The Function of Melanin or Six Blind People Examine an Elephant

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Summary

The pigment melanin is found in all living kingdoms and in many different structures and forms. When its various functions are examined separately, its behaviors seem disparate and conflicting. It has a clear role in camouflage and sexual display. Other major roles are examined critically. It can act as a sun screen but is not a very effective one. It can also scavenge active chemical species, but this, too, is not done very effectively. It produces active radicals that can damage DNA. It binds to drugs in ways that are either beneficial or deleterious. Aside from camouflage, its other roles can be brought together by a unifying hypothesis as first proposed by Proctor and McGinness nearly 20 years ago. Melanin is envisaged as an energy transducer with the properties of an amorphous semiconductor. It can absorb many different types of energy and dissipate them in the form of heat. However, if the energy input is too great, the output can be expressed in the form of activated chemical species that can damage cellular macromolecules resulting in cell death, mutations and cancer. The protective aspect of melanin in dark skin is seen as resulting from its high concentration and its confinement to ellipsoidal and densely packed organelles that can effectively shield the nucleus. In light skin, its radical nature is seen as potentially participating in the carcinogenic process, particularly when overwhelmed by intense episodes of sunburn.

Introduction

The great pigments of living things are the hemoglobins, chlorophylls, carotenoids, flavanoids and melanins. The most neglected of these are the melanins - and not without reason. The prosthetic groups of the first four substances are orderly arrays of single and double bonds. Their protein moieties are easily studied using conventional techniques. When melanins are isolated from living tissue, they produce an insoluble and amorphous mud that defies analysis by classical techniques.

The melanins are nearly ubiquitous and are found in some organisms of all biological kingdoms. They fall into three major categories: eumelanins: brown and black pigments derived from dihydroxyphenylalanine (DOPA); phaeomelanins: red and yellow pigments derived from DOPA and cysteine; and certain plant melanins: brown and black pigments derived from phenols and catechols and lacking nitrogen.

Phaeomelanins are found mainly in hair and feathers and possibly in freckles associated with red hair in humans. The ink cloud produced by the cuttlefish, *Sepia officinalis*, is almost pure eumelanin, as is the pigment in black hair characteristic of orientals. In mammals, melanins are found not only in hair, but in skin, in sensory organs and in many internal tissues, most notably the brain and the nervous system. Insect cuticles, eggplants and over-ripe bananas owe their color to melanin.

In human skin, melanin is synthesized in melanocytes - specialized pigment cells derived from the neural crest - that are located near the base of the epidermis. These cells, like their neural counterparts, have dendritic processes that stretch out among the keratinocytes, the most abundant cells of the skin. Melanin synthesis occurs in specialized organelles termed melanosomes. As these structures mature, they migrate into the dendrites which are then phagocytized by the keratinocytes. Keratinocytes arise in the basal layer of the epidermis and migrate upward with some additional replication toward the surface of the skin. Near the end of their journey, they extrude their nuclei to form the dead protective outer layer called the stratum corneum. The assimilated melanosomes are by now post-mature and have turned into melanin dust. The migration of the keratinocytes and their interactions with the melanosomes result in a pigment gradient with a maximum melanin concentration toward the base of the epidermis. This topsy turvy configuration - akin to an inverted umbrella - has led to much speculation regarding the efficacy of melanin as a sun screen.

The location of melanins in obscure internal body sites, their exotic chemical and physical properties, the sequestering of the pigment in protective subcellular particles and the disease states resulting from the absence of melanin all lead to speculation that melanins have other functions than simple solar protection.

This sun screen dogma is based primarily on the fact that people with dark skin are resistant to sunburn. Moreover, they rarely get skin cancer. Furthermore, tumors of melanocytes, melanomas, are frequently resistant to radiation therapy.

The purpose of this review is to contemplate the various aspects of the melanins in order to develop a unifying hypothesis. Our investigation is similar to that of the six blind people who set out to define an elephant, as depicted in Figure 1. In the end, given an opportunity to compare notes, they might still conjure up an imperfect picture of this remarkable mammoth. Let us now see what each would say. For the sake of simplicity, "melanin" will be used in a generic and unqualified sense, referring primarily to the animal pigment eumelanin.

