. Knockdown of the essential autophagy gene Atg7 in these mice leads to accumulation of defective mitochondria and ROS, increased senescence, decreased proliferation, and increased apoptosis[86].

Inhibition of $BRAF^{V600E}$ with vemurafenib induces autophagy by inhibition of the mTOR signaling pathway, and autophagy has been shown to promote survival of melanoma cells after vemurafenib[81,85]. Combined inhibition of autophagy and mTOR signaling enhances cell death[78] and impairs metastasis[88] in $BRAF^{V600E}$ mutant melanomas. Vemurafenib-resistant melanoma cells also have enhanced autophagy, although inhibition or genetic modulation of autophagy was insufficient to regain sensitivity to vemurafenib[89]. Combined inhibition of autophagy and MEK signaling was sufficient to restore vemurafenib sensitivity[89].

Additional conflicting evidence implicates decreased autophagy in melanoma cells, sup orting dual roles for autophagy in melanoma. High levels of autophagy adaptor protein and substrate p62 constitute a prognostic marker of malignant melanoma[90], although other work indicates that p62 expression increases, then decreases late in disease progression[91]. Atg5 expression has also been reported to decrease as melanoma progresses from benign to malignant[92]. Atg5 knockdown promotes proliferation, further suggesting that reduced autophagy at the early stages may contribute to tumorigenesis[92]. Atg5 loss of heterozygosity is found in many advanced melanomas and correlates with poor overall survival[93]. Atg5 LOH increases melanoma metastasis *in vivo* in a $BRAF^{V600E}$ and PTEN-deficient mouse model[93].

Expression of the autophagy inducer Beclin1 decreases as melanoma progresses[94,95]. One study reports that $BRAF^{V600E}$ overexpression in melanoma cells decreases basal autophagy levels relative to BRAF wild-type cells through a Beclin1-dependent mechanism[96]. Furthermore, BH3-family proteins Bcl-XL and MCL-1, which disrupt the activation of autophagy by Beclin1, are upregulated in metastatic melanomas[97]. Interactions between BH3-only protein Noxa and MCL-1 have been shown to disrupt inhibition of Beclin1 by MCL-1 and promote autophagy[98]. Recent work has shown that the BH3-only protein Noxa is upregulated in melanoma cells and promotes autophagy to inhibit apoptosis[99].

Expression of MITF, which correlates with increased lysosomal gene expression in melanoma cells[100], decreases with disease progression[97,101]. LC3 has similarly been reported to decrease during melanoma disease progression[92]. In heavily pigmented

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melanoma cells, however, LC3 is highly expressed[102]. In these cells, LC3 regulates MITF expression and ultimately, melanin production[102]. As MITF plays a critical role in melanoma growth and metastasis, this link between MITF expression and autophagy may be an important link in melanoma progression.

Inflammation in melanoma

Inflammation and immune response to melanomagenic conditions are critical for melanoma development and therapeutic response. UVB regulates the recruitment of inflammatory cells into the skin, including macrophages[103,104] and neutrophils[105,106]. UVB induces macrophage infiltration of melanomas by upregulating Ccr2[103] and ATF2[104]. Upon recruitment, IFN-γ signaling from macrophages triggers further upregulation of Ccl8, a Ccr2 ligand, in melanocytes[103]. This positive feedback loop increases melanoma growth *in vivo* by reducing melanoma cell death[103]. Depletion of macrophages inhibits UV-induced melanocyte proliferation in mouse skin[107]. Melanoma-derived factors also trigger the upregulation of CCL2 and MMP-9 in macrophages, which in turn promote invasion of melanoma cells[108]. UVB-mediated neutrophil recruitment further promotes melanoma metastasis by stimulating angiogenesis and increasing migration of melanoma cells toward blood vessels[105].

Melanoma-associated inflammation involves multiple regulatory pathways. For example, interleukin 23 (IL-23) induces DNA damage repair in melanocytes, including XPC and XPA expression and γ-H2AX foci formation[109]. DNA damage repair induced by IL-23 inhibits melanomagenesis[109]. IL-23 also inhibited regulatory T cell expansion and limited IFN-γ production[109]. The IFN- γ receptor on melanocytes inhibits UV-induced apoptosis[110], suggesting that suppression of IFN- γ by IL-23 suppresses melanomagenesis by clearing damaged cells.

