Commentary

UV or Not UV: Metals Are The Answer

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Advances in our understanding of the etiology of cutaneous melanoma over the past decade have implicated constitutive heredity alterations in a small percentage of cases (5-8%). Using the power of competitive genomic hybridization, melanomas located in intermittently sun exposed areas have been associated with BRAF abnormalities whereas those located in chronic sun-exposed areas have not shown such an association (1). A large number of abnormalities in many signaling pathways have been described by us and others in melanoma (2, 3) although the genetic basis per se for most of these alterations is unknown. Squamous cell cutaneous cancer is strongly associated with lifetime cumulative sunlight exposure, and classic UV light mutations are consistently detectable nearby and within the malignancy (4).

In contrast, the epidemiology of cutaneous melanoma is complex at best but strongly suggests that blistering sunburns during childhood and adolescence are particularly important in establishing a risk for subsequent carcinogenesis (5, 6), particularly in high-risk individuals; for example, in individuals with red hair color (RHC), melanocortin-1 receptor (MC1R) genotypes (7) or individuals with a large number of nevi, particularly those that are dysplastic (8). Epidemiology studies also support the notion that adults who experience intense intermittent sunlight exposure (e.g., indoor workers, sunlamps) are at increased risk for melanoma compared with those who receive their sun exposure chronically (6). In both the childhood and adult situations, there seems to be a long latent period before the end point of melanoma becomes manifest.

What Could Account for These Epidemiologic Observations and Cause Such a Phenomenon? We propose that redox-active metals are the missing link, the cocarcinogens that provide a biological rationale for the epidemiologic observations and the process of the pathogenesis of cutaneous melanoma (Fig. 1). We propose that the first step in the pathogenic process is the photoinduced release of a pool of iron cations (9-11) in response to a blistering sunburn and binding of Fe^{2+} and/or Fe^{3+} to at-risk melanin (i.e., pheomelanin and certain types of eumelanin, especially when partially oxidized), thereby initiating a low-level oxidative stress. Recent studies indicate that exposure of melanocytes to UV light results in up-regulation of nucleotide excision repair (12), the expression of which is determined by the MC1R genotype (being less vigorous in those with a RHC phenotype), which itself is a major determinant of the type of melanin made (13). We have recently shown that the multifunctional base excision repair protein apurinic/apyrimindinic endonuclease/redox effector 1 is also transiently up-regulated in response to UVB,[3] a property that melanoma cells seem to acquire permanently (2). Another prominent feature of the photobiological response (at least in keratinocytes) is the up-regulation of metallothioneins, which are responsible for metal transport (11).

How Can These Diverse Epidemiologic and Molecular Observations Be Reconciled? We have developed experimental evidence that UVB does not produce its permanent effect via a direct genetic change but rather epigenetically by causing partial oxidation of melanin and the establishment of a low-level redox cycling in susceptible individuals; that is, in individuals with at-risk melanin as determined by the multitude of factors that regulate melanin synthesis and melanosome construction (e.g., MC1R genotype; ref. 14).

We further propose that for the redox cycling to progress beyond a low level, which can generally be managed by the melanin of most individuals, a second hit is required, and that second hit is either repeated large doses of sunlight exposure with generation of high levels of reactive oxygen species *or* an increased uptake of a redox-active metal into the melanocyte. The latter event could occur in one of two major ways: increased uptake of available heavy metals due to a polymorphism in one of the many metallothioneins that regulate heavy metal uptake or by exposure to high environmental levels of metals that overwhelm normal metallothionein regulation of metals (see below). Although no direct measurements of metallothioneins and their association with melanoma risk have yet been reported, several studies document that metallothionein expression in primary melanomas is a strong prognostic factor for survival, even in thin melanomas (15). This should not be too surprising as large amounts of Cu^{2+} become available as the tight compartmentalization of melanin synthesis (which is governed by the copper dependent enzyme tyrosinase) in the melanosome (a solid matrix type of

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[3] Yang and Meyskens, unpublished data.