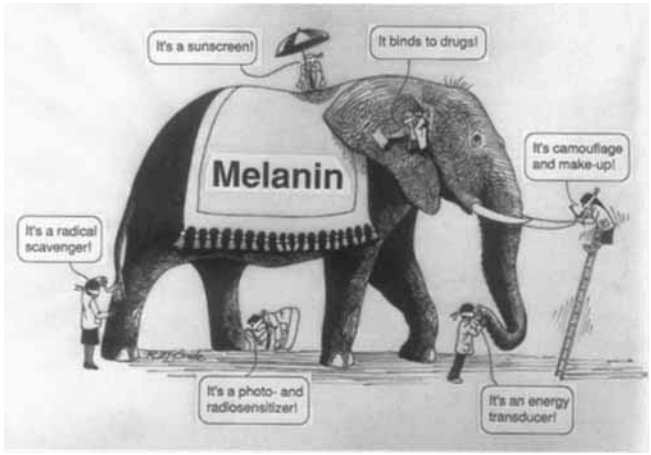

Fig. 1. The six blind people examine the elephant.

First Blind Person: "I Know What Melanin Does! It Acts as Camouflage and Adornment."

These are certainly functions of melanin. In mammals, for example, the tremendous variations in hair coloration are all the result of the melanin paint brush. Curiously, however, animals with dark fur usually have unpigmented skin and melanin synthesis occurs only in the melanocytes of the hair follicles. On the other hand, polar bears (Fig. 2) have black skin under their white fur. In this case, melanin probably serves as a thermoregulator. Himalayan albino rabbits have dark fur on their feet and ears. Their tyrosinase, the principal enzyme involved in melanin synthesis, is temperature-sensitive and active only in cooler regions of the epidermis. In amphibians, pigment bearing organelles in melanophores, analogous to melanocytes, aggregate to make the animal pale and disperse to make the animal dark. These responses are under hormonal control.

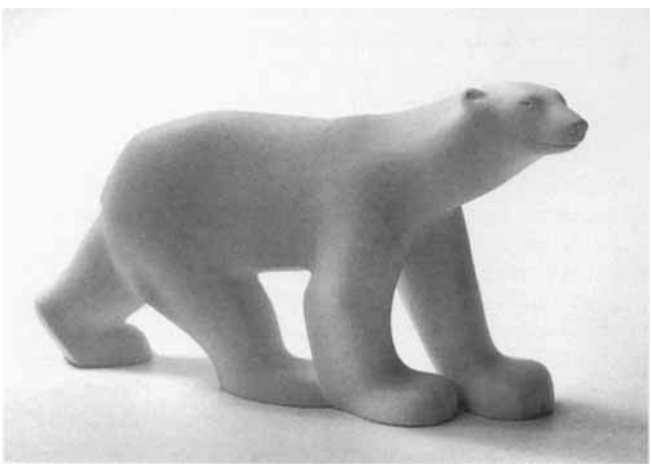

Fig. 2. Polar bears have white fur and black skin. This polar bear is a small version of the Metropolitan Museum of Art's replica of the marble polar bear by Francois Pompon (1855-1933).

In many animals, coloration patterns serve both as camouflage and mating cues. In plants, melanins and related pigments may be metabolic by-products. For example, some fruits such as apples turn brown when cut or wounded. The pigments produced are polyphenolic relatives of melanin. The lignins which impart woodiness to wood are very similar to melanins.

The leopard would be ill-advised to change his spots.

Second Blind Person: "I Know What Melanin Is! It Is a Sunscreen."

Photons from sunlight produce DNA damage in two ways: by direct interactions and by producing free radicals and active oxygen species mostly in water, the major chemical constituent of cells. These reactive oxygen species react in turn with DNA to produce so-called indirect effect type damage. Pyrimidine dimers are prototype direct effect DNA base damage. Strand breaks and oxidized bases such as glycols are indicative of indirect effect damages. Both direct and indirect types of DNA damage can be lethal, mutagenic and presumably carcinogenic. Figure 3 demonstrates the various types of interactions of photons with DNA[1].

Sunlight is a mixture of UV, visible and infrared wave lengths. UVC has the shortest wave length, the highest energy and is the most deleterious. It is also completely absorbed by the earth's atmosphere and does not penetrate to its surface. UVC causes mainly direct effect type damage in cellular DNA. UVB, on the other hand, does reach the surface in significant amounts and is thought to play a dominant role in skin cancer induction. It causes both direct and indirect effect type damage in DNA. The indirect effect damage is probably mediated through intracellular photosensitizers which are activated by their interactions with UVB photons. UVA, UV light of the longest wave length, has the lowest energy. It causes damage to cellular DNA exclusively through the indirect effects of photosensitizers. Visible light can also damage DNA in this manner.

