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Skin Pigmentation and Melanoma Risk

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1. Introduction

Malignant melanoma of the skin ranks as the number one cause of death from skin cancers. Affecting over 125,000 people worldwide and nearly 70,000 persons annually in the United States alone (Linos et al., 2009), melanoma incidence has been increasing steadily over the last several decades (Erickson and Driscoll, 2010). According to the World Health Organization, approximately 20,000 people worldwide die from melanoma each year. One of the most striking clinical aspects of melanoma is the profound difference in incidence between persons of fair and dark skin complexions (Garbe and Leiter, 2009). Deposition of UV-blocking melanin pigment in the epidermis accounts for much of the protection realized by persons of dark skin complexion, however risk for melanoma does not simply correlate with amount of melanin in the skin. There is now ample evidence that suggests that pheomelanin, the red/blonde sulfated melanin pigment expressed in persons of light complexion may promote UV-mediated oxidative damage to melanocytes and thus contribute to carcinogenesis (Kvam and Tyrrell, 1999; Kadekaro et al., 2006; Abdel-Malek et al., 2008; Smit et al., 2008). In addition, as many as a third of melanomas arise from areas of the skin not generally exposed to UV light, suggesting that UV-induced mutagenesis only partly accounts for melanoma susceptibility. Recent work has shown a link between some of the genes involved in the control of pigmentation and other cancer-relevant processes. In particular, we and others are interested in the melanocortin 1 receptor (MC1R) signaling pathway in melanocytes which determines not only melanoma risk but also the efficiency by which an individual can adaptively tan and repair UV-induced photolesions after UV exposure. Data are now emerging that link this signaling pathway with the DNA repair pathway responsible for clearing UV-induced photodamage from the skin (Kadekaro et al., 2005; Hauser et al., 2006; Robinson et al., 2010). In this chapter, we review the link between melanoma and skin complexion, focusing on the genes that control innate and adaptive skin pigmentation and the mechanisms by which pigmentation differences may account for melanoma risk.

2. Melanoma - A growing problem

According to the World Health Organization, about 132,000 people will be diagnosed with malignant melanoma of the skin each year. Mainly a disease of fair-skinned individuals, it is most prevalent in Western nations in which the majority of the population has descended from Northern European ancestry (Tucker, 2009; Rigel, 2010). In the United States, for example,

malignant melanoma of the skin currently ranks in the top ten most commonly diagnosed cancers of either men or of women. In 2010, for example, it is estimated that 68,130 individuals (38,870 men and 29,260 women) were diagnosed with the disease and that it claimed the lives of 8,700 people (Croyle, 2011). Melanoma ranks as the second most common cancer in women between the ages of 20 and 35, and represents the leading cause of cancer death in women ages 25 to 30. The melanoma burden is predictably largest in countries with large populations of fair skinned individuals living in sunny climates including the United States, Australia, New Zealand and Europe (Marks, 2000). Worldwide, Australia reports the highest incidences of melanoma (on the order of 40-60 cases per 100,000 individuals) due most likely to their geographic proximity to the equator and the high proportion of their population being fair-skinned immigrants from Europe (Lens and Dawes, 2004).

Race is the primary risk factor for developing melanoma, with fair-skinned races at greater risk than darker-skinned races. For example, fair-skinned Americans are 20 times more likely to develop melanoma than their dark-skinned counterparts (Fig. 1). Ultraviolet radiation in the form of natural sun exposure and, more recently, artificial UV from tanning salons, is also a clear risk factor for melanoma (Linos et al., 2009). The presence of melanin in the skin is thought to explain much of the racial predilection of the disease, with less pigmented individuals having skin of a more UV-permeable nature (Veierod et al., 2010). Because more UV radiation can penetrate the skin, fair-skinned individuals accrue more cancer-causing UV-induced mutations when compared with highly pigmented individuals.

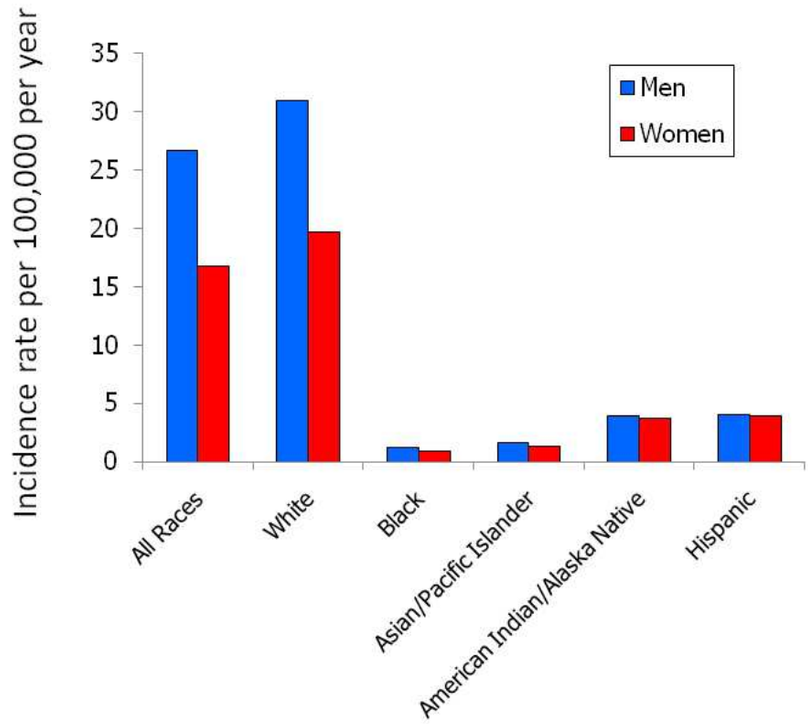


Fig. 1. Incidence of Melanoma by Race in the United States of America, 2004-2008. Note that the disease is much more prevalent among fair-skinned persons (Croyle, 2011).

Nonetheless, melanoma can afflict even the darkest individuals, and there are data to suggest that the disease tends to be diagnosed at a more advanced stage and is therefore associated

with a worse prognosis in such persons (Fleming et al., 1975; Halder and Bridgeman-Shah, 1995; Bradford, 2009). Despite advances in many areas of cancer detection and treatment, melanoma incidence and mortality have been rising for the past several decades (Berwick and Wiggins, 2006). The lifetime risk of an American developing melanoma has increased from one in 1500 in 1935 to currently about one in 50 (Fig. 2) (Croyle, 2011). According to the American Cancer Society (ACS), the incidence rate for melanoma has more than doubled since 1973 alone, increasing at annual rate on the order of 3-7% (Fig. 3) (American Cancer Society, 2011). The reason(s) for this alarming increase remain controversial and are likely multifactorial, however, it cannot be argued that melanoma's increasing incidence and high rate of metastatic disease present a legitimate public health problem (Markovic et al., 2007).

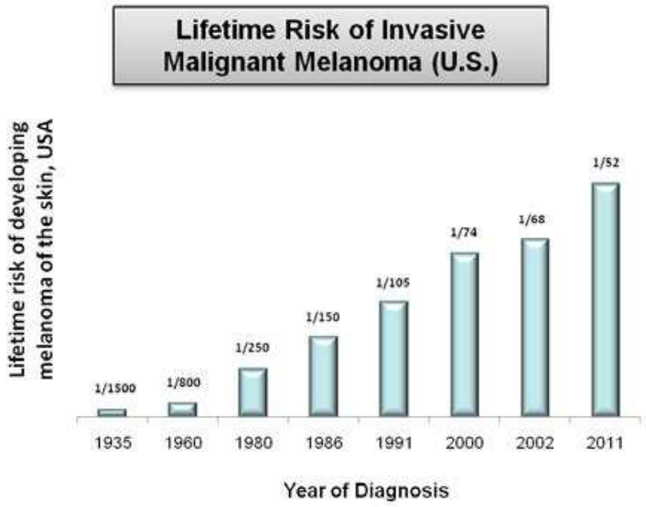


Fig. 2. U.S. Lifetime melanoma risk, 1935 - 2011 (Lens and Dawes, 2004).

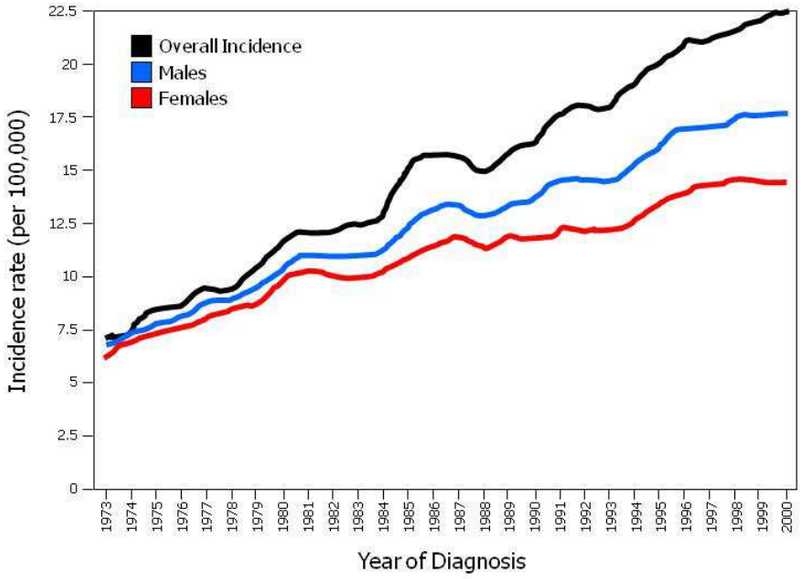


Fig. 3. U.S. Melanoma incidence, 1973–2000 (data from the SEER Program of the National Cancer Institute), adapted from Lens, et. al. (Lens and Dawes, 2004).