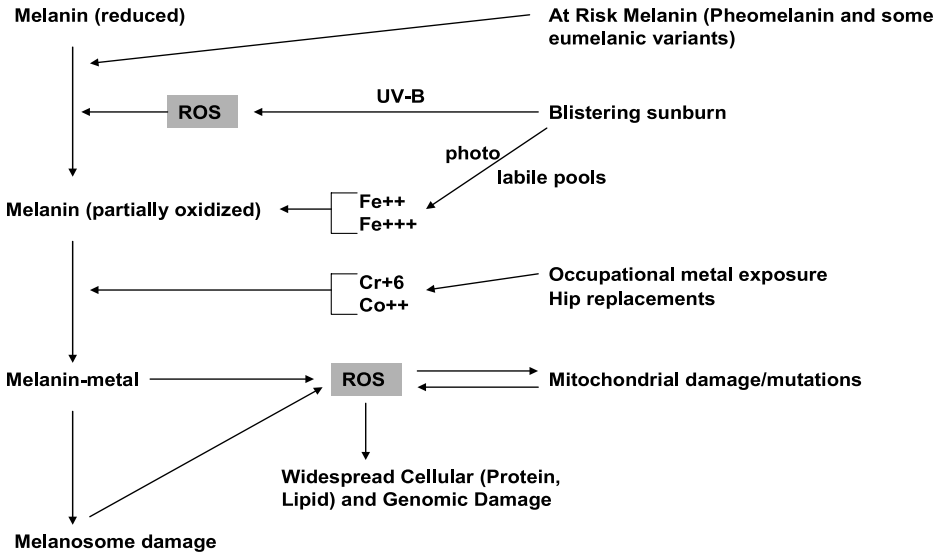

Figure 1. The initial carcinogenic event in melanomagenesis is epigenetic and is dependent on the presence at melanin.

synthesis) becomes progressively disrupted during melanomagenesis (16), and one feature of melanosome biology that is largely ignored is that this organelle can be duplicated (without nuclear genetic input) and passed on to the next generation of cells. An alternative explanation for the melanosomal disruption is that matrix proteins are mutated and the lattice on which melanin formation and deposition occurs is a primary event with melanin oxidation as secondary.

What Type of Environmental or Epidemiologic Evidence Supports the Notion that Increased Metal Exposure Is a Risk Factor for Melanoma? Most important is the long-known and well-documented binding of many natural and industrial metals to melanin (17), an observation that has been used to develop gallium for clinical imaging of melanoma (18). Since an extensive general review of the occupational epidemiology of melanoma and the general observations of Austin and Reynolds (19) that the mortality from melanoma was associated with a number of chemical-associated exposures, specific studies have addressed this issue. Three types of evidence have been accumulated: specific occupational epidemiology, groundwater studies, and follow-up observations on hip replacement patients. At least five studies of printers/lithographers from five different countries indicate an increased risk for these workers, from a proportionate mortality ratio of 460 (20) to relative risks of 3.4 (21) and 2.8 (22) and odds ratios of 1.6 (23) and 2.6 (24). Additionally, there has been reported an increased significant risk of melanoma in the electronics/electrical industries from five studies (24-28). A particularly informative result was the retrospective cohort study of 138,905 electrical utility workers (28) in which polychlorinated biphenyl (which bind to melanin) exposure showed a significant dose-response relationship with mortality from melanoma (relative risk, 1.23-1.93). A study of arsenic exposure, based on toenail measurements of arsenic and ecologic associations of water source among melanoma cases, has also shown a dose-response relationship that was further enhanced by a prior diagnosis of nonmelanoma skin cancer, suggesting perhaps a higher UV exposure (29).

Perhaps the most intriguing epidemiologic data is the long-term follow-up of patients who have had hip or knee replacements. No increased incidence of cancers (or melanoma) was seen in those patients who had a metal-on-plastic hip replacement (abandoned in the early 1990s due to a high failure rate) or knee replacements (no direct metal-on-metal contact). However, and in contrast, the situation in patients with metal-on-metal hip replacements suggested quite a different pattern. Nyren et al. (30) showed that the standard incidence ratio (SIR) of three cancers was increased: melanoma [SIR, 1.23 (95% confidence interval, 1.00-1.50), prostate [SIR, 1.13 (95% confidence interval, 1.00-1.50)], and kidney [SIR, 1.13 (95% confidence interval, 1.04-1.22)]. A large meta-analysis that analyzed all published articles from 1966 to 2004 with more than 1,435,356 person-years of follow-up confirmed these findings (31)—melanoma: SIR, 1.15 (95% confidence interval, 1.01-1.30); prostate: SIR, 1.12 (95% confidence interval, 1.08-1.16). Finally, a third study of the Nordic inpatient registry (which may have been partially included in the large meta-analyses) was subsequently published and confirmed these results with almost identical findings (32). Extensive longitudinal studies of hip replacement patients indicate that serum Cr^{6+} and Co^{2+} levels increase to 5×10 times normal in the first 2 years after operation for metal-on-metal replacements and then stay elevated at two to three times normal levels indefinitely; this does not occur in metal-on-plastic hip replacements (33).

Based on the studies discussed above, our preliminary findings have led us to postulate that a second cocarcinogen is needed for melanomagenesis to occur in many, if not most, cases, perhaps more so in those in which low actinic damage is not a prominent feature (1). We propose that redox-active metals, which are widely dispersed in modern societies, provide a basis for a second hit and are the cocarcinogens that lead to reactive oxygen species generation along with the melanin-bound Fe waiting *in situ* since the blistering sunburns of childhood, and that mutations eventually occur that lead to the transformed state. We have recently developed systems to directly test the role of redox-active metals

and UV in the melanocyte transformation process; the role of potential chelators in blocking this event needs to be examined as well (34). More to come...

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