UV Signaling Pathways within the Skin

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The effects of UVR on the skin include tanning, carcinogenesis, immunomodulation, and synthesis of vitamin D, among others. Melanocortin 1 receptor polymorphisms correlate with skin pigmentation, UV sensitivity, and skin cancer risk. This article reviews pathways through which UVR induces cutaneous stress and the pigmentation response. Modulators of the UV-tanning pathway include sunscreen agents, melanocortin 1 receptor activators, adenylate cyclase activators, phosphodiesterase 4D3 inhibitors, T-oligos, and microphthalmia-associated transcription factor regulators such as histone deacetylase inhibitors. UVR, as one of the most ubiquitous carcinogens, represents both a challenge and an enormous opportunity in skin cancer prevention.

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INTRODUCTION

The incidence of melanoma and non-melanoma skin cancers has continued to rise over the past few decades. The etiology is multifactorial with discrete genetic pathways and environmental factors. Although genetic factors may contribute significantly, environmental factors can be modified to potentially decrease the risk of developing deadly diseases such as melanoma. Exposure to UVR from sunlight is well established as a significant risk factor for melanoma development. However, indoor tanning is a source of preventable UVR exposure that represents a growing, multi-billion dollar industry (Levine *et al.*, 2005). UVR is a major environmental risk factor that contributes to carcinogenesis through DNA damage and immune modulation via inflammatory and immunosuppressive pathways (Tran *et al.*, 2008; Liu and Fisher 2010; D'Orazio *et al.*, 2013; Weinstock 2013). It has long been appreciated that tanning, through increasing epidermal melanin content, is the skin's major photoprotective response against acute and chronic UV damage. DNA damage from UVR induces signaling cascades that ultimately lead to activation of pigmentation machinery to produce the tanning effect. This process can be synthetically perturbed at different points along the pathway to upregulate driver signals or to suppress inhibitory feedback, thereby promoting a UVR-independent protective tanning response. These strategies range from broad, such as transcriptional activators, to narrow, such as molecular analogs. Because the UV-tanning pathway is essential for both melanogenesis and protection from skin cancers, we summarize here the consequences of the UV signaling pathway deficiencies and strategies to regulate the the UV signaling pathway.

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Abbreviations: DOPA, dihydroxyphenylalanine; MC1R, melanocortin 1 receptor; MITF, microphthalmia-associated transcription factor; α-MSH, alpha melanocyte-stimulating hormone; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; SUMO, small-ubiquitin-like modifier; Tyrp1, tyrosinase-related protein 1

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FEATURES OF UVR AND UV-INDUCED MUTAGENESIS

UVR, spanning the 200 to 400 nm wavelengths of the electromagnetic spectrum, is a high-energy component of solar radiation. UVR is divided into three categories based on wavelength: UVA (400–320 nm), UVB (320–290 nm), and UVC (290–200 nm). Over 95% of UVA and 1–10% of UVB radiation reaches the earth's surface, whereas almost 100% of solar UVC is absorbed by the atmosphere and the ozone layer. Thus, most of the research on the effects of UVR has focused on UVA and UVB. A history of sunburn in childhood and continued unprotected exposure to UVR through adolescence and adulthood contribute to skin cancer risk. However, many adolescents and adults continue to seek a tan, either from direct sun exposure or from tanning beds.

UVR directly targets macromolecules in the skin such as proteins, lipids, and nucleic acids, with the latter resulting in signature mutations characteristically found in melanomas and other skin cancers. When these mutations occur within genes regulating apoptosis, cell cycle progression, and genetic repair machinery, they may initiate oncogenic transformation (Schulman and Fisher 2009; Fisher and James 2010). UVR photoexcitation of the direct chromophore DNA produces excited electron states and toxic by-products, leading to direct and indirect DNA damage. This often produces signature mutations dependent on the insult and mechanism of damage. We will focus on mutations resulting from UVA and UVB specifically.

