HHS Public Access

Author manuscript

JAMA Dermatol. Author manuscript; available in PMC 2017 January 18.

Published in final edited form as:

JAMA Dermatol. 2016 July 01; 152(7): 751–753. doi:10.1001/jamadermatol.2016.0524.

Red hair, light skin, and UV-independent risk for melanoma development in humans

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A key gene which regulates pigmentation in humans is the Melanocortin-1-Receptor (MC1R), that encodes a seven transmembrane G-protein coupled receptor which regulates cAMP levels in melanocytes. MC1R is activated by Melanocyte Stimulating Hormone (MSH) that is secreted by UV-irradiated keratinocytes in the “tanning” response [1]. MC1R loss-of-function is one means of generating light skin that likely facilitates vitamin D biosynthesis. This plausibly provided an evolutionary selective advantage in preventing lethal vitamin D deficiency at high latitude geographic locations. Negative selective pressure may have arisen at low latitude (higher UV intensity), due to photolysis of vital factors such as folate or potentially increased skin cancer risk in lightly pigmented individuals.

In Fitzpatrick skin type 1 individuals with light skin and red hair, >80 percent bear a dysfunctional variant in both MC1R alleles [2]. MC1R signaling upregulates tyrosinase, whose strong enzymatic activity results in synthesis of brown/black eumelanin. In contrast, loss-of-function MC1R variants produce lower cAMP and tyrosinase levels which induce formation of pheomelanin pigment. Pheomelanin not only lacks efficient ultraviolet (UV) shielding capacity, but it (or its biosynthetic intermediates) actively induce formation of reactive oxygen species (ROS) as well as DNA damage [3]. Of skin type 2 patients, ~60 percent carry a single loss-of-function MC1R allele, whereas less than 20 percent of all individuals with skin type 3 or higher show one dysfunctional allele [2].

Melanoma incidence has risen over 30-fold in the last century [4]. Within the United States, melanoma incidence is about three fold higher in individuals of European descent than in Asians, and ~15 times higher than in individuals originating from South America and Africa [5]. As melanin levels largely influence melanoma risk, studies have examined the effect of yellow-red pheomelanin and brown-black eumelain on this melanoma risk [6].

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Conflict of Interest Disclosures:
None reported.

Author Contributions: Drs Roider and Fisher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Roider and Fisher. Acquisition, analysis, and interpretation of data: Roider and Fisher. Drafting of the manuscript: Roider. Critical revision of the manuscript for important intellectual content: Fisher. Statistical analysis: Roider and Fisher. Obtained funding: Fisher. Administrative, technical, or material support: Fisher. Study supervision: Fisher.

Financial Disclosure: None reported.

While UV is a key contributor to melanoma risk, with numerous UV signature mutations typically found throughout the melanoma genome, certain studies have suggested that additional mechanisms may contribute to melanoma risk. One of the suggested contributors is pheomelanin.

In a preclinical model, Mitra and colleagues studied mice carrying a conditional allele of BRAF V600E, that on a genetically black (Mc1r wildtype) background produces benign nevi. When crossed onto an Mc1r loss-of-function background, ~50% of the mice developed invasive melanomas. To ask whether the melanoma risk was related to the pheomelanin pigment in the Mc1r loss-of-function mice, (or a different biological consequence of having low cAMP signaling), a tyrosinase mutant allele (albinism) was crossed onto the red/Mc1r-mutant BRAF(V600E) background, and was seen to ablate the melanoma risk. These studies suggested that pheomelanin or the pathway downstream of tyrosinase that is responsible for pheomelanin synthesis, contributes significantly to melanoma risk in this UV-independent genetically defined system [7]. In the absence of UV the skin of these redhaired mice also contained significantly increased lipid peroxidation and oxidative DNA damage as compared to skin from genetically matched albino-red animals. Recognition of pheomelanin and oxidative stress as UV-independent drivers of murine melanoma formation raised the question of how important this effect might be in humans. An intrinsic challenge to defining a UV-independent role of pheomelanin in human melanoma arises from difficulties in controlling for UV exposure among melanoma patients.

In this issue of JAMA Dermatology, Wendt et al. addressed this challenge by performing a case control study including 991 melanoma and 800 control patients, investigating the effect of MC1R variants on melanoma formation in UV-dependent and UV-independent contexts. Their study showed that individuals carrying two MC1R variants were at higher melanoma risk independent of UV-exposure symptoms, as compared to wild-type carriers.

Patients were stratified according to their MC1R mutation status, and five high-risk variants (“R”, complete loss of function, Ins86_87A, R142H, R151C, R160W, 146 D294H) and five low-risk variants (“r”, partial loss of function, V60L, D84E, V92M, I155T, R163Q) were genotyped. Adjustment for age and gender confirmed that more than 12 sunburns in life, 10 or more sunburns below the age of 20, and severe signs of actinic skin damage were associated with significantly increased melanoma risk. Melanoma risk increased with the number of MC1R variants, suggesting that in this UV-dependent, but age and gender independent context, carriers of two or more variants were exposed to an over 2-fold higher risk (OR 2.13, 95% CI, 1.66–2.75; $p<0.001$) and single variant carriers to a 1.35 (95% CI, 1.05–1.73; $p=0.02$) to 1.94-fold (95% CI, 1.45–2.60; $p<0.001$) increased risk.

