Human pigmentation: A side effect adapted from a primitive organism's survival. Part 2: The melanocyte as mentor of the keratinocye

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ABSTRACT

Pigmentation featured millions of years ago and perhaps began with an amoeba frightening off a predator with some agent such as dopamine to prevent its attachment for phagocytosis by an enemy. This paper suggests that the environmental forces of grip and stick, rather than pure chemical influences, deserve greater emphasis, and that the influence of the mechanical forces involved in grip and stick or release from attachment, all point to control of proteases as a function underlying pigmentation. How and why pigmentation varies with temperature and sunlight is discussed. The toxicity of melanin, pH, transepidermal water loss, and the influence of endocrine factors are also addressed.

Key words: Melanocyte, keratinocyte, temperature, sunlight, water loss

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.137793

Quick Response Code:

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THE BASAL KERATINOCYTE AND ITS MENTOR THE, MELANOCYTE

The term "epidermal melanin unit" is used to describe each melanocyte along with keratinocytes to which it supplies melanosomes.[1] The basal cell keratinocyte has most of its surface in contact with other keratinocytes. There is a complex attachment to the dermis at its base and over its nonbasal surface with the dendrites of the melanocyte. It is possible that the cytoplasm of most of the basal cell is organized so that it is able take up and distribute the melanosome, but that this is not the case at the base of the cell where it has other things to do such as stick and grip to the basement lamina. The location of melanosomes is not a cap so much as a sparer of the base. The melanocyte's dendrites are often illustrated as if holding the basal cell in place in the basal layer, electron microscopy (EM) suggests a looser, somewhat more relaxed extension of dendrites. As shown in melasma, the melanocyte can be easily displaced into the dermis without similar displacement of basal keratinocytes, probably due to activation of proteases and the massage effect of rubbing the skin.

Chung *et al*.[2] found the keratinocyte's production of laminin-332 essential for the adhesion of both the keratinocyte and melanocyte to the basement lamina. McClenic *et al*.[3] had determined that both fibronectin and laminin have a role for such grip and stick. Hirobe[4] reviewed just how complex and numerous are the co-factors by which the keratinocyte interacts with the melanocyte [Figure 1]. Moretti *et al*.[5] showed that keratinocytes in vitiligo manufacture more mRNA for tumor necrosis factor-alpha and interleukin-6 (IL-6) and it is this that contributes to loss of melanocyte affinity for the keratinocyte. The opportunity for proteases to play a role is obvious. It is discussed by Lee exploring another influence, PI3K/AKT and E-cadherin-catenin complex.[6] The skin of vitiligo has more mast cells and according to Schallreuter *et al*. long-standing explanations of vitiligo,[7] it is rich in epinephrine, presumably derived from dopamine with an influence on grip and stick as discussed in Part 1. Others describe these agents of local homeostasis of the skin as a neuroendocrine system.[8] Vitiligo melanocytes do not grow well in culture, have ultrastructural defects and according to Jimbow *et al*. have stubby dendrites.[9] Kumar *et al*.[10] correlate this with impaired expression of matrix metalloproteinase-2, needed for detachment and degradation of denatured collagen and collagen Types IV, V, VII, IX, and X. It plays a role in migration through laminin. Kumar *et al*.

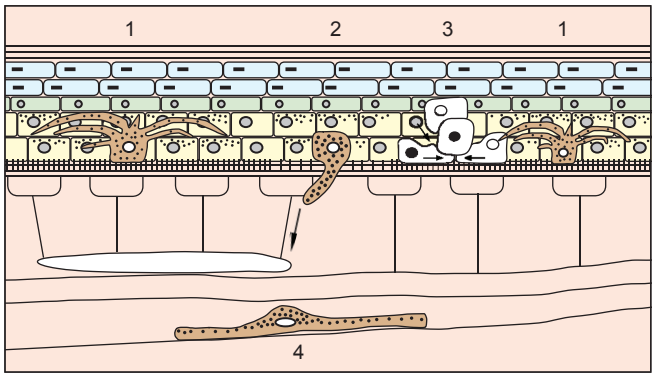

Figure 1: The melanocyte's affinity for the keratinocyte and for elastin has much to do with grip and stick by the employment and inhibition of proteases. (1) Melanocyte inoculates keratinocytes with melanosomes and like many cells derived from the neural crest determines organ shape and relationships. (2) Melanocyte lyses epithelial basement lamina and uses elastin to guide it to the lymphatic. (3) Basal keratinocytes lose grip and stick to basal lamina and melanocyte while in mitosis and one is jostled out of contact with basement lamina. (4) Melanocyte contacting mid-dermal horizontal elastin fibers take up a horizontal orientation

postulate that the transcription factor Ets-1 is involved and that in vitiligo skin samples it is absent.[10]

