Human pigmentation: A side effect adapted from a primitive organism's survival, acting through cell attachment with an affinity for the keratinocyte and for elastin: Part I

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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 deserve greater emphasis and that mechanical forces involved in grip and stick or release from attachment, all point to control of proteases underlying pigmentation. There is an affinity for elastin as a pathway for melanin to exit its peripheral location in the epidermis into lymphatics and play a humeral role in defense mechanisms. The hair follicle follows the epidermal-dermal pattern of behavior with an affinity for elastin, a controlling function of melanin and through the bulge, an influence of mechanical forces and control by protease inhibitors.

Key words: Evolution, keratinocyte, melanocyte, pigmentation, skin color

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INTRODUCTION

History of an evolving function

The color of the polymer melanin is over emphasized. Other roles of the melanocyte or the precursors of melanin, such as dopamine deserve greater emphasis. Its biological, clinical and sociological complexity, are reviewed by Borovansky and Riley[1] Nordlund *et al*.[2] Jablonski[3] Connor[4] and Lahiri *et al*.[5] found throughout the animal and plant kingdoms and in species such as fungi, it existed well before life on earth used it as protection against the sun or as camouflage. "What then, is its function?" In the human, in whom total production amounts to 1 g, it is found mostly in the skin, where it is credited for sun protection. Melanin is found in the hair root, well away from the sun's ultraviolet-B (UVB) rays and in the amphibian and in early animal development, it is often seen around blood vessels rather than in the epidermis. The location of melanin, in the inner ear, surrounding the cochlea's striae vascularis, in adipose tissue, in the midbrain and in the valves of the heart, suggests other functions. As in feathers its function of display developed millions of years after its first appearance.

In the human, melanin is mostly seen in the basal layer where the melanocyte deposits the pigment in the cytoplasm of the basal keratinocyte [Figure 1], apparently shielding the nucleus. However, in the elongated rete peg, with the orientation of the basal cell frequently lying on its side, that seems a less satisfactory explanation than not being where the keratinocyte is too busy making links to the dermis. Other functions to be discussed below include free radical detoxification and the provision of dopamine and related adrenochrome products in the primitive brain especially for the specialized attachment process of synapse formation. In the heart, other functions are linked to the autonomic nervous system, or to the need for a physicomechanical perspective in the snap back of the valves.

The early history of cells surviving in a biochemical soup is one of the evolution of adhesion of cells to each other to accomplish a greater range of activities and to respond to mechanical forces temperature and pH, migration from darkness toward light, utilization of oxygen and protection from irradiation and microbes included making the best use of an initially accidental polymer, melanin, as well as 1, 25(OH) 2D a precursor of

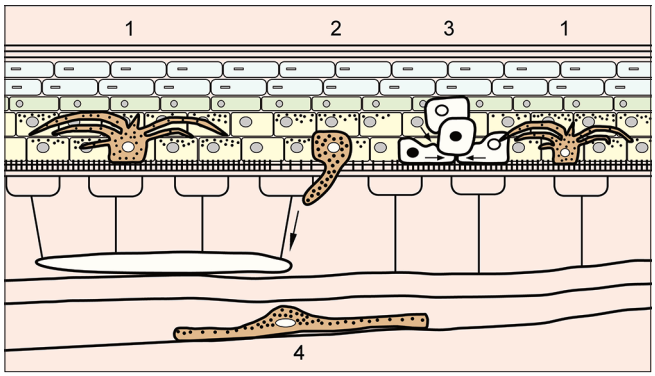

Figure 1: The melanocyte's affinity for the keratinocyte and for elastin has much to do with grip and stick by the employment and inhibition of proteases. (1) Melanocyte inoculates keratinocytes with melanosomes and like many cells derived from the neural crest determines organ shape and relationships. (2) Melanocyte lyses epithelial basement lamina and uses elastin to guide it to the Lymphatic. (3) Basal keratinocytes lose grip and stick to the 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

vitamin D. But one can step back a little and note tyrosinase as a developmentally specific major determinant of peripheral dopamine production.[6] Dopamine is a precursor of the fright and flight agents adrenaline and noradrenaline and in some very primitive organisms it protects against being selected by its enemies as food and hence that attachment does not automatically.[7]

