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1. Introduction

1.1. Melanoma a growing problem

The U.S. National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review estimates over 70,000 people will be diagnosed and 9,000 will die from melanoma in the United States in 2012. Though melanoma can affect persons of essentially any age, it is mainly a disease of adulthood, with median ages of diagnosis and death between 61 and 68 years, respectively (Weinstock, 2012). Nonetheless, melanoma incidence is increasing across age groups, over the past several decades in the United States (Fig. 1) (Ekwueme et al., 2011). In 1935, the average American individual had a 1 in 1,500 lifetime risk of developing melanoma. In 2002, the approximate risk of developing melanoma increased to 1 in 68 individuals (Rigel, 2002). Globally, Australia and New Zealand have the highest incidence rate of melanoma, an abundance of fair-skinned residents living in a UV-rich geography widely believed to be a major factor (Lens and Dawes, 2004). The current melanoma risk for Australian and New Zealander populations may be as high as 1 in 50 (Rigel, 2010). Considering melanoma is being diagnosed more often in young adults, could be prevented by UV-avoiding behaviors, and can be associated with extensive morbidity and mortality, it is truly an emerging public health concern. Part of the apparent increase in melanoma incidence may be due to better surveillance and earlier detection (Erdmann et al., 2012) however, even with heightened melanoma awareness and screening, there seems to have been a real increase in melanoma incidence over the past several decades.

1.2. The ultraviolet connection

Historically, humans have been exposed to UV radiation primarily as a consequence of unprotected exposure to sunlight (Holman et al., 1983; Holman et al., 1986; Woodward and
Boffetta, 1997). Since the early 20th century, a tanned appearance has been culturally associated with health and well-being in Western civilizations. The desire to sport a dark tan has been matched by increased opportunities for sunbathing outdoors as well as proliferation of indoor tanning salons. UV radiation has many deleterious effects on cells (Zaidi et al., 2012), producing both direct and indirect DNA damage, resulting in mutations that can contribute to carcinogenesis 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. 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 (Kadekaro et al., 2003; Pfeifer et al., 2005; Maddodi and Setaluri, 2008). Both (6,4)-photoproducts and cyclobutane dimers can result in characteristic transition mutations between adjacent pyrimidines. “UV signature mutations” involving T-to-C or C-to-T changes are a common feature of UV-induced malignancies such as skin cancers (Kanjilal et al., 1993; Nataraj et al., 1996; Soehnge et al., 1997; Sarasin, 1999). UV radiation also damages cellular macromolecules indirectly, through production of oxidative free radicals [20]. Several DNA modifications can result from oxidative injury, including 7,8-dihydro-8-oxoguanine (8-oxoguanine; 8-OH-dG), which promotes mutagenesis (specifically GC-TA transversion mutations) (Kino and Sugiyama, 2005). Both direct and indirect DNA changes interfere with transcription and replication, and render skin cells susceptible to mutagenesis. It is estimated that one day’s worth of sun exposure can cause up to 100,000 potentially mutagenic UV-induced photolesions in each skin cell (Nakabeppu et al., 2006).

Figure 1. Increasing incidence of melanoma of the skin, US. Data are reported as lifetime risk and are taken from NCI SEER reports.
Much of solar UV energy is absorbed by stratospheric ozone, and gradual depletion of stratospheric ozone over the last several decades has resulted in higher levels of solar UV radiation striking Earth’s surface (van der Leun et al., 2008). Increased ambient UV radiation from global climate change may be an important factor to explain the burgeoning prevalence of melanoma (Schmalwieser et al., 2005). Increased exposure to ambient UV radiation is a feature of global climate change because of thinning of atmospheric ozone and increased outdoor occupational and recreational activities associated with a warming climate (de Gruijl et al., 2003; van der Leun et al., 2008; Andrady et al., 2010; Makin, 2011; McKenzie et al., 2011; Norval et al., 2011). UV exposure in youth seems particularly important, affording the longest amount of time for the gradual accumulation of mutagenic UV lesions. Thus, high UV exposures in childhood, adolescence and young adulthood are strongly linked to risk of skin cancer later in life. For example, first exposure to indoor tanning before the age of 35 years raises lifetime risk of melanoma by seventy five percent (Schulman and Fisher, 2009).