ELONGATED RETE PEGS IN BOTH ATROPHY AND HYPERTROPHY

This interaction between melanocytes and keratinocytes is essential for skin pigmentation. There are several pigmented conditions in which increased pigment in the basal cell layer is associated with elongated rete pegs viz.: Acanthosis nigricans, Dowling–Degos disease, seborrhoeic keratosis, senile lentigo. Unver *et al*.[11] studied senile lentigo, which features mostly on the back of the hand and on the face in sun damaged and usually atrophic skin. Mitotic figure counts gave no indication of proliferation nor were there proliferation cytokines such as Ki-67.[11] Melanocytes in the basal cell layer were not markedly increased but there was more melanin within them and melanogenesis-associated genes were all increased. There was "massive dermal uptake" of melanosomes in predominantly factor XIIIa + dermal dendrocytes of the dermis. Compare this to the elongation of rete pegs in wound healing or psoriasis in which there are often no melanocytes but a high rate of keratinocyte turnover.

THE MELANOCYTES CONTRIBUTION TO TRANSEPIDERMAL WATER LOSS AND THE ACID MANTLE

One much discussed role for the melanocyte is the preserving of the integrity of the epidermis in its preferred environment. Since the control of transepidermal water loss (TEWL) is a prime function of the epidermis studies of the influence of the melanocyte on TEWL have received recent publicity. A hypothesis that an early role for the melanocyte was to prevent xerosis, often induced by a threatening climate, has had added to it the importance of the acid mantle and the probable contribution of the melanosome to surface acidity and prevention of a high pH. The story propounded is that man moved from the humid forest to the drying savanna, lost hair, developed sweating, spread the sweat by surface sebum, prevented droplet loss from scalp eyebrows and trunk hair, tackled the problem of skin infection by bacteria and fungi and did all of this by making use of the melanocyte to slow down epidermal turnover allowing an orderly death of the keratinocyte and maintaining at least one cell after mitosis attached to the basement lamina. The other cell is acidified and is jostled on its way to the surface. Elias *et al*.[12] and others before and after them propose an evolutionary advantage from an incremental improvement in TEWL and cutaneous antimicrobial defense that is in part determined by the move of the melanocyte from the hair follicle to the interfollicular epidermis.

Epithelial surfaces and neutrophils produce defensins and cathelicidins against bacteria. This intervention is upregulated by 1, 25$(OH)_2$D and by calcipotriol. Melanin production from dopamine, optimal at 30°C in studies of insect protective mechanisms against bacteria reminds one of an important early and perhaps still present function of this pigment.[13]

Of relevance is the fact that the skin of albinism in Tanzania has a higher density of common bacteria, especially Gram-negatives, compared to their pigmented sibling.[14]

It has been questioned whether albinism could protect against leprosy, as they are not recorded together where as in Africa both oculocutaneous albinism and until recently, leprosy have a high prevalence. Both leprosy and tuberculosis share genes with albinism.[15] Cytokeratin 10 is similar to the lepra soluble antigen heat shock protein-65. Since ultraviolet (UV) radiation decreases the granulomatous response to lepromin in humans. It could be that the mycobacterium leprae is more effectively destroyed in the dermis when there is no blocking of the effects of sunlight by melanin?[16]

Gunathilake *et al*.[17] showed that more heavily pigmented subjects had lower surface pH, and enhanced stratum corneum integrity as demonstrated by repair of TEWL after tape stripping. In heavily pigmented subjects the melanocyte dendrites were more acidic and passed more melanosomes to the skin surface. Sustained serine protease activity is induced by a prolonged increase in pH and it leads to profound alterations in stratum corneum integrity.[18]

Liu *et al*.[19] examining the depigmented skin of vitiligo demonstrated delayed epidermal TEWL recovery but were not convinced about pH changes in a differing racial group.

