Melanin

Melanocyte Biology

Jean L. Bolognia MD, in Dermatology, 2018

Regulation of Melanin Biosynthesis

This section will begin with a review of the melanin biosynthetic pathway and then examine the factors, both external and internal, that can influence the level of melanin production. The "starting material" for the production of melanin, both the brown–black eumelanin and the yellow–red pheomelanin, is the amino acid tyrosine. The key regulatory enzyme in the pathway is tyrosinase, which controls the initial biochemical reactions in this pathway (Fig. 65.11). It should then come as no surprise that the initial investigations into the molecular basis of OCA focused on the gene that encodes tyrosinase.

In OCA1A, the form of OCA where mutations in both copies of the tyrosinase gene lead to complete loss of enzyme activity, no melanin is found in the hair, skin, or eyes (seeTable 65.1). However, in OCA1B, where there is decreased enzyme activity, pheomelanin is produced, especially in the hair as the patient ages. The formation of pheomelanin requires less tyrosinase activity than does the formation of eumelanin (seeFig. 65.11) and therefore the formation of pheomelanin can be thought of as a default pathway.

The activity of tyrosinase is enhanced by DOPA and is stabilized by tyrosinase-related protein 1 (TYRP1) (see below). Competitive inhibitors of tyrosinase activity include hydroquinone, which is used to treat disorders of hyperpigmentation such as melasma, and L-phenylalanine. In patients with phenylketonuria (PKU), there is a diffuse pigmentary dilution due to elevated levels of L-phenylalanine resulting from a deficiency in the enzyme L-phenylalanine hydroxylase that converts L-phenylalanine to L-tyrosine[15]. The characteristic blonde hair of PKU can undergo darkening when the patient is on a low-phenylalanine diet. Of note, tyrosinase is a copper-requiring enzyme and it has two copper-binding sites. Rare cases of copper deficiency can lead to diffuse cutaneous pigmentary dilution, and in patients with Menkes disease, where a transmembrane Cu^{2+}-transporting ATPase that delivers copper to the trans-Golgi network and melanosomes is dysfunctional[29], the kinky hair is hypopigmented.

In a test tube, L-DOPA can spontaneously oxidize to form melanin, an insoluble biopolymer. For this reason, it was originally thought that tyrosinase was the sole enzyme involved in melanin biosynthesis. However, by the late 1970s, it was becoming clear that there were additional control points in the pathway (seeFig. 65.11). For example, dopachrome tautomerase, also known as tyrosinase-related protein 2 (TYRP2), which like TYRP1 shares

similarities in its amino acid sequence with tyrosinase, converts DOPAchrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA). In mice and humans, TYRP1 stabilizes tyrosinase[30] and mutations in both copies of*TYRP1* lead to OCA3 (seeTable 65.1).

Decreased function of yet another transmembrane protein, the P protein, leads to OCA2[31] (Fig. 65.12). Based upon its amino acid sequence, a prediction was made that the P protein was involved in the transport of small molecules across the membrane of the melanosome. Tyrosine, the initial precursor in the melanin biosynthetic pathway, was considered the most likely candidate for transmembrane transport. However, the nature of what might be transported by the P protein remains unclear. Data suggest that the P protein regulates processing and trafficking of tyrosinase, possibly via control of pH or glutathione content within intracellular compartments[32].

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M. Naoi, ... P. Riederer, in Encyclopedia of Movement Disorders, 2010