1.3. Geographic location

UV radiation varies with altitude and with proximity to the equator. Since UV radiation can be absorbed, reflected back into space or scattered by particles in the atmosphere, ambient UV doses on the surface of the Earth vary according to the amount of atmosphere solar radiation must pass through. The more atmosphere solar radiation passing through, the weaker the corresponding UV content of the sunlight realized on the surface of the Earth. Sunlight strikes Earth most directly at the equator and more tangentially toward the poles. The more direct the sunlight’s path, the less atmosphere radiation has to traverse and the more powerful the UV component will be (Fig. 2). Thus, UV content of sunlight is most powerful in equatorial locations and weakest in polar extremes. Equatorial locations are also typically the hottest environments, therefore people living in such places tend to wear lesser amounts of clothing. Fabrics and other materials used for clothing typically block large amounts of UV radiation, as evidenced by the pattern of “farmer tans” among people who wear short sleeve tee shirts. Persons living in cold, polar climates would be expected to realize far less UV radiation from sunlight both because the UV dosage in ambient sunlight is weaker in such locations and because people living there probably are covered with more clothing. Thus in general, individuals living in equatorial locations typically receive much higher ambient UV doses than persons inhabiting temperate climates (Lee and Scotto, 1993). In the United States, risk of melanoma is higher in the South than in the North (Crombie, 1979). Worldwide, melanoma rates are highest in UV-rich environments such as Australia (Franceschi and Cristofolini, 1992; Elwood and Koh, 1994; Marks, 1995). One study examining the low rates of melanoma in Scandinavia pointed to data showing that ambient UV levels in Norway were significantly lower than most of the world because of its high latitude (Moen et al., 2009). Altitude and the amount of particulate matter in the atmosphere also influence the amount of UV found in a particular geographic location. The higher the altitude, the nearer the location to the sun and the more powerful the sunlight’s UV dose will be. Similarly, the more particles in the atmosphere, the higher the likelihood of interference with UV and the weaker the UV energy at the earth’s surface (Atkinson et al., 2011).
Figure 2. **Strength of ambient UV varies with geographic location.** UV radiation in sunlight can be blocked by the atmosphere. Consequently, the longer the distance sunlight must travel, the weaker the UV component hitting Earth will be. The highest UV doses in sunlight are found at the equator, where the sun hits the Earth at a direct angle.

### 2. Risk factors

#### 2.1. Older age

Melanoma incidence increases markedly with advancing age (Fig. 3), presumably because of the time it takes to accumulate mutations in melanocyte-relevant genes that drive carcinogenesis (Gilchrest et al., 1999). However other factors may also be relevant, including a more permissive environment for tumors to develop because of the natural age-related decline in cellular immunity (Weiskopf et al., 2009; Malaguarnera et al., 2010). According to the SEER data, from 2005-2009, the median age of melanoma diagnosis was 61 years. Nonetheless, although older adults are more at risk for melanoma, the incidence of melanoma in young adults, especially in young adult women, is increasing at a faster rate (Reed et al., 2012). For women and men between the ages of 20-29, melanoma is the second and third most commonly diagnosed cancer respectively (Siegel et al., 2012).

#### 2.2. Solar UV exposure

Decreasing UV radiation exposure, from both sun exposure and artificial UV light, may be the single best preventable factor for decreasing the incidence rate of melanoma (Lucas et al.,...
The ultraviolet portion of sunlight is divided into UVC (<280 nm), UVB (280-315 nm) and UVA (315-400 nm), with wavelengths below 290 nm being absorbed by stratospheric ozone (Fig. 4). UVB constitutes 5-10% of solar UV irradiation and is mainly absorbed by the epidermal layer of the skin. The most frequent form of DNA damage induced by UVB are molecular rearrangements resulting in the dimerization of pyrimidines, generating 2 classes of mutagenic lesions, cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts (6-4 PP) through direct absorption by DNA. CPDs are formed through a ring structure involving C5 and C6 of neighboring bases whereas 6-4 PP are formed with a non-cyclic bond between C6 and C4 (Budiyanto et al., 2002). These photoproducts promote cytosines (C)- thymines (T) and CC-TT transitions, with regions of DNA containing 5-methylcytosine being hot spots for UVB-induced mutations. Radiation in UVA range is associated with lower energy but has the ability to penetrate deeper into the dermis. In contrast to UVB, UVA is poorly absorbed by DNA, but excites numerous endogenous chromophores, generating reactive oxygen species (ROS) e.g. singlet oxygen and hydroxyl radicals. The predominant ROS-induced lesions formed are oxidized bases, such as 8-oxo-dG with DNA single and double strand breaks (Mouret et al., 2006). Both ultraviolet A radiation (320 to 400 nm) and ultraviolet B radiation (290 to 320 nm) contribute to the development of melanoma (Gilchrest et al., 1999).
Figure 4. Electromagnetic spectrum of visible and UV radiation and biologic effects on the skin. The diagram shows the subdivision of the solar UV spectrum with the shorter UV wavelengths (i.e. UVC) being entirely absorbed by stratospheric oxygen, and the majority of UVB (> 90 %) being absorbed by ozone. UV light penetrates the skin and is absorbed by different layers in a wavelength-dependent manner. The visible and UVA components of solar radiation penetrates deeply into the dermis reaching the dermal stratum papillare. In contrast, UVB is almost completely absorbed by the epidermis, with only ~20 % reaching the epidermal stratum basale. UVA and visible light make up the majority of the total terrestrial solar energy and are able to generate reactive oxygen species that can damage DNA via indirect photosensitizing reactions. UVB is directly absorbed by DNA which causes molecular rearrangements forming the specific photoproducts CPD and 6-4 PP. Mutations and cancer can result from a variety of modifications to DNA.