TEMPERATURE CONTROL AND THE HEAT OF INFLAMMATION

One only has to Google cold adaptation to read how enzymes can over time change their optimal temperature and for some the temperature range over which they are effective is small. The human body temperature is 37°C but much of the skin, and hence most melanocytes, is nearer 30°C. Elongation of the rete pegs with excess pigment favors the warmer flexures in Dowling–Degos disease. Immediate pigment darkening (IPD) prefers 37°C, but is inhibited by heating above this,[20] but less so in chronically damaged skin. One theory concerning the role of melanin is that it is anti-inflammatory and one role of inflammation is to bring the skin temperature up to 37°C, especially for repair. Acutely traumatized skin switches on inflammation and is an effective way to bring the optimal temperature of the epidermis closer to 37°C. Erythema ab igne is atrophy with dermal pigmentation induced by heat and pressure.

One form of albinism maintains loss of pigmentation only of the peripheries and their cooling might also be the explanation. Experimental cooling of the skin takes longer in vitiligo and local heating is faster in vitiligo patches.[21]

Temperature control is evolved in animals and includes the change to white fur of many animals in the cold. Long haired animals transfer the pigment needed from the epidermis to the hair, except for where there is short hair such as the ear, tail, nose or paw. Insulation by hair brings the underlying skin to a higher temperature?

The hair turns white in vitiligo and alopecia areata? Some of this is linked to stem cells in the bulge of the hair. The bulge is attached to the arrector pili, adding a mechanical stretch factor to hair growth. It is much under the influence of fright and flight stimuli and temperature control as well as mood to make the hair stand on end to provide insulation or cause goose pimples in the cold.

An elastic lamina is located between the retinal pigment epithelium and the vascular bed. It is believed to act as a functional and physical barrier. Early age related macular degeneration is characterized by a break down in this barrier and allows penetration of newly formed blood capillaries. Both *in vitro* and *in vivo*, this is restored by heat and there is increased production of anti angiogenic agents such as endothelin and thrombospondin-1. Heat treatment of retinal pigment epithelium induces the production of elastic lamina components and suppresses angiogenesis.[22]

Okun[23] has questioned the role of a close site relationship with mast cells as in urticaria pigmentosa. Conversely, mast cells are noted to be present at an increased density in the center of vitiligo lesions. The mast cell is a key cell in inflammation, in which participation by the melanocyte may be key, perhaps as a stimulus when pure melanin is released or a pacifier when folded in a trapping devise such as the melanosome.

KERATINOCYTE CONTROL AND LOSS OF GRIP AND STICK

In Dowling–Degos disease (http://dermnetnz.org/colour/dowlingpdegos.html) the pigmentation occurs in the flexures, which are of course notably at a body temperature nearest 37°C. Gene defects seem to result in a failure to produce keratin-5, which is involved in the transfer of melanin to the keratinocyte. Galli–Galli's disease is an acantholytic form of the disease. Other variants are reticulate acropigmentation of Kitamura, Haber disease and symmetrical acropigmentation of Dohi. This recalls the supra-basal acantholysis of Darier's and Hailey-Hailey disease, which is explained by a defect in the gene controlling the calcium pump and also can present with pigment disorders, but in this case it is a "confetti" depigmentation. Burge *et al*. have shown excessive plasminogen in Darier's disease, in the supra-basal epidermis where there are acantholytic cells.[24]

Becker *et al*.[25] and Werner *et al*.[26] demonstrated disruption of supra-basal connectivity of keratinocytes through such interventions as elastase release of fibroblast growth factor-2 (FGF-2) and significant reduction of elastin. At the molecular level Foxn-1 stimulates keratinocytes to call on FGF-2 to make melanocytes link to keratinocytes [Part 1[1]]. The receptor for FRG-2, which is FRG-2r2 when receiving an antisense oligonucleotide does not inhibit melanocyte activity whereas antisense oligonucleotide to FRGR-1 does inhibit activity. The supernatant of keratinocytes treated with tacrolimus stimulates melanocyte growth.[27] In retinitis pigmentosa in which elastin is damaged, there are low levels of FRG-2, and inhibition of FGF-2 increases elastin.[27] The keratin-5 gene is implicated.

Attachment between melanocytes and keratinocytes determines the expression of proteinase-activator receptor 2, which when activated increases the transfer of melansomes. It is controlled by the agents that control fibrinolysis[28] and hence it is of interest that UVB inhibits fibrinolysis in the upper dermis by the release of PA1. UVA which penetrates deeper activates fibrinolysis. In porphyria, another disease with blisters, the stimulus to the dermis by UVA does not attract white cells but is characteristically pigmented.

