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News and views

Epidermal pigmentation in the human lineage is an adaptation to ultraviolet radiation

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Skin color is one of the most biologically significant and socially salient aspects of the human phenotype and an understanding of its evolution is of fundamental importance. In a series papers, Elias et al. (2009, 2010) and Elias and Williams (2013) presented the hypothesis that epidermal pigmentation evolved primarily to enhance the barrier functions of the epidermis, specifically that increased melaninization of the skin evolved to provide "a competent permeability barrier, [as] a requirement for life in a desiccating terrestrial environment" (Elias and Williams, 2013: 688). They cite evidence that darkly pigmented skin possesses a more competent skin barrier than lightly pigmented skin (Gunathilake et al., 2009), and that it prevents transepidermal water loss (TEWL) when humans are traveling over long distances. Further, they claimed that darkly pigmented skin is more resistant to infections because it is drier, more acidic, and capable of producing more antimicrobial peptides (Wassermann, 1965; Mackintosh, 2001). They also proposed that reduced epidermal pigmentation at higher latitudes was determined by natural selection for reduced levels of the protein filaggrin (FLG) in the stratum corneum, leading to enhanced cutaneous synthesis of pre-vitamin D_3 in extreme northern latitudes. A second driver of depigmentation, they stated, was the "ever-present imperative to conserve energy," specifically, that retention of genes for eumelanin production was no longer necessary under low UVR conditions, and mutations to "weed out energy-consuming processes [became] beneficial, and favored by natural selection" (Elias and Williams, 2013: 690).

The barrier properties of darkly pigmented skin

Elias and Williams' central claim is that darkly pigmented skin possesses a more competent permeability barrier than lightly pigmented skin, and that evolution of genes promoting dark pigmentation occurred under xeric conditions and the threat of high TEWL. The proximate mechanism for the superior barrier functions of darker skin is proposed to be acidification of the stratum corneum (SC) by transfer of more eumelanin-containing melanosomes from the dendrites of darkly pigmented melanocytes into the outer epidermis (Gunathilake et al., 2009; Elias and Williams, 2013). One of the most consistent findings to emerge from recent comparative studies of the barrier functions of the human SC is that darkly pigmented African or African–American skin exhibits the highest rate of TEWL among modern humans (Reed et al., 1995; Wesley and Maibach, 2003; Rawlings, 2006; Muizzuddin et al., 2010). It is not less "leaky," especially under dry conditions (Elias and Williams, 2013: 688). What comparative studies (including many by Elias) consistently have revealed is that the skin of darkly pigmented Africans and African Americans has a more compact SC with significantly thicker corneocyte envelopes (Gunathilake et al., 2009; Muizzuddin et al., 2010). These properties have nothing to do with pigmentation per se, but with the high amount of covalently bonded proteins and the enhanced rigidity of the corneocyte envelope (Muizzuddin et al., 2010).

Skin pigmentation is most strongly correlated with UVR not aridity

The pattern of geographical variation in skin pigmentation is well known and is its most significant feature. Skin reflectance is

Abbreviations: 5-MTFH, 5-methyltetrahydrofolate; 7-DHC, 7-dehydrocholesterol; 25(OH)D, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D, or serum vitamin D; ASIP, agouti signaling protein; DHFR, dihydrofolate reductase; MC1R, melanocortin 1 receptor locus; MITF, microphthalmia-associated transcription factor; NTDs, neural tube defects; ROS, reactive oxygen species; SC, stratum corneum; SLC24A5, solute carrier family 24 (sodium/potassium/calcium exchanger), member 5, SLC24A5; TEWL, transepidermal water loss; UVR, ultraviolet radiation; UVB, ultraviolet B radiation; UVA, ultraviolet A radiation.

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highly correlated with latitude, and even more highly correlated with UVR (Walter, 1958; Jablonski and Chaplin, 2000; Chaplin, 2004). Approximately 86% ($r = 0.927$) of the variation in human skin reflectance can be accounted for by autumn levels of UVMED (primarily UVB) alone (Chaplin, 2004). The highest correlations are between UVMED and skin reflectance measured at 545 nm (green visible light), which is close to one of the absorption peaks of oxyhemoglobin (Mahmoud et al., 2008), and indicative of the epidermal pigmentation conferring protection against damage to circulating blood in cutaneous arterioles (Jablonski and Chaplin, 2000; Chaplin, 2004). Any hypothesis that seeks to explain the evolution of epidermal pigmentation must be in accord with these facts.