Another inflammation and immunological regulatory pathway is Programmed cell death 1 (PD1) and its ligand PD-L1. Anti-PD-1 immunotherapy has shown efficacy in melanoma, but fewer than half of all melanoma patients treated with anti-PD-1 immunotherapy have a prolonged response[5]. Current efforts are aimed at understanding the differences between immunotherapy responders and non-responders. PD-L1 expression in melanoma cells is not associated with $BRAF^{V600E}$ mutation, and cells expressing PD-L1 recruit tumor-infiltrating lymphocytes (TILs) independent of BRAF status[111]. BRAF inhibitor-resistant melanoma cells increase PD-L1 expression in a MEK-dependent manner, and inhibition of MEK and BRAF increases apoptosis and decreases PD-L1 expression[112]. Cyclooxygenase-2 (COX-2) expression is also correlates with PD-L1 expression in primary melanomas, and inhibition of COX-2 by celecoxib downregulates PD-L1 in melanoma cells[113].

Inflammation and response to immune therapy are also regulated by PTEN status. Loss of PTEN in melanoma cells allows PI3K-mediated activation of immunosuppressive cytokines[114,115]. PTEN expression represses PD-L1 expression, promoting an immune response against tumor cells. PTEN loss was associated with non-brisk (localized) immune response in tumors[114,115]. Other work shows that PTEN loss in melanoma cells inhibits both T cell recruitment into tumors and targeted killing of tumor cells by T cells[115]. PTEN loss is also associated with poor response to anti-PD-1 therapy[115]. Treatment with a PI3Kβ

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inhibitor improved response to immune therapies *in vivo*, further supporting a role for PTEN loss in immunosuppression in melanoma[115].

Vitamins and Melanoma

Vitamin A—Vitamin A, which has a number of forms, including retinol, retinoic acid, and beta-carotene, is tumor suppressive in melanoma. Vitamin A inhibits growth, invasion, and metastasis of melanoma cells[116–118]. Vitamin A has been suggested to impair UV-induced tumorigenesis by preventing UV-induced oxidative stress accumulation[118]. Clinically, multiple studies have shown an inverse correlation between retinol intake and melanoma risk, while vitamin A and beta-carotene have no association[119,120].

Vitamin C—Vitamin C, or ascorbic acid, has been suggested to play a dose-dependent role in melanoma growth and progression. High concentrations of vitamin C inhibit invasion and survival of melanoma cells[121]. Conversely, low concentrations of vitamin C promote melanoma cell growth, migration, and invasion, and protect against stress[121]. Another study found that ascorbic acid reduces HIF-1α activity and protein levels in metastatic melanoma, reducing invasion of melanoma cells[122]. Ascorbate, a reduced form of vitamin C, induces DNA damage and cell death in melanoma cell lines *in vitro*, and inhibits tumor growth *in vivo*[123].

Vitamin D—UVB absorption in skin leads to the conversion of 7-dehydrocholesterol to previtamin D3, an isomer of vitamin D3[124]. Vitamin D3 production is induced by UVB in a dose-dependent manner[125–127] and depends on melanin levels and skin type[128,129]. Dietary intake of vitamin D was initially explored as a promising preventative strategy for melanoma, but many studies have found no association between dietary vitamin D uptake and risk of melanoma[130–133]. Some controversy remains, however, as several have identified both a positive correlation[134] and inverse association between Vitamin D3 intake and melanoma risk[135].

Similarly, serum levels of vitamin D3 have been explored as a diagnostic target in melanoma, and results have been unclear. In several studies, normal serum levels of vitamin D3 at the time of diagnosis correlate with a better prognosis[136,137]. In another study, lower serum vitamin D3 levels were associated with advanced stages at diagnosis, worse disease-free survival, and poorer overall survival[138]. Lower serum vitamin D was associated with higher-stage melanomas[139,140]. Conversely, one large study found no association between serum vitamin D levels and melanoma risk[141].