3. Risk factors

Risk factors for melanoma include both inherited and environmental variables (Cho et al., 2005). Understanding their interaction and relative impact is crucial to optimizing clinical practice and public health efforts.

3.1 Age

According to the most recent Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute (NCI) based on data collected between 2004-2008, the average age at which new patients were diagnosed with melanoma was 60 years (Dennis, 1999; Croyle, 2011). In fact, more than half of all new melanoma diagnoses are made in persons older than 45 years of age (Fig. 4). It should be noted, however, that melanoma can strike persons of any age, and it has been increasingly diagnosed in children and young adults (Cust et al., 2011). The reason(s) why melanoma incidence increases with age are not clearly understood, but may reflect the typical long latency required for accumulation of sufficient mutations caused by environmental factors (in this case UV radiation) to result in carcinogenesis (Liu and Soong, 1996).

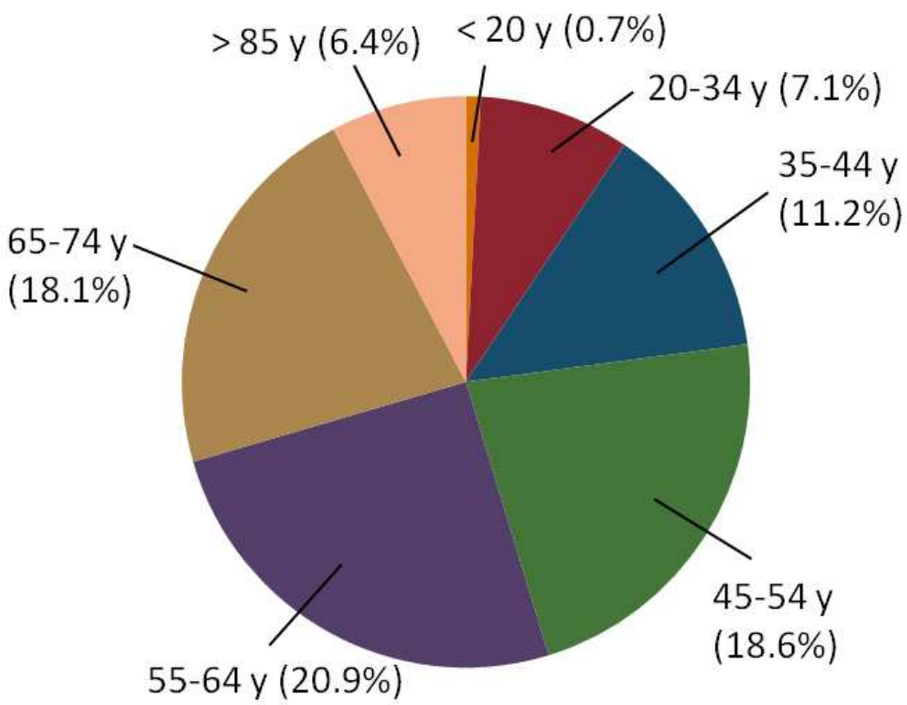


Fig. 4. Age at diagnosis, US Melanoma cases, 2004-2008 (SEER data, NCI).

3.2 UV radiation

Though many factors predict melanoma risk (Table 1), UV radiation, in the form of ambient sunlight and artificial UV sources such as tanning beds (Lim et al., 2011) is among the most important. Strong epidemiologic evidence clearly links UV exposure, particularly blistering sunburns early in life, with subsequent melanoma development (MacKie and Aitchison, 1982; Gandini et al., 2005). However, in contrast to squamous cell

carcinomas (SCC) and basal cell carcinomas (BCC) which are thought to arise from keratinocytes rather than melanocytes (Leiter and Garbe, 2008), the mechanism of UV-mediated carcinogenesis of melanocytes is not well-characterized. In keratinocyte malignancies, characteristic "UV-signature" transitional mutations between thymidine and cytosine residues are frequently noted in relevant cancer-specific genes such as p53 (Giglia-Mari and Sarasin, 2003); such changes are not typical in melanoma isolates. Nonetheless, most melanomas occur in UV-exposed anatomic locations, and melanoma incidence correlates geographically with doseage of ambient UV. It has been suggested that the mechanism of UV-mediated carcinogenesis in melanocytes may differ fundamentally from that in keratinocytes, possibly mediated by free radicals and oxidative species (Autier et al., 2011), however this has not yet been definitively proven. Because UV is composed of different subtypes (e.g. UV-A, -B and –C) and each are capable of inducing different cellular and DNA damage, the exact wavelengths and mechanisms whereby UVR contributes to the development of melanoma are not clear (Seo and Fisher, 2010). Different exposure patterns appear to predict different cutaneous malignancies (Rass and Reichrath, 2008). Intermittent intense sun exposure such as that received by a fair-skinned vacationer in a sunny environment imparts a significant increase in risk for developing melanoma (Molho-Pessach and Lotem, 2007) whereas chronic sun exposure, typically through occupational or recreational exposure, seems more relevant to keratinocyte malignancies (Gandini et al., 2005). In one study, a history of sunburn at any age, used as a surrogate for periods of intense exposure, conferred a relative risk of melanoma of 2.03 (Tucker, 2009). Serial sunburns across childhood, adolescence, and adulthood result in a dose-dependent increase in risk for melanoma (Dennis et al., 2008).

In 1988, 1% of Americans used a tanning bed. By 2007, that number increased to 27% (Fisher and James, 2010). There are currently roughly 25,000 indoor tanning facilities in the United States alone. The tanning industry represents a multi-billion dollar industry that employs more than 150,00 people and that actively seeks to dispel information linking tanning bed use with skin cancer risk (Fisher and James, 2010). Nonetheless, the UV energy emitted by tanning beds is usually anywhere from two-to ten-fold more intense than direct sunlight, and currently there is no mechanistic way to "get a tan" without assuming the mutagenic risk of UV radiation and the subsequent risk of malignancy. In fact, the profound rise in tanning bed use over the last several years may account for a significant fraction of increased melanoma incidence, particularly among young women. Persons who have ever used a tanning device have a 50% increased risk of BCC and more than a 100% increased risk of SCC (Karagas et al., 2002). Tanning bed use also clearly increases melanoma risk, as determined by at a number of separate clinical studies (Walter et al., 1990; Westerdahl et al., 1994; Chen et al., 1998; Schulman and Fisher, 2009; Lazovich et al., 2010; Mogensen and Jemec, 2010). Together, such meta-analyses suggest that regular use of tanning beds triples or quadruples the risk of developing melanoma, and that first exposure to indoor tanning before 35 years of age raises lifetime risk of melanoma by 75% (Fisher and James, 2010).

Cutaneous UV injury produces both direct and indirect DNA damage, and each can result in accumulation of mutations in skin cells. Direct damage occurs when DNA absorbs UV photons, and undergoes cleavage of the 5-6 double bond of pyrimidines. When two adjacent pyrimidines undergo this 5-6 double bond opening, a covalent ring structure referred to as a cyclobutane pyrimidine dimer (thymine dimer) can be formed.

• Age	The incidence of melanoma increases dramatically with age.
• Sun exposure	Occupational or recreational UV exposure, living in UV-rich geographies (e.g. equatorial locations), living at altitude.
• Tanning bed use	First exposure to indoor tanning before 35 years of age raises lifetime risk of melanoma by 75%
• Fair skin complexion	Deficiency of the highly UV-protective eumelanin epidermal pigment allows more UV to penetrate into the skin and promote mutagenesis.
• Chronic exposure to heavy metals	Chromium, cobalt and other metals may promote oxidative mutagenesis in melanocytes.
• Poor ability to tan	A propensity to burn rather than tan after sun exposure correlates with increased melanoma risk.
• History of sunburn	One or more severe blistering sunburns as a child or teenager increases risk
• Personal history of melanoma	Once a person has been diagnosed with a melanoma, their risk for others is heightened. Up to 10% of melanoma patients will develop a second melanoma in their lifetime.
• Family history of melanoma	Inherited CDKN2A defects (the gene that encodes the p16INK4A and p14ARF tumor suppressors) are associated with familial melanoma
• Having a large number of moles (nevi)	Many melanomas appear to arise from pre-existing moles. Benign nevi and melanoma both frequently exhibit gain-of-function mutation in the B-Raf gene.
• Immune suppression	Immunosuppressive therapies, for example, as used to prevent rejection of solid organs in transplant recipients, are associated with melanoma.
• DNA repair deficiency	Xeroderma pigmentosum (XP) patients who lack one of at least eight enzymes in a common nucleotide excision repair (NER) pathway have a 2,000-fold increased risk of skin cancers, including melanoma.