2.3. Sunburns

While squamous cell carcinoma of the skin has been closely associated with long term occupational exposure to the sun, risk of developing melanoma seems to be more associated with intermittent, high intensity sun exposure (MacKie and Aitchison, 1982; Lew et al., 1983). Prevalence of sunburns among children is high, with one study finding that approximately 69% of adolescents experienced sunburn the previous summer and only 40% used sun protection methods (Buller et al., 2011). Positive association between severe, painful sunburn and the development of melanoma and a negative association between Early found a positive melanoma and long-term recreational/occupational sun exposure (MacKie and Aitchison, 1982; Lew et al., 1983). Sunburn represents an inflammatory response of the skin to a significant amount of acute UV damage. It is mediated by a complex series of cellular and hormonal
events, including the generation of cytokines and mediators of vasodilatation. Risk of sunburn is related not only to UV exposure, but also to innate melanin content of the skin. Thus, sunburn mostly occurs in fair skinned people without sun protection exposed to high intensities of UV radiation, for example in equatorial or high altitude locations. Various epidemiologic studies support the finding that the number of severe sunburns and total childhood sun exposure are positively associated with the development of melanoma (Holman et al., 1986; Scotto and Fears, 1987; Cust et al., 2011; Newton-Bishop et al., 2011; Volkovova et al., 2012). The carcinogenic effects of sunburn have also been demonstrated experimentally using transgenic mice forcing overexpression of the hepatocyte growth/scatter factor (HGF/SF) in melanocytes. In these mice, HGF over-expression altered the distribution of melanocytes to create a “humanized” model, which mimics human skin with melanocytes located in the basal layer of the epidermis, rendering them more susceptible to DNA damaging effects of UVR. Remarkably, a single erythemal UV dose to neonatal mice caused the development of melanomas in roughly half of animals at one year of age (Noonan et al., 2001). This animal model has been used by several laboratories to study a variety of melanoma susceptibility genes in context of UV-induced childhood sunburn and melanoma initiation and metastasis (Recio et al., 2002).

2.4. Indoor tanning

Whereas only one percent of Americans ever used a tanning bed in 1988, now more than twenty five percent have participated in indoor tanning. With more than 25,000 facilities in the US alone, indoor tanning represents a multi-billion dollar industry.Employing over 160,000 people, the tanning industry has a customer base of nearly thirty million people and exerts political influence through powerful lobbying efforts. Nonetheless, there are clear health risks associated with indoor tanning. UV radiation emitted by tanning lamps is typically more powerful than direct ambient sunlight. It is estimated that half an hour in a tanning booth yields the same UV damage to skin as much as 300 minutes in unprotected sun. Levels of UVA/UVB emitted by tanning beds are unpredictable, widely unregulated, and much higher than environmental exposure. A study of 62 tanning salons in North Carolina found that the average UVA output of a tanning bed was 192.1 W/m² (vs. average UVA summer solar output at noon in Washington D.C. of 48 W/m²) and the average UVB output of a tanning bed was 0.35 W/m² (vs. average UVB summer solar output at noon in Washington D.C. of 0.18 W/m²) (Hornung et al., 2003). Tanning bed use is clearly associated with skin cancers of all varieties. Persons who have ever used a tanning bed have a 50% increased risk of basal cell carcinoma and more than a 100% increased risk of squamous cell carcinoma (Karagas et al., 2002).

The risk association between melanoma development and indoor tanning has been well substantiated (Autier, 2004; Rados, 2005; Han et al., 2006). Data accumulated from several studies suggest that the use of a tanning salon before the age of 35 is associated with a 75% increased lifetime risk of melanoma, while over-use of tanning salons was associated with a 15% increased risk of melanoma (Fig. 5) (Schulman and Fisher, 2009). Risk of carcinogenesis is enhanced for all types of tanning beds (UVA, UVB and mixed output) and increases with years of use, number of sessions, and hours exposed (Lazovich et al., 2010). There currently is no “safe” way to tan by UV without the inherent risk of photodamage and malignancy. The
use of tanning salons despite the established risks, however, remains popular, especially in female young adults and adolescents. A recent survey found that 18.1% of female and 6.3% of male Caucasian adults reported using a tanning salon in the past 12 months (Choi et al., 2010). Among 10,000 adolescents across the 50 states, 24.6% of girls under 18 reported tanning, with prevalence of use steadily increasing from age 12 to 18 years (Geller et al., 2002). California and Vermont have recently banned (January 2012 and July 2012 respectively) use of indoor tanning beds for minors, while many other states require parental permission or have proposed legislation for restricting the use of tanning beds for minors. The use of tanning salons by adolescents did not decline from 1998 to 2004, even though more states restricted use by minors (Cokkinides et al., 2009), which suggests that these partial restrictions may not be effective. Predictors of using tanning salons for women were residing in the Midwest and the South and using spray tan products, while men who lived in metropolitan areas were more likely to visit tanning salons.

Figure 5. Relative risk of melanoma associated with exposure to indoor tanning. Results of seven studies and overall estimate. Values higher than 1.0 indicate heightened risk of melanoma. Modified from (Schulman and Fisher, 2009).