Vitamin D production in the skin protects against irradiation and likely suppresses melanomagenesis. Vitamin D reduces UV-induced DNA damage, including oxidative and genotoxic DNA damage, and induces DNA damage repair[126,142,143]. It inhibits proliferation and invasion of melanoma cells *in vitro* and *in vivo*[118,144]. Importantly, vitamin D synthesis is not inhibited by sunscreen use[145], but strict physical avoidance of sunlight increases risk of vitamin D deficiency[145,146].

Vitamin E—Vitamin E has 2 major forms, tocotrienols and tocopherols. Vitamin E succinate, a tocopherol, inhibits melanoma cell growth and induces apoptosis by blocking

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cell cycle progression *in vitro*[118,147] and *in vivo*[147]. Tocotrienols similarly induce apoptosis in melanoma cells *in vitro* by inducing ER stress response[148]. Tocotrienols also induce degradation of melanosomes in the lysosome by promoting lysosomal and endosomal fusion[149]. δ-Tocotrienol alone reduces melanin content[150], suppresses cell proliferation[151], and induces apoptosis[151] of melanoma cells *in vitro*. *In vivo*, tocotrienols inhibit melanomagenesis and progression[148]. Taken together, this work indicates that vitamin E suppresses melanoma growth and progression.

Vitamin K—Little work has explored the effects of vitamin K on melanoma cells. Several forms of vitamin K, including Vitamin K3 and K5, inhibit proliferation and increase apoptosis of melanoma cells[152]. *In vivo*, the vitamin K analog menadione inhibits growth of melanoma xenograft tumors[153].

UV and Melanoma Risk

Childhood exposure to UV radiation is a major risk factor for skin cancer development, particularly at doses high enough to achieve sunburn[154]. Some studies suggest that childhood sunburns could as much as double the risk of melanoma[155]. This effect is highly dependent on skin tone, however. In red haired and freckled individuals, childhood UV exposure is a particularly potent risk factor for melanoma development[156]. Conversely, in light-skinned individuals prone to tanning, childhood UV exposure can be protective against melanoma[157]. Exposure to UV early in life is associated with the development of BRAF mutant melanomas, while NRAS mutation is more commonly associated with high UV exposure later in life[158].

In addition to childhood UV exposure, ease of access to indoor tanning has provided teenagers and young adults with further opportunities to increase UV radiation exposure. Indoor tanning at a young age increases melanoma risk[159]. Use of indoor tanning beds increases as children enter adolescence, and this shift is accompanied by a ~50% drop in sunscreen use[160]. In the US, it is estimated that 40–50% of teenagers have utilized tanning beds[161]. Furthermore, approximately 70% of tanning salon customers are females under 30[162], and indoor tanning before age 30 leads to a 75% increase in melanoma risk[163]. Data suggest that melanoma rates in women ages 15–39 are nearly double that of men of the same age group[164].

Despite links between early age sunburn and melanoma, one study has found that melanoma risk was associated with the number of sunburns throughout life[165]. Some studies have found a similar dose-dependent effect of indoor tanning independent of age[166], although another found that tanning increased risk for young women[167]. Indoor tanning also likely contributed to an epidemic of melanomas on the trunk in young Icelandic women in the early 2000s[168]. Furthermore, misunderstandings persist about the ability of an all-year tan to protect against melanoma[155].

Sunscreen has been linked to a paradoxical increase in sun exposure and sunburns[169]. The sun protection factor (SPF) of sunscreen correlates with increased intentional sun exposure[170]. A similar paradoxical increase in risk is seen in indoor workers, who have a higher risk of melanoma than outdoor workers[171]. UVB exposure has also been linked to

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decreased rates of melanoma mortality[172], and in mouse models, sunscreen is ineffective at preventing melanomagenesis[173]. Recent meta-analyses of published epidemiological data have found no link between sunscreen use and melanoma risk, however[174,175]. In the United States, use of sunscreen and physical barriers, such as clothing and sunglasses, is increasing[159], but many Americans still report receiving at least one sunburn in the last year[159].

Prevention of UV-induced Melanoma

Chemoprevention—A recent review from Chhabra et al. [176] has explored recent advancements in chemoprevention in-depth, and therefore we will not address it here.