The heat-absorbing properties of melanin are well known from in vivo experiments on human performance under both hot-wet and hot-dry conditions. Baker and colleagues found that after 2 h of vigorous exercise, individuals with darkly pigmented skin showed significantly higher rectal temperatures than those with lightly pigmented skin, but no significant difference in heat storage or in evaporated sweat (Baker, 1958a, b). Heat storage was balanced by increased long wave radiation to the environment (Baker, 1958b).

The primary and most important function of eumelanin in human epidermis is protection against damage caused by UVR (Brenner and Hearing, 2008). Eumelanin absorbs and scatters UV photons, thus reducing the amount of damage caused to important biomolecules and structures within and below the dermis (Kobayashi et al., 1998; Moan et al., 1999; Meredith and Sarna, 2006; Nielsen et al., 2006; Yamaguchi et al., 2006). The strongest evidence in support of the photoprotective role of eumelanin comes from studies examining regulation of its production and its location within the skin, in supranuclear melanin caps within keratinocytes and as 'melanin dust' within the SC. Exposure to UVR upregulates production of eumelanin through the immediate and delayed tanning responses, which results in darkening of the skin and enhanced photoprotection (Quevedo and Smith, 1963; Routaboul et al., 1999; Tadokoro et al., 2005; Garcia-Borron, 2008; Moan et al., 2012). The tanning cascade is initiated by UVR exposure and is tightly controlled by the transcription factor MITF, which regulates melanogenesis and melanocyte activity (Schallreuter et al., 2008; Liu and Fisher, 2010). Production of melanin is not upregulated by increased dryness or environmental aridity. The most important effect of reduced atmospheric moisture is increased transmission of UVB, as observed in remotely sensed UVR data (Jablonski and Chaplin, 2000, 2010). The inhabitants of hot deserts do not have skin with the highest melanin content (Baker, 1958a). The darkest skin colors in the world are found among people (such as the Chopi of Mozambique and the natives of Bougainville) who live in humid coastal environments and experience high levels of direct and reflected UVR (Jablonski and Chaplin, 2000; Norton et al., 2006). When the skin is moistened by environmental moisture or sweat, hydration of the horny layer of the epidermis leads to a shift in the UVR absorption spectrum of the stratum corneum and greater UVB transmission through forward scattering and refractive transmission (Moehrle et al., 2000; Chaplin, 2004). These conditions appear to favor darker skin, up to a threshold past which no further melanization appears to be possible (Chaplin, 2004).

The physiological challenges of high UVR

UVR causes damage directly through mutagenic and cytotoxic DNA lesions, and by generation of ROS, which lead to damage of collagen and elastin, immunosuppression, and the photolysis of nutrients including folate (Branda and Eaton, 1978; Cleaver and Crowley, 2002; Fisher et al., 2002; Fukuwatari et al., 2009). Folate is universally important in the body because it carries one-carbon groups for methylation reactions, is required for nucleic acid synthesis and repair, and maintains the epigenome (Lucock et al., 2012). UVR degrades folate and its vitamers, especially in the presence of natural photosensitizers and uroporphyrin (Steindal et al., 2008; Tam et al., 2009). Folate's direct connection to reproductive success derives from its role in cell division, thence spermatogenesis and normal embryogenesis. Folate deficiencies elevate the risk of neural tube defects (Bower and Stanley, 1989; Fleming and Copp, 1998; Lucock and Daskalakis, 2000) and result in reduced sperm viability or inhibition of spermatogenesis (Mathur et al., 1977; Wallock et al., 2001; Boxmeer et al., 2009). UVR exposure also produces increased demands for folate in the skin because of the demands of DNA repair and melanin synthesis (Williams et al., 2012). Folate's role in stimulating specialized cells of the immune system suggests a novel mechanism by which the immune system detects microbial infections (Chua and Hansen, 2012).

We originally advanced the hypothesis that the primary driver of increased epidermal pigmentation in hominins was reduction of UVR-induced folate photolysis because of its direct effects on reproductive success (Jablonski, 1992, 1999; Jablonski and Chaplin, 2000). This hypothesis has been tested vigorously in many types of in vitro and in vivo experiments involving measurement of serum folate and 5-MTHF following exposure of human serum and human subjects to different wavelengths of UVR (Gambichler et al., 2001; Off et al., 2005; Steindal et al., 2006, 2008; Fukuwatari et al., 2009). The immediate pigment darkening reaction, which constitutes the first phase of the tanning response, appears to be especially protective against UVA-induced sensitization of folate (Moan et al., 2012). A recent review of these studies confirmed that UVR degrades folate and its synthetic form, folic acid, in human blood, but that the dearth of epidemiological studies demonstrating direct effects of UVR on health precludes definitive assessment of the significance of the effect (Borradale and Kimlin, 2012). Direct photolysis of folate by UVR is best seen as one of several mechanisms whereby UVR exposure adversely affects folate metabolism, overall health, and reproductive success. Melanin production itself requires pterin compounds, which are produced by conversion of folate by DHFR (Schallreuter et al., 1994, 2008; Spencer et al., 2005; Schallreuter, 2007). Selective pressure for increased epidermal pigmentation is, thus, best viewed as the result of reduced bioavailability of folate caused by the manifold effects of UVR stress (Jablonski and Chaplin, 2010; Lucock et al., 2010).