Human skin pigment properties are divided into six solar response categories. Type I skin always burns and never tans. These individuals have blond or red hair and often have freckles. Type VI skin rarely burns (although all skin can sunburn, given enough exposure of sufficient intensity). These individuals have very dark skin. Solar reactions of skin are measured in MED (minimal erythema dose), by which is meant the time it takes, under standard conditions of noonday sun or sunlamp exposure, for skin to redden.

Many people assume that the MED is proportional to skin pigment type[2]. However, recent careful measurements using more objective and sophisticated techniques show that there is a better inverse correlation between skin type and the rate of production of erythema than there is a direct proportionality between

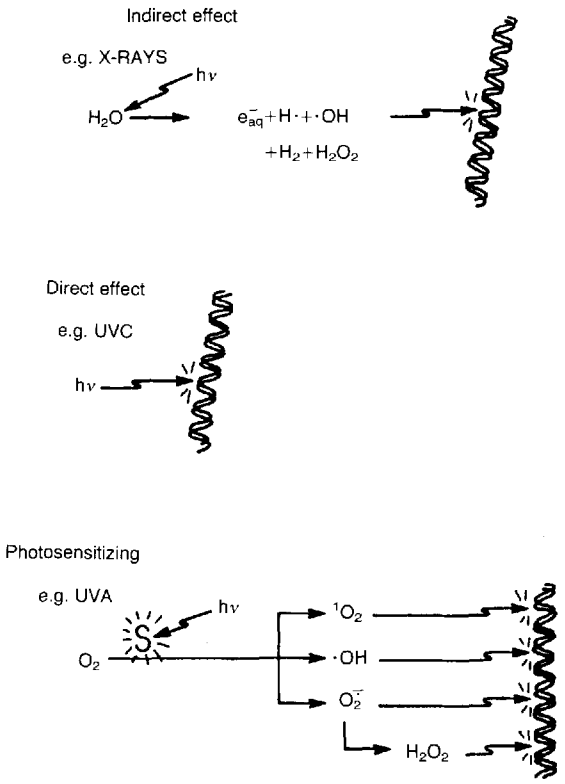

Fig. 3. Radiation damage to DNA. Indirect Effect: photons of low LET ionizing radiations interact with matter, mainly water in biological systems, to produce ionizations which ultimately result in the formation of free radicals, the most important of which is the hydroxyl radical. This, in turn, reacts with biological molecules to produce damage. The target for lethal, mutagenic and carcinogenic damage is almost certainly DNA. Direct effect: photons of UVC and UVB interact directly with biological molecules to produce damage. Photosensitizing: photons of UVB and UVA activate an intracellular photosensitizer such as flavin or a porphyrin which causes the formation of active oxygen species which can in turn react with target molecules such as DNA. Reproduced by permission of Telford Press[1].

skin type and MED[2]. This suggests that the protective role of skin pigmentation is not that of a sun screen because a sun screen would raise the threshold.

Cells in tissue culture that vary in melanin provide a simple model system to study the influence of the pigment on direct effect damage to UV. However, extrapolations to skin must be made with caution because cellular monolayers will have different light-absorbing and scattering properties than the multilayers of skin.

A sunscreen should protect cellular DNA from direct effect UV-induced damage in the same way that a venetian blind blocks sunlight from entering a window. Hill and Setlow found that intracellular melanin protected melanoma cell DNA from direct effect UVC damage, but not from similar damage induced by longer

