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News and views

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

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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., 2004), providing an approximate date for the population of interfollicular epidermis by melanocytes. That epidermal pigmentation conferred significant survival benefits is shown by the strong conservation not only of MC1R (Harding et al., 2000), but also of several other genes involved in pigment production (Graf 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 S-methyl tetrahydrafolate, 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

Abbreviations: α-MSH, alpha-melanocyte-stimulating hormone; 7DHC, 7-dehydrocholesterol; FLG, filaggrin; ka, thousands of years ago; Ma, millions of years ago; POMC, pro-opiomelanocortin; pre-D3, pre-vitamin D; SCC, squamous cell carcinoma; Skh1, albino hairless mice; Skh2, pigmented hairless mice; UV-B, ultraviolet-B; VD3, vitamin D3; VDBP, VD3 binding protein.

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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 (Moan 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 (Cicarma et al., 2010; Juzeniene et al., 2010). Nor do folic acid levels decline with repeated sun exposure (Cicarma 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 (Elias 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 depigmented 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 (Fluhr and Elias, 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 moister environment (Elias, 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 (Elias, 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 (Schroder 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 threatened 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 mid-day 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),