

MELANOMA AND SUN EXPOSURE.

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Although melanoma incidence and deaths continue to increase in most populations,^{1 2} until recently, there has been uncertainty as to precisely which wavelengths of light cause melanoma or the exact mechanisms of action involved in melanoma induction. This has greatly hindered the development of new sunscreens, and led to consumer confusion.

There is now abundant evidence linking short and long wavelength UVA rays to melanoma. This evidence includes both animal models and epidemiological evidence.

MELANOMA ISSUES.

It has been recognized for a long time that there is an association between the development of melanoma and sun exposure, particularly acute intermittent exposure. Important genes have now been linked to the development of melanoma. However, it is still unclear exactly how melanoma develops, and which wavelengths of light are involved, UVB, long or short wavelength UVA, or both? Which genes are involved? Although all is not known, there are a few animal models and epidemiological data that does help to paint a picture of what is causing sun induced melanoma.

WHAT IS KNOWN ABOUT MELANOMA

There is significant epidemiological and genetic evidence showing that UVA exposure is the cause of sun induced melanoma^{3 4 5 6}, whereas other skin cancers (squamous cell and basal cell carcinomas) are largely a UVB phenomenon.

High energy UVB rays are able to produce direct DNA damage. They actually produce “signature mutations” such as pyrimidine dimers and 6-4 photoproducts. These characteristic UVB fingerprints are seen commonly in non-melanoma skin cancers (squamous cell and basal cell carcinoma) but **are not** seen in melanomas. Further; BRAF

¹ Longstreet, J. (1988). Cutaneous malignant melanoma and ultraviolet radiation: a review. *Cancer Metastasis Rev* 7, 321-333.

² Woodhead, A.D., Setlow, R.B., & Tanaka, M. (1999). Environmental factors in nonmelanoma and melanoma skin cancer. *J Epidemiol* 9, S102-S114

³ Moan, j., Dahlback, A., & Setlow, R.B. (1999). Epidemiological support for a hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 70, 243-247.

⁴ Oliveria, S., Dudek, J., & Berwick, M. (2001). Issues in the epidemiology of melanoma. *Expert Rev Anticancer Ther.* 453-459.

⁵ Wang, S., Setlow, R., Berwick, M., Polsky, D., Marghoob, A., Kopf, A., et al. (2001). Ultraviolet A and melanoma: a review, *J Am Acad Dermatology* 44, 837-846.

⁶ Garland, C., Garland, F., & Gorham, E. (2003) Epidemiologic evidence for different roles of ultraviolet A and B radiation in melanoma mortality rates. *Ann Epidemiol* 13, 395-404.

mutations, common in melanomas occurring on sun exposed areas,^{7 8 9} are not seen in melanomas occurring on sun protected sites.^{10 11 12} About 90% of BRAF mutations occurring in sun exposed melanomas involve a single nucleotide substitution -T1799A¹³, a mutation not caused by UVB rays, (pyrimidine dimers or photoproducts), but oxidative damage secondary to UVA exposure.¹⁵ In addition to BRAF, there are other “oxidative signature” gene mutations, such as NRAS that are found in melanomas.

Although there are rare UVB signature (pyrimidine dimer) mutations in melanomas on sun exposed sites, these are found in similar frequency in non-sun exposure mucosal site melanomas¹⁶. This is strong evidence that sun induced melanomas are caused not by UVB damage, but oxidative stress damage from exposure to long wavelength UVA rays.

SO HOW DOES UVA EXPOSURE CAUSE THE OXIDATIVE DAMAGE NECESSARY FOR DEVELOPMENT OF MELANOMA

Given that environmental sunlight is a mix of different wavelengths, and of different strengths, the study of human subjects to determine a mechanism of action for development of melanoma is problematic to say the least. One is left to the study of animal models. The best of these is the fish *Xiphophorus* model. In this fascinating study by Dr. Richard Setlow, there were melanoma induction peaks in not only the long wavelength UVA I region, but even extending into the visible light range. This is disturbing, as many sunscreen manufacturers have argued that there is no reason to continue to push sunscreen development further into the long wavelength UVA I range. It was not until recently that scientists have understood the true damage posed by UVA rays, particularly long wavelength UVA I rays.