Characteristics of Melanin and Neuromelanin (NM) – Similarity and Dissimilarity

Melanin is a black pigment synthesized nonenzymatically or enzymatically from dopamine, l-DOPA and l-tyrosine. Melanin-containing cells, including catecholaminergic (CA) cells in the brain and melanocytes of the hair and skin, pigment cells in the inner ear, iris, and choroid of the eye, originate from the neural crest. However, the synthesis pathway, chemical structure, and function of melanin are quite different in the neural versus peripheral cells. In adult CA neurons of the substantia nigra (SN), locus coeruleus (LC), and additional brain stem loci, NM is produced in the cytoplasm mainly by autooxidation of dopamine. However, enzymatic synthesis of NM by tyrosine hydroxylase, peroxidase, prostaglandin H synthase, and macrophage migration inhibitory factor has also been proposed. In melanocytes, tyrosinase synthesizes l-DOPA and then DOPA-quinone from l-tyrosine in melanosomes. Tyrosinase mRNA and promotor activity are detected in the SN, but the tyrosinase-dependent synthesis does not occur in human brain, even though it does occur in the retinal pigmented epithelium.

NM isolated from the human SN is present in a large, aggregated structure, composed of three major components, melanin, protein, and lipid, with different electron density. Melanin polymer has the highest density and the protein component shows intermediate density, whereas the third lipid component is translucent. Melanin component is a mixture of melanin classes, black–brown ‘eumelanin’ and yellow–red ‘pheomelanin’ in a ratio of 4~3 to 1. Eumelanin is composed of indole derivatives produced by autooxidation of dopamine, whereas pheomelanin contains benzothiazine molecules from incorporated cysteine or GSH with dopamine–quinone derived from dopamine by autooxidation. The protein components are covalently bound to NM, make up 5–15% of the isolated molecule, and include mostly lysosomal proteins, in addition to mitochondria-, cytosol-, and endoplasmic reticulum-

associated protein, as detected by subcellular proteomics. The protein components are derived from a reaction of melanin polymer and proteins, or dopamine (quinone) bound to cysteinyl residue of peptide chains. The lipid components account for up to 20% of the mass and are identified to be 1% cholesterol and 14% poly-isoprenoid dolichol. The lipid component is adsorbed to NM, not integrated in the structure. It was proposed that NM granules originate from lipofuscin, a lipid-containing pigment, but this hypothesis is now challenged by the fact that lipofuscin is localized in the lysosomes and produced also in glia and distributed ubiquitously in the brain.

The higher structure of the NM molecule is a multilayer three-dimensional structure similar to synthetic and naturally occurring melanin, as shown by X-ray diffraction studies. More recently, atomic force microscopy has revealed a spherical structure of NM granules with a diameter of ~30 nm. The spherical structure of NM is composed of a pheomelanin core with a higher oxidation potential and a less redox-reactive eumelanin surface. However, this model cannot explain the occurrence of free sulfhydryl (SH) residues on the NM surface.

NM binds iron most strongly, and zinc, copper, manganese, chromium, cobalt, mercury, lead, and cadmium for 1.5% of the mass, and other 2–5% is due to sodium, potassium calcium and other inorganic compounds. Iron binds to NM at two distinct sites, the catechol groups forming metal centers in a lattice and the small-sized iron–oxygen frameworks in an insoluble NM matrix. In dopamine neurons of the SN, iron binds mainly to NM and accounts for 10–20% of the total iron, and the remainder is stored in microglia as bound to ferritin.

Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii)

John E. Bennett MD, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 2020

The production of melanin is observed in many fungi, including some pathogenic species.[43] *C. neoformans* possesses a laccase, an enzyme that catalyzes the conversion of diphenolic compounds such asl-3,4-dihydroxyphenylalanine (DOPA), norepinephrine, epinephrine, and other related aromatic compounds to quinones, which rapidly autopolymerize to form melanin. The production of this pigment can help identify the yeast in the laboratory, but it is also a major virulence factor for the yeast. Laccase is bound to the inner aspect of the yeast's cytoplasmic membrane, and a site-directed mutant for the gene encoding for it has been created. This laccase-negative or albino mutant has been attenuated for virulence in animal models.[161]

One proposed mechanism by which melanin may protect the yeast is through its ability to act as an antioxidant, and it has been shown that yeast cells without the ability to form melanin are more susceptible to oxidative stress. Other potential mechanisms by which melanin protects the yeast from host damage involve the following: (1) cell wall support or integrity, (2) alteration in cell wall charge, (3) interference with T-cell response, (4) abrogation of antibody-mediated phagocytosis, and (5) protection from temperature changes and antifungal agents.