Table 1. Melanoma Risk Factors

Alternatively, a pyrimidine 6-4 pyrimidone (6,4)- photoproduct can result when a 5-6 double bond in a pyrimidine opens and reacts with the exocyclic moiety of the adjacent 3' pyrimidine to form a covalent 6-4 linkage (Sarasin, 1999). One day's worth of sun exposure can cause up to 100,000 potentially mutagenic UV-induced photolesions in each skin cell, and UV radiation can also damage cells by free radical formation and oxidative stress (Hoeijmakers, 2009). Oxidative DNA lesions are also mutagenic and form after UV-induced free radical attack (Meyskens et al., 2001). One particularly well-characterized oxidative lesion is 7,8-dihydro-8-oxoguanine (8-oxoguanine; 8-OH-dG), which promotes mutagenesis since this guanine derivative can pair equally well with cytosine (normal pairing) and adenine (abnormal) and consequently cause GC-TA transversion mutations (Schulz et al., 2000). Interestingly, although the cutaneous inflammatory response to solar radiation (sunburn) is clearly caused by the UVB component of solar radiation, it is the UVA component (which actually represents about 95% of ambient sunlight) that penetrates most deeply into the skin. Each has been implicated in skin cancer/melanoma formation. UV energy in the UVA range (roughly 315-400 nm) promotes mainly oxidative damage to DNA (e.g. 8-oxo-guanine formation) although

photodimers can result from UVA exposure as well (Cadet et al., 2005). UVB photons (290-320 nm) mainly result in thymine dimer formation but can also cause (6,4)-photoproducts and oxidative adducts to form. Each of the DNA changes caused by UV radiation is potentially mutagenic and actively repaired by cells. Thus, carcinogenesis that results from UV exposure (e.g. melanoma) is influenced not only by the amount of environmental UV exposure but also by the degree to which damage can be repaired.

The mechanism of UV-mediated carcinogenesis for keratinocyte malignancies seems to correlate with direct UV-induced DNA damage (e.g. cyclobutane dimers) because more than half of basal cell and squamous cell carcinomas are found to have signature "UV mutations" in cancer-associated genes like p53 (de Gruijl et al., 2001; Cleaver and Crowley, 2002; Bolshakov et al., 2003). However, in primary human melanoma samples, such C-T transition mutations have not been found with any degree of frequency in known cancer-related genes (Lacour, 2002; Greenman et al., 2007; Rass and Reichrath, 2008). Thus, although UV exposure is clearly linked with melanoma incidence, the actual molecular mechanism of carcinogenesis is unclear. Many groups have hypothesized that UV-induced free radicals and subsequent oxidative damage may be relevant carcinogenic events in melanocytes (Kvam and Tyrrell, 1997; Runger, 1999; Larsson et al., 2005; Runger and Kappes, 2008).

3.3 Heavy metal exposure

There is growing interest in the contribution of heavy metals (such as chromium and cobalt) to melanoma risk. Epidemiologic studies of cohorts exposed either occupationally or through joint-replacement (in patients with metal-on-metal hip arthroplasties) to to redox-active heavy metals suggest that such exposure may be a risk factor for melanoma (Meyskens and Berwick, 2008). Through fenton chemistry, heavy metals may contribute independently and in conjunction with UV (particularly UVA) to free radical formation in melanocytes; the interaction between UV and heavy metals is a field of intensive investigation (Meyskens and Yang, 2011). There is also great interest in determining whether heavy metals may influence the ability of melanocytes to recover/repair UV-mediated DNA damage (Beyersmann and Hartwig, 2008; Joseph, 2009; Whiteside et al., 2010).

3.4 Large number of moles

Since many melanomas arise from nevi (moles), it is not suprising that having a large number of moles increases an individual's risk for melanoma (Bataille et al., 1996). It is estimated that relative risk for melanoma increases from 1.47 for individuals with 16-40 nevi to 6.89 in people with 101-120 nevi (Tucker, 2009). The moles that seem particularly relevant to melanoma are dysplastic nevi, which are characterized by histologic atypia (Barnhill and Roush, 1990) and may represent a mole in evolution to a less benign state (Hussein, 2005). Still, there is a lack of consensus as to whether melanomas grow from existing benign nevi or whether nevi and melanomas may share one or more genetic factors. Individuals with many nevi are more likely to develop melanomas of the trunk whereas those with lower nevus counts require more sun exposure and typically develop cancer in sun-exposed areas of the body (Whiteman et al., 2003), suggesting that host factors that drive nevus formation may also play a role in carcinogenesis. The role of the BRAF oncogene has been prominently emphasized in recent years, and may represent a critical genetic link between nevi and melanoma. Gain-of-function signaling mutations in the BRAF gene are found in 60-80% of human melanoma isolates (Brose et al., 2002; Davies et al., 2002). Furthermore, about 80% of BRAF-mutated melanomas display a common mutation - the V600E mutation wherein

valine is substituted by glutamic acid at position 15- and this very same mutation is found in a large number of benign nevi (Pollock et al., 2003; Yazdi et al., 2003). This mutation leads to increased signaling through the MAP kinase cascade, and is thought to be a contributing factor to melanocyte proliferation.

3.5 DNA repair

Nucleotide excision repair (NER) is an evolutionarily-conserved mechanism for repairing bulky DNA lesions, including UV-induced photodimers and (6,4)-photoproducts which, if left unrepaired, underlie characteristic "UV-signature" pyrimidine transition mutations (de Laat et al., 1999; Cleaver et al., 2001). Patients with inherited recessive deficiencies of the NER DNA repair pathway are at much heightened risk of developing melanoma and other skin malignancies (Leibeling et al., 2006). The NER pathway involves the following basic steps: (1) recognition of damage and recruitment of a multiprotein repair complex to the damaged site, (2) nicking the damaged strand several nucleotides away on each side of the damaged base(s) and excision of the damaged region between the two nicks, 3) filling in the resultant gap by a DNA polymerase using the non-damaged strand as a template and (4) ligating the final nick to seal the strand. Xeroderma Pigmentosum (XP) is a rare autosomal recessive condition of defective NER caused by homozygous loss-of-function in any one of eight or more genes central to NER function. XP patients exhibit profound UV hypersensitivity beginning in early childhood, and develop epidermal thinning, telangiectasias, lentigenes and patchy hypo- or hyper-pigmentation by adolescence(Eugene and Joshi, 2006). Furthermore, despite UV-avoidance, most XP patients develop actinic keratosis and frank skin malignancies in the first decade of life (with a median age of 8 years) (Jen et al., 2009). XP patients have at least a 1,000-fold increased risk of skin cancers, and have a median age of onset for non-melanomatous skin cancer roughly fifty years younger than that of the general population. Similarly, XP patients have a markedly higher incidence of cutaneous malignant melanoma, particularly on UV-exposed skin (Van Patter and Drummond, 1953; Lynch et al., 1967; Jung, 1978), highlighting the central relevance of the NER pathway in melanoma prevention. Even though clinical XP has been described in the setting of defects in any one of eight genes (XPA, ERCC3 (XPB), XPC, ERCC2 (XPD), DDB2 (XPE), ERCC4 (XPF), ERCC5 (XPG), and POLH (XP-V)), mutations in XPA or XPC account for at least half of all clinical cases. Though XP is a dramatic phenotype that, fortunately, affects only a small fraction of the population, the mechanistic defects underlying XP may have relevance to the greater population at risk for sporadic melanoma. The contribution of polymorphisms in NER response in the general population's risk of melanoma is an area of active investigation (Li et al., 2006; Millikan et al., 2006; Applebaum et al., 2007).

Resistance to oxidative DNA damage is accomplished on a cellular level by anti-oxidant cellular defenses (e.g. glutathione levels) as well as via repair of oxidative lesions by the base excision repair (BER) pathway, a highly conserved pathway initiated by one of at least eleven damage-specific, monofunctional or bifunctional glycosylases that scan the DNA for specific base alterations (Tudek et al., 2006; Russo et al., 2007). After recognition, altered bases are cleaved from the phosphodiesterase backbone by glycolases and repair is achieved via involvement of an apurinic intermediate which is cleaved out and then replaced (David et al., 2007; Hazra et al., 2007; Klungland and Bjelland, 2007). Each of the distinct types of mutagenic lesions in the DNA of UV-exposed cells (cyclobutane dimers,(6,4)-photoproducts and oxidative lesions such as 8-OH-dG and abasic sites) can promote mutation through aberrant repair and/or incorrect base pairing during replication. Much as is the case with NER,

variations in the resistance or repair of UV-induced oxidative lesions may be relevant in determining mutagenesis in the skin and subsequently risk of melanoma (Phillipson et al., 2002; Kadekaro et al., 2006; Runger and Kappes, 2008; Song et al., 2009).

3.6 Personal or family history of skin cancer

Either because of inherited predisposition or through environmental factors, individuals who have had melanoma once have as much as an 8% chance of developing a second primary melanoma distinct from their original tumor (Ferrone et al., 2005). Similarly, melanoma risk is higher in people with first-degree relatives affected by melanoma (Gandini et al., 2005). Melanoma-prone family cohorts have been described with mutations in the CDKN2A gene which encodes the p16INK4A and p14ARFtumor suppressors, highlighting the importance of the integrity of this pathway in the ability of melanocytes to resist malignant degeneration (Hussussian et al., 1994; Kamb et al., 1994; Meyle and Guldberg, 2009; Hansson, 2010). Perhaps because of increased surveillance, familial melanoma is characterized by younger age at diagnosis, thinner lesions, better survival, multiple primary lesions, as well as higher incidence of non-melanoma neoplasms (Kopf et al., 1986).

