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Role of Ocular Melanin in Ophthalmic Physiology and Pathology

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ABSTRACT The mammalian eye consists of several layers of pigmented tissues that contain melanin. The eye is a unique organ for pigment cell research because one can isolate and compare melanosomes from different tissues and embryonic origins. Retinal, iris and ciliary pigment epithelial cells are derived from the neural ectoderm, more specifically from the extremity of the embryonic optical cup, which is also the origin of the retina. In contrast, the pigment-generating cells in the choroid and in the stroma of the iris and ciliary body, uveal melanocytes, are developed from the neural crest, the same origin as the melanocytes in skin and hair. This review examines the potential functions of ocular melanin in the human eye. Following a discussion of the role of melanins in the pigment epithelium and uveal melanocytes, three specific topics are explored in detail-photo-screening protective effects, biophysical and biochemical protective effects, and the biologic and photobiologic effects of the two main classes of melanins (generally found as mixtures in ocular melanosomes)- eumelanin and pheomelanin.

INTRODUCTION

The wall of the human eye consists of three layers, the transparent cornea and opaque white sciera, the uveal tract and the retina (1). The uveal tract, a highly vascularized connective tissue, is further composed of three parts, from anterior to posterior-the iris, the ciliary body and the choroid. The choroid supports and nourishes the retina, which is located on the inner side of the choroid. The retina further consists of two layers-the retinal pigment epithelium (RPE) and the neural retina. The neural retina contains photoreceptor cells, which are involved in the primary processes of visual transduction, and other neurons, which encode and transfer the visual information to the brain. The RPE (derived from the neuroectoderm), a monolayer of postmitotic pigment cells that lies between the uveal tract and the neural retina, is

responsible for important metabolic support for the entire retina and is involved in phagocytosis of the photoreceptor outer segment disks, which are constantly being shed (2). The RPE extends to and is contiguous with the iris pigment epithelium (IPE) and ciliary pigment epithelium. A sagittal horizontal section of the adult human eye is shown in Fig. 1.

Melanin is found in several of these tissues. Pigmented cells are of two different types-the uveal melanocytes located in the uveal tract, and the pigment epithelial cells (1-4). The uveal melanocytes in the uveal tract are derived from the neural crest and can be divided into iridal, ciliary and choroidal melanocytes (1-4). Melanocytes in the iris and ciliary body are located in the stroma. Melanin is also found in all three of the pigment epithelium cell types, of which the RPE is the most studied.

The function of melanin in these various tissues is not fully elucidated. Melanin tends to protect the eye against several ocular diseases that can cause blindness, including uveal melanoma and age- related macular degeneration (AMD) (4-6). However, the exact mechanism by which melanin protects the eye, whether the protective function depends on the type of the melanin, and whether the melanin- related protection changes with age, remains mostly unknown. This article examines the current hypotheses for the role melanin plays in the physiology and pathology of the eye. Because many of these hypothesized roles are linked to its interaction with light, we first summarize the accessibility and exposure of ocular different pigment cells to sunlight and UV radiation (7).

Environmental light impinging on the eye consists of the visible and UV regions of the electromagnetic spectrum. The UV region is further subdivided into UVA, UVB and UVC. According to the International Commission on Illumination, the wavelength ranges of the regions in the UV are-UVC: 100-280 nm, UVB: 280-315 nm and UVA: 315-400 nm. Definitions based on biologic effects modify these rangesUVC: 180-290 nm, UVB: 290-320 nm and UVA: 320400 nm. UVC in sunlight is normally completely screened by stratospheric ozone, but it is important to note that artificial light sources can also produce UVC.

Not all wavelengths of light impinging on the surface of the eye illuminate the various melanin-containing cells in the eye. The iridal melanocytes are located behind the cornea and anterior chamber (containing the aqueous humor). The cornea is transparent to visible light, but it absorbs all of the UVC, part of the UVB (22- 73% at 320-300 nm) and a very small amount of UVA (6-20% at 400-330 nm) (8). Therefore, in vivo the iridal melanocytes are exposed only to visible light, UVA and some of the UVB spectrum. The ciliary body and choroidal melanocytes are covered internally by the retina and densely pigmented ciliary and retinal pigment epithelia and externally by thick and nontransparent sciera. In infancy and in early childhood, there is a window of transmission of nearly 8% of UV radiation around 320 nm through the lens, and about 30% of the transmitted UV is absorbed by the RPE before impinging upon the uveal melanocytes (8,9). As a result of the transmission properties of the cornea and lens, only visible light reaches the RPE in the adult human eye (7).

