Title
Re-appraisal of current theories for the development and loss of epidermal pigmentation in hominins and modern humans

Permalink
https://escholarship.org/uc/item/7kv045kn

Journal
Journal of Human Evolution, 64(6)

ISSN
0047-2484

Authors
Elias, PM
Williams, ML

Publication Date
2013

DOI
10.1016/j.jhevol.2013.02.003

Peer reviewed
Re-appraisal of current theories for the development and loss of epidermal pigmentation in hominins and modern humans

Peter M. Eliaa,b,* , Mary L. Williams c

a Dermatology Service, Department of Veterans Affairs Medical Center, 4150 Clement Street, MS 190, San Francisco, CA 94121, USA
b Department of Dermatology, University of California, San Francisco, CA, USA
c Departments of Dermatology and Pediatrics, University of California, San Francisco, CA, USA

When and why epidermal pigmentation evolved

Population genetic techniques show that the gene encoding the melanocortin 1 receptor (MC1R) stabilized in hominins around 1.2 Ma (millions of years ago) (Harding et al., 2000; Rogers et al., 2005; Lao et al., 2007; Parra, 2007), indicating strong evolutionary pressure to retain interfollicular pigmentation among humans residing in Sub-Saharan Africa today. But melanin is a significant heat absorber (Blum, 1961; Hill, 1992), which would have posed substantial difficulties in thermoregulation. Therefore, the benefits of pigmentation must have been quite robust to offset this formidable disadvantage.

Among competing hypotheses put forward to explain the development of epidermal pigmentation, the ‘genotoxic hypothesis’ is untenable because the vast majority of skin cancers occur well past peak reproductive age. Likewise, epidermal pigmentation did not evolve to protect against UV-B-induced destruction of nascent eccrine sweat glands, as proposed by Jablonski and Chaplin (2000) and Chaplin (2004) because these glands reside deep in the dermis, where they are fully protected from UV-B exposure (Parrish et al., 1982). Though the heat of equatorial Africa can obstruct eccrine ducts, leading to heat intolerance and difficulties with thermoregulation, darkly-pigmented skin is just as prone to sweat gland dysfunction as is lightly-pigmented skin.

Protection against folate degradation and vitamin D toxicity

In 1967, Loomis provided maps that showed latitude-dependent differences in skin coloration, and suggested that epidermal pigmentation evolved in ancestral hominins in order to protect against vitamin D intoxication (‘yin’) (Murray, 1934). As humans moved northward out of equatorial Africa into regions with less exposure to ultraviolet light, he proposed oppositely that pigmentation faded in order to augment cutaneous production of Vitamin D (‘yang’) (see also Neer, 1975; Branda and Eaton, 1978; Chaplin and Jablonski, 2009; Jablonski, 2010; Yuen and Jablonski, 2010). To generate vitamin D, a distal precursor of cholesterol, 7-dehydrocholesterol (7DHC), is first synthesized in the epidermis (Holick et al., 1980), then photo-converted to pre-vitamin D3 (pre-D3), and finally, thermally converted to vitamin D3 (VD3) (Holick et al., 1980). Intense sun exposure never results in vitamin D intoxication (Holick et al., 1981), because excess pre-VD3 is shunted toward two biologically-inactive metabolites, tachysterol and lumisterol.

Vitamin D is now paired with folic acid (vitamin B9) in an antipode of ‘drivers’ of skin coloration (Jablonski and Chaplin, 2010). According to this formulation, epidermal pigmentation evolved to protect folic acid and its metabolites, tetrahydrofuran and 5-methyltetrahydrofolate, from being destroyed by UV irradiation. Folic acid protects against the development of congenital neural anomalies, such as failure of spinal fusion (‘spina bifida’) (Rayburn et al., 1996; Wilson et al., 2003, 2007). Hence, epidermal pigmentation could confer a considerable evolutionary advantage should it protect...
against photo-induced folic acid deficiency (Jablonski and Chaplin, 2010). Yet, most neural tube defects are too mild to interfere with reproductive success (Rayburn et al., 1996; Wilson et al., 2003, 2007), and the overall prevalence of congenital anomalies (∼1/2000 pregnancies) is quite low (Rayburn et al., 1996; Rasmussen et al., 1998; Northrup and Volcik, 2000). While highly susceptible to photodegradation by UV-B, and to a lesser extent by UV-A in vitro (Moa et al., 2012), a final concern with the folate hypothesis is whether folic acid and its metabolites are vulnerable to photodegradation in vivo. The blood vessels that transport folate and its active metabolites lie well beneath the epidermis, where insufficient UV-B can penetrate to impact circulating folate (Anderson and Parrish, 1981). Though UV-A can penetrate to such depths, it is unlikely to degrade folate in vivo, because intense doses of UV-B and UV-A, when administered repeatedly in the treatment of patients with inflammatory skin diseases, do not provoke folic acid deficiency (Cicarna et al., 2010; Juzeniene et al., 2010). Nor do folic acid levels decline with repeated sun exposure (Cicarna et al., 2010; Juzeniene et al., 2010). Therefore, epidermal pigmentation likely did not develop to protect against UV-B-induced folic acid deficiency.