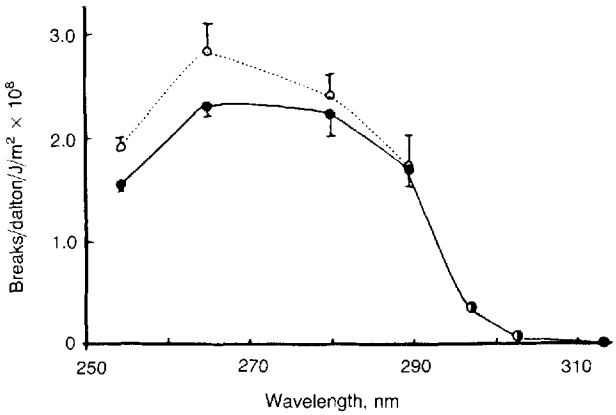

Fig. 4. DNA damage produced by UV irradiation is induced in non-melanotic carcinoma cells (open circles) and melanotic melanoma cells (closed circles) under conditions that preclude any DNA repair. At wavelengths below 290 nm there is less direct effect DNA damage (pyrimidine dimers - equivalent to the DNA strand breaks induced by UV-endonuclease, an enzyme that makes breaks at dimers) in melanotic cells, but above this wavelength, the damage is the same. Because of the ozone layer, UV light of wavelengths below 290 nm does not penetrate to the surface of the earth, thus the shielding by melanin as exemplified by these experiments may be irrelevant. Reproduced by permission of Pergamon Press[2].

wavelength UVB light[3]. Their findings are shown in Figure 4.

The findings of Hill and Setlow imply that melanin's sun screening efficiency is greatest at biologically irrelevant wave lengths. Niggli compared direct effect DNA damage in melanoma cells containing little pigment and in the same cells induced with cholera toxin to form large amounts of melanin[4]. In contrast to the results of Hill and Setlow, he found that the damage induced by UVC was the same, regardless of the amount of pigment in the cells. After UVB, the overall direct effect damage was much less than that induced by UVC - DNA absorbs UVB much less efficiently than UVC - but again, pigmentation appeared to have no effect in this case, in agreement with the earlier study. The discrepancy between the two UVC studies needs to be resolved. Different methods were used to analyze the DNA damage in the two studies. Hill and Setlow measured enzyme sensitive sites (see legend, Fig. 4) while Niggli degraded the DNA to bases and determined pyrimidine dimers directly.

UV light can produce crosslinks between DNA and its associated proteins. These lesions are caused by direct effect interactions with DNA by UVC, by indirect interactions of UVA and by both types of interactions by UVB[5]. Hill, Peak and Peak[6] found that intracellular melanin had no effect on UVC-induced (direct effect) DNA protein crosslinks.

So, if melanin is a sunscreen, it may not be very good one.

Third Blind Person: "I Know What Melanin Is! It Is a Radical Scavenger."

X- and gamma rays, both of which are low LET ionizing radiations, act mainly by causing water to ionize and form a complex array of radical species. These include hydroxyl radicals, aqueous electrons, hydrogen radicals, also small amounts of hydrogen peroxide and hydrogen gas. Hydroxyl radicals are the most reactive and damaging to cellular constituents. Superoxide anion radical is another important active oxygen species. It is an incidental by-product of cellular oxidizing reactions, especially respiration. In most cells, superoxide dismutase rapidly converts it to hydrogen peroxide which in turn is converted by catalase to water and oxygen. Superoxide anion radical and hydrogen peroxide produced in these reactions can interact with each other, especially in the presence of metal ions, to form hydroxyl radical.

Reactive species produced by UVB and UVA in cells are similar to those produced by ionizing radiations. However, some photosensitized interactions may produce singlet oxygen which can also damage cellular macromolecules[7].

Free radicals and active oxygen species interactions produce DNA strand breaks, base damage and DNA-protein crosslinks. They are also lethal, mutagenic and carcinogenic.

Synthetic melanins have properties that are similar in many ways to natural melanins. However, they are easier to study because some of them are soluble. Sarna et al.[8] examined the ability of synthetic melanins to scavenge radicals produced by ionizing radiation. Melanin scavenged hydroxyl radicals most efficiently. The rank order of scavenging was the same as the rank order of the rate of production by ionizing radiation of the various radicals. Other studies demonstrate that melanin can scavenge molecular oxygen as well as active oxygen species when it is exposed to UV light[9,10].

In aqueous solutions, melanins reduce the ionizing radiation-induced destruction of pyrimidine bases - the building blocks of DNA. They do this more efficiently than other macromolecules[11]. Melanin can also prevent the ionizing radiation-induced formation of thymine glycols in DNA[12]. This type of DNA damage is caused by active oxygen species. The protection of DNA by melanin is shown in Figure 5 (but melanin also damages DNA - see below).

In UVA-treated cells cellular melanin has been shown to quench the photosensitized reaction that produces DNA-protein crosslinks[6]. This is in contrast to its ineffectiveness as regards UVC-induction of such lesions in the same cells.