Public Health/Outreach Efforts—Given the extremely high incidence of skin cancers, making significant strides in prevention will require large-scale public health campaigns. Australia implemented one such campaign in the 1980s, which has led to a shift in the behavior and attitude toward UV exposure[177,178], particularly in young adults[178,179]. Incidence of melanoma on the trunk and shoulders, sites subject to intermittent UV exposure if left unprotected, was significantly decreased in Australian young adults[179].

Recent efforts have aimed to reach teenagers and young adults via social media[180,181] and texting[182], in addition to determining the efficacy of positive vs negative/fear-based messaging[183]. Targeted messaging to parents of adolescents was effective at starting conversations between mothers and daughters about the concerns of indoor tanning[184]. In households receiving these messages, fewer daughters reported a desire to go indoor tanning than non-intervention households[184]. Fathers and sons were largely unaware of the messaging, however, suggesting that additional avenues are needed to engage men in awareness of the dangers of UV radiation exposure. A survey of young women who indoor tan indicates that, while they are overwhelmingly supportive of policies limiting indoor tanning for minors and placing stronger warnings of indoor tanning risks on tanning beds, they do not support a total ban[185].

Tanning-related regulations vary across the US. Many states have age-based tanning bans, some requiring parental consent, and others simply require warning signs to be placed in tanning salons[186]. As of 2014, FDA regulations require displays on indoor tanning devices warning of skin cancer risk[186]. Similar restrictions exist worldwide, with many countries banning indoor tanning under the age of 18[186]. Enforcement of these laws is lax, however, and there are likely high rates of non-compliance by users and owners of tanning salons[186].

A nationwide 10% tax on indoor tanning was implemented in the US in 2010 with the passing of the Affordable Care Act in an attempt to curb tanning bed use. A drop of approximately 25% in tanning salon patronage accompanied the tanning bed tax, although other salons reported customers were indifferent to the tax[187].

Even more recently there has been a push to name tanning bed use an addiction, as frequent users can exhibit many of the classic signs of addiction[188,189]. A study of indoor tanning users found that those who met standards for addiction to indoor tanning exhibited higher anxiety-related symptoms and substance abuse than those who did not[189]. This suggests that

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for some indoor tanning salon users, taxes and regulations will be insufficient to prevent tanning.

Discussion and Future Directions

Melanoma presents a significant clinical problem, as its incidence is rising worldwide and current therapeutic options are ineffective for many patients. The European Cancer Organization has predicted that melanoma death rates will fall by 2050, but the number of deaths will increase unless more effective treatments are developed[190]. Improvements in both prevention efforts and therapeutic targeting of melanomas will be necessary to reduce melanoma-related deaths.

Prevention of melanoma can be improved by optimization of sunscreen designs, as significant research suggests that sunscreen is ineffective at reducing melanoma risk. Sunscreens could also be optimized to account for improper application and duration of use. Educational programs can be optimized to target young women and to more readily engage men, two groups who are likely to ignore warnings about the negative effects of UV exposure. Furthermore, by approaching tanning as a potentially addictive behavior, techniques could be adapted from substance abuse treatment and prevention.

Recent therapeutic advancements have made significant strides toward achieving sustained progression-free survival for a subset of metastatic melanoma patients. However, there remain a number of opportunities for improving melanoma treatment. Little work has focused on understanding the role of UV exposure in response to immunotherapy. Currently, research does not indicate that vitamins will be beneficial therapeutic options for melanoma, although more work could clarify specific opportunities in melanoma. Autophagy appears to have a highly context-specific role in melanoma, but further research will determine whether careful modulation of autophagy would benefit melanoma patients. Furthermore, our overall understanding of melanoma pathogenesis is far from complete. Future investigation is required to elucidate the molecular and cellular basis by which melanocytes become cancerous melanoma cells, and the mechanism by which melanoma cells evade immune surveillance and become resistant to targeted therapy or immunotherapy. These future studies will improve our ability to prevent melanoma development and resistance to therapies.