3.7 Immunodeficiency

Individuals with defective immunity, particularly T cell immunity, are at increased risk of melanoma. Thus, patients with inherited or acquired immune defects, patients on chronic immunosuppressive therapies such as cyclosporine, tacrolimus or sirolimus (e.g. following solid organ or stem cell transplantation) and cancer patients treated with immunosuppressive chemotherapy all have a higher risk of melanoma than their immunocompetent counterparts (Otley and Pittelkow, 2000; Calista, 2001; Berg and Otley, 2002; Reutter et al., 2007).

3.8 Fair skin complexion and defective tanning response

Fair-skinned individuals, especially those who fail to tan after sun exposure, have a much higher lifetime risk of melanoma than individuals with darker complexions (Rees and Healy, 1997). Melanoma occurs about twenty times more frequently in fair-skinned individuals than in their melanized counterparts (Evans et al., 1988; Franceschi and Cristofolini, 1992). Though dark-skinned persons can develop melanoma, the disease is rare in non-white persons and tends to occur in less pigmented sites such as the subungual regions, the palms of the hand and the soles of the feet (Kabigting et al., 2009). Although the incidence of melanoma in non-white patients is lower, the mortality rate is higher, perhaps reflecting the disease's tendency to be diagnosed later at a more advanced stage and thus associated with a poorer prognosis (Bradford, 2009). Many genes have been described that contribute to skin pigmentation , often first identified in animal models with coat color or other pigmentary defects. In our discussion, we will focus on one gene in particular- the melanocortin 1 receptor (MC1R)- because its function seems particularly relevant to melanoma development.

4. Skin pigmentation

4.1 Melanocytes

Melanocytes are dendritic-type cells derived from the neural crest and are traditionally defined by their ability to produce melanin. Comprising 5-10% of total cells in the epidermal

basal layer, there are estimated to be between 1,000 and 2,000 melanocytes in every square millimeter of human skin (Nordlund, 2007). They are found both in dermal hair follicles (where they impart pigment to hair) and in the interfollicular epidermis in the stratum basale where they manufacture pigment that accumulates in the outer layers of the epidermis and that blocks UV penetration into the deeper layers of the skin. Melanocytes cells are the sole manufacturers of melanin in the skin and are thought to be the precursor cell that, upon malignant degeneration, develop into melanoma. Via their dendritic projections, melanocytes in the stratum basale may be in intimate contact with as many as 30-50 maturing keratinocytes. Numerous studies have shown robust contact-dependent as well as paracrine signals between melanocytes and keratinocytes. The "epidermal melanin unit" is a term coined to describe the close association between one melanocyte and numerous keratinocytes in the epidermis (Jimbow et al., 1991). As melanocytes manufacture melanin pigments, they transfer melanin to interdigitating keratinocytes where it accumulates in the epidermis (Seiberg, 2001). Melanin functions as a "natural sunscreen" to protect the skin against harmful effects of UV radiation such as oxidative damage and DNA mutagenesis. The more eumelanin present in the skin, both basally and after UV exposure, the more UV-protected and cancer-resistant is the individual (Vincensi et al., 1998). Persons with albinism have normal numbers of melanocytes in the skin but lack melanin pigments due to loss-of-function of any one of a number of pigment biosynthetic enzymes (Oetting, 1999). Because they lack melanin, albinos are much more UV sensitive than either fair-skinned pheomelanotic or dark-skinned eumelanotic individuals (Oetting, 2000).

4.2 Melanin pigments

Skin pigmentation is determined mainly by the type and amount of melanin pigments deposited in the epidermis. Melanin is a large bio-polymer composed of subunits of different melanotic pigment species formed by sequential oxidation and cyclization of the amino acid tyrosine (Riley, 1997) (Fig. 5). Biosynthetic reactions are catalyzed by several pigment enzymes, including tyrosinase, the critical rate-limiting enzyme that catalyzes the first two steps in melanogenesis (conversion of tyrosine into DOPA and then conversion of DOPA into DOPAquinone) (Prota, 1980; Rosei, 2001). Most of the enzymes involved in melanogenesis are exclusively found in melanocytes. The final amount and type of melanin produced in the melanocyte depends upon both inherited and environmental factors (Hearing, 1999).

There are two basic types of melanin: eumelanin and pheomelanin. Eumelanin is a brown-black chemically inert and poorly-soluble pigment polymer that is preferentially expressed in persons of darkest complexion. In contrast, because of incorporation of cysteine into the molecule, pheomelanin is a more red-yellow sulfur-containing compound (Ito et al., 2000). Eumelanin absorbs more UV radiation (is a better "sunscreen") and is much more chemically inert than pheomelanin. The first two reactions of melanin formation are common to both eumelanogenesis and pheomelanogenesis; biosynthetic pathways diverge after the formation of dopaquinone (Fig. 5). Eumelanins are derived from metabolites of dopachrome whereas pheomelanins are produced from sulfhydryl-reduced metabolites including cysteinyldopa (Prota, 2000). UV resistance is mainly determined by the absolute amount of eumelanin in the skin. Thus, while epidermal pheomelanin levels are fairly similar between light-and dark-skinned persons, dark-skinned individuals have much more eumelanin in the skin and are therefore much more UV-resistant (Simon and Peles, 2010). Besides being a poorer blocker of UV energy, pheomelanin may actually contribute to UV-induced cellular and DNA damage. UV radiation of pheomelanin is associated with

generation of reactive oxidative species (Hubbard-Smith et al., 1992; Hill et al., 1997) and photosensitized UV-induced DNA damage when added to melanocytes *in vitro* (Wenczl et al., 1998). Moreover, pheomelanin is much more soluble than eumelanin, even being found in the serum and urine of fair-skinned persons(Ito et al., 1983; Ito and Wakamatsu, 1989), raising the possibility that UV-exposed pheomelanin (or its metabolites) could leach out of melanosomes, diffuse into the nucleus, and interact with DNA to promote mutagenesis especially in the context of UV radiation. The contribution of pheomelanin to UV-induced carcinogenesis is an ongoing area of investigation.

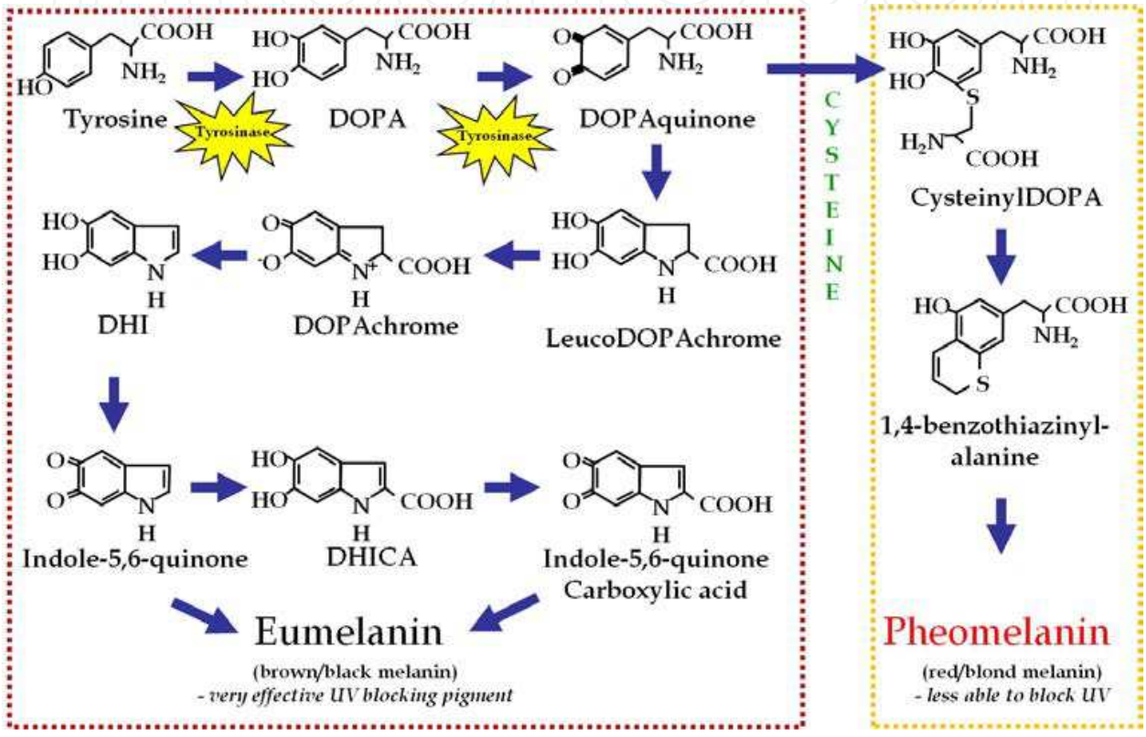


Fig. 5. **Melanin Biosynthesis.** Melanin is a large bioaggregate composed of pigmented chemical species synthesized from the amino acid tyrosine. It is present in two major forms: (1) the brown/black highly UV-protective "eumelanin" pigment and (2) the red/blonde UV-permeable "pheomelanin". Eumelanin and pheomelanin both are synthesized from the amino acid tyrosine. Tyrosinase, the enzyme that catalyzes the rate-limiting synthetic reaction for either melanin species, is the enzyme that is defective in the most common type of albinism. Incorporation of a cysteine into pheomelanin results in the retention of a sulfur moiety into the pigment, which may contribute to UV-mediated oxidative injury. The melanocyte stimulating hormone (MSH) - melanocortin 1 receptor (MC1R) signaling axis is a major determinant of the type and amount of melanin produced by melanocytes in the skin.