To investigate UV-independent effects, the analysis was adjusted not only for age and gender, but also for variables related to sun exposure, such as a history of sunburns in childhood and adolescence, as well as clinically visible signs of actinic sun damage. Most interestingly, this adjustment revealed a significant correlation between melanoma risk and MC1R variant status, resulting in a 1.5 (95% CI, 1.01–2.21; $p=0.04$) to 2.63-fold (95% CI, 1.82–3.81; $p<0001$) risk increase. Overall, this carefully performed study indicates that individuals carrying MC1R variants display a UV-independent significant intrinsic risk,

highlighting a need to better understand how MC1R variants, pheomelanin and ROS impact melanoma development and how to protect these individuals at elevated risk.

Morgan and colleagues proposed, a concept in which pheomelanin might either reduce or consume major antioxidants, or increase ROS generation directly [8]. Panzella and colleagues studied how pheomelanin, originating from human red hair, impacts the cellular redox system and autoxidation of reduced glutathione (GSH). GSH, a major cellular antioxidant, and reduced nicotinamide adenine dinucleotide (NADH), were both significantly diminished by pheomelanin [9]. The question of whether MC1R may also control various redox genes, like 8-oxoguanine DNA glycosylase and the apurinic apyrimidinic endonuclease 1 [10], or might influence lipid peroxidation via pheomelanin-metal complexes [11] has not yet been fully clarified.

Understanding the danger originating from excessive cutaneous ROS, the question of how to protect individuals from an elevated intrinsic melanoma risk arises. Clearly, the correct and continuous application of UV-filter sunscreen reduces melanoma formation, and limits additional UV-induced ROS exposure as well as other UV-mediated carcinogenic events. As demonstrated in a large-scale carefully conducted randomized controlled trial in Australia, sunscreen application significantly reduced melanoma formation, by about 50% [12]. In BRAF(V600E) mice, a broad-spectrum sunfilter delayed the onset of UV induced melanomas, offering partial protection [13]. Although these studies strongly support efforts made in public health promotions encouraging usage of sunscreens, currently available sunfilters and prevention recommendations might not fully cover additional “intrinsic” risk factors, such as those associated with UV-independent pheomelanin related chemistry.

As UVA, a major ROS inducer, likely plays a significant role in melanoma formation, sunscreen manufacturers are seeking to incorporate ingredients that broadly filter both UVA and UVB. However, about half of all sunfilters promoted as "broad spectrum" protection exhibited only “low” or “medium” protection from UVA [14]. Therefore implementation of stricter guidelines, and implementation of extra sun care actions, such as physical sun protection and sun avoidance, must still be emphasized.

Carrying the findings of Wendt et al further, it may be valuable to consider whether UV-independent (pheomelanin-related) carcinogenic risk might occur in lightskinned non-redhaired individuals. While redhaired individuals usually contain MC1R redhair variant alleles, it is possible that other individuals with light skin (eg Fitzpatrick phototype II) may harbor related chemical events within their skin, perhaps to a lesser degree. The finding by Wendt et al is also consistent with the observation that melanoma is more likely to occur on non-sun-exposed anatomic locations of lightly pigmented individuals, as compared to non-melanoma skin cancers (which are more tightly linked to UV).

One controversial preventative strategy might be to utilize anti-oxidants within sunfilters. While anti-oxidants might produce direct antagonistic chemical activities against pheomelanin associated reactive oxygen generation, several studies have demonstrated worsening behavior of various cancers, including melanoma [15] following use of the thiol antioxidant N-acetyl cysteine. It is possible that such anti-oxidants are inadvertently

protecting existing malignant (or premalignant) cell clones, from oxidative stress intrinsic to malignant transformation. If so, then it may be difficult—and hazardous—to utilize antioxidants as a preventative strategy. Such “shotgun” approaches seem ill-advised given our current understanding of the underlying chemistry. However it may be valuable to better understand which precise pro- and anti-oxidant species are involved, how the skin’s intrinsic antioxidant defenses work, and consider the role(s) of cutaneous pigments (especially dark brown/black eumelanin).

There are likely to be valuable lessons available to learn from nature, since humans with dark skin pigmentation or easy tanning capacity, exhibit profoundly lower risk of both melanoma and non-melanoma skin cancers. This lower risk occurs despite the relatively weak SPF value of eumelanin. Perhaps dark pigment is a more optimal anti-oxidant species which does not exert a survival benefit to pre-malignant cells. However the use of UV to produce dark pigmentation would clearly be a suboptimal and hazardous strategy.

The study by Wendt and colleagues provides valuable insight into a silent UV-independent melanoma risk that has no clear current preventative strategy. For now, lightly pigmented individuals need to understand the risks associated with sun exposure, and should utilize physical sun protection whenever possible. Regular skin examination and thorough self-examination remain valuable steps towards halting melanoma mortality.

Acknowledgments

Funding/Support: This study was supported in part by NIH grants (5P01 CA163222-03 and 5R01 AR043369-19) and the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation. Funding/Sponsor was not involved in the design and conduct of the study, collection, management, analysis, interpretation of data, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

The authors grateful acknowledge members of the Fisher Lab for useful discussions.

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