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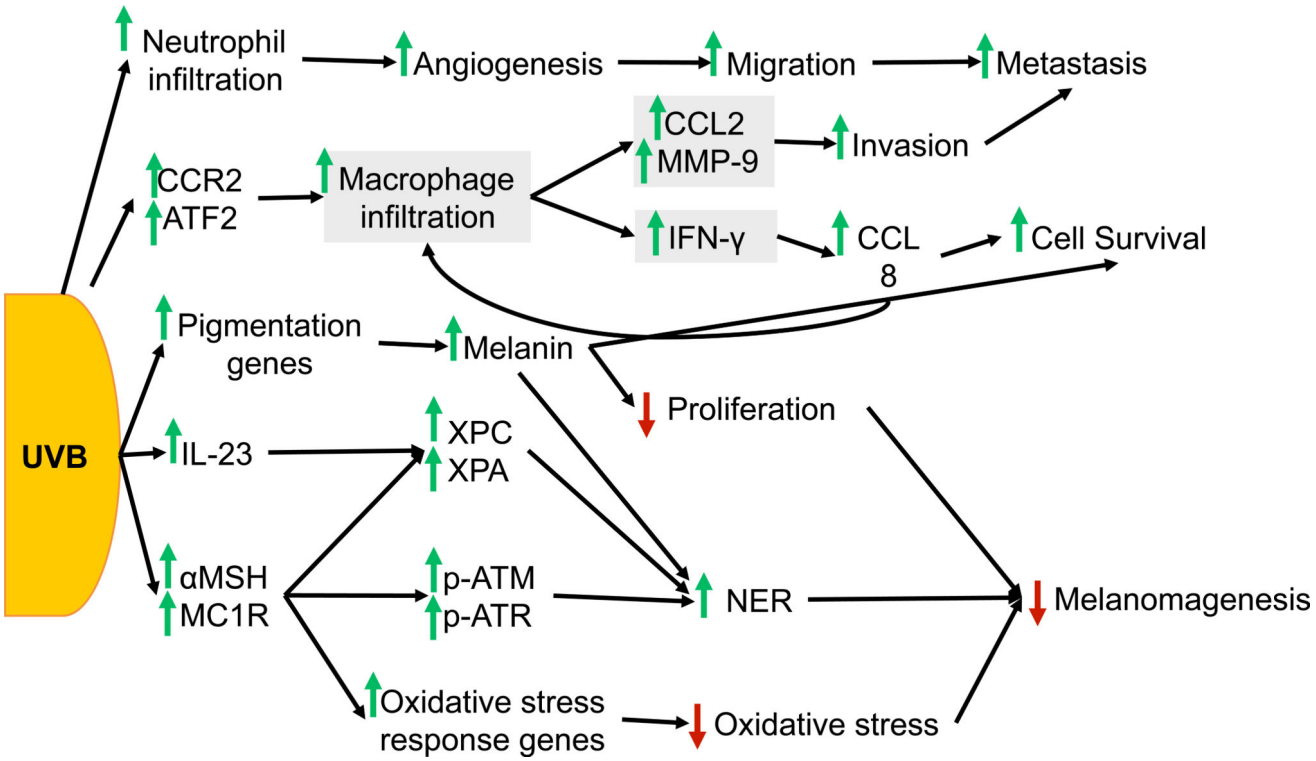

Figure 1. UVB response in melanoma

UVB exposure triggers macrophage and neutrophil infiltration into the skin. Upregulation of CCR2 and ATF2 in melanocytes promotes recruitment of macrophages into the skin, which in turn stimulates production of CCL2, MMP-9, and IFN-γ in macrophages. IFN-γ signaling from macrophages promotes a positive feedback loop between melanocytes and macrophages, in which melanocytes upregulate CCL8, a CCR2 ligand, and promote further recruitment of macrophages. The inflammatory response created by macrophage and neutrophil recruitment promotes angiogenesis, as well as melanoma cell invasion, survival, and metastasis. UVB also independently regulates melanin production and MC1R signaling. Induction of pigmentation genes and subsequent increase in melanin production following UVB increases cell survival and NER, but decreases proliferation and ultimately, melanomagenesis. Signaling through MC1R is induced by UVB and activates DNA damage response. Signaling through αMSH and MC1R promotes phosphorylation of ATM and ATR, upregulates XPC, and promotes XPA recruitment to stimulate NER. αMSH also activates oxidative stress response genes to reduce oxidative stress in melanocytes/melanoma. UVB-induced expression of IL-23 also activates XPC and XPA to induce NER. IL-23 signaling, melanin production, and MC1R signaling can all inhibit melanomagenesis induced by UVB.