**Barrier requirements likely stimulated the development of epidermal pigmentation**

If pigmentation developed neither to prevent skin cancer, nor to protect against eccrine gland destruction, vitamin D intoxication, or folic acid deficiency, then why did hominins become darkly pigmented? The answer almost certainly relates to the most critical function of the skin: the provision of a competent permeability barrier, a requirement for life in a desiccating terrestrial environment (Elas et al., 2009, 2010). Darkly-pigmented human skin possesses a more competent skin barrier than does more lightly-pigmented skin, differences that correlate solely with pigment-type, rather than race, and are independent of latitude (Reed et al., 1995; Gunathilake et al., 2009). Moreover, patients with vitiligo, in which pigment loss occurs in localized patches due to an absence of melanocytes, display reduced barrier function in de-pigmented regions (Liu et al., 2010). Finally, pigmented hairless mice (Skh2) display a superior permeability barrier in comparison with the non-pigmented albino (Skh1) mice (Man et al., 2013). Mechanistic studies show that it is the reduced pH of darkly-pigmented skin that accounts for these differences (Gunathilake et al., 2009). Indeed, a reduced pH is highly beneficial for multiple epidermal functions, including barrier homeostasis (Flurh and Elas, 2002).

Dark skin is also more resistant to infections (Mackintosh, 2001), and it is well-known that darkly-pigmented hunter-gatherers experienced fewer skin infections than their co-habitating, light-skinned neighbors (Wassermann, 1965; Mackintosh, 2001). Why is dark skin more resistant to infections? First, the more competent barrier of pigmented skin generates a drier skin surface, which is inimical to colonization by pathogenic microbes that prefer a moist environment (Elas, 2007). Second, the more acidic surface pH of pigmented skin is hostile to the growth of bacterial pathogens (Korting et al., 1987, 1990). Cutaneous antimicrobial defense is pH-dependent (Elas, 2007) by several mechanisms, including: i) increased cohesion of adjoining corneocytes (Gunathilake et al., 2009), which inhibits the penetration of pathogens; and ii) increased quantities of antimicrobial lipids (i.e., acidic free fatty acids), which inhibit the growth of gram-positive bacteria and yeasts (Miller et al., 1988; Drake et al., 2008). In addition, melanin and its metabolites display potent antimicrobial activities (Montefiori and Zhou, 1991). Melanin granules are distributed evenly throughout the cytoplasm in darkly-pigmented skin, and these more robust granules persist high into the outer nucleated layers, and even into the stratum corneum, where they discharge pigment granules (and protons) into the extracellular spaces of the stratum corneum (Man et al., 2013). Furthermore, pigmented epidermis also produces increased qualities of non-melanin-derived antimicrobial peptides (Mackintosh, 2001), a highly-conserved class of molecules, that are found in epithelial barriers throughout the plant and animal kingdoms, and are inimical to the growth of many disease-causing pathogens (Schröder and Harder, 2006; Nakatsuji and Gallo, 2012). Thus, the evolution of darkly pigmented skin equipped hominins to withstand the ‘infectious soup’ of the tropics (Wassermann, 1965; Mackintosh, 2001).

The climate that dominated Sub-Saharan Africa at the time of pigment development in Homo erectus was not only UV-B enriched, but also extremely arid (DeMenocal, 2004; Blome et al., 2012), a condition that would have placed further stress on the permeability barrier. Because the vapor pressure at the skin surface is the primary determinant of transepidermal water loss, low environmental humidity steepens the gradient of water loss across the skin, inevitably imposing additional demands for a highly competent skin barrier. While the evolutionary development of eccrine sweating permitted hominins to hunt more actively on the savannah, the combination of sweating to dissipate heat, coupled with an inefficient (leaky) skin barrier would have quickly threaten these hunter-gatherers with dehydration. But the development of a highly competent permeability barrier, through the generation of interfollicular pigmentation, would have allowed movement by hominins over longer distances, even during midday hours.