Skin contains reduced forms of the antioxidants thioredoxin and glutathione that can detoxify free radicals and active oxygen species. Enzymes that catalyze the detoxifications are thioredoxin reductase, glutathione peroxidase, superoxide dismutase and catalase. Resulting oxidized forms of thioredoxin and glutathione are reduced by their respective reductases. Schallreuter et al. found that levels of thioredoxin reductase correlated with skin pigment type, more enzyme being associated with darker skin[13]. In addition, ten patients with vitiligo - epidermal pigment loss - all had lower activities of this enzyme in their affected skin than in their normal skin. Based on their observations, Schallreuter and Wood proposed that melanin synthesis in human skin is inhibited by reduced thioredoxin. Exposure to sun causes the oxidized form to accumulate, resulting in activation of tyrosinase and melanin synthesis[14]. The actual protective agents in skin could be the antioxidants, while melanin synthesis reflects a response to stress.

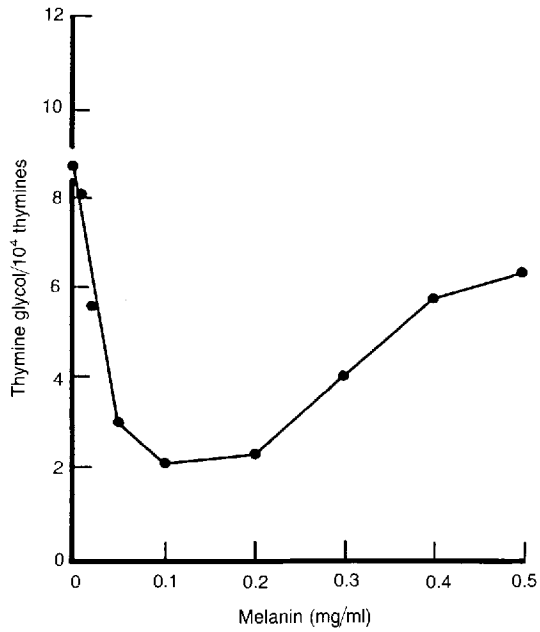

Fig. 5. Melanin is a two-edged sword. Oxidative base damage - thymine glycols - induced in calf thymus DNA by ionizing radiation is reduced by low concentrations of melanin. At high melanin concentrations, the pigment itself produces DNA damage[11]. DNA and melanin in aqueous solution were exposed to 200 gray equivalents of gamma-rays. Thymine glycols were quantitated in a competitive ELISA using an anti-thymine glycol antibody. Reproduced by permission of Academic Press.

Melanins can scavenge radicals and appear to do so *in vivo*.

Fourth Blind Person: "I Know What Melanin Is! It Is a Photo- and Radio-sensitizer."

To be sure, melanin can absorb free radicals and active oxygen species. But when it does so, free radicals and active oxygen species are also produced. Melanins are unique among biological molecules in that they continuously emit a free radical signal[15]. The free radicals associated with this signal are called "melanin-

free radicals". When melanins are irradiated with UV, or when melanins absorb superoxide anion radical, the melanin-free radical signal is enhanced and, depending on the conditions, superoxide anion radical, hydrogen peroxide and hydroxyl radical are produced[10]. Melanin-mediated radical production is potentially lethal to cells[16]. For this reason, phaeomelanin - the putative pigment in freckles - which is more photoreactive than eumelanin is believed to enhance solar-induced carcinogenesis in type I skin[17].

Active radical species appear to be associated with melanins even in the absence of any stimulation. When melanins are incubated with melanoma cells in tissue culture, single strand breaks in DNA are rapidly produced at melanin concentrations that are also lethal to the cells[18]. Synthetic melanin can also induce the formation of thymine glycols and strand breaks in DNA[12] (see Fig. 5).

Lethal species are produced by melanin in UVC-irradiated cells *in vivo*[19]. Melanotic melanoma cells accumulate thymine glycols in DNA at a rate that is greater than that seen in amelanotic melanoma cells of similar origin. Carcinoma cells lacking in melanin do not produce detectible glycols under similar conditions. Figure 6 shows the results of experiments that demonstrate this phenomenon. In our laboratory we find that both UVC and UVB are more lethal to melanotic melanoma cells than to related amelanotic melanoma cells, suggesting that intracellular melanin may play a biologically significant role in enhancing lethal damage in these cell lines[20].