As seen in the person affected by albinism, this melanization phenomenon can be done without. A long life is not dependent on it, some with albinism have a normal lifespan, even though those who are not protected against sunlight do die early from skin cancer. In contrast as shown in the literature on dopamine antagonists and receptor blockers, protease activity and agents such as protein kinases are linked to control by or of proteases. Furthermore, there is a gradient of dopamine activity maximal in the in the basal layer of the keratinocyte where amongst many actions, it accelerates barrier function repair[8] and upregulates interleukin 6 (IL-6) and IL-8 production.[9] It also has a role in the control of the adipose cell in subcutaneous tissues.[10]

The neural function employs dopamine and deposits melanin

The enlarged multicellular organism learned to control attachment of its cells to each other, its size and shape determined by utilizing the properties of privileged cells, which manufactured dopamine and ensured safe attachment and synapses. These were later found in the neural crest and neural tube. Grip and stick had to be moderated by the additional control of proteases so that detachment was easily made and controlled. The many functions determined by attachment are best distinguished so that organ development and synapse formation stops short of phagocytosis. Schwann cells must wrap round nerve axons, but not eat them. Nerves must make synapses as controlled attachments to transfer information and dopamine is involved.

Melanin biosynthesis and the neural relationship

The initiation of melanin formation and employment of tyrosine and dopamine is linked with adrenochrome systems. The pigment that lies in the midbrain was thought to have a different role to that in the skin and has long raised greater questions about its link with dopamine.[11,12] The stages of the conversion of DOPA to melanin seem, as was once believed, almost accidental; a polymerization that requires no energy nor oxygen and has been adopted for multiple purposes during evolution. Most likely it is the readiness with which the quinones will bind with several alternative chemicals such as cysteine that determines which direction or pathway is taken. Duplication and new gene creativity make contemporary interpretation of the tyrosinase enzymes more complicated. Several of these prove useful in evolution, making decisions about the prime purpose of melanin more difficult, some being antibiotic or anti-inflammatory. For example, they are believed to prevent the bacterial breakdown of feathers and may explain superficial cutaneous mycoses control by darker skin. The spontaneous formation of pigment proves useful in camouflage and display and in particular, its protection against UV radiation proves of value.

While melanocytes are the cells that produce the melanin-containing melanosomes it cannot be forgotten that their origin is in the neural crest and they have some features which remind one of cells of the nervous system as they migrate preferentially to the basal layer of the epidermis. There have been theories focused on the hypopigmented anesthetic patch observed in leprosy, that the melanocyte, having reached the epidermis does not entirely lose its neuronal sensory properties.[13] However, no cell loses stem cell properties during maturation as completely as was once believed. Stem cell progenitors of the Schwann cell need to be in contact with nerves and when they are not, the Schwann cell turns into a melanocyte. The polymerization processes leading to pigment formation does not necessarily require tyrosinase.

IT TAKES TIME TO PERFORM THE FUNCTIONS OF THE MELANOCYTE

Gfeller[14] emphasizes that the melanocyte must be given time. Neuromelanin is not found in animals with a short gestation time, but it is in sites where pigment formation is slow or where the gestation period in the fetus is prolonged. Marsden[12] also stated that melanin was seen only when the phenothiazine prescription was prolonged. The polymerization of adrenaline applied to the eye topically for glaucoma, takes several months before melanin is produced.[15] The Cambridge anatomist Boyd[16] wrote that initially the cells of the neural crest have no pigment and that melanin is chronologically a product that

is naturally a late production; a theme that recurs over and over again in the study of skin disease, the hair cycle and the amelanotic melanoma. Whether or not they produce such pigment shows great variation in the site during evolution having either a whole body or only patchy presence and allowing time for distribution of pigment along dendrites, to keep up with keratinocyte cell turnover.

SYMMETRY

One of the prominent features of the nervous system and of pigmentation is its symmetry. Both were studied by Whimster[17] when in the gecko he determined cell migration, skin color and the role of the sympathetic nerve system. Whimster argues that studies of symmetrical patterns of pigmentation, of amphibians and of diseases such as neurofibromatosis, show that they can only be explained through an influence of the autonomic nervous system. The latter is influenced by mood, temperature, stress and that these are linked not just to a biological role but a social role in control of privacy and display and hence of camouflage. Stress modulates skin color through melanocyte activity[18] inclusive of the effects of dopamine and related by products for flight and fight.