UVA radiation, upon exciting endogenous chromophores, can generate reactive oxygen species capable of causing oxidative DNA damage. Through generation of singlet oxygen ($^1O_2$) or type-1 photosensitization reactions, UVA is able to cause oxidative base modifications, predominately at guanine

bases. This process leads to generation of 7,8-dihydro-8-oxoguanine lesions, which have been shown to induce specific DNA mutations if not repaired. (Garibyan and Fisher 2010).The major UVA-induced mutations are G→T transversions and G→A transitions. Like UVB, UVA may also trigger DNA damage through cyclobutane pyrimidine dimer (CPD) formation.

UVB contact with DNA activates a photochemical reaction that usually occurs between adjacent pyrimidine nucleotides and leads to formation of photoproducts known as CPDs and pyrimidine 6-4 pyrimidones. After the formation of CPDs and pyrimidine 6-4 pyrimidone photoproducts, either spontaneous reversion may occur (for CPDs), or DNA repair enzymes participate in the correction of the damage. Incorrect repair of these damaged DNA lesions leads to mutations in epidermal cells that may initiate oncogenesis. When UVB-induced CPDs and pyrimidine 6-4 pyrimidones are incorrectly resolved, certain signature mutations may form, including C→T and CC→TT transition mutations (Tran *et al.*, 2008; Garibyan and Fisher 2010).

These characteristic mutations are not exclusively induced by UVR from sunlight. DeMarini and colleagues compared the mutagenic effects of radiation from three common sources using Salmonella assays and determined that mutagenic ability was most potent in radiation from tanning salon beds, followed by sunlight. White fluorescent light represented the least mutagenic source of radiation. The most common mutations were G:C→A:T transitions. The CC→TT transitions characteristic of UVB exposure represented 83% of mutations induced by tanning bed radiation exposure, demonstrating that both solar and non-solar sources of UV radiation are capable of inflicting signature UV mutations (DeMarini *et al.*, 1995; Besaratinia and Pfeifer 2008).

Although UVB mutations have comprised the majority of the traditional UVR-associated mutations, little overlap exists between these mutations and those observed in codon V600 of the *BRAF* gene, the most common location of the well-established BRAF mutations in melanoma. BRAF V600 variants can be attributed to G→A transitions and T→A, T→G, and G→T transversions (Thomas *et al.*, 2006; Besaratinia and Pfeifer 2008). In contrast, traditional UVB-induced mutations from exposure to sunlight are characterized by single or tandem C→T transitions at dipyrimidine nucleotides. Damage from UVA radiation has been characterized more recently, with one mechanism being the generation of DNA cross-links and lesions through oxidative damage from UVA-induced photosensitization reactions. Certain of these UVA-induced DNA lesions resemble mutations in BRAF V600 variants from sun-exposed melanomas, suggesting a greater role for UVA in melanomagenesis than traditionally thought (Garibyan and Fisher 2010). Importantly, BRAF V600 mutations may also occur in non-sun-exposed malignancies, such as colon, lung, and thyroid, potentially consistent with oxidative damage as a common carcinogenic mechanism (in those cases independent of UVA). Other important melanoma-associated genes such as INK4A, PTEN, FGFR2, and N-RAS may also possess mutations attributable to UVR (Mar *et al.*, 2013).

UV SIGNALING PATHWAYS FOR TANNING

The core component of the skin response to sunlight is the epidermal melanin unit, comprised of the melanocyte and its associated keratinocytes. UV exposure induces DNA damage in keratinocytes and results in stabilization of the p53 tumor suppressor protein. This promotes p53 transcriptional activation of proopiomelanocortin, which is enzymatically cleaved to produce α–melanocyte-stimulating hormone (α-MSH). α-MSH is released by keratinocytes and binds the MC1R on melanocytes. MC1R activation by α-MSH triggers an increase in cAMP levels within the melanocytes, which increase transcription of microphthalmia-associated transcription factor (MITF) via CRE-binding protein/activating transcription factor 1. Binding of MITF to the E-box sequences in promoter regions triggers transcription of numerous pigmentation genes (Tran *et al.*, 2008; Hearing, 2011a,b). These genes act to synthesize, mature, and traffic melanin, the most common types of which are brown-black eumelanin and yellow-red pheomelanin. The melanin is packaged in melanosomes which are exported to keratinocytes, where they localize over the nucleus and may protect the genomic material from further UVR-induced damage (Figure 1 and Figure 2).