4.3 Fitzpatrick scale and UV sensitivity

Skin color, mainly determined by the amount of eumelanin in the epidermis, correlates well with UV resistance. Thus, the darker a person's skin, the more eumelanin it contains and the better that person's skin is able to withstand acute (e.g. sunburn) and chronic (e.g. cancer)

effects of UV. Dermatologists use the "Fitzpatrick Scale", created in 1975 by a Harvard dermatologist named T.B. Fitzpatrick, to describe skin tone (Andreassi et al., 1999). This scale is comprised of six categories that define individual phototypes by basal skin color and by response to UV radiation (Scherer and Kumar, 2010) (Table 2). Minimal erythematous dose, often abbreviated "MED", is a measure of the skin's response to ultraviolet radiation using erythema (redness, inflammation) as an endpoint. Much more UV radiation is needed to "burn" dark skin, and therefore MED is lowest in fair-skinned persons (Lu et al., 1996; Andreassi et al., 1999; Kawada, 2000). In most cases, phototypes show a strong correlation with MED (Ravnbak, 2010).

Fitzpatrick Phototype	**Phenotype**	**Epidermal eumelanin**	**Cutaneous response to UV**	**MED (mJ/cm^2)***	**Melanoma risk**
I	Unexposed skin is bright white Blue/green eyes typical Freckling frequent Northern European/British	+/-	Always burns Peels Never tans	15-30	++++
II	Unexposed skin is white Blue, hazel or brown eyes Red, blonde or brown hair European/Scandinavian	+	Burns easily Peels Tans minimally	25-40	+++/++++
III	Unexposed skin is fair Brown eyes Dark hair Southern or Central European	++	Burns moderately Average tanning ability	30-50	+++
IV	Unexposed skin is light brown Dark eyes Dark hair Mediterranean, Asian or Latino	+++	Burns minimally Tans easily	40-60	++
V	Unexposed skin is brown Dark eyes Dark hair East Indian, Native American, Latino or African	++++	Rarely burns Tans easily and substantially	60-90	+
VI	Unexposed skin is black Dark eyes Dark hair African or Aboriginal ancestry	++++++	Almost never burns Tans readily and profusely	90-150	+/-

Minimal erythematous dose (MED) is defined as the least amount of UVB radiation that will result in reddening and inflammation of the skin 24h after exposure (i.e. the lowest UV dose that causes a sunburn). The more UV sensitive an individual is, the lower the MED of their skin.

Table 2. Fitzpatrick Scale of Skin Phototypes

Although innate pigmentation is a major determinant of sun sensitivity, there are other genetic and environmental factors that determine how prone to UV damage an individual

will be (Rees, 2003). In particular, UV sensitivity correlates well with the degree to which epidermal melanin can be up-regulated after UV exposure. Adaptive pigmentation, or tanning, is the natural physiologic response of the skin to UV exposure. Adaptive pigmentation involves both an increase in the amount of melanin pigment made by melanocytes as well as epidermal thickening mediated by proliferation of keratinocytes. Both changes serve to increase melanin accumulation in the epidermis so that the skin is better protected against subsequent UV exposures. Individuals with defective adaptive pigmentation are particularly sun-sensitive and melanoma-prone. Thus, individuals with skin phototypes I and II burn easily, have difficulty tanning, and suffer the highest incidence of melanoma whereas persons of higher skin phototypes are much more sun-tolerant and have much lower incidence of melanoma (Ravnbak, 2010).

4.4 Genetic determinants of skin color

Several genes are known to be associated with basal pigmentation in humans and natural variation in skin color. Most pigment-determining genes are associated with melanin synthesis or melanosome structure/function (Table 3) (Parra, 2007). Others, such as microphthalmia (MITF) or Kit ligand (KITLG) control melanocyte migration and development (Fleischman et al., 1991; Giebel and Spritz, 1991; Tassabehji et al., 1994}. With the exception of tyrosinase, defects in melanin biosynthetic enzymes generally lead to dilutional pigmentary effects whereas defects that result in defective melanocyte survival or development result in more profound phenotypes such as piebaldism. Many pigmentation genes were identified through detailed study of coat color mutations in mice and other model organisms (Steingrimsson et al., 2006). Tyrosinase deficiency underlies oculocutaneous albinism type I (OCA1) wherein melanocytes are present in normal numbers and distribution in the skin but they fail to make any melanin pigments at all. As a result, individuals with this severe form of albinism are highly UV-sensitive and tend to avoid outdoor activities throughout life. In comparison, SLC45A2**,** also known as MAPT, encodes a membrane-associated transporter protein (MATP), which when mutated is responsible for the milder OCA4 form of albinism (Newton et al., 2001; Inagaki et al., 2006). Many genes regulate either the ratio or absolute levels of eumelanin or pheomelanin expressed in the skin. For example, solute carrier family 24 member 5 (SLC24A5), purported to encode a cation exchange protein in melanosomes, may account for up to 40% of skin color differences between Europeans and Africans (Lamason et al., 2005) and polymorphisms that result in some decrease in the activity of *TYR, OCA2, MC1R, ASIP* and *IRF4* have been reported to affect skin color in European populations (Sturm, 2009; Edwards et al., 2010; Scherer and Kumar, 2010). Thus, it seems that the protein products of several genes together influence basal skin pigmentation in humans.

4.5 Rickets and pigmentation

It would at first seem highly illogical that fair skin would have been evolutionarily selected for over time, as being fair-skinned clearly limits an individual's ability to function in ambient sunlight. However, by considering the native geographical regions from which lightly-pigmented persons originated, we might infer why light skin complexion may have developed in humans over time. Simply put, fair complexion probably evolved so that people living in geographic areas of the world with less intense sun exposure (e.g. celtic populations) would have less risk of rickets. Before widespread

supplementation of foods with vitamin D, the major source of this essential vitamin was the natural sunlight-mediated direct chemical conversion of 7-dehydrocholesterol into previtamin D3 that occurs naturally in the epidermis. After synthesis in the skin, previtamin D3 then can be modified sequentially by liver and kidney to form the active hormone cholecalciferol which is intricately involved in a host of homeostatic mechanisms. Deficiency of vitamin D underlies the pathophysiology of rickets, a disease state in which altered calcium metabolism leads to a host of severe health consequences, including osteomalacia and osteoporosis that lead to delayed growth, chronic pain, muscle weakness and disfiguring skeletal abnormalities including bowed legs, scoliosis and abnormal bone structure. Since epidermal eumelanin is a potent blocker of UV penetration and of the direct chemical conversion of 7-dehydrocholesterol into previtamin D3, more UV is needed in dark skin to manufacture sufficient previtamin D3. Therefore, as populations moved away from the equatorial regions in which humans evolved to more polar climates in which the UV energy of sunlight is much weaker, natural selection mechanisms would have favored reduced basal eumelanin in the skin and a lighter skin complexion. Moreover, there would have been much less of a need for photoprotection in such environments, therefore there would have been no evolutionary pressure to maintain a dark phenotype. By gradual lightening of the skin (mediated by reduced melanocytic eumelanin production), sufficient UV-mediated vitamin D production in the skin would still occur in regions with less ambient sunlight so as to prevent rickets (Holick, 1981; Jablonski and Chaplin, 2000). In contrast, in high-UV regions, evolutionary pressure would have favored the photoprotection afforded by eumelanin, as evidenced by the fact that populations native to these regions (e.g. Africans, Australian Aborigines, Indian subcontinent, etc.) typically having much more epidermal melanin than their more-polar counterparts. Thus, it is postulated that the evolution of fair skin may have been a positive adaptation due to the requirement of UV-dependent Vitamin D synthesis (Jablonski and Chaplin, 2000).

4.6 The melanocortin 1 receptor (MC1R) and the adaptive tanning response

There are many genes that control human skin pigmentation (Table 3), but we will focus on melanocortin 1 receptor (MC1R), which is a critical locus involved in both pigmentation and the tanning response. More relevant to melanoma, pioneering work done by Jonathan Rees and colleagues in the mid-90's showed that loss-of-function polymorphisms of MC1R correlated directly with melanoma risk. Studies of the interaction between melanocyte stimulating hormone (MSH) and its receptor, the melanocortin 1 receptor (MC1R) have led to some understanding of the molecular basis for differences in inherited and adaptive skin pigmentation. The MC1R is a seven-transmembrane domain G-protein-coupled receptor belonging to the melanocortin receptor subfamily. Ligand-mediated signaling through Mc1r involves G-protein activation and resultant increases in levels of intracellular cAMP. Production of eumelanin is favored with higher intracellular cAMP concentrations, and pheomelanin is preferentially synthesized when cAMP levels are low (Abdel-Malek et al., 2000). Fairness of skin (and melanoma susceptibility) correlates with polymorphisms of the MC1R associated with diminished transmission of MSH signals and a muted cytoplasmic cAMP response (Valverde et al., 1995; Rees and Healy, 1997). Genetic support of this hypothesis is revealed by studies of the C57BL/6 *extension* mutant ($MC1R^{e/e}$) in which red/blonde pigmentation occurs as a result of defective MC1R signaling (Robbins et al., 1993).