Cells arising from the neural crest and neural tube migrate in various directions. Some stop on this journey making a small in size but important contribution to the function of many organs such as the ear, eye and even the heart; one of the first functioning organs. Most, melanocytes will make their final stop in the epidermis. Here, they are encouraged to interact with keratinocytes and to produce melanin prompted by local, hormonal and external stimuli, especially postpartum, such as UV rays. The melanocyte may align itself to where there is a horizontal bed of elastin, as in the Mongolian blue nevus and Ota's nevus. Here the melanocytes are strikingly elongated horizontally, orientated parallel to horizontally disposed elastin fibers. Sometimes those that stop on the neural crest pathway to the epidermis, spread out in the deeper dermis, sparing the upper dermis in large areas of the skin and adjacent tissues; a well-known example of this is neurofibromatosis.

Developmental studies of half a century ago

Half a century ago, the investigation of pigment cells derived from the neural crest relied on extirpation and grafting and resulted in a huge literature. Boyd[16] studied how they appear in only one or more layers of the skin or in hair and feathers. Its product, melanin is frequently transferred to other cells not of neural crest origin. As Boyd emphasized, cells derived from the neural crest have a role in detaching the grip and stick of fused epithelium of the newborn eyelids or foreskin and are probably retaining melanocyte features including protease activity.

Melanocyte behavior is clearly under genetic control but it is now well recognized that such control is greatly influenced by local environmental factors. These may be through close contact as with the keratinocyte or of far distant origin as from UV rays. The latest environment for the melanocyte to be identified is adipose tissue where there is evidence from Baronova's laboratory of ectopic synthesis in human adipose tissue.[19] There too,in the burning of fat,there is a role for the autonomic nervous system and for influences such as dopamine.

We conclude that the melanocyte has evolved as a controller of cell relationships, picked up the property of melanin production and evolved ways to protect tissues from its toxicity. Ultimately melanin has to be disposed of safely. High rates of epidermal turnover can accelerate loss of melanin from the skin's surface, somewhat slower as a constituent of hair and hardly at all in the choroid or retina.

Biochemical control at different ages by attachment and transmission of mechanical forces: the role of proteases and protein kinases

Some 40 years ago when Ryan was exploring the morphological range of shapes of the upper dermis and its capillary bed it was suggested that melanin plays a role in the control of these changing relationships and their final shape.[20,21] It was reported that the melanocyte behaved quite differently in its control of endothelium compared with the keratinocyte. Blood vessels tending, when in the presence of epithelium, to be branching and to make networks. This is not the case with endothelium under the influence of melanocytic tumors in which there is no branching but a radial distribution of elongated capillaries.[22] Significantly, it may be the melanin precursor dopamine that plays the greater role in such angiogenesis.[23] Always from the perspective of the blood vessel, it later became an interest of the field of tumor blood supply to explore control of proteases activated and inhibited by mechanical stresses[24] induced by blood flow and later to write a review about the transduction of biochemical signals by mechanical forces.[25]

This 1989 review included a number of concepts: (i) Mechanical forces are transmitted to cell membranes by adhesion complexes between solid elements in the extracellular environment and the cytoskeleton; (ii) the adhesion complexes require inhibition of proteases to maintain their adhesion; and (iii) hydrostatic pressure is a mechanical stress on solid elements in the tissues and it is controlled by the microcirculation and lymphatic system through provision and removal of tissue fluid. Hypotheses include the following: (i) Mechanical forces act on the cell membrane and induce inhibitors of proteases, thereby maintaining the adhesion complexes; (ii) the transduction of chemical signals-protease inhibition-is more flexible in young cells, wounds and psoriasis. In old tissues, protease inhibition is more sustained; and (iii) cell shape, cell migration and mitosis are in part controlled by such mechanisms. These hypotheses are supported by evidence from the literature and observations of many co-workers in the fields of microcirculation, lymphatic systems, angiogenesis, wound healing and proteases.

This review was updated 2 years ago in this journal.[26] The concept is again revised, this time inclusive of the melanocyte, with the suggestion that the control of attachment of cells is a prime function.

These studies in the 1970s were followed by an examination of the lymphatic system and its supporting elastin fibers and the identification of an affinity for plasminogen activator inhibitor (PAI) and vitronectin[27] by the elastin fibers. This affinity extended also to decay accelerating factor.[28] It is the pigment cell that has a liking for elastin rather than the polymer product melanin alone.