SKIN EXPOSED TO SUNLIGHT

Skin exposed to sunlight is associated with an increased number of active melanocytes when compared with skin

protected from the sun within the same individual. Friedman and Gilchrest[29] were the first to demonstrate that cultured melanocytes show a decrease in proliferation, but an increase in pigmentation when exposed to UV radiation. UV radiation also leads to elongation and branching of melanocyte dendrites and an increase in the size, as well as number, of melanocytes.

Exposure to sunlight results in two phases of darkening: Early and late. The late manufacture of melanin as stated above depends in part on spontaneous polymerization that takes time. There is a need for an immediate provision, while this process is underway. Proposed mechanisms of IPD are controversial. They include photo-oxidation of "premelanin," changes in the distribution pattern of microfilaments and microtubules, movement of melanosomes to melanocyte dendrites, increased transfer of melanosomes to keratinocytes, and changes in the melanosome distribution pattern in keratinocytes.[30] IPD could be elicited and reversed *in vitro* in full-thickness skin and in epidermal sheets, provided that the cells are viable. Its production was not inhibited by repeated freezing and thawing, or by formalin fixation. However, the temperature of 37°C induced by inflammation is preferred.

Immediate pigment darkening could not be blocked by substances that disrupt the microfibrillar or microtubular system (cytochalasin B, colcemid, and vincristine). As shown with a monoclonal antivimentin antibody, IPD-producing UVA doses did not induce changes in the cytoskeleton of melanocytes. No changes in number and distribution pattern of melanosomes were observed EM and by morphometric analysis of EM micrographs. Production of IPD does not depend on the structural and functional integrity of the melanocyte cytoskeletal apparatus, whereas its reversibility is. The fact that no increased melanosome transfer occurs may explain the lack of a UV protective action.

As melanin collects in a melanosome, it migrates into the dendrites of the melanocyte via microtubules, ready for transfer to keratinocytes. This process requires an intact cytoskeleton and "motor proteins." Hypopigmentation (the Griscelli syndrome) results if this transfer process is disrupted.

Hara *et al*.[31] discuss how intracellular centrifugal movement is determined by kinesin whereas centripetal movement is determined by cytoplasmic dynein. Application of kinesin antisense oligonucleotides to UV irradiated skin *in vitro* and *in vivo* results in decreased transfer of melanin and shows that kinesin plays a major role in tanning. There is species variation in this respect. The control of metalloproteases is influenced by plasminogen activator inhibitor, which is released by UVB.[32]

In a review by Ortonne and Bissett,[33] they favored publications that indicated that the increased pigmentation following sun exposure was postinflammatory, we would say antiinflammatory, and they especially referred to how easy it was to produce such pigment by irritating the skin with lauryl sulfate, a standard inducer of inflammation used in investigative dermatology. IL-1α, endothelin-1, stem cell factor, superoxide and nitric oxide were likely agents mediating the response. Destruction of elastin by proteases is another. Proteases tend to be activated in the early stages of inflammation and mast cell stimulation induces early inflammation. Injury that affects the dermis may stimulate mast cells to produce histamine and proteases; acting primarily on dermal tissues but within in a short time activating a response from the epidermis. Damage to the epidermis causes it switch on a repair mode to call upon the blood vessels in the dermis to bring in all that is necessary from the bloodstream for repair and to raise skin temperature for optimum repair.

The sensory nervous system may be stimulated to release acetylcholine and nor-epinephrine which rapidly disperse dermal melanosomes, but have no effect on epidermal melanocytes.[34] The melanosomes are quickly dispersed in the presence of melanin stimulating hormone (MSH) and these aggregate in its absence. In the frog, epidermal melanocytes are spread by MSH and the melanosomes rapidly aggregate when it is washed out. MSH renders the epidermis insensitive to the aggregating effects of melatonin, acetylcholine or norepinephrine. Dermal melanocytes will contract rapidly with these agents even in the presence of MSH. There is thus an additional modulating effect of keratinocytes on the effect of MSH.

FOLATE METABOLISM

Another more contemporary view of the function of melanin has been postulated by Juzeniene *et al*. group[35] in several publications that it is specifically protective of keratinocyte folate metabolism.

Folate deficiency is linked to disturbances of human skin color, serious birth defects, pregnancy complications, male infertility and cardiovascular diseases. The photodegradation of 5-methyltetrahydrofolate (5-MTHF) in aqueous solutions exposed to UVB, UVA or visible light in the absence or presence of riboflavin, uroporphyrin, and conjugated bilirubin was investigated by absorption spectroscopy. 5-MTHF is stable under exposure to visible light and UVA radiation, whereas it is slowly photo-oxidized under UVB exposure. However, it is rapidly oxidized by UVA or visible radiation in the presence of riboflavin or uroporphyrin, but not in the presence of conjugated bilirubin, which acts in a protective manner.