Gene	Pigmentation Disorder	Proposed Function	General Structure
Tyrosinase (TYR)	Oculocutaneous albinism type 1 (OCA1)	Rate-limiting enzyme in melanin biosynthesis	Type I transmembrane protein
Tyrosinase-related protein-1 (TRP1)	Oculocutaneous albinism type 3 (OCA3)	Melanin biosynthesis; tyrosinase stabilization	Type 1 transmembrane protein
Microphthalmia (MITF)	Waardenburg syndrome type 2	Myc-like master transcription factor essential for melanocyte differentiation and survival	basic-helix-loop-helix-leucine-zipper transcription factor
Dopachrome tautomerase (TRP2)	Unknown	Melanin biosynthetic enzyme	Type 1 transmembrane protein
Solute carrier family 24 member 5 (SLC24A5)	Fair skin	Melanosomal cation exchange	Membrane transporter
stem cell factor/ kit ligand (KITLG)	Piebaldism	Transmits survival and differentiation signals to melanocytes	Membrane tyrosine kinase
Pmel17 (gp100; ME20)	Unknown	Striation formation; melanin polymerization	Type 1 transmembrane protein
P/OCA2	Oculocutaneous albinism type 2 (OCA2)	Melanosome acidification	12-transmembrane domain-containing protein
OA1 receptor	Ocular albinism (OA)	Maintenance of melanosome size	G-protein-coupled receptor
Melanocortin 1 receptor (MC1R)	Red hair, freckling, defective tanning	Binds to melanocyte stimulating hormone and generates cAMP signal	7 transmembrane Gs-coupled receptor

Table 3. Partial list of major genes that determine human skin color (Marks and Seabra, 2001).

Inability to tan in response to sunlight is a cardinal feature of fair-skinned, UV-sensitive, melanoma-prone individuals. Normally, melanocytes respond to UV exposure through proliferation and up-regulation of melanin production, the "tanning response". While it is possible that some of this response occurs by direct UV-mediated effects on melanocytes themselves, it is likely that the tanning response depends on signals from other cells. In particular, the melanocyte stimulating hormone (MSH)- melanocortin 1 receptor (MC1R)

signaling axis appears to be central to the adaptive tanning response. MSH, the agonistic ligand for MC1R, binds to MC1R on the surface of melanocytes and promotes increases in cytoplasmic cAMP. Basal pigmentation likely results in part from this MSH-MC1R interaction from MSH secreted either central from the pituitary gland or from keratinocytes in the epidermis. There are three common polymorphisms of the MC1R found in UV-sensitive and melanoma-prone individuals: Arg151Cys (R151C), Arg160Trp (R160W) and Asp294His (D294H). These so-called "red hair color" (RHC) mutations correlate with red hair, freckling and tendency to burn rather than tan after UV exposure. Molecularly, the RHC MC1R variants display a muted ability to activate adenylate cyclase after MSH binding, and thus are associated with a blunted cAMP signaling response. Importantly, these loss-of-function polymorphisms of MC1R are also influence susceptibility to melanoma and other skin cancers. Thus, persons with defective MC1R signaling have higher risk of melanoma than their MC1R-intact counterparts.

Using a congenic C57Bl/6 mouse model with humanized skin, we showed that Mc1r signaling is critical to adaptive pigmentation. Thus, animals with intact Mc1r responded to repeated UV exposure by depositing eumelanin in the epidermis, whereas animals that were genetically identical except for loss of Mc1r failed to melanize at all in response to the same UV exposure (Fig. 6). We also found evidence of a cutaneous MSH-MC1R signaling axis in the skin induced by UV and involving MSH production by epidermal keratinocytes. Thus we concluded that adaptive pigmentation is dependent on an effective MSH-MC1R signaling axis in the skin.

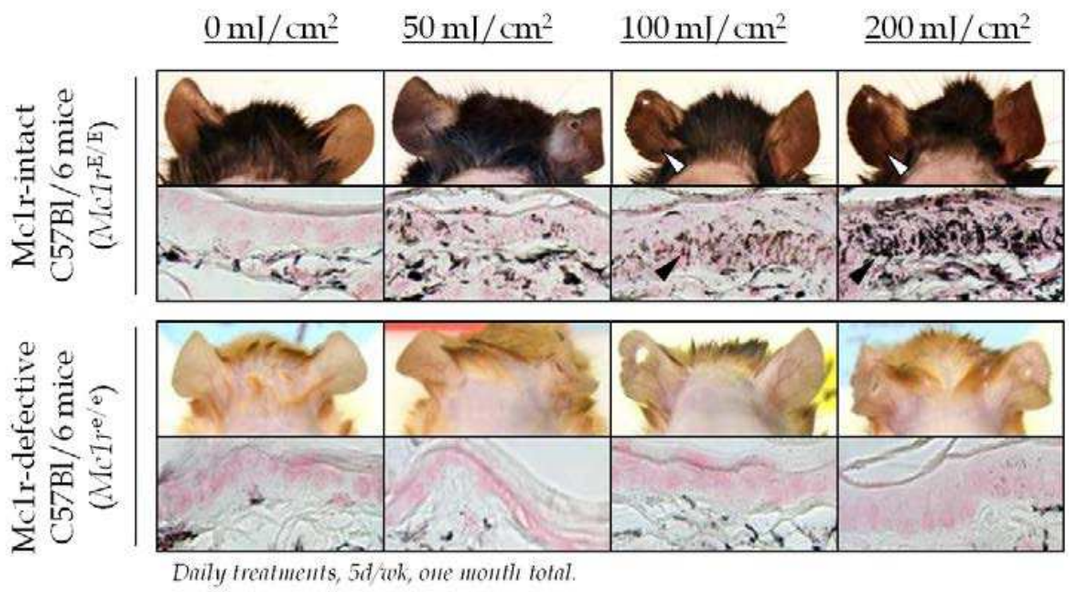


Fig. 6. **Critical role of the melanocortin 1 receptor in the adaptive tanning response.** C57Bl/6 mice genetically identical except for being either wild type ($Mc1r^{E/E}$) or mutant at the MSH receptor ($Mc1r^{e/e}$) were treated with the indicated dose of UV. Top-most rows show UV-induced ear skin darkening, with corresponding skin sections stained for melanin immediately below to show melanin accumulation (black deposits). Note the UV-induced skin darkening (black triangles) and melanin accumulation (white triangles) in $Mc1r^{E/E}$ but not in $Mc1r^{e/e}$ animals (as originally published, D'Orazio, 2006).