Mechanical control linked to cell shape, grip or stick and release from attachment for mitosis or migration

The melanocyte is part of a caring community of cells surviving in a threatening environment; a nurse maid that uses the electromagnetic spectrum and mechanical forces and evolves over 500 million years to a point at which its original behavior is forgotten and skin color and its social influence dominates the literature read by dermatologists.

Cell adhesion requires adhesion proteins and calcium pump activity. Its release is determined by proteases which induce lysis of such adhesion proteins only when there are no inhibitors of proteases dominating the immediate environment. Ryan *et al*.[29-32] and more recently Bhadal *et al*.;[33] Ogura *et al*.[34] in a series of studies of the grip and stick behavior of fibroblasts, relevant to the specialty dermatology, showed that protease activity, in part dependent on protein kinase C, varied in its ability to sustain PAI-1 release depending on whether its origin was from young or old tissues.

Melanosomes influence the calcium pump.[35] In the skin context, it is relevant that the confetti hypopigmentation of Darier's disease is a consequence of a loss of suprabasal adhesion involving a genetic defect in the calcium pumping control by cadherin. The keratinocytes in the hypopigmented areas are empty of melanosomes even though adjacent melanocyte dendrites are stuffed full of them. It is in the heart valve that a role for melanin, calcium and elastin have been shown to be interrelated in determining mechanical responses.[36]

A rise in intracellular Ca(2+) may precede cellular changes that lead to calcification and fibroblasts have been shown to exhibit increases in intracellular Ca(2+) in response to mechanical strain. Strain induces intracellular Ca(2+) accumulation through stretch-activated calcium channels.[37]

It is puzzling that heart valves, the uveal tract of the eye and the aorta feature together in literature, on the stiffening and snap back of such organs. The idea that the properties required to make the melanocyte act in this way are relevant to the behavior of the basal cell of the epidermis finds support from Uehara *et al*.[38] Ryan has long believed that what is needed is a rethink of the factors controlling direction of growth whether in the neural crest or fully mature tissues, with tissue spatial relationships better understood as activity or inactivity, hypertrophy or atrophy and not to be misled by two dimensional interpretations.[39,40] The 1970 article led to a response by the leading thinker on histopathology, Pinkus.[41] The concept put forward was that the basal keratinocyte prefers to be in contact with the dermis and that only when in mitosis does it get jostled out of position. Given a chance it will grow inwards.[42,43]

There was a further discussion on the vertical disposition of basal epidermal cells and their horizontal cleavage by Smart[44] and Ryan.[45]

Fitzpatrick developed his views on the positioning of the melanocyte in part while in Oxford working with Ryan's tutor Blaschko, but Ryan at that time failed to note that it was a position that might well stabilize the keratinocyte and prevent it being jostled out of position on its "migration outwards." Elongation of rete pegs or complete flattening of the epidermis can be seen in either atrophy or hypertrophy, that is slow growth or fast growth and the presence of melanocytes or mitotic figures can be a clue to which process is taking place.

Ryan was the first to show PAI-1 release from the epidermis especially when traumatized.[46] This additional factor, the release of PAI-1 needs to be examined when plotting changing morphological relationships, cell shape changes, attachment grip and stick, or release from attachment. These underlie the interpretation of "activity."[31,47]

Adherence, Jostling, incontinence and dropping out

There are three cell types in the epidermis and there is no biological advantage to their position anywhere other than in the basal cell layer. Suprabasally there is deprivation and orderly death in the preparation of the inert barrier between the epidermis and dermis. The language used to describe the jostling for an advantageous position for nutrition from infrabasal blood supply and displacement from the epidermis (termed incontinence) is nonsensical [Figure 1]. There is no active migration outwards and the occasional evacuation of inanimate material to the surface is a clue to the passive process of outward movement also once termed "Catharsis."[48]