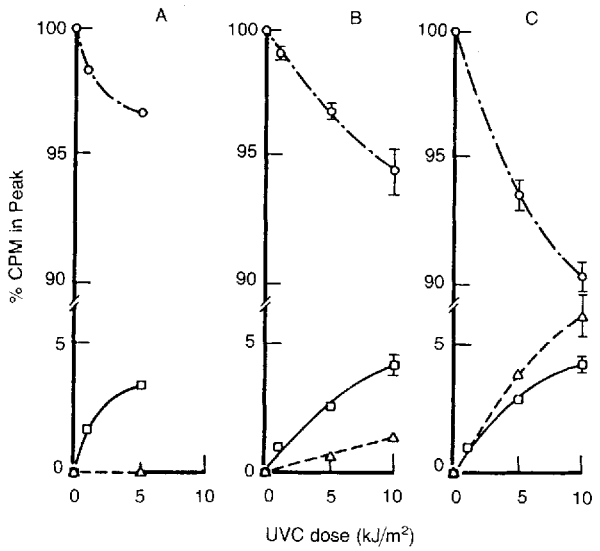

Fig. 6. In whole cells, oxidative DNA base damage - thymine glycols - is induced by UVC. None is seen in DNA of mammary carcinoma cells (A), a small amount is induced in hypomelanotic melanoma cells (B) and a large amount is induced in melanotic melanoma cells (C). Circles, thymine remaining in the DNA; squares, direct effect DNA base damage - thymine dimers; triangles, indirect effect DNA base damage - thymine glycols[18]. Reproduced by permission of Wiley-Liss, Inc.

Unrepaired double strand breaks in DNA that are caused by ionizing radiations are almost certainly lethal events. In our laboratory, under conditions that release melanin from melanosomes, we find that greater numbers of double strand breaks are induced by radiation in melanotic cells than in hypomelanotic cells. The induction of breaks is further reduced in mammary carcinoma cells that contain no melanin at all. These findings suggest that melanin is potentially a radiosensitizer[21].

Sometimes melanins may do more harm than good.

Fifth Blind Person: "I Know What Melanin Does! It Binds to Drugs."

Many chemicals and drugs are retained in tissues that contain melanin. Much of the binding can be attributed to electrostatic forces due to the strong negative charges of the carboxyl groups in melanin. This drug binding can be both beneficial and detrimental. Anaesthetics such as lidocaine bind to melanin in the ear and can be used to relieve tinnitus[22]. Ototoxicity and deafness are undesirable side effects of some drugs such as chloroquine and phenothiazines[23]. Such drugs can also affect the eye and the nervous system. A number of human melanomas are found at anatomic sites that are not exposed to sunlight. These could be caused by the accumulation of such carcinogens in melanin-containing cells[24].

Perhaps the most dramatic instance of melanin-drug interaction was observed in California several years ago. Two drug addicts developed symptoms of Parkinson's disease which were of such severity that they ultimately died. Autopsy confirmed the loss of pigment in the substantia nigra diagnostic of Parkinson's. The cause of the problem was traced to an impurity in the street heroin that the addicts had obtained. The substance was ultimately purified and demonstrated to bind to melanin[25]. The substance produces Parkinson-like symptoms in animals but only in those species that contain high levels of neuromelanin in the substantia nigra[26]. It also preferentially kills melanoma cells containing high levels of melanins[27]. There is some indication that the drug-neuromelanin complex produces active oxygen species and hydrogen peroxide[28].

Other drugs only bind to melanin as it is synthesized. These are called false melanin precursors[23]. Drugs that bind to melanin and false precursors can be used to target melanomas. One example of such targeting is found in ^{10}boronophenyl-alanine[29]. Once this drug has reached its optimum concentration in the tumor, the tumor is bombarded with thermal neutrons that cause the ^{10}boron to decay, producing charged particles which kill the tumor cells.

Drug-melanin interactions may be a two-edged sword.

Sixth Blind Person: "I Know What Melanin Does! It Transforms one Kind of Energy into Another."

Melanins can participate in electron transfer reactions[30]. They can transform light energy into electrical energy and into heat[31]. They can also store electrical energy and convert it slowly to heat. Melanins are said to act like amorphous semiconductors[32]. That is, absorbed light and electrical energy - activation energy - is quantized. Crystalline semiconductors absorb discreet quanta of energy. Amorphous semiconductors differ from this in that the energy of quanta absorbed by different domains of the molecule may be different and therefore cannot be evaluated.