It remains unclear whether the catecholamine-rich CNS, with its excellent substrates for melanin formation, provides some tissue tropism or a rich environment that enhances this yeast's ability to produce disease. For instance, it has clearly been shown that melanin is formed in yeast cells within the brain.[162,163]

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Functions of Fungal Melanins

Daniel P. Agustinho, Joshua D. Nosanchuk, in Reference Module in Life Sciences, 2017

Abstract

Melanins are elusive pigments produced by a remarkably wide range of organisms, including fungi. Melanins play an important role in the protection against environmental stresses, and in pathogenic fungi, melanins have pleotropic beneficial effects, ranging from protecting fungal cells against environmental oxidative stresses to manifesting as important virulence factors during mammalian infections. However, the biochemical structure and the dynamics of melanin in the fungal cell wall remain enigmatic. Nevertheless, our current knowledge of fungal melanin has led to critically important insights into the pathogenesis of fungal infections and facilitated the development of novel therapies. This article details our current understanding of key functions of melanin in fungi.

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Lasers and Other Energy-Based Therapies

Jean L. Bolognia MD, in Dermatology, 2018

Treatment of Melanin-Containing Lesions

Ephelides and Lentigines

Since melanin has a broad absorption spectrum (seeFig. 136.3), many lasers can be used to treat melanin-containing lesions. At the lower end of the therapeutic window, the penetration of green lasers is limited to the superficial papillary dermis. These lasers are best

utilized for epidermal pigmented lesions. Thus, the frequency-doubled Nd:YAG (532 nm), either Q-switched or normal mode, effectively treats lentigines and ephelides in most skin types with limited recurrence[36]. Of note, in patients with a history of systemic gold therapy, Q-switched lasers can induce darkening of these pigmented lesions. Additional lasers, e.g. the 800 nm diode, as well as IPL can also be used to treat epidermal pigmented lesions (Table 137.3). While the PDL is most commonly used for vascular lesions, 595 nm light is also well absorbed by melanin and can be used to treat pigmented lesions. By incorporating compression, the vascular component of the skin is blanched out and melanin-containing lesions can be targeted. Newer PDL systems have incorporated such a "compression handpiece".

In general, the Q-switched ruby and alexandrite lasers are more effective when treating more deeply situated pigmented lesions (e.g. nevus of Ota), as these wavelengths have an increased depth of penetration. Q-switched ruby (694 nm) laser light is better absorbed by melanin than is alexandrite (755 nm) laser light, which might be an advantage in lighter-skinned individuals, but problematic in darker-skinned patients, given the increased likelihood of nonspecific heating of normal epidermal melanin. Q-switched Nd:YAG laser light is much less well absorbed by melanin, but reaches deeply into the skin; therefore, it is primarily used to treat dermal pigmented lesions.

For the treatment of lentigines, ephelides, and café-au-lait macules as well as nevus of Ota, understanding these profiles allows one to choose the optimal device. The clinical response of pigmented lesions to Q-switched lasers is determined by where the pigment is localized (epidermal, dermal or mixed) and whether it is intracellular or extracellular, as well as the composition of the pigment (usually melanin)[37].

Benign Melanocytic Nevi

Laser removal of acquired and congenital nevi is controversial since no specimen is submitted for tissue diagnosis and margin assessment. Furthermore, the future biologic behavior of laser-resistant cells and the effect (if any) of laser thermal injury on these cells is unknown. Since the clinical standard of care is excision for any atypical pigmented lesion, laser treatment of melanocytic lesions should only be considered for clinically banal lesions in patients with no personal or family history of melanoma.