It was suggested that the junction of the epidermis is a barrier that discourages passage into the dermis which is where all the needs of the epidermis can be met. So called migration outwards within the epidermis is in fact more a process of jostling out of position to where the environment is increasingly anaerobic and is certainly less compatible with life. One may question whether the keratinocyte's link to the melanocyte discourages that cell's migration outwards and also protects it

against being jostled out of position. It is interesting to examine what it is it that holds the melanocyte in position and compare that to the basal epithelial cell. Several authors have noted that conditions with increased mitotic figures in the basal layers of the epidermis such as psoriasis develop preferentially in vitiliginous sites where there are no melanocytes.[49]

While there is no increase in prevalence of psoriasis in patients with vitiligo[50] they share the phenomenon of the Koebner response which occurs only when the basement lamina is disrupted at a predisposed site[50,51] and when they occur together psoriasis preferentially locates to vitiliginous sites.[52]

Elongation of the rete peg, the inward migration of the anagen hair, the invasive melanoma or cancer, all have some linkage to the relationship between melanin, elastin and the lymphatic and a further discussion takes one back in evolution to the early development of immune-surveillance and skin as a barrier between the body and the environment the basement lamina between the epidermis and the dermis.

Cells cannot "drop" into the dermis and the phenomenon of cells moving there is not explicable by a concept of incontinence. In the basal cell layer of the epidermis keratinocytes will grip and stick until mitosis calls up proteases and releases them from attachment. At this stage jostling to preserve a position of advantage at the basement lamina forces one or more cells upwards into the suprabasal position [Figure 1]. All of this is dependent on the control of and by proteases that manage the grip and stick process. The higher the rate of mitosis, the more cells are moved passively outwards.

The morphology of the epidermal-dermal junction ranges from flat to up and down. The latter is more usual in hyperplasia as in the acanthosis of psoriasis determined as much by the outward growing dermal dermal vasculature of the papillae and the space for expansion is limited by size. In such a condition proteases play their part also on the surface of the melanocyte releasing it for outward carriage to the surface. Flatness is a feature of extreme atrophy with pigmentation as in poikiloderma but it is also a feature of the rapidly growing organism only when there is plenty of available space as in the fetus and in the edge of a wound with migrating epithelium. In this case, the epidermis is not atrophic.

Melasma a model of loss of grip and stick

Melasma, fully discussed in[5] is a very common acquired cause of circumscribed hypermelanosis, in which the melanocyte escapes through a basement lamina disrupted by proteases. It is mostly seen symmetrically distributed in three typical sun exposed and rubbed sites; centrofacial, malar and mandibular.[53] It can be exacerbated by pregnancy, progesterone and oral contraceptives it fades during the winter months.[54] Autoimmune thyroid disease, phenytoin and other phototoxic drugs are also potential exacerbating factors for melasma.

It is hypothesized that hyperfunctioning melanocytes in affected skin produce increased amounts of melanin compared with unaffected skin.[55] In addition, mitochondria, Golgi apparatus and rough endoplasmic reticulum are increased in number or amount, supporting the hypothesis that the melanocytes are overactive.

Under illumination with Wood's lamp, the pigment may be seen at several levels of dispersal; epidermal, dermal, mixed or indeterminate. In the dermal layer, an increase in number of melanin-containing macrophages may be observed. There may be an increase in number of melanocytes, which have enlarged dendrites. However, histological findings do not correlate well with reported Wood's light examination findings.[5,54,56] Epidermal hypermelanosis is more amenable to topical treatments and chemical peels, while dermal pigmentation is very difficult to treat.[5]

In melasma the melanocytes appear to be displaced into the dermis,[5,57] in part due to protease activity weakening the basement lamina.[5,58] It is alike to the migration of melanocytes observed by Yasutomi in the metamorphosIs of the tadpole.[59] The number of epidermal melanin-containing cells of the skin decreases during metamorphosis in the frog; Yasutomi concluded that this decrease was due to the migration of epidermal melanocytes to the dermis. Epidermal melanocytes and epidermal cells are initially tightly associated with each other in the young tadpole. "The association becomes looser at the metamorphic stage and occasionally, small breaks in the basement membrane are seen. These breaks may facilitate the migration. The migration was observed exclusively at the metamorphic stage, in spite of careful observation of other stages under the electron microscope. The migration of epidermal melanophores was induced by treatment with thyroxine of cultured skin from tadpoles at stage 15 and this hormone may act directly on epidermal melanophores." 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.[60] UVB inhibits fibrinolysis in the upper dermis by the release of PAI-1. UVA, which penetrates deeper, activates fibrinolysis.[61] In Porphyria the stimulus to the dermis is UVA which is characteristically pigmented but white cells are not attracted. Moreover in this respect activation of proteases may be a feature as in melasma. There is some evidence of hypersensitivity to sunlight, even when tested on the non melasma sites. However, the pigmentation of melasma is without the inflammatory phase of sunburn. Immediate pigment darkening is a feature. Sun blocks are helpful and sandalwood is commonly used for this purpose in Asia.