Semiconductors have the property that the conductivity increases as the temperature increases, in contrast to metals in which conductivity decreases with increasing temperature. The conductivity of melanins, like that of semiconductors, increases with temperature[33]. Melanins are dielectric materials and can be polarized. Their relaxation times are slow, a characteristic of amorphous semiconductors[34].

Melanins are important in the inner ear[35]. Albinos frequently suffer from hearing loss and experiments have shown that the extent of induced temporary hearing loss is inversely related to skin pigment type[36]. Melanins may convert acoustic energy into heat[37].

Is melanin a biological solenoid?

The Blind People Compare Notes

Blind person Number 1 thinks the major role of melanin is camouflage and sex appeal. Number 2 concludes that melanin is not a very good sunscreen and blind person Number 3 concludes that it is not even a very good radical scavenger. Blind person Number 4 thinks that melanin can produce free radicals and damage cellular macromolecules including DNA, while blind person Number 5 believes that the function of melanin is to detoxify xenobiotics. Blind person Number 6 feels that the answer lies in energy transductions.

The Elephant Speaks

The key to understanding melanin can be found in a series of papers based on physico-chemical studies of melanin and the associations of disease states with melanization[38-42]. The picture that emerges more closely resembles the observations of blind person Number 6, but unites those of all but Number 1.

Melanin can transform different types of energy into heat and by this means dissipate them. Blind persons 1 and 2 are correct in their observations regarding screens and radicals. Melanin can absorb photons, electrons, noise, free radicals and active oxygen species. But melanin can be overwhelmed. When this occurs, free radicals and active oxygen species are produced. Melanin has the capacity to act as a pseudo-superoxide dismutase and can convert superoxide anion radical to hydrogen peroxide. But melanin also binds metals. It

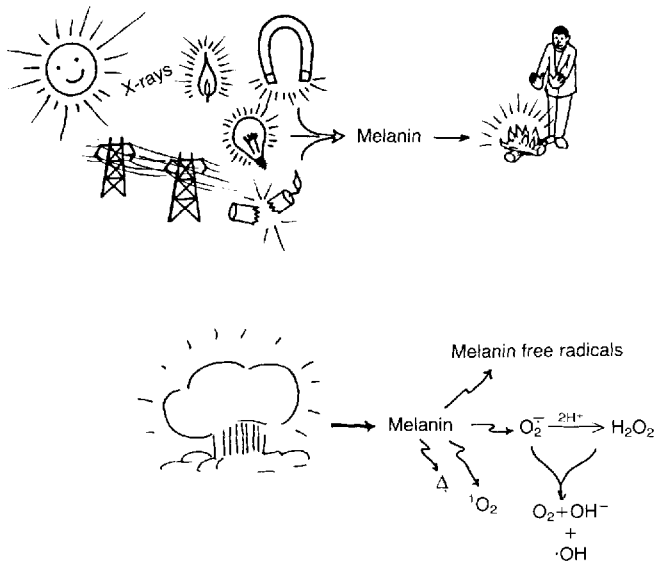

Fig. 7. Many different forms of energy are absorbed by melanin and dissipated as heat. If the energy input is too great, the capacity of the pigment to detoxify the radicals is exceeded and potentially damaging radical species - hydroxyl radicals (·OH) - are produced.

now becomes a generator of hydroxyl radical, the most evil of the active oxygen species. These concepts are depicted in Figure 7.

Blind person Number 1 is also correct. Melanin provides camouflage and sex appeal.

The Blind People Query: "Why Is It That Dark-skinned Individuals Don't Get Skin Cancer and Light-skinned Individuals Do?"

Melanosomes tend to aggregate around the cell's nucleus. However, in the first place, there is a lot more melanin in dark skin so there is more of it to absorb and convert photon- and solar-generated free radical energy into heat. In the second place, melanosomes in dark and light skin are different. Dark skin melanosomes are ellipsoidal, single and densely melanotic. Their shape allows them to overlap to form a solid light-absorbing and scattering screen. Radicals generated within them would be self-absorbed. Caucasian melanosomes are round, aggregated and lightly melanotic. They form a poor screen and radicals can easily escape (see Fig. 8)[1]. In the third place, the coupling of constitutive skin pigmentation to radical modulating systems may further protect dark skin from sun damage. Solar-induced melanin synthesis, now thought by many to be a wounding response, may enhance the intracellular generation of free radicals and provide little additional protection. This would have little impact in dark skin but could actually contribute to skin cancer induction in light skin. For melanoma, there is epidemiological evidence that short, intense exposure to sunlight at an