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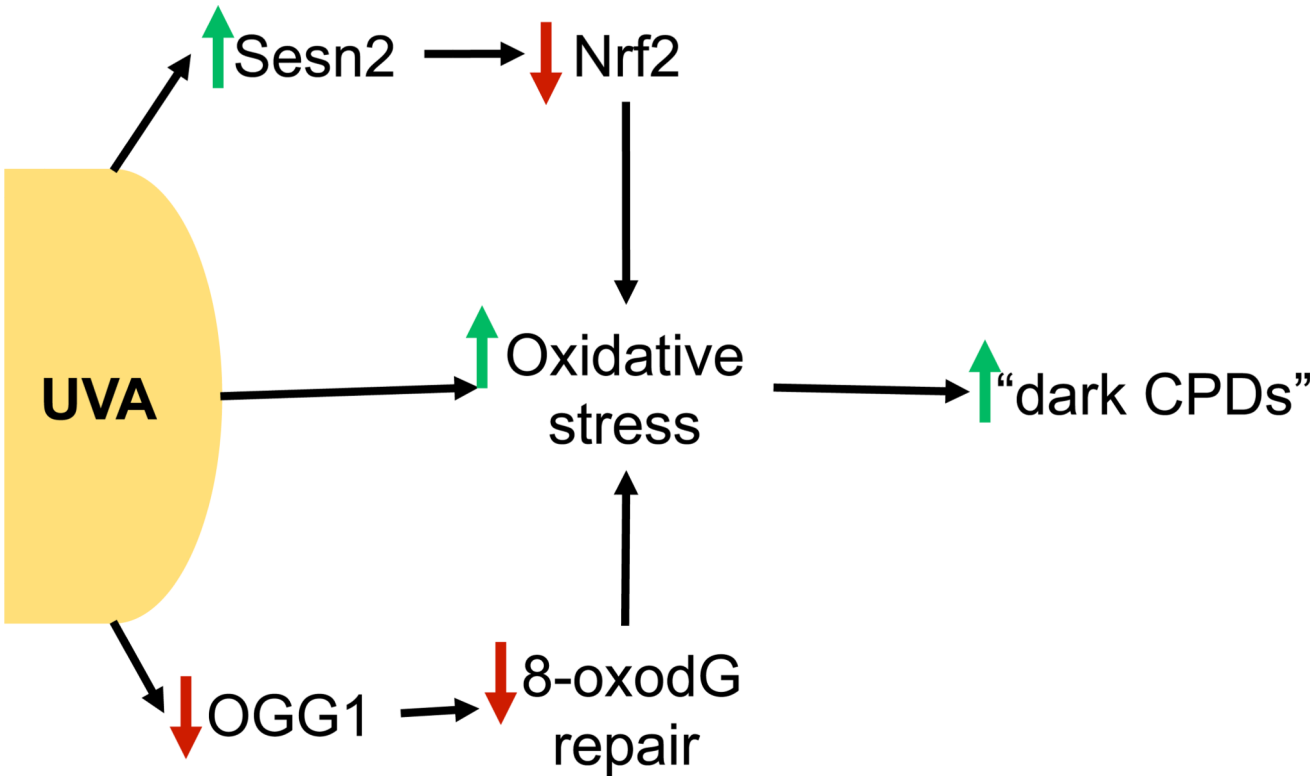

Figure 2. UVA response in melanoma

UVA is known to directly induce oxidative stress in melanocytes, but recent work suggests that UVA perpetuates the accumulation of oxidative stress through several mechanisms. UVA induces Sestrin2, a negative regulator of Nrf2 to promote oxidative stress accumulation in melanocytes. Furthermore, UVA suppresses OGG1, impairing repair of oxidative lesions and furthering oxidative stress. Oxidative stress can ultimately lead to the accumulation of "dark CPDs" hours after UVA exposure.