Elias and Williams (2013) question the evolutionary significance of folate depletion because they consider the neural tube defects (NTDs) caused by folate deficiency to be biologically insignificant because they state that the prevalence of neural tube defects resulting from folate deficiency is 'quite low.' Prior to widespread antenatal screening and, in many countries, mandatory folic acid fortification of flour, prevalence of NTDs as a percentage of all conceptions was much higher (Forrester et al., 1998; Frey and Hauser, 2003). Folic acid supplementation has resulted in a 25–60% reduction in prevalence of NTDs at birth (Jägerstad, 2012). Melanization of the skin prevents depletion of, and competition for, folate under conditions of low dietary folate intake and/or environmental UVR-induced stress.

The physiological challenges of low UVR

Human skin pigmentation is significantly lighter outside of the tropics and is markedly lighter in populations living at latitudes greater than 46°. Some populations exhibit extremely light constitutive pigmentation and limited or no tanning abilities, and

others (including Alaskan Inuit and indigenous Greenland populations) exhibit light to moderate constitutive pigmentation and high facultative tanning abilities. Elias and Williams state that "lighter pigmentation resulted from an accumulation of genetic polymorphisms in the melanocortin 1 receptor… and in other genes that regulate melanin synthesis or the acidification of melanosomal contents" (Elias and Williams, 2013: 688–689). They claim, first, that Paleolithic inhabitants of high latitude environments would have included significant amounts of vitamin D-rich fish and meat in their diets, thus obviating the need for depigmentation to facilitate production of vitamin D in the skin. Second, they state that there is no evidence of rickets in the archaeological record. Third, they speculate that if there had been natural selection for depigmentation then loss of pigmentation "should have been lost preferentially on sun-exposed surfaces, such as the face and extremities…" (Elias and Williams, 2013: 689). Finally, they suggest that "the vitamin D hypothesis also fails to explain why hair simultaneously became lightly pigmented, though hairs are not involved in vitamin D synthesis" (op. cit.).

In an earlier paper, we established probable causality between skin pigmentation and UVR using 'Hill's Criteria' (Chaplin and Jablonski, 2009). Loss of epidermal pigmentation at high latitudes was not the result of an accumulation of mutations (Brace, 1963), but involved positive selection for depigmentation in order to facilitate cutaneous production of the important secosteroid hormone, vitamin D.

Using an empirical F_{ST} approach, Norton and colleagues demonstrated the action of strong positive directional selection for depigmentation in two sets of pigmentation loci: ASIP and OCA2, which played roles in skin lightening in many populations living outside of equatorial latitudes, and SLC24A5, MATP, and TYR, which were under positive selection in the ancestors of Europeans (Norton et al., 2007). They concluded that depigmentation in the ancestors of modern Europeans and Asians occurred independently, and under the influence of positive directional selection. In Europeans, cutaneous depigmentation was accomplished largely by a selective sweep that brought a variant allele of SLC24A5 into a high proportion of the population (Lamason et al., 2005). At the same time that this was occurring, relaxation of the functional constraint on monomorphism in the MC1R locus saw the development of various loss-of-function mutations at the locus (Rees, 2000). In Europeans, polymorphisms at the MC1R locus do not have significant effects on skin color, but do affect hair color (Latreille et al., 2009). In East Asian populations, polymorphism at the MC1R locus is higher than in African populations, but lower than in Europeans (Harding et al., 2000; Makova and Norton, 2005) and is not associated with hair color variation. Positive selection for loss of epidermal pigmentation in Europeans and Asians acted independently on different genetic loci, and hair only became lightly pigmented in Europeans as the result of loss-of-function MC1R polymorphisms that were not under positive selection. Neanderthals, who lived in dry, peri-glacial environments, also underwent depigmentation by yet a different mechanism. Distinct loss-of-function MC1R polymorphisms discovered in ancient DNA recovered from Neanderthals also indicated that at least some individuals would have had red hair (Lalueza-Fox et al., 2007).