Both acquired and congenital melanocytic nevi have been treated with Q-switched ruby, alexandrite, and Nd:YAG lasers[38]. The 694 and 755 nm devices can improve the appearance of acquired junctional melanocytic nevi without scarring[39]. In general, smaller and thinner lesions are typically more treatment-sensitive. While congenital nevi can be lightened, complete eradication is much more difficult and recurrence is common. Laser therapy decreases the number of pigmented nevus cells in the papillary dermis, but is unlikely to affect deeper seated, non-pigmented cells that are closely associated with adnexal structures.

This has been demonstrated histologically as persistent nests of nevus cells in the mid papillary and deeper dermis at depths of 0.16–0.44 mm. Deeper components of these nevi located within muscle or under fascia will also remain unaffected by laser surgery.

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Metabolism of Amino Acids

Gerald Litwack Ph.D., in Human Biochemistry, 2018

Melanin is derived from tyrosine, and more directly from **DOPA**. Melanin is a family of pigments having different colors. In this case, DOPA is the product of the enzyme, tyrosinase (**diphenol oxidase**). Differently from tyrosine hydroxylase, tyrosinase, a copper enzyme, uses molecular oxygen directly [without tetrahydrobiopterin (BH4)] as is the case with tyrosine hydroxylase) to form DOPA from tyrosine. The synthesis of melanin occurs in the melanocyte, and the reactions starting with tyrosine are shown in Fig. 13.25.