2.5. PUVA therapy

Ultraviolet A radiation therapy (PUVA) is a common and effective treatment for psoriasis that was first introduced in the 1970s. Since UVA exposure from the sun and artificial sources like tanning beds is a clear risk for melanoma, there is concern that PUVA therapy may predispose to malignancies including melanoma. One large cohort study that followed patients for 20
years found that there was a 10-fold increase in the incidence of invasive melanoma in patients who had received PUVA therapy versus age matched controls (Stern, 2001). Increased risk began at 15 years post-PUVA therapy exposure, and there was a stronger association with patients exposed to higher doses of PUVA therapy, more treatments (greater than 250), and in patients with fair skin. Thus, limiting exposure to PUVA to minimal doses and carefully selecting appropriate patients for the treatment can maximize the effectiveness of this treatment and minimize the risks. Patients who receive PUVA therapy should be carefully followed to facilitate early detection of melanoma and other skin cancers.

2.6. Skin pigmentation

Although individuals from any race or skin pigmentation group can be affected by melanoma, risk of disease is much higher in fair-skinned persons (Fig. 6) (Beral et al., 1983; Rees and Healy, 1997; Sturm, 2002). Created by Dr. Thomas Fitzpatrick in 1975, the Fitzpatrick scale is commonly used to describe skin tone and resultant UV sensitivity (Draelos, 2011). Skin complexion is mainly determined by the amount of black melanin in the epidermis. This pigment, called eumelanin, is a potent blocker of UV radiation. Thus the more eumelanin in the skin, the less UV penetrates into the deep layers of the epidermis, and the less UV-mediated mutagenesis will occur. Risk of sunburn is also heavily influenced by epidermal eumelanin content. In fair-skinned individuals with low Fitzpatrick skin types, it takes a much lower dose of UV to induce inflammation. The amount of UV needed to cause a sunburn is termed the “minimal erythematous dose” (MED), and a lower MED correlates with low levels of epidermal eumelanin and a higher risk of melanoma (Ravnbak et al., 2010) (Fig. 7). Thus, risk of melanoma for Caucasian males and females is 31.6 and 19.9 per 100,000 respectively, while risk for African American males and females is only 1.1 and 0.9 per 100,000 in comparison (Ekwueme et al., 2011; Park et al., 2012).

Figure 6. Racial Disparity in Melanoma Incidence (US). Incidence rates based on NCI SEER data. Note that in general, the darker a race’s average skin tone, the lower their incidence of melanoma, irrespective of gender.
Figure 7. Melanoma risk varies according to skin complexion. Skin complexion can be estimated by the Fitzpatrick scale wherein the higher the number, the more deeply melanized and pigmented the skin is. Fair-skinned individuals are much more UV sensitive and tend to burn rather than tan after UV exposure. Melanoma risk is highest in fair-skinned individuals.

2.7. Nevi

The majority of melanomas arise out of pre-existing moles (nevi), therefore the more nevi a person has, the higher the likelihood that a melanoma may develop (Grob et al., 1990; Newton-Bishop et al., 2010). One study found a seven-fold increased relative risk for melanoma if a patient has more than one hundred nevi (Gandini et al., 2005). Most patients, however, do a poor job in estimating their own mole counts (Melia et al., 2001), and a patient’s self assessment of nevus count should not be relied upon in lieu of a full skin exam for melanoma screening (Psaty et al., 2010). Despite the link between nevi and melanoma, risk of any given mole progressing to malignancy is very low (Metcalf and Maize, 1985; Halpern et al., 1993). One study estimated the 60 year risk of malignant transformation to be 1:11,000 for an individual nevus on a 20 year-old woman (Tsao et al., 2003).

A molecular link between benign nevi and malignant melanoma was established in 2003 when Pollock and coworkers reported that a gain of function mutation in the BRAF gene was common to the majority of benign nevi and melanomas (Pollock et al., 2003). Specifically, the V599E amino-acid substitution in BRAF results in enhanced MAPkinase signaling which stimulates melanocytes to proliferate. Clearly other genetic and/or epigenetic cellular events, such as loss of the tumor suppressor p16, are required for full malignant transformation, as BRAF mutation is sufficient for nevi formation but not melanomagenesis.

Congenital melanocytic nevi are pigmented lesions found on individuals at birth (Zaal et al., 2005; Krengel et al., 2006). Those that are particularly large (>20 cm in diameter) seem particularly prone to malignant transformation, and are associated with a lifetime melanoma risk of approximately 10% (Krengel et al., 2006). Smaller congenital melanocytic nevi have a significantly lower risk of malignant degeneration. Given their relatively high malignant potential,
large congenital melanocytic nevi warrant consideration for prophylactic excision (Psaty et al., 2010) preferably during childhood, since up to 70% of melanomas associated with congenital melanocytic nevi occur by the individual’s tenth year (Marghoob et al., 2006).

Atypical Mole Syndrome (also referred to as Dysplastic Nevus Syndrome or Familial Atypical Multiple-Mole Melanoma Syndrome) has emerged as one of the most significant risk factors for the development of melanoma (Carey et al., 1994; Slade et al., 1995; Seykora and Elder, 1996). In the general population, dysplastic nevi are relatively common: found on 2-8% of Caucasians especially among those under 30 (Naeyaert and Brochez, 2003). A combination of both UV exposure and genetic susceptibility is believed to contribute to dysplastic nevi formation (Naeyaert and Brochez, 2003). Atypical Mole Syndrome is an important melanoma risk factor (Halpern et al., 1993); individual melanoma risk approaches 82% in affected individuals by the age of 72 (Tucker et al., 1993).