Elias and Williams' assertion that people, regardless of their skin pigmentation and diet, can make sufficient vitamin D to satisfy their physiological needs by exposing small areas of skin to summer sunshine is wrong. Most indigenous populations, including those receiving of high insolation and UVB, have low to marginal status of circulating vitamin D_3, 25(OH)D (Chaplin and Jablonski, 2009). Maintenance of healthy 25(OH)D status is difficult because of the effects and interactions of several variables such as skin pigmentation and the natural sunscreen properties of eumelanin, the UVR wavelength mixtures that obtain in different places (especially the relative proportions of UVB and vitamin D_3-photodegrading UVA), age, reproductive status (for females), levels of stored 25(OH)D, duration and area of exposure to UVB, and the consumption of vitamin D_3-rich foods in the diet. The theoretical potential of large amounts of pre-vitamin D_3 manufacture in the skin is never realized in a natural setting because the conversion of the precursor, 7-DHC, to pre-vitamin D_3 is rarely complete, the rate-limited nature of the reaction leads to breakdown of the pre-vitamin D_3, and vitamin D_3 made in the skin can be readily broken down by UVA (Chaplin and Jablonski, 2009). Within the tropics with dual peaks of high UVB during the year, the need for storage of 25(OH)D is never longer than a month on either side of the solstices (Jablonski and Chaplin, 2010). At the northern limits of large population settlements at 55°N, duration of vitamin D storage would need to be at least six months for people with darkly pigmented skin. This is three times longer than the half-life of 25(OH)D stored in adipose tissue (Mawer and Davies, 2001).

Today, widespread vitamin D_3 deficiencies and their sequelae exceed the cost of high UVB exposure (Lucas et al., 2008). In light of these considerations, Elias and Williams' contention that melanin pigmentation was lost in high latitude populations as the result of an accumulation of mutations and because of the importance of conservation of metabolic energy is untenable and cannot account for the high correlation of skin pigmentation with UVB even within a geographically restricted region of low insolation such as the British Isles (Relethford, 1997; Chaplin and Jablonski, 1998).

Elias and Williams' suggestion that depigmentation for purposes of maximizing vitamin D production would have occurred only on exposed regions of the body such as the face and dorsum of the hands is not tenable in light of the regional action of pigmentation genes in primates (Mundy and Kelly, 2006). Their suggestion that natural selection for loss-of-function mutations in the stratum corneum structural protein filaggrin would have enhanced UVB penetration of the epidermis and promoted cutaneous vitamin D_3 production in far northern populations (Thyssen et al., 2012) is also unlikely and contradicts their argument that sufficient vitamin D_3 can be produced in the human skin from short periods of summer sun exposure regardless of pigmentation and latitude and that properties of the skin associated with vitamin D production have not been the object of natural selection.

Conclusions

Elias and Williams set out the hypothesis that epidermal pigmentation was primarily determined by the requirements for establishing and maintaining the barrier functions of the SC. The primary evolutionary force leading to increased melanization of human skin in their view was enhancement of the physical barrier functions of the epidermis under conditions of high environmental aridity by incorporation of acidic, eumelanin-containing melanosomes or their by-products into its structure. We have demonstrated that their hypothesis is not supported by the data at hand. Darkly pigmented skin indeed has different barrier functions, but most of these are unrelated to the presence of eumelanin dust within the SC or to the presence of intact eumelanin-containing melanosomes beneath the SC.

Elias and Williams' hypothesis fails to account for several key attributes of skin pigmentation. Foremost among this is the process and evolution of tanning, which can occur in all except the most depigmented human skin. The fact that increased melanization of the skin is provoked only by increased UVR, and not by other changes in the physical environment is obvious. Melanocytes are located in the basal layer of the epidermis below the SC. Many melanosomes produced by melanocytes become localized within

keratinocytes as supranuclear melanin caps, a position that emphasizes their front-line role in protection of DNA against UVR. Secondly, Elias and Williams' establishment of a causal relationship between increased pigmentation and enhanced competence of barrier functions including abrasion and bacterial resistance cannot account for the depigmented skin on the lips and on the volar surfaces of the hands and feet of all humans and some non-human primates. These areas have the highest abrasion loads and the most contact with pathogens, and yet are conspicuously unpigmented. Thirdly, their hypothesis cannot account for the consistent pattern of sexual dimorphism in human skin pigmentation, with females being consistently lighter than males in all indigenous populations studied (Jablonski and Chaplin, 2000). Fourthly, it fails to account for the evolution of eumelanin concentrations inside the body (such as the inner ear and brain) that are not subject to abrasion, desiccation, or UVR, but experience high ROS loads (Hearing, 2009). Lastly, their hypothesis cannot account for the high correlation of skin color to solar strength worldwide or locally within Africa or within Europe.

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