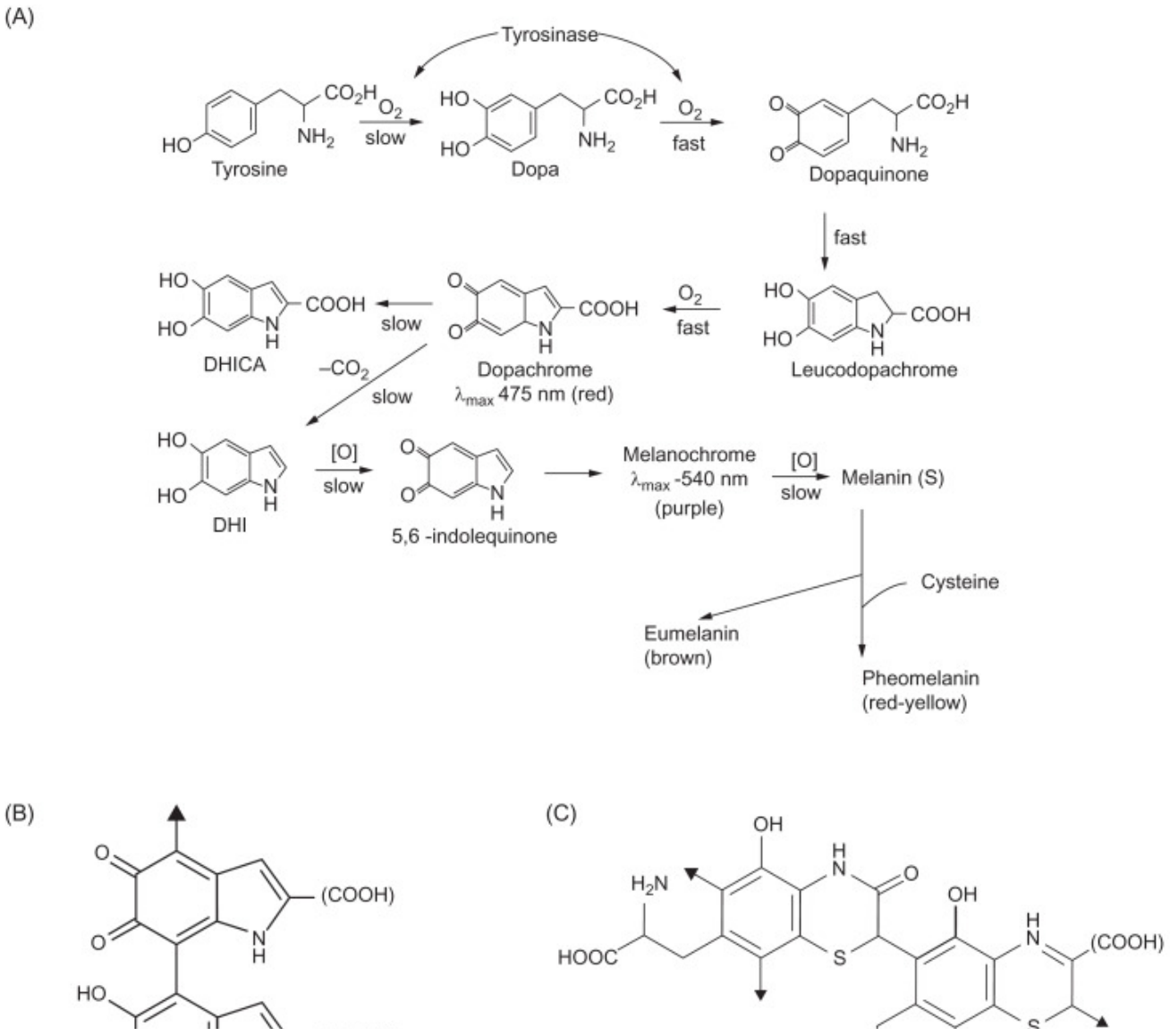

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Figure 13.25. Synthesis of melanin from tyrosine. *DHI*, dihydroxyindole; *DHICA*, dihydroxyindole catecholamine. In the presence of cysteine another pigment called **pheomelanin** can be formed that has a *red-yellow* color compared to **eumelanin** that has a *brown* color. Melanins are the pigments that produce the color of the eye. The arrows at the top of the structures of eumelanin and pheomelanin indicate the point at which polymerization can occur.

After the formation of **DOPA** from tyrosine, the further conversion of DOPA to **DOPAquinone** follows. Then, a number of intermediates are formed ending in **indolequinone** that polymerizes to form **melanin**. The more common product is **eumelanin** (*brown*) but in the presence of cysteine, **pheomelanin** can be formed (*red* to *yellow*). Melanin is formed primarily in the **melanocyte**, located in the inner layers of the skin where melanin and carotene blend to produce the skin color as well as the color in the eyes and hair. Red hair is produced by pheomelanin in spherical melanosomes (melanin granules). Black-colored melanin is formed in oblong melanosomes. Melanin granules are distributed uniformly in the skin cell in order to absorb UV rays from the sun and protect, at least partially, from injurious rays.

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Spectral Imaging in Dermatology

D. Ho, ... R.M. Levenson, in Imaging in Dermatology, 2016

Melanin is obviously a prominent skin constituent, and is associated (perhaps causally) in melanomagenesis [60]. Unfortunately, at least for imaging scientists, melanin proves to be not autofluorescent (or only very weakly autofluorescent) when excited in the visible range, although it is apparently possible to induce bright yellow autofluorescence of melanin by combining exposure to peroxide compounds with UV irradiation [61]. Native melanin autofluorescence, however, can be generated using femtosecond-pulse excitation or single-photon NIR illumination [62,63]. It is thought that melanin autofluorescence may be induced by stepwise two-photon excitation, which allows for a brief interval in the arrival of the two photons, as opposed to the requirement for near-simultaneous cooccurrence that

seems necessary for exciting other cellular fluorophores. Under conditions of nanosecond irradiation, with a relatively lower total photon flux, melanin autofluorescence becomes more readily detectable and, intriguingly, the peak melanin emission from malignant melanomas differs from that of benign nevi, possibly reflecting alterations in the pheomelanin and eumelanin contributions [64]. Similar findings using pump-probe imaging for enhancement of the spectral signal to segment melanin distribution have been reported (see Pump-Probe Microscopy section, below).