Anti fibrinolytic agents, transexamic acid, are therapeutic for melasma.[62] In a later paper these authors Li *et al*.[63] emphasize that this plasmin inhibitor has a greater effect on the affected melasmic skin than on normal skin and supposed that this was due to the greater amount of vasculature and mast cells in the affected skin. They also pointed out that mast cell tryptase degrades basement lamina collagen type IV. Li *et al*.[63] also report another serine protease inhibitor, pigment epithelium derived factor, which they find inhibits migration of outer root sheaf cells of the hair follicle and may be an inhibitor of vascular endothelial growth factor in the hair follicle. It has a role in the determination of some retinal degenerative diseases.

Elastin guidance on leaving the epidermis into the dermis

Once in the dermis, cells meet elastin for the 1st time. Elastin of the upper dermis is orientated tangentially to the epidermis and at the junction of the upper and middle dermis.[24,64-67]

Elastin is coated with vitronectin and PAI-1 and affinity between the melanocyte and the elastin guide wire is an important influence.[27] In the upper dermis, the tangential elastin deposition encourages passage into the lymphatics and in the mid and deep dermis the horizontal disposition of the elastin fibers encourages the melanocyte to stretch out in a horizontal pattern. The preferential guidance by elastin in the upper dermis explains why melanin is a common feature of lymph nodes draining the skin. In a well illustrated paper using electron microscopy, Ono *et al*. demonstrated dermal melanocytes aligned along the long axis of elastin fibers, encircling and embracing them.[68]

Passage of cells passively into the lymphatics, depends on massage and the seldom static condition of tissues in a living organism. When reconstituted skin is in cell culture without vibratory stimuli, stacking of cells is sometimes observed along elastin fibers. This does not happen in a healthy, mobile skin in which movement of the tissues hastens the passive movement of cells along elastin fibers, into and along the lymphatics.

The melanocyte, when attached to the keratinocyte, is well separated from elastin fibers components until it is dislodged through a disrupted basement lamina as in melasma or as in the prototype incontinentia pigmenti, in which the whole elastin fibers can be shown to have moved closer to the basal cells of the epidermis. A study by Wong *et al*.[69] and Daroczy and Feldmann[70] observed ultrastructurally similar phenonomen in incontinentia pigmenti the Bloch-Sulzberger syndrome in which a dendritic process of the melanocyte could be seen extending through the discontinuous basement membrane into the upper dermis. Electron Microscopy shows that pseudopodia from the keratinocyte when activated as in dermographism[42] have an increase in number of protrusions into the basement lamina. This is an example of the effect of dermographism, the edema from scratching, which is due to the stimulus of the dermal mast cell and illustrating its inflammatory role. Melanin is also spread hematogenously and found in circulating leucocytes.[71] Since melanin is a macromolecule it can only get into the bloodstream via the lymphatics, either as an isolated macromolecule, or having been phagocytosed by a white cell. Melanin is an endogenous pigment that can be found habitually within lymph nodes. Thus, it is a normal finding in black-skinned mice and is not considered to be pathological lipomelanic reticulosis, reviewed by[72] it is a feature of most lymph glands draining any form of dermatitis. The melanin is often within macrophages.

Ryan has long hypothesized that on leaving the epidermis, the route ultimately taken is along a tangentially orientated elastin fibers “guide wire” into the lymphatics. This was first observed in the mesentery.[73] With faulty guide wires it gets taken up by macrophages or drifts toward hemosiderin.