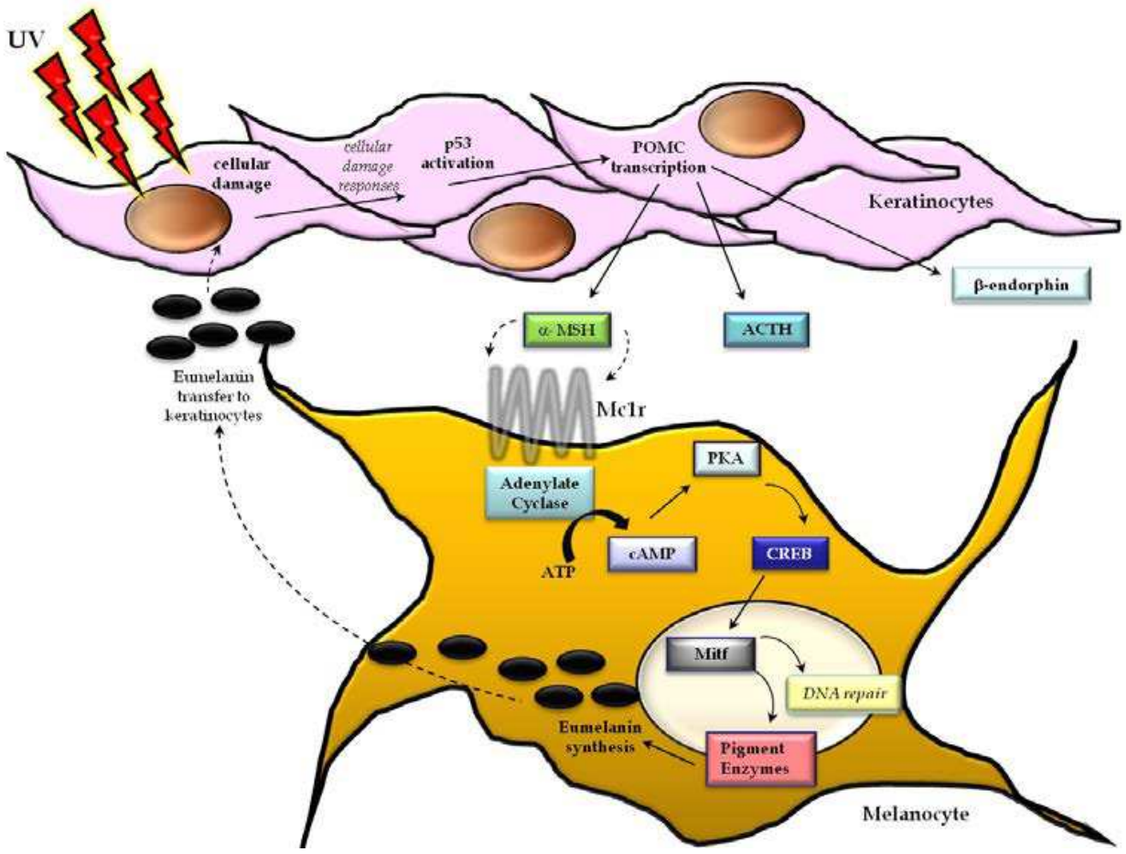


Fig. 7. **The adaptive tanning response.** Epidermal keratinocytes receive the brunt of UV damage because of their proximity to the surface of the body and because they are the most abundant cells in the epidermis. DNA damage in these cells induces activation of the global damage response protein p53, which mediates transcriptional activation of the pro-opiomelanocortin (POMC) gene. The POMC gene encodes a propeptide that is cleaved into three protein products: β-endorphin, adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH). MSH is thus produced and secreted from UV-exposed keratinocytes, where it is postulated to interact in a paracrine manner with melanocortin 1 receptors (MC1R) on neighboring melanocytes in the basal epidermis. If MC1R signaling is intact, MSH binding induces generation of the second messenger cAMP via activation of adenylate cyclase. In melanocytes, elevated cAMP levels trigger a number of downstream events including activation of protein kinase A- and subsequent up-regulation of both the cAMP responsive binding element (CREB) and microphthalmia (Mitf) transcription factors. CREB and Mitf mediate up-regulation of melanin production by induction of tyrosinase and other melanin biosynthetic enzymes. Thus, MSH-MC1R signaling leads to enhanced pigment synthesis and subsequent transfer of melanin (in the form of melanosomes) to epidermal keratinocytes. In this manner, the skin is more protected against subsequent UV insults. Recent data suggest that MSH-MC1R signaling may also enhance nucleotide excision repair (NER) in melanocytes, which would favor recovery from potentially mutagenic UV damage.

In subsequent work, David Fisher's group showed that adaptive pigmention was also dependent on p53 function (Cui et al., 2007). Normally thought of in the context as a tumor suppressor, p53 is a central DNA damage response mediator that binds to the POMC promoter and induces its expression. As a result, UV-exposed keratinocytes produce and secrete α-melanocyte stimulating hormone (α-MSH) which may then interact with MC1R on melanocytes and thereby signal the cells to ramp up production of melanin pigment (particularly eumelanin) so that the skin will be more able to cope with subsequent UV insults (Fig. 7). The skin's ability to respond to UV radiation correlates with melanoma risk. Persons with loss-of-function polymorphisms of the MC1R fail to respond to MSH signaling and demonstrate limited melanization in response to UV exposure. These very people with a defective "tanning response" are at very high risk of melanoma; their fair complexion favors accumulation of UV-induced mutation by failing to block UV penetration into the skin.

4.7 MC1R and DNA repair

We and others are now appreciating that the function of Mc1r in melanocytes clearly extends beyond adaptive pigmentation and synthesis of eumelanin. Using genetically heterogeneous human melanocytes transfected with *Mc1r* genes of variable functionality, various groups have reported a reproducible link between nucleotide excision repair (NER), the pathway responsible for clearing UV-induced thymine dimers and [6,4]-photoproducts and Mc1r function and/or cAMP signaling (Bohm et al., 2005; Hauser et al., 2006; Passeron et al., 2008; Smith et al., 2008). Using our congenic animal model divergent only at the Mc1r locus, we also observe a reproducible difference in the ability to recover from UV damage (Fig. 8). Others have also found a correlation between MC1R function and resistance to UV-mediated oxidative and free radical damage (Song et al., 2009). Determining the molecular mechanisms linking MC1R signaling and NER function is an active area of investigation in the melanocyte community.

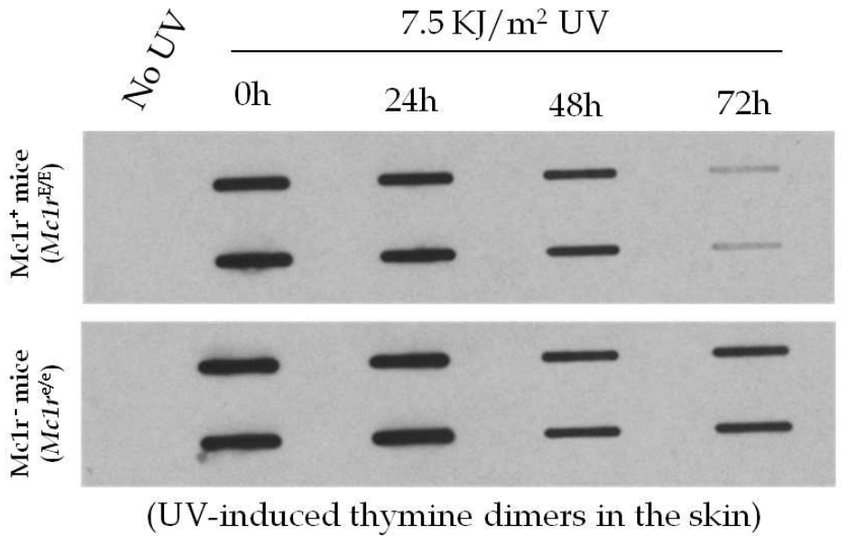


Fig. 8. **Mc1r function influences repair of UV-induced DNA damage.** C57Bl/6 mice differing only at the *Mc1r* locus were irradiated with UV and persistence of thymine dimers in the skin was followed over time. Shown are the results of two animals per group. Note that animals with intact Mc1r cleared thymine dimers more efficiently.

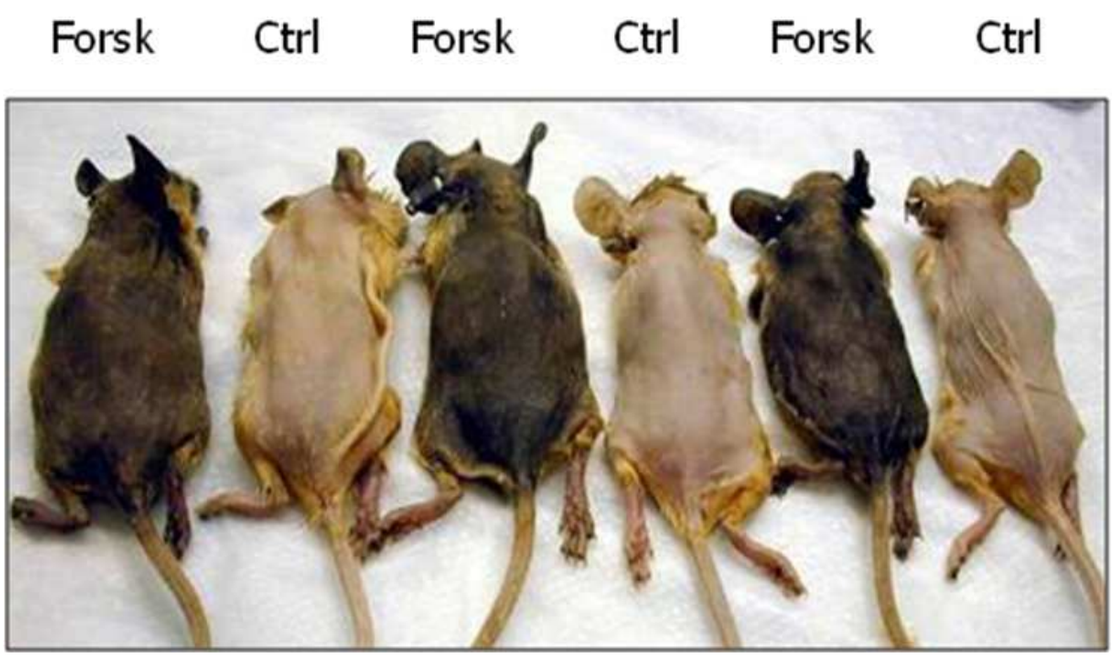


Fig. 9. Pharmacologic induction of melanin in an animal model of the fair-skinned human. C57Bl/6 mice harboring a loss-of-function mutation in the melanocortin 1 receptor ($Mc1r^{e/e}$) were treated daily with topically-applied control (propylene glycol/ethanol) or with forskolin, a drug that directly activates adenylate cyclase and raises cAMP in the skin. Photos of shaved mice were taken after 21 days. Note the robust skin darkening (which proved to be due to accumulation of eumelanin in the epidermis) in the forskolin-treated mice (D'Orazio et al., 2006).