2.8. Chemical exposure and occupational risk

Geographic discrepancy in melanoma incidence may be influenced by factors other than UV exposure and skin pigmentation (Fortes and de Vries, 2008). A number of environmental and occupational substances have been linked to development of malignant melanoma including heavy metals, polycyclic aromatic hydrocarbons (PAHs) and benzene (Ingram, 1992; Vinceti et al., 2005; Meyskens and Yang, 2011). As a result of working around many of these chemicals, petroleum workers, for example, have been reported to have up to an eight-fold increased risk of melanoma (Magnani et al., 1987). Polyvinyl chloride (PVC), a substance used widely in the clothing and chemical industries, is also linked to increased risk of melanoma (Lundberg et al., 1993; Langard et al., 2000). Printers and lithographers, through their exposure to PAH and benzene solvents, have up to a 4.6-fold increased risk of disease (McLaughlin et al., 1988). Ionizing radiation exposure, as might occur from medical radiation exposure or atomic energy occupational exposure has also been linked to melanoma risk (Fink and Bates, 2005; Lie et al., 2008; Korcum et al., 2009). Pesticide exposure was reported to almost triple melanoma risk (Burkhart and Burkhart, 2000). Clearly a better understanding of occupational risk factors, especially when coupled to UV risk, is needed to guide more targeted public health efforts for the prevention of melanoma (Fortes and de Vries, 2008).

2.9. Immunodeficiency

Immunodeficiency, either from inherited defects in cell-mediated immunity or from infection-associated immunosuppression (e.g. AIDS) clearly predisposes individuals for the development of melanoma (Silverberg et al., 2011). Furthermore, with the increasing prevalence of autoimmune disorders and solid organ transplantation requiring medical restraint of native immune function, iatrogenic immunosuppression is becoming an increasingly important risk factor for malignancy (DePry et al., 2011). The number of individuals in the US living with solid organ transplant has more than doubled since 1998 to more than 225,000 individuals (Sullivan et al., 2012). Although immunosuppressive agents expose patients to increased risk for a large number of malignancies, cutaneous cancer risk is particularly affected (Engels et al., 2011), and skin cancers in immunosuppressed patients may behave more aggressively than
those in immunocompetent persons (Brewer et al., 2011). Cancer patients treated with chemotherapy also have a higher incidence of melanoma, presumably either because of the mutagenic effects of chemotherapy on melanocytes or perhaps through immunosuppression (Smith et al., 1993). Therefore, solid tumor transplant patients, persons with inborn or acquired deficiencies of T cell function and anyone with a current or past pharmacologic history of chemotherapy or immunosuppressive medications should be advised to practice UV-avoiding strategies and be regularly screened for cutaneous malignancies.

3. Genetic factors

While UV exposure is the most significant environmental risk factor for melanoma, there are several genes that when mutated clearly influence melanoma risk (Meyle and Guldberg, 2009; Nelson and Tsao, 2009; Ward et al., 2012). These genes have been identified largely through studying melanoma-prone families or individuals with extraordinary UV sensitivity or melanoma predisposition. Some of these genetic defects cause bone fide familial cancer syndromes, characterized by heritable predisposition to one or more types of malignancy. Each cancer syndrome is associated with unique cancer risk. Clinical “clues” to melanoma familial cancer syndromes include: melanomas diagnosed at a young age (e.g. below forty years of age), multiple primary melanomas diagnosed in the same person over time, multiple family members affected by melanoma, and extreme UV sensitivity (D’Orazio 2010). It is estimated that up to twelve percent of patients diagnosed with melanoma will have a positive family history of melanoma, yet even among this group, there is often no identifiable melanoma susceptibility gene (Gandini et al., 2005). Many of these melanoma susceptibility genes can portend risk vastly exceeding that of the general population (Udayakumar and Tsao, 2009).

3.1. Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A)

The familial atypical multiple mole and melanoma (FAMMM) syndrome was first described in two families in which affected individuals harbored more than one hundred dysplastic nevi and had a lifetime cumulative incidence of melanoma approaching one hundred percent (Clark et al., 1978; Lynch et al., 1978). This syndrome, also called “dysplastic nevus syndrome” was associated with many of the features of a familial cancer syndrome, including melanomas at young ages (median age of 33 years in one study) (Goldstein et al., 1994). Heterozygous loss of CDKN2A function is associated with roughly 40% of cases of familial melanoma (Kamb et al., 1994; Holland et al., 1995)