Figure 1. A sagittal horizontal section of the adult human eye. Reprinted with permission from http://www.webvision.med.utah.edu.

The remainder of this review is organized as follows. First we briefly review the chemistry of melanins and the melanogenesis of ocular melanosomes. Second, we focus on the iris, examining the relationship between iris color and melanin composition, and eye diseases. This is followed by a general discussion of the role ocular melanin might play in the physiology and pathology of the eye. Three specific topics are explored-photo-screening protective effects, biophysical and biochemical protective effects, and the biologic and photobiologic effects of the two main classes of melanins (generally found as mixtures in ocular melanosomes)- eumelanin and pheomelanin.

MELANIN AND OCULAR MELANOGENESIS

There are different types of melanin present in the pigment epithelia and uveal melanocytes. The pigment epithelium is densely pigmented in all races and in all eye colors. Melanin in the pigment epithelium is mainly eumelanin, which is a brownblack substance derived from tyrosine or dopa. Eumelanin is formed in a series of oxidation and tautomerization reactions catalyzed by several enzymes, with the end product being a complex oligomeric material exhibiting a distinct particle nature (10-13). Key intermediates in the biosynthesis of eumelanin are 5,6-dihydroxyindole and 5,6- dihydroxyindole-2-carboxylic acid, as well as their oxidized forms.

Formation of melanosomes occurs in the RPE early in fetal development, then ceases within a few weeks (14). Polymerization of melanin within these melanosomes continues until, at approximately 2 years of age in humans, the RPE contains only mature melanosomes (14). Whether melanogenesis occurs in the RPE after approximately 2 years has not been definitely established. Premelanosomes, or partially melanized melanosomes, which are indicative of ongoing melanogenesis, have not been observed in adult human RPE. In addition, very little or no tyrosinase activity could be detected in adult bovine RPE cells (15,16). The melanin content of the RPE decreases significantly in aged human eyes (17-20). Therefore, melanin biosynthesis either is absent in adult human RPE cells or occurs only at a very slow rate; and whether there is turnover of RPE melanosomes remains unknown.

In uveal melanocytes, the quality and quantity of melanin vary with race and iris color. In the uveal pigments, pheomelanin is often present in addition to eumelanin (21-23). Pheomelanin is a lighter colored, yellowish pigment that is formed when cysteine or glutathione is present during the oxidation stage of dopa (24). 1,4- benzothiazynylalanine, derived from cysteinyldopas, is proposed to be a key intermediate in the biosynthesis of pheomelanin (24). The quantity of uveal melanin in eyes with dark-colored irides is greater than that in light-colored eyes (21,23,25). Uveal melanocytes contain both eumelanin and pheomelanin. In cells from eyes with dark-colored irides (brown and dark brown in color), the amount of eumelanin and the ratio of eumelanin/pheomelanin is significantly greater than that from eyes with light-colored irides (hazel, green, yellow-brown and blue in color) (23). The quantity of pheomelanin in uveal

melanocytes from eyes with light-colored irides is slightly greater than that from dark-colored irides, although the difference is not statistically significant (23).

The ocular melanin content differs among species. For example, Liu et al. (22) reported that pheomelanin content in bovine eyes is low in the choroid and RPE and moderate in the iris (containing both iridal melanocytes and IPE). In cultured human uveal melanocytes, the quantity and type of melanin in iridal melanocytes are not significantly different from that in choroidal melanocytes (23).

Both uveal melanocytes and pigment epithelium cells can be isolated and cultured in vitro (26-30). Human uveal melanocytes produce melanin to maintain a constant level of melanin in vitro. Cultured uveal melanocytes isolated from eyes with different iris colors maintain their inherent capacity for melanogenesis (31). Adult human pigment epithelium cells do not produce melanin in vitro and perhaps not in vivo either (32). The melanin content of cultured RPE decreases rapidly and in proportion to cell division. No melanin production could be demonstrated in cultured RPE under standard culture circumstances (27,30,32-34). Several authors have reported that cultured human adult RPE may produce melanin under special circumstances or when induced by certain stimulators (35-37). These reports have not provided a quantitative measurement of melanin in the cultured RPE cells, have proven difficult to replicate by others, and have not established that the pigment produced is the same as that naturally found in the cells. IRIS-RELATIONSHIPS BETWEEN COLOR, MELANIN COMPOSITION AND DISEASE

The IPE is located at the posterior surface of the iris. The IPE is pigmented in all races and colors. The pigment in the IPE provides only a background tint, receiving and reflecting light only through the filter of stroma arranged in front of this tissue (21,38- 41). The iris color is determined by the variation in pigmentation of the melanocytes in the stroma.