CONSEQUENCES OF UV SIGNALING PATHWAY DEFICIENCY

The loss of p53

As an important regulator of the genotoxic response, p53 is a key tumor suppressor gene that is mutated frequently in human cancer, including skin cancers. The p53 protein

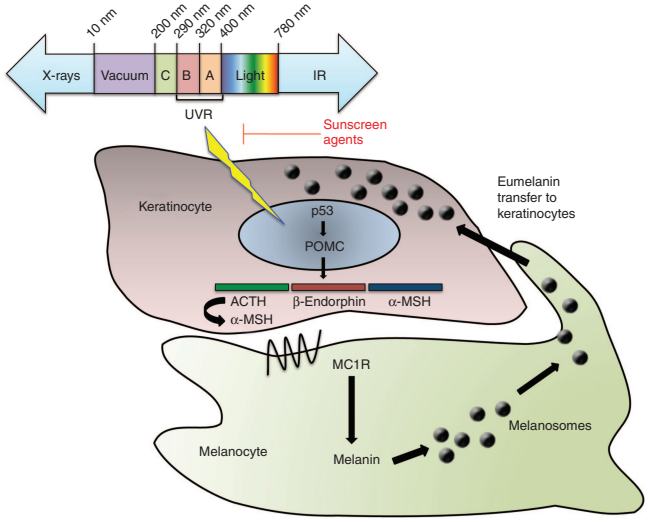

Figure 1. The epidermal melanin unit and tanning response to UV radiation. UV radiation induces DNA damage, which leads to activation of p53. In turn, p53 stimulates transcriptional upregulation of the proopiomelanocortin (POMC) gene, which is posttranslationally processed to adrenocorticotrophic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), and β-endorphin. Secreted α-MSH binds to the melanocortin 1 receptor (MC1R) on melanocytes, leading to production of melanin. The melanin is packaged within melanosomes and transported back to keratinocytes, where they localize over the nucleus as part of the protective tanning response to UV radiation.