4.8 Pharmacologic manipulation of MC1R signaling

Pharmacologic manipulation of melanocytic cAMP levels represents a promising and novel approach to alter UV sensitivity and melanoma risk. Pharmacologic MC1R mimetics include both small peptides that mimic MSH agonist activity (Abdel-Malek et al., 2009) as well as agents that bypass the MC1R to directly manipulate melanocyte cAMP levels. We reported that topical application of the adenylate cylase activating drug forskolin restored melanotic pigmentation in an animal model of the fair-skinned human (Fig. 10) and that this "sunless tanning" was potently protective against UV damage and carcinogenesis of the skin (D'Orazio et al., 2006). More recently, Khaled and coworkers showed that a similar UV-protected phenotype could be induced not by induction of cAMP generation, but rather by pharmacologic interference with clearance of cAMP by topical application of a phosphodiesterase inhibitor (Khaled et al., 2010). Small molecule-based approaches of cAMP manipulation may offer a critical advantage over MSH peptide mimetics in that fair-skinned, UV-sensitive persons most at risk of melanoma are frequently defective in MC1R signaling ability, and thus would not be expected to generate a brisk cAMP response upon MSH peptide binding. Of course, such agents would be expected to have effects in cells other than melanocytes, thus the more melanocyte-targeted approach of the MSH mimetics may offer selective advantages. In any case, rational development of pharmacologic agents capable of safely manipulating cAMP levels in epidermal melanocytes might offer UV- and melanoma protection by a variety of ways. First, by up-regulating melanin in the skin, fair-skinned

individuals would be better protected from UV. Second, sunless tanning by small molecules would represent a way to uncouple tanning from UV exposure. Fair-skinned persons seeking tans would no longer need to sunbathe or frequent tanning salons to enjoy the cosmetic and UV-protective benefits of improved skin pigmentation. Lastly, pharmacomimetics of the MC1R pathway hold the promise of enhancing the ability of melanocytes to repair UV-induced damage and would be expected to result in fewer mutations in UV-exposed skin.

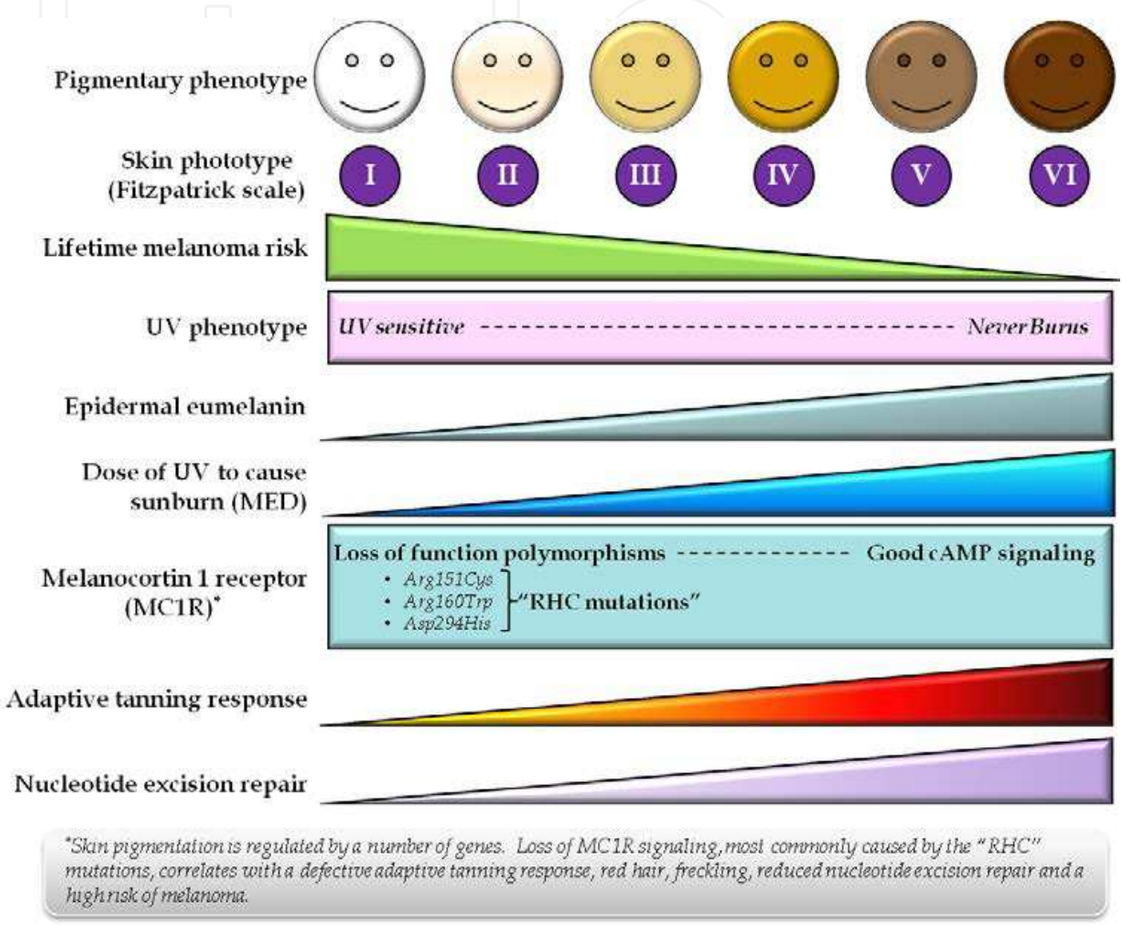


Fig. 10. **Summary of the influence of pigmentation on melanoma risk.** Fair-skinned individuals have a much higher risk of melanoma than their dark-skinned counterparts. Such individuals are much more UV sensitive, tending to burn rather than tan, after UV exposure. Their skin is characterized by much lower levels of epidermal eumelanin and consequently much less UV is needed to induce a sunburn (erythema). Furthermore, fair-skinned persons are more likely to harbor the so-called "red hair color" mutations in their melanocortin 1 receptors. These mutations are associated with a blunted MSH signaling response and reduced ability to tan. Recent data also suggests that MC1R mutations are associated with less efficient nucleotide excision repair. Reduced ability to clear UV-induced DNA photolesions would promote mutagenesis after UV exposure. Thus, MC1R-defective individuals not only suffer a higher realized dose of UV radiation because their skin has insufficient UV-blocking eumelanin but also may accumulate more mutations from UV exposure because of defective DNA repair.

5. Conclusions

One of the greatest risk factors for the development of cutaneous melanoma is having a fair skin complexion, which is characterized by comparatively low levels of a UV-blocking dark pigment called eumelanin in the epidermis. Unlike darker-skinned individuals, persons with light complexions suffer much greater skin damage from UV radiation because more UV light penetrates through the superficial epidermis to damage both keratinocytes and melanocytes in the deeper layers of the epidermis. As a result, fair-skinned individuals are exposed to higher "realized" doses of UV radiation in the skin. Thus, UV-induced mutations, which directly contributes to melanoma and other forms of skin cancer, might accumulate preferentially in fair-skinned persons over time. We and others are increasingly interested in the genetic factors that determine melanoma risk to be able to intervene in the carcinogenic process. One of the most important alleles that influences melanoma risk is the melanocortin 1 receptor (MC1R), whose function is central to the adaptive pigmentation (tanning) response in the skin. This protein mediates signals to melanocytes to induce pigment production after UV exposure (the tanning response). Besides regulating adaptive pigmentation (tanning), MC1R seems to have a powerful influence on the ability of melanocytes to repair UV-induced DNA damage by the nucleotide excision repair pathway. Thus, defective MC1R signaling as occurs with the common polymorphisms observed at high frequency in melanoma-prone fair-skinned people may predispose to malignancy by resulting in inadequate pigment deposition (which would favor UV penetration into the skin) and in a sluggish DNA repair response (which would allow UV-induced photodamage to promote mutagenesis). These new insights into the many ways in which MC1R function protects melanocytes from harmful consequences of UV may help explain why people with inherited defects of MC1R signaling suffer a disproportionately high incidence of melanoma (Fig. 10). Our long-term goal is to devise rational MC1R-rescue strategies that would reduce melanoma risk and UV sensitivity in high-risk, melanoma-prone individuals.

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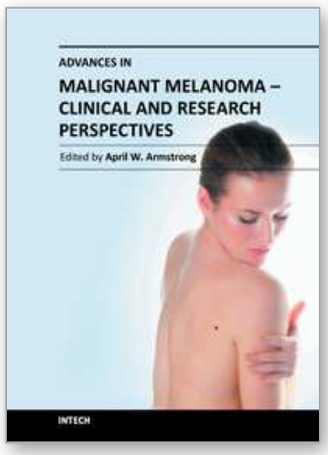
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This book titled Advances in Malignant Melanoma - Clinical and Research Perspectives represents an international effort to highlight advances in our understanding of malignant melanoma from both clinical and research perspectives. The authors for this book consist of an international group of recognized leaders in melanoma research and patient care, and they share their unique perspectives regarding melanoma epidemiology, risk factors, diagnostic and prognostic tools, phenotypes, treatment, and future research directions. The book is divide into four sections: (1) Epidemiology and Risk Factors of Melanoma, (2) Clinical Phenotypes of Melanoma, (3) Investigational Treatments for Melanoma and Pigmentary Disorders, and (4) Advances in Melanoma Translational Research. This book does not attempt to exhaustively cover all aspects of the aforementioned topics. Rather, it is a compilation of our authorsâ€™ pearls and unique perspectives on the relevant advances in melanoma during the recent years.

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