To further address the plausibility of this hypothesis, we must first examine the impact of UV-B irradiation on epidermal structure and function. Erythemogenic doses of UV-B damage DNA, induce keratinocyte cell death (apoptosis), and provoke inflammation (Anderson and Parrish, 1981; Parrish et al., 1982; Young et al., 1998; Honigsmann, 2002; Uchida et al., 2003). As an acute sunburn recedes, epidermal hyperproliferation propels layers of functionally-incompetent keratinocytes through the outer epidermis, where they transiently compromise the permeability barrier (Holleran et al., 1997; Haratake et al., 1997a, b). Yet paradoxically, lower (‘sub-erythemogenic’) doses of UV-B instead benefit skin barrier function, while also enhancing cutaneous antimicrobial peptide production (Hong et al., 2008). While even low doses of UV-B become toxic in lightly-pigmented humans, the endowment of hominin epidermis with dark pigmentation shifted the UV-B dose–response curve from a toxic toward a beneficial range.

**Basis for pigment dilution in modern humans**

An obvious feature of the northward dispersal of humans is a quasi-geographic reduction in pigmentation (Murray, 1934; Loomis, 1967; Chaplin and Jablonski, 2009). Coloration varies greatly among northerners. Native Inuit display medium-to-dark (type III/IV), rather than light pigmentation, and both northern- and central-dwelling Asians display medium (type III) pigmentation. Recent population genetic data show that the reduction in skin pigmentation occurred sporadically and incompletely in northern and Asian populations (Sturm, 2009). Moreover, while modern humans reached Central Europe ≈40 ka (thousands of years ago), they reached northern Europe only after the last ice sheets receded <11 ka. It is only these humans that display light pigmentation, and recent molecular genetic studies suggest that the very light pigmentation of northern Europeans did not develop until 5–6 ka (Norton et al., 2007; Norton and Hammer, 2008). Lighter pigmentation resulted from the accumulation of genetic polymorphisms in the melanocortin 1 receptor (Rana et al., 1999),
pigmentation provides additional thermal insulation (Hill, 1992). Likewise, the expression of the 1α- and 25-α hydroxylase enzymes; and VD3 receptor expression. It is likely that at least one of these mechanisms is upregulated in darkly-pigmented skin to provide sufficient VD3, even with reduced UV-B penetration into the skin. In fact, the lower incidence of osteoporosis in darkly-pigmented humans serves as eloquent evidence for increased bioavailability of VD3 independent of UV-B availability (Aloia, 2008; Vivanco-Munoz et al., 2012).

Vitamin D requirements can also be met by eating a diet enriched in oily fish, and in animals that eat fish (Chen et al., 2007; Bikle, 2010), as occurs in Arctic dwellers (Sharma et al., 2011). Although modern diets of highly refined, grain-derived foods, contain little vitamin D (Jew et al., 2009; Yuen and Jablonski, 2010), current dietary practices do not resemble those of the late Paleo-lithic, when few grains and cereal products were available. Indeed, a fish-enriched diet evolved in Central Europe over 20 ka, and the species of fish that inhabited inland waterways doubtlessly included some marine species (such as migrating Atlantic salmon), and oily freshwater fish, such as eels and catfish, that contain substantial vitamin D. Furthermore, Paleolithic humans likely wasted little in the food chain—vitamin D-storing tissues, such as fat, liver, kidney, bone marrow, and even skin and brain (Bikle, 2010) of wild game, likely would have been consumed.

Despite the many alluring examples of cave paintings from the Dordogne region of France, hunter-gatherers of this period were intimidated by these caves, which still were inhabited by dangerous species of cave bears, lions, and hyenas. They chose to live an outdoor life, which would have resulted in frequent exposure of their uncovered arms, legs, faces and hands to UV-B radiation (Robins, 2009). With the addition of fish to a diet already enriched in fatty tissues, and with an outdoor life associated with continuous exposure of portions of their body surface, it is unlikely that hunter-gatherers of the late Paleolithic, even if still fully-pigmented upon arrival in Central Europe, would have encountered difficulties in meeting their vitamin D requirements.