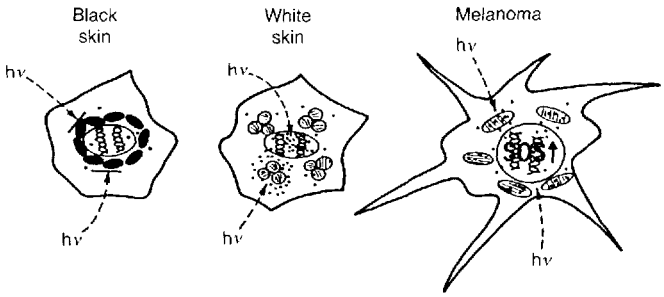

Fig. 8. In black skin, melanosomes are oval, single, densely packed with melanin and clustered around the nucleus. Incoming photons are blocked from the nucleus and free radicals are absorbed. In white skin, melanosomes are round, aggregated and lightly melanotic. Incoming photons can bypass the clusters to enter the nucleus and free radicals that impinge on melanin in melanosomes can be re-emitted. In melanoma, the constant slow bombardment of the nucleus with free radicals from melanin induces DNA repair functions (SOS). Enhanced repair results in less effective response to ionizing radiation as in radiation therapy. Reproduced by permission of Telford Press[1].

early age is a strong risk factor. This is consistent with the hypothesis that melanin can be overwhelmed and enhance the yield of free radicals.

"Why Are Melanomas Resistant to Radiation Therapy?"

Direct scavenging of radiation-induced radical species seems unlikely. However, melanin is constantly producing melanin-free radicals and other active radical species. Enhancement of radical modulating systems and of DNA repair capacity could render some melanomas radioresistant. There is evidence for enhancement of post-replication repair in melanomas[43] (see Fig. 8). Melanin in tumors is rarely quantitated but is anecdotally reported to be heterogeneous. So also is radiation response heterogeneous[44]. Some melanoma cells in vitro and in nude mice have been shown to be very radiosensitive, while others are very radioresistant. If melanization and radiation response were correlated, this could have some predictive value. Radiation therapy is used infrequently in the treatment of melanoma. In some cases, it could be beneficial.

"Why is There Such Variation in Human Skin Pigmentation?"

This bears on a theory of pigment loss in nordic peoples. The theory states that in colder climates, the deleterious effects of melanin outweigh the beneficial effects. People with dark skin would be less fit, being more prone to debilitating skin ailments[45]. This hypothesis relies in part on frost bite studies from the Korean and earlier wars. These are open to criticisms based on the possible differential treatment of soldiers according to race. But animal studies - cold treatment of black and white areas of guinea pig skin - demonstrate a greater sensitivity of the dark skin.

Other theories do not stand up well to criticism. These include: 1) the skin cancer hypothesis, that dark skin has a selective advantage in areas with high sunlight because it protects against skin cancer - but this cancer does not appear until after reproductive age; 2) the greater susceptibility to sunburn of light skinned people makes them less fit for the chase in areas with high sunlight; 3) the vitamin D hypothesis - that dark skin in low sunlight environments prevents activation of vitamin D precursors in the skin - but racial pigmentation does not interfere with normal production of active forms of vitamin D[46].

There is good reason to retain dark skin for its solar protection and heat modulating properties. The selective advantage of the loss of pigment in northern climates is not at all clear. Given the exotic properties of melanin it seems unlikely that its loss occurred by chance....Eskimos do not have light colored skin.

The species *Homo sapiens* is believed to be descended from a small group or tribe that originated in Africa or western Asia. The members of the founding group presumably had uniform pigmentation, possibly intermediate between the extremes known today. The present diversity must have arisen as a result of selective pressures imposed as the species multiplied and radiated away from its site of origin. The present locations of people may be unrelated to their sites of origin. Synthesis and retention of functions that are not needed are energetically costly for cells and organisms. During evolution, camouflage, light absorption and scattering, energy modulation and heat retention must all have been balanced against the cost and benefit of retaining a complex organelle system that requires the synthesis of an energetic and radical-generating pigment.

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