An interesting link is described with elastin viz., the use of elastin immunostaining improving the evaluation of melanomas associated with naevi[74] and melanocyte precursors expressing elastin binding protein and elastin-derived peptide (VGVAPG) to stimulate melanogenesis and dendrite formation.[75]

Water surrounds the elastic fiber and may hydrate materials moving along the guide wire. Melanocytes manufacture metalloproteinases making it a viable hypothesis that migration is enhanced, but the possibility of PAI control should not be ruled out. It also might explain how readily melanin and related nevus cells appear in lymph nodes if not phagocytosed by macrophages. Patterson,[76] discussing nodal melanocytic nevi in lymph nodes, notes how frequently their presence is a finding. Nevus cells tend to be rounded, unlike the elongated bipolar melanocyte when it lies in the dermis. Kamino *et al*.[74] have more recently observed that nevus cells have elastin around them in the lymph node, but melanoma cells do not. Patterson[76] argues that a theory of arrested migration of nevus cells is less likely than mechanical transport.

The melanocyte and the hair

When examining the hair's direction of growth, mechanical forces, control of grip and stick through protease activation and inhibition, the influence of temperature and the affinity of the melanocyte for the keratinocyte or for elastin, all become part of the story but clearly cyclically and regulated by hormones. So does the role of dopamine as a factor in control of hair melanization. A study by Eisenhofer *et al*.[6] established tyrosine as a developmentally specific major determinant of peripheral dopamine production.

In the mature hair follicle, active melanocytes, sans melanin, are readily detectable in the basal cell layer of the infundibulum and around the upper dermal papilla. Amelanotic melanocytes (dopa-negative, but immunopositive) appear in the mid to lower outer root sheath.[77] Whatever the etiology,

it begins as a default in epidermal melanocytes followed by pigmented cells in the hair follicle. The final stage is an attack on the amelanotic cells in the hair follicle at which stage the alopecia areata becomes irreversible. White hair (poliosis) in vitiligo is a bad prognostic sign.

Melanocytes in the follicular-melanin unit, which is believed to be immunologically privileged, are larger with longer dendrites than in the epidermis. They take a long time to emerge in the hair shaft keratinocyte at the surface.[78]

The feature of anagen hair is that at least part of the epithelium appears to be growing inwards and this is at a stage when there is an increase in elastin in the papilla. The question should be asked whether cells with the properties of a melanocyte placed immediately deep to the embryonic epidermis in a hyperplastic dermis induce budding by slowing growth at that site and at a later stage a hair follicle when it is attached deeply to elastin perhaps through melanocyte affinity in the papilla extends the adnexa. The concept of inward growth is a misinterpretation.

The elastin in the papilla was first described in the rat hair cycle by Divano *et al*.[78] The elastin in the hair literature has been renamed Arao-Perkins bodies and their presence or loss in hair disease are commonly referred to.[79] In this physiological review, the authors write of the downward growth pressure of the anagen hair and the role of proteases in making a way through the collagen and elastin bed. The role of mast cells versus catechol amines is also a feature of the cycle. During anagen mast cells increase and there is more histamine and heparin in the hair bulb environment. Conversely catechol amines decrease during anagen and are at their highest during telogen.[80-84] Shape changes due to different rates of cell growth in adjacent tissues would be determined the distribution of the secretions of mastcells and melanocytes.

Using fibrinolysis autography Ryan (unpublished) noted a cyclical variation in fibrinolysis in the dermal papilla, increased in anagen, but absent in telogen. If, as some believe, all the proteases active in tissue are remodeling and wound healing, then the hair cycle is a good illustration of PAI-1 as a significant control factor. The bulge too is playing a part and it cannot be ignored that it is under the influence of the mechanical force of the arector pili, which is in turn under the influence of the nervous system when the hackles rise and goose pimples indicate the influence of temperature. So far a large literature invoking a control role for PAI-1 has not linked the melanocyte-PAI-1 relationship with the hair cycle changes in melanocyte activity. Nor, unlike Ryan,[25] has the transduction of biochemical signals by the mechanical forces occurring in the hair follicle been examined. Cohen and Chen[85] discuss the mechanical control of stem cell differentiation. Both externally-applied and cell-generated mechanical forces are pivotal to the differentiation responses. Muscle contraction is one such force and relevant to the hair follicle bulge and its attachment to the arector pili. Where a stem cell lies in parallel to other cells experiencing mechanical forces it may be released from tension. In this way, it is proposed that some cells with enhanced grip increase their inhibition of proteases while a cell in parallel may be exposed to the releasing effects of proteases. Multicellular growth imparts expansile forces and shape changes that require some cells to enhance the pulls and stretches while others in parallel relax them.

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