Linkage studies performed in melanoma pedigrees identified loss of heterozygosity in the chromosome 9p21 region (Fountain et al., 1992). Later, the cyclin-dependent kinase inhibitor 2A gene was identified through positional cloning to be the tumor suppressor on 9p21 that was mutated in many melanoma-prone families (Kamb et al., 1994; Weaver-Feldhaus et al., 1994). Interestingly, affected individuals were not only at higher risk of malignant melanoma of the skin, but also for central nervous system gliomas, lung cancers and leukemias (Nobori et al., 1994). CDKN2A actually encodes two distinct tumor suppressor proteins- p16 and
p14ARF that are transcribed in alternate reading frames directed through the use of alternative first exons (Chin et al., 1998; Sharpless and DePinho, 1999; Sharpless and Chin, 2003). p16/INK4a is produced from a transcript generated from exons 1α, 2 and 3, and p14/Arf is generated in an alternative reading frame, from a transcript of exons 1β, 2 and 3 (Udayakumar and Tsao, 2009). The majority of melanoma-associated mutations impacting exon 1β, which is specific for p16INK4a. Most germline mutations in CDKN2A found to contribute to melanoma susceptibility are loss-of-function missense or nonsense mutations of p16 (Goldstein et al., 2006; Goldstein et al., 2007).

The p16 tumor suppressor protein acts to regulate cell proliferation at the G1/S cell cycle checkpoint by inhibiting the cyclin-dependent kinases CDK4 and CDK6 to prevent entry into S-phase of the cell cycle (Serrano et al., 1993; Ohtani et al., 2001). Cyclin-dependent kinases in complex with cyclin D function jointly to inactivate the retinoblastoma (RB1) by phosphorylation. Once phosphorylated, RB1 is released from the transcription factor E2F-1, thereby permitting E2F-dependent transcription of genes that propel cells into proliferation. By binding to and inhibiting CDK4, p16 acts to prevent cell cycle progression, and when p16 function is lost, cells lose regulatory control over CDK/cyclin activity and proceed into unregulated cell division (Bartkova et al., 1996; Chin et al., 1998; Liggett and Sidransky, 1998). As with many other tumor suppressor genes, it is thought that inactivation or underexpression of both alleles of CDKN2A may be required for a cancer phenotype to emerge (the “two-hit” hypothesis) (Knudson, 1996; Tomlinson et al., 2001; Payne and Kemp, 2005). Thus individuals with inherited loss of one copy of p16 are at risk for p16-dependent malignancies such as melanoma (Ranade et al., 1995), with cancers developing only if the remaining p16 allele is inactivated to a sufficient extent either through mutation or epigenetic inactivation (Berger et al., 2011).

3.2. Cyclin-Dependent Kinase 4 (CDK4)

Several melanoma-prone kindreds have been discovered who carry mutations not in CDKN2A, but in its target- cyclin-dependent kinase 4 (CDK4) (Zuo et al., 1996; Soufir et al., 1998; Goldstein et al., 2000). Unlike CDKN2A whose p16 protein product acts as a tumor suppressor by negatively regulating melanocyte proliferation, CDK4 is an oncogene whose activity enhances cell division. The gain-of-function mutations in CDK4 melanoma-prone families typically result in amino acid changes that render the CDK4 enzyme insensitive to p16 inhibition, thereby resulting in a functional p16 null phenotype (Zuo et al., 1996; Newton Bishop et al., 1999; Goldstein et al., 2000).

3.3. Xeroderma Pigmentosum (XP) genes

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder of the nucleotide excision DNA repair (NER) pathway caused by homozygous deficiency of any one of at least eight genes (XPA, XPB, XPC, XPD, XPE, XPF, XPG and XPV) that work in complex to repair bulky DNA lesions such as mutagenic DNA photoproducts caused by UV radiation (Leibeling et al., 2006) (Fig. 8). NER functions by recruiting a protein complex known as XPC-hHR23B to UV-induced photoproducts in the DNA, with XPE aiding lesion verification. TFIIH, a transcription factor that plays a key role in gene transcription, is also essential for NER. TFIIH is a complex of nuclear proteins that promote transcription and DNA repair, and its dysfunction can lead to increased susceptibility to skin cancer.
factor containing multiple enzymes including XPA, XPB and XPD then unwind the DNA in
the vicinity of the damaged bases, and then two endonucleases XPF-ERCC1 and XPG incise
the lesion on either side of the photodamage to release the damaged DNA section. Finally,
using the undamaged strand as a template to ensure fidelity, DNA polymerase, PCNA, RFC
and DNA ligase I act in concert to synthesize and ligate the new DNA fragment. In this manner,
the NER pathway is the cell’s major defense against DNA damage and if defective, UV-induced
mutations accumulate in the genome.

Figure 8. UV-induced cyclobutane dimers- structure (A) and repair by the Nucleotide Excision DNA Repair
(NER) pathway (B). The NER pathway is mediated by at least eight enzymes that work together to identify bulky DNA
lesions that distort the structure of the double helix, excise the damaged portion and replace the excised region by
DNA synthesis directed by the complementary strand. Homozygous deficiency in any one of the NER enzymes leads to
the clinical condition known as Xeroderma Pigmentosum (XP). Please note that although not shown, NER can also be
initiated in actively transcribed regions of the genome by involvement of the Cockayne syndrome proteins A and B.