⁷ Gordon, A., Osman, I., Gai, W., He, D., Huang, W., Davidson, A., et al. (2003). Analysis of BRAF and N-RAS mutations in metastatic melanoma tissues. *Cancer Res*, 1276-1286.

⁸ Pollock, P.M., Harper, U.L., Hansen, K.S., Yudt, L. M., Stark, M., Robbins, C. M., et al. (2003). High frequency of BRAF mutations in nevi. *Nat Genet* 33, 19-20.

⁹ Goldenberg-Cohen, N., Cohen, Y., Rosenbaum, E., Herscovici, Z., Chowers, I., Weinberger, D., et al. (2005) T1799A BRAF mutations in conjunctival melanocytic lesions. *Invest Ophthalmol Visual Sci* 46, 3027-3030.

¹⁰ Edwards, R., War, M., Wu, H., Medina, C., Brose, M., P.V., et al. (2004). Absence of BRAF mutations in UV protected mucosal melanomas. *J Med Gen* 41, 270-272.

¹¹ Helmke, B.M., Mollerhauer, J., Herold_Mende, C., Benner, A., Thome, M., Gassler, N., et al. (2004). BRAF mutations distinguish anorectal from cutaneous melanoma at the molecular level. *Gastroenterology* 127, 1815-1820.

¹² Wong, C., Fan, Y., Chan, T., Chan, A., Ho, L., Ma, T., et al. (2005). BRAF and NRAS mutations are uncommon in melanomas arising in diverse internal organs, *J. Clin Pathol* 58, 640-644.

¹³ Brose, M. S., Volpe, P., Feldman, M., Kumar, M., Rishi, I., Gerrero, R., et al. (2002). BRAF and RAS mutations in human lung cancer and melanoma. *Cancer Res* 62, 6997-7000.

¹⁴ Davis, H., Bignell, G. R., Cox, C., Stephens, P., Edkins, S., Clegg, S., et al (2002). Mutations of the BRAF gene in human cancer. *Nature* 417, 949-954.

¹⁵ Edwards, R., War, M., Wu, H., Medina, C., Brose, M., P.V., et al. (2004). Absence of BRAF mutations in UV protected mucosal melanomas. *J Med Gen* 41, 270-272.

¹⁶ Ragnarsson-Olding, B.K., Karsberg, S., Platz, A., & Ringborg, U.K. (2002). Mutations in the TP53 gene in human malignant melanomas derived from sun-exposed skin and unexposed mucosal membranes. *Melanoma Res* 12, 453-463.

Part of this confusion arose from studies of albino mice in which UVA exposure **does not** cause melanoma induction. It is now thought, and studies support, the idea that melanin is the key sensitizing chromophore in melanocytes. Melanin granules, within the melanocyte, together with exposure to UVA light, are necessary to initiate the process of turning a melanocyte into melanoma. Melanin granules, not present in the albino mice, are necessary for the development of melanoma.

Some of the best evidence for the necessity of melanin granules involves epidemiologic observations of sun damage in albino African-Americans and versus non-albino African-Americans. African-Americans rarely develop sun induced melanomas (or other skin cancers)¹⁷. Melanin granules produced by melanocytes are transported out of the cells and deposited within the epidermis. This not only makes African-Americans dark, but melanin provides a protective effect, keeping UVA from rays penetrating beyond the epidermis. However, albino African-Americans who do not produce melanin granules and as such they quickly develops skin cancers (basal cell and squamous cell carcinomas), but they **do not** develop melanomas. They have lost the protective effect of melanin deposition in the epidermis (thereby developing basal cell and squamous cell carcinomas), but this same lack of melanin granules within the melanocytes prevents the development of melanoma.