There are still other, serious problems with the vitamin D hypothesis. It is true that a severe deficiency in vitamin D can produce rickets in growing children, and can narrow the pelvis, obstructing childbirth (Chaplin and Jablonski, 2009). However, severe cases of rickets are rare, and milder or later onset vitamin D deficiency likely would not have exerted deleterious effects on reproduction. Moreover, evidence for rickets in the fossil record only became prevalent after the Industrial Revolution darkened the skies over Europe (Robins, 2009). Finally, the vitamin D hypothesis fails to explain why pigment was lost in sites that remain unexposed to light. If vitamin D requirements 'drove' pigment dilution, pigmentation should have been lost preferentially on sun-exposed surfaces, such as the face and extremities, particularly since sufficient vitamin D can be generated with only limited exposure of these areas (Holick, 1995; Goding, 2007; Gilchrest, 2008). Moreover, the vitamin D hypothesis also fails to explain why hair simultaneously became lightly-pigmented, though hairs are not involved in vitamin D synthesis. Finally, population genetic studies have found few polymorphisms in genes that encode the VD3 synthetic pathway or VD3 receptor (Ahn et al., 2010).

A non-pigment-based mechanism that likely enhances vitamin D bioavailability

While pigment dilution likely did not enhance VD3 generation in northerners, other mechanisms could have evolved to enhance
its production. Not all incident UV-B is blocked by melanin—a substantial proportion (~35%) is absorbed by proteins and protein metabolites in the stratum corneum, even in darkly-pigmented humans (Thomson, 1955). One protein has just emerged as a candidate to explain enhanced V3D production, i.e., the stratum corneum structural protein, filagrin (FLG) (Thyssen and Elias, 2013). The link between FLG and UV-B bioavailability can be explained by the proteolytic processing of FLG into one of its constituent amino acids, histidine, followed by the deamination of histidine by the enzyme, histidine ammonia-lyase (histidase) into the carboxylic acid, trans-urocanic acid (t-UCA) (Scott, 1981; Brown and McLean, 2012). t-UCA is a key endogenous sunscreen of the stratum corneum (Kripke, 1984), with an action spectrum in the UV-B spectrum (Brookman et al., 2002; Haralampos-Grynavski et al., 2002; McLoone et al., 2005). Moreover, FLG knock-down results in sub-normal levels of t-UCA and an increased susceptibility to UV-B-induced apoptosis (Mildner et al., 2010). Population genetics show that a substantial number (~15%) of normal Scottish, Irish and Scandinavians exhibit loss-of-function mutations in FLG (Irving et al., 2011), with much lower prevalence in Central Europeans (<1%) (Thyssen and Elias, 2013). Furthermore, while FLG mutations provoke defects in cutaneous barrier function that predispose to atopic dermatitis (Fallon et al., 2009; Scharschmidt et al., 2009; Gruber et al., 2011), northern Europeans with FLG mutations, with or without atopic dermatitis, exhibit higher-than-normal circulating V3D levels (Thyssen et al., 2012). Hence, a deficiency of t-UCA due to FLG deficiency would inevitably result in substantially more UV-B transmittance, likely leading to increased intracutaneous V3D generation in extreme northern latitudes (Thyssen and Elias, 2013).

Conservation of metabolic energy

Then, what could have been the benefit of reduced pigmentation in widely-separated northern and Asian populations? The most likely explanation is the ever-present imperative to conserve energy; i.e., metabolic conservation. Briefly, when there is no biological advantage to expend metabolic energy in support of no-longer-needed functions (Gabay and Kushner, 1999), mutations that reduce out-energy-consuming processes become beneficial, and favored by natural selection. Thus, a declining need to heavily-pigment the epidermis favored the retention of mutations in genes that reduced pigment synthesis, thereby diverting energy toward the production of more urgently-needed proteins. An eloquent demonstration of the metabolic cost of pigment accumulation occurs in children with protein malnutrition (i.e., kwashiorkor), who manifest marked lightening of the skin and hair (Latham, 1955). One protein has just emerged as a driver of dermal pigmentation in humans. The skin barrier as an innate immune element. Semin. Immunol. 29, 3–72.


Norton, H.L., Hammer, M., 2008. Sequence variation in the pigmentation candidate gene SLC45A4 and evidence for independent evolution of light skin in European and East Asian populations. Presented at the 77th Annual Meeting of the American Association of Physical Anthropologists, April 9–12, Columbus, OH.