As a result of the inability of the skin to recover after UV exposure, intense sun sensitivity is
one of the first manifestations of XP. Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the US (Robbins et al., 1974). Beginning in the first or second year of life, UV-exposed skin (e.g. on the face and arms) develops areas of hypo- or hyper-pigmented macules, telangiectasias and atrophy, all signs of chronic sun exposure that normally take decades to develop. Premalignant lesions such as actinic keratoses develop, and typically malignancies such as basal cell carcinomas, squamous cell carcinomas and melanomas start appearing by the age of ten years. XP patients have more than a thousand-fold increased risk of skin cancer and develop malignancies decades earlier than unaffected patients (Van Patter and Drummond, 1953; Lynch et al., 1981; Cleaver, 2005; Jen et al., 2009; Rao et al., 2009; Wang et al., 2009). Melanomas isolated from XP patients clearly bear evidence of “UV signature mutations”, lending support to the concept that defective repair of UV-induced photodimers underlies carcinogenesis of melanocytes (Takebe et al., 1989; Sato et al., 1993). Beside skin cancer, XP patients suffer a 20-fold increased risk of other malignancies including lung cancer, gastric carcinoma and brain cancer, perhaps reflecting the importance of NER in the repair of damage produced by agents other than UV. Overall, approximately 70% of persons with XP
die by the age of 40 years from cancer. Currently there is no accepted therapy for treating XP other than avoidance of sunlight and careful surveillance and local control of pre-malignant or malignant lesions as they appear. The use of topical DNA repair enzymes such as T4 endonuclease V which cleaves UV-induced photolesions (Cafardi and Elmets, 2008) and novel UV-protective strategies such as the pharmacologic induction of cutaneous melanin levels which block penetration of UV radiation (D’Orazio et al., 2006) are being developed and may hold great promise for these exceptionally UV-sensitive individuals.

Intriguingly, although the homozygous condition known as XP reveals much about the importance of the NER pathway in melanoma resistance and ability of UV radiation to fuel melanomagenesis, evidence is accumulating that polymorphisms in NER enzymes in the general (non-XP) population may influence melanoma risk. For example, several studies have found an association between polymorphisms in certain NER enzymes and melanoma including XPD (Tomescu et al., 2001; Mocellin et al., 2009), XPC and XPF (Winsey et al., 2000; Baccarelli et al., 2004; Blankenburg et al., 2005; Debnak et al., 2006). Some groups have posited that multiple NER variants in a single individual may be required to influence melanoma susceptibility (Li et al., 2006).

3.4. Melanocortin 1 Receptor (MC1R)

The MC1R is a seven transmembrane Gs-coupled protein that, when bound by melanocyte stimulating hormone (MSH), activates adenylyl cyclase and cAMP generation (Fig. 9). This cAMP second messenger signaling leads to activation of the protein kinase A (PKA) cascade which, in turn, leads to up-regulation of the MITF and CREB transcription factors that together induce expression of melanin biosynthetic enzymes such as tyrosinase and dopachrome tautomerase (Yasumoto et al., 1994; Bertolotto et al., 1996; Fang and Setaluri, 1999). In this manner, MC1R signaling enhances the production and export of melanin by melanocytes to maturing epidermal keratinocytes, thereby controlling the melanin levels and innate UV resistance of the skin (Fig. 9). When MC1R signaling is defective, then melanocytes alter the type and amount of melanin they manufacture. Specifically, a red/blonde sulfated pigment known as pheomelanin is produced rather than the brown/black eumelanin species. Pheomelanin is a much poorer blocker of UV photons and may even contribute to oxidative damage within melanocytes, itself a possible mutagenic mechanism.

Loss-of-function polymorphisms have been identified in MC1R, with the vast majority of allelic variation occurring in European and Asian populations. The most prevalent MC1R mutations (D84E, R142H, R151C, R160W, and D294H) are known as the “RHC” (red hair color) alleles because of the association with a blonde/red hair color, freckling and tendency to burn rather than tan after UV exposure (Scherer and Kumar, 2010). RHC MC1R alleles are also associated with a relatively high lifetime risk of melanoma (increased odds ratio of 2.40 in one study) (Williams et al., 2011). MC1R variants may also modify other melanoma-relevant alleles (van der Velden et al., 2001; Demenais et al., 2010; Kanetsky et al., 2010; Kripper et al., 2010). In an Australian cohort, for example, co-inheritance of either the MC1R variants R151C, R160W or D294H with CDKN2A mutations and decreased latency for melanoma by approximately 20 years (Box et al., 2001). A more recent study found that MC1R variants significantly
increased penetrance and lowered the age of melanoma diagnosis in people with CDKN2A mutations, (Fargnoli et al., 2010).

In addition to its role in skin melanization, MC1R may influence melanoma development by non-pigmentary pathways as well (Matichard et al., 2004; Goldstein et al., 2005). Specifically, we and others have found that MC1R signaling influences the ability of melanocytes to recover from UV-induced DNA damage (Hauser et al., 2006; Abdel-Malek et al., 2009; Song et al., 2009). MC1R signaling directly enhances NER in melanocytes, and studies are underway to discover the molecular mechanisms linking MC1R signaling to the NER DNA damage repair pathway. Overall, there is much evidence placing MC1R as a “master regulator” of melanocyte UV physiologic responses.