It is also worth noting that UVB light is poorly transmitted through skin, whereas UVA rays penetrate deeply to the epidermal junction and beyond, where melanocytes reside.

MELANIN AS A PHOTSENSITIZER

Illumination of melanin by UVA rays, generates reactive melanin radicals (RMR) that react with oxygen to produce oxidants such as superoxide, which ultimately result in the formation of hydrogen peroxide and hydroxyl radicals. In the fish *Xiphophorus* model, these melanin sensitized free radicals are the central key event causing melanoma. Further work has shown the ability of UVA light to produce these RMR's extends way into the long wavelength UVA region and into the visible light range, the region in which most sunscreens either provide little or no protection^{18,19}.

$H\nu + RMR \rightarrow O_2 + H_2O_2 + HO \rightarrow \text{Cell Damage} \rightarrow \text{Melanoma mutation} \rightarrow \text{Melanoma}$

It is hypothesized that a certain UV threshold is necessary to deplete a melanocytes of antioxidant defenses. This may account for the strong association of melanoma with episodes of acute sunburn producing UV exposure.

¹⁷ Moan, j., Dahlback, A., & Setlow, R.B. (1999), Epidemiological support for a hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 70, 243-247.

¹⁸ Setlow, R.B., (1999). Spectral regions contributing to melanoma: a personal view. *J Investig Dermatology Symp Proc* 4, 46-49.

¹⁹ Setlow, R. B., & Woodhead, A. D., (1994). Temporal Changes in the Incidence of Malignant-Melanoma: explanation from Action Spectra. *Mutat Res* 307, 365-374.

TAKE HOME POINTS

If the above hypothesis is correct, UVA and not UVB rays are the main cause of melanoma. This brings up a couple of issues:

1. The total flux or amount of UVA and longer wavelength rays at the earth surface vastly exceeds that of UVB rays. UVA and longer wavelength rays remain relatively constant throughout the day and throughout the year, unlike UVB rays.
2. Most sunscreens do not provide adequate protect against UVA/melanoma. There is little that is as controversial as this statement, but sunscreens were designed to protect against UVB induced sunburns, and the SPF system only rates the level of UVB protection. Studies by Dr. Richard Setlow showing that 90% of melanomas are caused by wavelengths longer than UVB rays are important because many sunscreens, even newer sunscreens boasting high UVA protection have been proven to be insufficient. Further, poorly designed sunscreens with high UVB, but low UVA protection may actually facilitate longer exposure to UVA inducing melanoma rays.
3. **SEEK OUT PRODUCTS WITH A UVA RATING.** Consumers looking for high levels of UVA protection need to look for products with a UVA rating. PPD or persistent pigment darkening has been used in Japan and Europe for years and is the basis for the PA rating of + to +++ . Although better than nothing, this rating suffers from multiple issues, including only rating the protection provided from the first half of the UVA spectrum, and it is somewhat subjective.

Critical wavelength by contrast is a good in-vitro test that is a accurate measure of both long and short wavelength UVA protection (for sunscreens with a SPF 15 and higher). The American Academy of Dermatology recommends that consumers look for products with a critical wavelength of 370nm or higher. The AAD is actually urging that an absolute critical wavelength value be placed on every bottle of sunscreen- it is that important.

Last year the FDA proposed a four star UVA rating system based on the two systems above, PPD and a variation in the in-vitro UVA rating developed by Brian Diffey. It is on indefinite hold.

Consumers are left to look for a sunscreen with an absolute critical wavelength of 370nm or above, or a PA +++ . This information is provided by some of the better UVA protecting products. It is important enough to do some digging.

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²⁰ Lund, L. & Graham, T. (2007). Melanoma, long wavelength ultraviolet and sunscreens: Controversies and potential resolutions. *Pharmacy & Therapeutics* 114, 198-207.