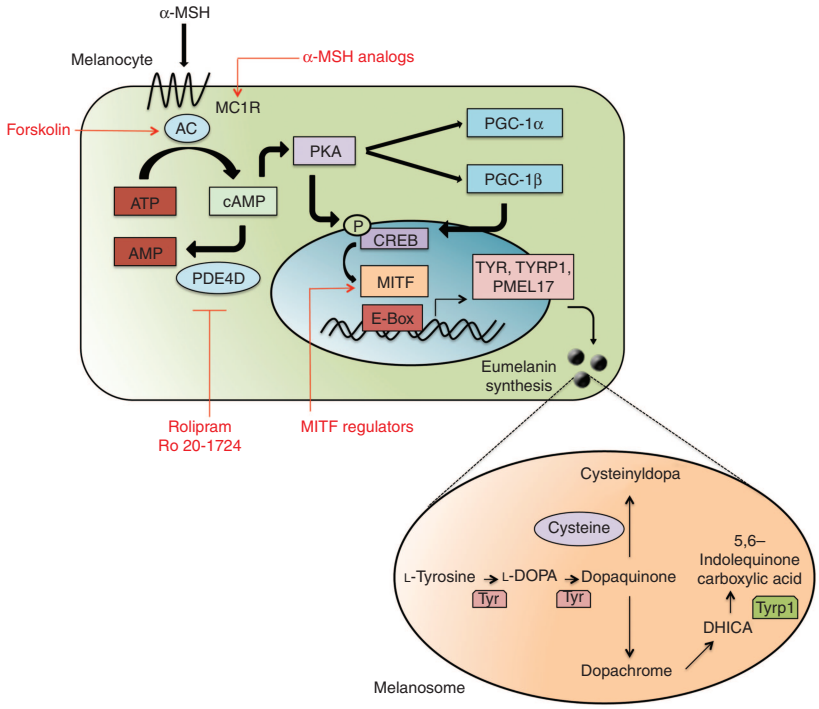

Figure 2. Melanin synthesis and strategies to regulate the tanning response. Secreted α-melanocyte-stimulating hormone (α-MSH) from keratinocytes binds melanocortin 1 receptor (MC1R) on melanocytes, leading to upregulation of cAMP, which stimulates expression of microphthalmia-associated transcription factor (MITF). MITF then transcriptionally activates expression of enzymatic machinery including tyrosinase and tyrosinase-related protein 1 (Tyrp1), which are critical in the synthesis of melanin within melanosomes. Tyrosinase catalyzes the initial conversion of tyrosine to dihydroxyphenylalanine (DOPA) and dopaquinone. Dopaquinone may then combine with cysteine to form the pheomelanin precursor cysteinyldopa, or it may enter a separate pathway catalyzed in part by Tyrp1 to produce the eumelanin precursor. The matured melanin is then transported in vesicles called melanosomes to the overlying epidermal keratinocytes. Strategies such as MC1R activators, adenylate cyclase activators, phosphodiesterase 4D3 inhibitors, and MITF regulators are shown to regulate the UV-tanning response by targeting different components of this pathway.

regulates multiple signaling pathways in response to stimuli such as DNA damage, oxidative stress, hypoxia, heat shock, membrane compromise, and other stresses (Cui *et al.*, 2007). p53 is thought to participate in DNA repair via multiple mechanisms, including control of cell cycle checkpoint activity as well as regulation of the DNA repair machinery. Lesions with mutant p53 are readily found in UV-exposed hairless mouse skin and sun-exposed healthy human skin. These mutations tend to be localized to dipyrimidine sequences and consist of C→T or CC→TT transitions (Beaumont *et al.*, 2008; Weinstock 2013).

MC1R mutations in skin cancers

The MC1R gene is highly polymorphic in humans, with over 80 variants identified. Certain variants are closely associated with red hair color (RHC) phenotype, which is accompanied by fair skin, poor tanning ability, high sunburn risk, and the highest risk of melanoma for any skin pigmentation type. Other MC1R polymorphic variants with weaker melanoma associations are known as ''non-red hair color'' variants. Three RHC variants of MC1R that are associated with fair skin and poor tanning are Arg151Cys, Arg160Trp, and Asp294His (Han *et al.*, 2006). The 151Cys variant was associated with increased risks of the three types of skin cancer after controlling for hair color, skin color, and other skin cancer risk factors. Women with medium or olive skin color carrying one non-red hair color allele and one red hair color allele had the highest risk of melanoma (Han *et al.*, 2006; Fargnoli *et al.*, 2010).

One mechanism by which MC1R polymorphisms affect melanoma risk may be through repair of DNA damage (Kadekaro *et al.*, 2005). Human melanocyte cultures exposed to varying levels of UVR were found to have CPD levels that correlated with MC1R genotype and function. In the melanocytes with non-functional MC1R, treatment with forskolin to directly activate adenylate cyclase appeared to enhance CPD repair (Hauser *et al.*, 2006).

Eumelanin and pheomelanin synthesis contributes to melanomagenesis

In addition to its direct effects on DNA damage repair, MC1R may also affect oncogenic drivers through regulation of pigmentation. MC1R signaling and cysteine availability govern the balance in production of eumelanin and pheomelanin. The amino acid cysteine is required for pheomelanin synthesis but not eumelanin synthesis. When MC1R signaling is strong, cysteine stores are insufficient to keep pace with the rate of generation of pigment precursors, and eumelanin production is favored. When the MC1R signal is weak as in redhead

melanocytes, cysteine stores keep pace with the slower formation of pigment precursors, leading to formation of cysteine-containing pheomelanin. In our 2012 study using redhead mice with inactivating MC1R mutations, UVR was not necessary for increased melanoma development in these mice when compared with black mice expressing an activating BRAF mutation in their melanocytes. This study supports carcinogenic potential of the pheomelanin synthetic pathway through an UVR-independent mechanism.

Oxidative stress appeared to have a role in pheomelanin-mediated melanomagenesis (Mitra *et al.*, 2012). We hypothesize two possible mechanistic pathways to explain the observed pheomelanin-dependent oxidative DNA damage that drives melanomagenesis. First, pheomelanin might generate reactive oxygen species that directly or indirectly cause oxidative DNA damage. Second, pheomelanin synthesis might consume cellular antioxidant stores and make the cell more vulnerable to other endogenous reactive oxygen species (Morgan *et al.*, 2013).