TOXICITY OF MELANIN AND SKIN CANCER

It is notable that the Quinone intermediates that are precursors of melanin are toxic to cells and the melanosome confines them

thus protecting against their harmful effects.[36] Rees believes the reason melanin has to be compartmentalized is because it is toxic in excess and melanoma is a side effect.[37] A view also expressed by Hallberg and Johansson[38] and Shipman *et al* 2011[39] Melanosomes are specialized organelles found within the cytoplasm of melanocytes. These when formed in the choroid and retina remain dormant for years and contain the proteins that regulate the synthesis of melanin. In macrophages melanin is also packaged and rendered harmless. The rate of melanosome degradation once migration to keratinocytes has taken place partly depends on the size of the individual melanosomes; in light skin, the melanosomes are smaller and degraded more quickly than in darkly pigmented skin.

Melanoma is a highly malignant tumor, which appears to be provoked by previous exposure to sunlight. It provokes antibodies, which are similar to those found in vitiligo and in halo nevi, and which some argue protect against malignancy.

There is an acral lentiginous form occurring on the soles of the feet. It is a site without sun exposure, cooler than other parts of the skin, subject to pressure and shearing strains and without the hair follicle source of melanocytes.

The case has been strongly made that absence of a protective shield against sun light provided by melanin predisposes to skin cancer. Not everyone believes this is proven; "most melanoma occurs on skin that is only intermittently exposed; individuals with high continuous sun exposure have lower rates than those exposed intermittently; and there seems an important interaction between skin type and incidence of melanoma."[38] It is unexplained why albinism, with melanocytes present, but no melanin, has a high prevalence of cancer and not of melanoma whereas vitiligo, with no melanocytes, has a low prevalence of cancer. Erythema ab igne is atrophy with pigmentation induced by heat, which predipose to skin cancer as was well demonstrated in an African tribe.

IS PIGMENTATION IN THE ABSENCE OF SUN MOSTLY UNDER THE DIRECTION OF THE ENDOCRINE SYSTEM?

The metamorphosis of the amphibian is under endocrine influence and the changes in the behavior of the melanocytes are a response to hormones under pituitary control.

Wasserman[40,41] believed the darker African races were genetically prone to greater influences of an endocrine kind. Exposure to sunlight isn't the only thing that can darken skin. Certain diseases and conditions also may play an important role. For example, hyperpigmentation, or excessive skin darkening, is a key symptom of Addison's disease, a disorder that results when the adrenal glands fail to produce sufficient amounts of critical hormones. The increase in pigmentation is caused by a rise in blood levels of melanocortins derived from the pituitary gland. Hormonal changes during pregnancy also may increase the body's production of melanin, leading to blotchy skin on the upper lip, nose, cheekbones or forehead. Endocrine, paracrine and autocrine factors influence melanogenesis mostly by increasing tyrosinase activity, like estrogen, which is one well-studied example of an endocrine influence increasing melanogenesis.

Within the skin, the life of the melanocyte continues, while the keratinocyte it feeds manufactures keratin and aims for an effective barrier function. It also seems little influenced by the change in the keratinocyte as it switches from a resting state to a repair phase, manufacturing dermal stimuli such as eiconisides, cytokines and growth factors.

In a recent review Ortonne and Bissett[33] wrote "there are 1500 genes products (proteins) expressed in melanosomes of all developmental stages with 600 of them being expressed at any given time and 100 of them apparently expressed at any given time unique to the melanocyte. They emphasize that the genetic factors affecting relationships with the keratinocyte and other cells are ripe for further study.

We do not wish to downgrade pigmentation and the complex late development of a genes and biochemistry to control color and free radical formation.

In this essay, we have given still greater emphasis to the keratinocyte in the basal layer, to elastin and to the lymphatic and we regard activators and inhibitors of proteases under the influence of both biochemical and mechanical factors as key to the range of pigmentation interactions in the skin.

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Cite this article as: Arianayagam S, Ryan TJ. Human pigmentation: A side effect adapted from a primitive organism's survival. Part 2: The melanocyte as mentor of the keratinocye. Indian Dermatol Online J 2014;5:328-33.

Source of Support: Nil, **Conflict of Interest:** None declared

This is Part 2 of two articles written by the author. Part 1 is available in the previous issue of the journal.