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Design and Evaluation of Ophthalmic Delivery Formulations

Vandana Soni, ... Rakesh K. Tekade, in Basic Fundamentals of Drug Delivery, 2019

13.10.6 Melanin Binding

Ocular melanin is found in the retina and influences the ocular BA of the topically applied drug. Drug binding to melanin affects drug response, toxicity, and duration of activity, which may be due to its distribution and retention in pigmented ocular tissues. Melanin binds to the drugs by electrostatic and van der Waals forces or by simple charge transfers (Rimpelä et al., 2016). Melanin binding in the iris–ciliary body influences the drug concentrations in anterior ocular tissues as well as drug response. Melanin binding may significantly lower the pharmacological activity. Drugs similar to ephedrine and timolol bind to the melanin with an intense binding efficiency. Melanin loaded drugs are not available for receptor and for absorption, hence require large dosage for action (Gaudana et al., 2010). Melanin also absorbs the excess radiation via facilitating the transmittance of visible light to the retina. It also serves as a photoprotector by quenching reactive oxygen species, as well as other radicals, created as a result of the elevate oxygen dependency of the retina for its metabolism (Rozanowska et al., 2009). Melanin additionally can bind various pharmaceuticals that can produce ocular toxicity.

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Mechanisms and Morphology of Cellular Injury, Adaptation, and Death1

Margaret A. Miller, James F. Zachary, in Pathologic Basis of Veterinary Disease (Sixth Edition), 2017

Melanin.

Melanin is the pigment responsible for the color of the hair, skin, and iris. It also colors the leptomeninges in black-faced sheep (Fig. 1-44) and cattle and may be present multifocally in oral mucosa in various species. Localized deposits of melanin (melanosis) are common in the

aortic intima in ruminants with pigmented coats and in the lungs (Fig. 1-45) of red or black pigs. The localized deposits in congenital melanosis are merely a color change and not a lesion because they are not a response to injury and have no ill effect on the animal.

The melanocytes that synthesize and secrete melanin are derived from the neural crest and migrate to the site of pigment production during embryonic development of the structure. In the skin, melanocytes reside in the stratum basale of the epidermis and follicular epithelium. Melanin is formed in organelles called melanosomes, then transferred through dendritic cell processes to adjacent keratinocytes. In the keratinocyte, melanin granules are mainly in the apical cytoplasm, where they may shield the nucleus from ultraviolet light. Histologically, melanin granules are small (usually less than 1 μm in diameter), brown, and nonrefractile.

Melanin pigment can be diminished or excessive in disease. The first step in melanin synthesis is the conversion of tyrosine to dihydroxyphenylalanine (DOPA), catalyzed by the copper-containing enzyme, tyrosinase. Thus a lack of tyrosinase results in albinism (lack of melanin pigmentation), and sheep and cattle with copper deficiency have defective tyrosinase and fading of coat color. Partial albinism in Chédiak-Higashi syndrome (CHS) (recognized in people, mink, Persian cats, mice, and other species) is caused by a mutation of the *LYST* gene that codes for a lysosomal trafficking regulator protein. The mutation causes abnormal lysosomal structure and function in leukocytes and in melanocytes. The melanocytes of animals with CHS have enlarged melanosomes, but the melanin pigment is not transferred effectively to keratinocytes, so coat color is a pastel shade of what it should have been. Normally pigmented skin and hair can also become depigmented because of an immune-mediated attack on melanocytes (vitiligo) or basilar keratinocytes (see Chapter 17). The dead keratinocytes spill their melanin into adjacent dermis in a process called pigmentary incontinence, where it is phagocytized by macrophages (melanophages).

The term hyperpigmentation implies excessive melanin. This finding can be a common epidermal response to chronic injury and appears as darkened skin. Endocrine skin disease, especially hyperadrenocorticism, is often associated with hyperpigmentation. Histologically, melanin granules are numerous, not only in the basilar keratinocytes, but in all layers of the epidermis, even the stratum corneum. Neoplasms of melanocytes can be darkly pigmented or not pigmented at all (amelanotic) (see Chapters 6 and 17).