STRATEGIES TO REGULATE THE PIGMENTATION SIGNALING PATHWAY

The UV signaling pathway can be synthetically perturbed at different points to regulate the activity of MC1R, adenylate cyclase, cAMP, and MITF. Such strategies could induce a UV-independent tanning response, potentially conferring a photoprotective effect against UVR-mediated melanomagenesis. Here, we will discuss targetable processes at each level in detail.

MC1R activators (analogs of α-MSH)

In addition to the use of sunscreen agents, one strategy for melanoma prevention is based on analogs of α-MSH that function as MC1R agonists (Marwaha *et al.*, 2005). These include products such as melanotan I, melanotan II, afamelanotide, Ac-His-D-Phe-Arg-Trp-NH2, and n-Pentadecanoyl- and 4-Phenylbutyryl-His-D-Phe-Arg-Trp-NH2. Those analogs were more potent than α-MSH itself in stimulating melanogenesis, as well as reducing apoptosis, decreasing release of hydrogen peroxide, and enhancing repair of DNA photoproducts in melanocytes exposed to UVR. The photoprotective and other biological effects of α-MSH analogs await full determination (Hadley *et al.*, 1998; Langan *et al.*, 2010; Miller and Tsao 2010; Schulze *et al.*, 2013).

Some pathologic processes can alter levels of α-MSH and indirectly affect melanogenesis. α-MSH, like ACTH and thyroid-stimulating hormone, is secreted by the anterior pituitary gland. In Addison's disease (chronic adrenal insufficiency), lack of negative feedback from cortisol induces the anterior pituitary to produce greater levels of ACTH. As a by-product, more MSH is also produced, leading to hyperpigmented lesions in these patients. The classical hypothalamic-pituitary-adrenal axis is a negative feedback neuroendocrine pathway that is essential for the systemic response to external or internal stress. Emerging evidence has indicated that a fully functional cutaneous equivalent participates in the response of skin to local stress as well as other homeostatic contexts (Slominski and Wortsman 2000; Zbytek *et al.*, 2006; Slominski *et al.*, 2000, 2007, 2012). This local system can modulate the function of skin and follicular melanin units following UVR exposure and maintain or restore immune privilege in hair follicles. In the tanning pathway, the epidermal melanin unit comprised of the keratinocyte and melanocyte can be recognized as a functional equivalent of the hypothalamic-pituitary-adrenal axis in the skin.

Adenylate cyclase activation

Another strategy to promote the tanning response is through direct stimulation of adenylate cyclase activity downstream of MC1R. UVR-induced tanning is defective in numerous fair-skinned individuals, some of whom possess functional disruption of the MC1R. Although UVR is capable of inducing α-MSH production in keratinocytes, loss of MC1R function in red-haired mouse models results in inability to produce a tanning response upon UV exposure. However, pigmentation can be rescued by topical application of the cAMP agonist forskolin. This process can occur without UVR, demonstrating that the pigmentation machinery is available despite the absence of functional MC1R (D'Orazio *et al.*, 2006).

Alternative strategies

cAMP is an ATP-derived secondary messenger that functions in signal transduction for a variety of intracellular pathways. Levels of cAMP are controlled by its production, catalyzed by adenylate cyclase, and its hydrolysis, catalyzed by the phosphodiesterase class of enzymes. Phosphodiesterase 4D3 was identified as a direct target of the MSH/cAMP/MITF pathway (Khaled *et al.*, 2010). Its activation creates a negative feedback loop that induces refractoriness to chronic stimulation of the cAMP pathway in melanocytes. This highlights a potent mechanism controlling melanocyte differentiation that may be amenable to pharmacologic manipulation (Khaled *et al.*, 2010). Telomere-related oligonucleotides also have shown promise in augmenting the tanning pathway while bypassing UV-stimulation to confer a protective effect on skin (Arad *et al.*, 2006). This strategy was born from an understanding of telomeric-derived oligonucleotides as inducers of DNA repair responses in melanocytes, as well as concomitant inducers of melanogenesis (Atoyan *et al.*, 2007; Gilchrest *et al.*, 2009).