**Figure 9. The central role of the melanocortin 1 receptor (MC1R) in the epidermal response to UV radiation.** UV-induced cellular and DNA damage to epidermal keratinocytes 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 melanocyte stimulating hormone (MSH) along with β-endorphin and adrenocorticotropic hormone (ACTH). MSH secreted from UV-exposed keratinocytes then is hypothesized to bind melanocortin 1 receptors (MC1R) on melanocytes in the basal epidermis. MSH binding induces generation of the second messenger cAMP via MC1R-mediated activation of adenylate cyclase in melanocytes. Generation of cAMP triggers a number of downstream events including activation of the protein kinase A signaling pathway and up-regulation of the cAMP responsive binding element (CREB) and microphthalmia (Mitf) transcription factors. CREB and Mitf induce melanin production through transcriptional up-regulation of melanin biosynthetic enzymes. Thus, MSH-MC1R signaling leads to enhanced pigment synthesis and subsequent transfer of melanin to epidermal keratinocytes. In this manner, the skin is more protected against subsequent UV exposure. MSH-MC1R signaling may also enhance nucleotide excision repair (NER) in melanocytes, which would enhance recovery from UV damage.
3.5. Microphthalmia (MITF)

Mitf is a myc-like transcription factor that is critical to melanocyte development and survival (Levy et al., 2006). Defective Mitf leads to disorders of melanocyte function and pigmentation (Fisher, 2000; Goding, 2000; Widlund and Fisher, 2003; Steingrimsson et al., 2004). In humans, for example, Waardenburg syndrome type 2 is caused by inactivating mutations of Mitf, and is characterized by pigmentary defects due to the congenital absence of melanocytes in distinct anatomic locations (hair, skin eyes) (Hughes et al., 1994; Tassabehji et al., 1994). Mitf Immunohistochemical staining has long been used to identify surgical tumor isolates as melanomas (King et al., 1999; Salti et al., 2000), but its oncogenic contribution to melanoma wasn’t realized until Garraway and colleagues reported Mitf to be amplified in a subset of melanomas, particularly in aggressive disease (Garraway et al., 2005). Mitf may be amplified in up to 20% of metastatic melanomas and is associated with activation of the hypoxia inducible factor (HIF1A) pathway (Busca et al., 2005; Cheli et al., 2012) and reduced patient survival (Ugurel et al., 2007).

More recently, melanoma predisposition due to point mutations of Mitf (rather than gene amplification) were described. The E318K Mitf variant correlated with a positive melanoma family history, multiple primary melanomas or risk of melanoma and renal cell carcinoma in the same patient. Mechanistically, it is thought that the E318K Mitf variant leads to gain-of-function in Mitf by impairing its SUMO-mediated clearance (Bertolotto et al., 2011; Yokoyama et al., 2011). Thus whether by increased gene dosage or increased protein stability, Mitf seems to be a relevant melanoma oncogene, and current research efforts are attempting to devise pharmacologic targeting of MITF (Flaherty et al., 2010).

4. Conclusions

An explosion of information regarding the molecular pathways involved in melanoma development has been witnessed in the last several years. The MAPkinase cascade, for example, has emerged as a critical oncogenic pathway that drives the majority of cases of melanoma. Gain of function mutations in BRAF, most notably the V600E point mutation that results in unregulated BRAF signaling, have been described in at least half of all cutaneous melanomas (Davies et al., 2002; Pollock and Meltzer, 2002; Pollock et al., 2003). Oncogenic BRAF mutations lead to constitutive activation of kinase activity of BRAF, providing continuous growth signals in the absence of extracellular stimuli (Nikolaou et al., 2012). In many melanomas in which BRAF has not been mutated or in melanomas treated with BRAF inhibitors, N-Ras oncogene upregulation has been observed, leading again to increased signaling through the MAPkinase cascade (Padua et al., 1984; van ’t Veer et al., 1989; Ball et al., 1994; Carr and Mackie, 1994; Wagner et al., 1995; Goydos et al., 2005; Nazarian et al., 2010). Though targeted inhibition of the MAPkinase signaling pathway has led to significant advances in the treatment of melanoma (Flaherty et al., 2010; Falchook et al., 2012), to date, somatic inheritance of MAPkinase activating mutations leading to melanoma predisposition, have not been reported.
The incidence of melanoma has risen at an alarming rate over the last several decades. The reasons for this increase are unclear, but probably represent the confluence of a variety of environmental and inherited risk factors. Though significant progress has been made over the last several years in immunotherapy (Hodi et al., 2010; Kaplan, 2011; Wilson, 2011) and targeted kinase inhibition against melanoma (Flaherty et al., 2010; Chapman et al., 2011; Flaherty et al., 2012; Sosman et al., 2012), clearly it would be better to prevent development of disease in the first place. As our understanding of the molecular mechanisms that underlie the malignant degeneration of melanocytes expands, so hopefully will our ability to develop rational interventions to prevent the development of melanoma.

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