Macroenvironment-gene-microenvironment interactions in ultraviolet radiation-induced melanomagenesis

Xuan Mo, ... M. Raza Zaidi, in Advances in Cancer Research, 2019

5 UVR-induced “dark CPD”

Melanin pigment is important for protecting the skin from UVR exposure. However, it is becoming clear that it is an imperfect process as more reports show a role for melanin in mutagenesis (Noonan et al., 2012; Premi et al., 2015). Premi et al. have shown that in addition to 8OH-G adduct formation, UVR-mediated chemiexcitation of melanin derivatives can also lead to the formation of "dark CPDs" in an unusual biochemical pathway that remains active long after UVR exposure ceases (Premi et al., 2015). This is in contrast with CPDs formed within 1 ps by direct UVR absorption, which does not require melanin (Schreier et al., 2007). Upon UVR exposure by either UVB or UVA wavebands, there is an increase in the superoxide radical ion $O_2^{\cdot -}$. The $O_2^{\cdot -}$ is generated directly from melanin during irradiation as well as from enzymatic activity of NOX [reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase], which provides a longer-lasting source (Chedekel et al., 1978; Takeuchi et al., 2004). The reaction of $O_2^{\cdot -}$ with iNOS-generated nitric oxide (NO  radical dot) produces peroxynitrite (ONOO  single bond) (Koppenol, Moreno, Pryor, Ischiropoulos, & Beckman, 1992). Both NOX and iNOS are rapidly induced by UVR exposure (Romero-Graillet et al., 1996). Peroxynitrite is stable enough to diffuse within the cell so that it can react with melanin monomers to form a dioxetane intermediate. Dioxetane is a strained four-member ring peroxide that undergoes spontaneous thermolysis to two carbonyls, one of which is in an electronically excited triplet state that contains the high energy of a UV photon. CPDs are generated from dioxetane thermolysis by energy transfer of the excited triplet state directly to the DNA (Lamola, 1971). The dark CPD reaction generates more CT and TC CPDs after UVA exposure similar to UVB exposure (Premi et al., 2015). Both eumelanin (black pigment) and pheomelanin (red pigment) can participate in this reaction, with pheomelanin-containing melanocytes accumulating double the amount of CPDs compared to eumelanin-containing melanocytes (Premi et al., 2015). Redheads, individuals with higher pheomelanin content, are at greater susceptibility to melanoma not only because pheomelanin is a poor shield against UVR but perhaps that it also generates more "dark CPDs." Currently, it is unclear how melanin would enter the nucleus after UVR exposure. Melanin monomers are found in the cytoplasm in perinuclear vesicles before being transported into melanosomes (Orlow, 1995; Seiji, Fitzpatrick, Birbeck, & Shimao, 1963). These monomers are lipophilic and would have the ability to cross the nuclear membrane. Additionally, melanin polymers are rapidly degraded by exposure to hydrogen peroxide and UVR, which is thought to also form a dioxetane and subsequent triplet carbonyls so that both melanin and melanin monomers can acquire the necessary excited-triplet state to form CPDs (Slawinska & Slawinski, 1982; Wakamatsu, Nakanishi, Miyazaki, Kolbe, & Ito, 2012). The monomers or degraded products may be released from UVR-damaged melanosome and vesicles and can migrate to the nucleus where the accumulation of melanin-aggregate-like vesicles are found after exposure to UVA (Premi et al., 2015). This has implications for skin cancer in general since dark CPDs are also found in keratinocytes, which receive melanin through melanosomes. So, it is not the synthesis of melanin but its presence that is required for dark CPD formation. Consequently, there is an emerging dual-role for melanin in tumorigenesis as it may also have mutagenic effects, considering that more than half of the CPDs formed are through this melanin-dependent dark CPD pathway (Premi et al., 2015).

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