Regulation of MITF through direct targeting and modification of posttranscriptional processes

Finally, strategies to regulate the tanning response may focus on MITF, which is required for melanocyte development and is an amplified oncogene in a fraction of human melanomas. In addition to its control of critical pigmentation genes, MITF also regulates target genes essential to cell cycle progression, apoptosis, and differentiation (Levy *et al.*, 2006). Therefore, pharmacologic suppression of MITF is of potential interest in a variety of clinical settings. However, MITF is not known to contain intrinsic catalytic activity amenable to direct small-molecule inhibition (Flaherty *et al.*, 2012). An alternative drug-targeting strategy is to identify and interfere with lineage-restricted mechanisms required for MITF expression. Multiple histone deacetylase inhibitor drugs potently suppress MITF expression in melanocytes, melanoma, and clear cell

sarcoma cells (which are sometimes pigmented). Although histone deacetylase inhibitors may affect numerous cellular targets, they have been shown to suppress skin pigmentation upon topical application in mice (Yokoyama *et al.*, 2008). High throughput screens to identify additional small molecules capable of modulating MITF activity are currently being conducted in the authors' lab, and candidate leads are under development.

A germline missense substitution in MITF (Mi-E318K) was found to occur in families with high incidences of melanoma in Australia, United States, Great Britain, and France (Bertolotto *et al.*, 2011; Yokoyama *et al.*, 2011). Codon 318 is located in a small-ubiquitin-like modifier (SUMO) consensus site (PsiKXE), (Miller *et al.*, 2005) and Mi-E318K ablated that SUMOylation event on MITF. The Mi-E318K mutation measurably increases MITF's transcriptional activity. An additional key posttranslational modification on MITF is its phosphorylation by mitogen-activated protein kinase (Hemesath *et al.*, 1998), which subsequently targets MITF for ubiquitination and proteolysis (Wu *et al.*, 2000). More recently, it was shown that MITF is targeted by the de-ubiquitinase USP13, a theoretically drug-able protease whose suppression results in strong downregulation of MITF protein levels (Zhao *et al.*, 2011).

Other MITF gene regulators and MITF gene co-factors

In addition to directly targeting MITF, potential strategies to regulate the tanning response can target factors upstream of MITF or genes that serve as co-factors for MITF. The peroxisome proliferator-activated receptor gamma coactivator proteins PGC-1α and PGC-1β are key mediators of α-MSH activation of MITF. PGC-1α and PGC-1β are stabilized through α-MSH signaling via phosphorylation by protein kinase A. The PGC-1 proteins subsequently activate MITF transcription, and inhibition of the proteins blocks expression of MITF and its target genes in the tanning pathway.

Recent studies in humans revealed polymorphisms in PGC-1β that associated with ability to tan and protection against melanoma (Shoag *et al.*, 2013). YY1, which functions as both a transcriptional repressor and activator, also cooperates with melanocyte-specific isoform MITF to regulate the expression of the piebaldism gene KIT and multiple additional pigmentation genes (Li *et al.*, 2012).

CONCLUSIONS

Tanning represents increased melanization of the epidermis following UV exposure. The UV-tanning pathway is a DNA damage-related stress and injury response. Targeting components of the UV-tanning pathway through small molecules such as α-MSH analogs may be one strategy to modulate skin pigmentation. α-MSH analogs would likely be less potent on the MC1R loss-of-function variants that are most frequently found in melanoma patients, but they might still function. The strategies targeting components downstream of MC1R show potential in rescuing deficiencies of the UV-tanning pathway. These include adenylate cyclase activators, phosphodiesterase 4D3 inhibitors, and telomere-derived oligonucleotides. Additional interventions which may suppress key melanoma survival factors include MITF regulators such as histone deacetylase inhibitors and candidates from ongoing high throughput screens for MITF regulators. Strategies may also target MITF posttranscriptional modification processes such as SUMO modification, dimerization, and ubiquitination/deubiquitination. Future mechanism-based studies of UVR are needed to help completely elucidate molecular pathways responsible for the carcinogenic effects of UVR on the melanocyte lineage. We hope to develop better strategies to regulate pigmentation and in doing so, identify further opportunities for prevention, early detection, and treatment of melanoma.

CONFLICT OF INTEREST

The authors state no conflict interest.

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