The quantity and types of melanin in the iridal melanocytes vary with iris color (21,23,42). However, it is important to emphasize that the iris color visible through the cornea results from different optical phenomena, such as multiple light scattering on pigment granules and other components of the connective tissue forming the stroma, as well as light absorption by various chromophores (26). Studies of human donor eyes under light and electron microscopes revealed that the difference in iris color is determined by the variation of the melanosome structure and composition within the iridal melanocytes, not by the number of iridal melanocytes present (38,40,41). Darker indes have larger melanin granules and greater granule density (38). In pathologic conditions, e.g. albinism, where the melanin content in the pigment epithelium is markedly decreased or even absent, very light-colored irides may vary from yellow to a pink color.

The incidence of two important eye diseases, uveal melanoma and AMD, appears to be correlated with the color of the iris. Uveal melanoma is the most common intraocular malignant tumor in human adults. A population-based study on the relationship between racial/ ethnic group and incidence of uveal melanoma found that the incidence of uveal melanoma is highest in non-Hispanic whites, followed by Hispanics,

Asians and blacks, with a white/black incidence ratio of uveal melanoma of 18:1 (43). These epidemiologic data suggest that the light-colored eye is at higher risk for the occurrence of uveal melanoma. In fact, several studies have shown that light-colored irides (blue, hazel, etc.) have a higher incidence of uveal melanoma (44-46). Recently, a meta-analysis based on 10 studies (1732 cases) revealed that a blue or gray iris is a statistically significant risk factor for the development of uveal melanoma (47).

AMD is a common ocular disease that is the major cause of blindness among the elderly in developed countries. AMD is at least an order of magnitude (48) more prevalent in the white population than in darkly pigmented races, suggesting that melanin may be protective against AMD development (49-52). Several authors have found an association between light-colored irides and the occurrence or progress of AMD, although the relationship between iris color and AMD is not so conclusive as that in uveal melanoma (20,50,53-57).

PROTECTIVE EFFECTS OF OCULAR MELANIN

The detrimental effects of UV radiation are a cause of the cellular gene mutation that leads to cutaneous melanoma. Reactive oxygen species (ROS), both UV-induced and biochemically produced, also play a role in the malignant transformation of uveal melanocytes. ROS can be either stable diamagnetic molecules or free radicals; when they are produced in the choroid and RPE they can damage the RPE and lead to the degeneration of photoreceptors in the neural retina, e.g. AMD.

The protective effects of melanin on the ocular cells and tissues occur by both physical and biochemical mechanisms; the pigment acts as a photo-screen and as an antioxidant, respectively (6). The photo-screening effect, purely physical in nature, dominates in the anterior segment (the iris), which is exposed to sunlight and UV radiation. The posterior segment is exposed to limited amounts of light and UV radiation. Visible light reaches RPE melanosomes but the exposure of choroidal melanosomes to light is very limited. In these regions the sole mechanism of protection must be biochemical (58). We now examine each of these effects in more detail.

Photo-screening protective effects

Melanin absorbs near-infrared, visible light and UV radiation with absorption increasing at the shorter wavelengths (6). In the anterior segment of the eye, the pigment epithelium and the melanocytes in the iris absorb and block both visible light and UV radiation, thus protecting the rest of the eye from the deleterious effects of these wavelengths. A significant amount of light escapes the absorption by photoreceptor cells, and so even in the posterior segment of the eye (e.g. RPE), melanosomes absorb light. In fact, absorption by the RPE is believed to aid in minimizing spurious signals that may appear because of light reflection and scatter from the fundus (5). Based on experimental measurements, it has been estimated that the absorbance of the RPE, resulting mostly from absorption by RPE melanosomes, is in the range 0.2-0.9. Thus, the amount of light reaching the choroidal melanocytes is much lower than that

reaching the iris and RPE, but remains a concern. These uveal melanosomes may still act as a photo-screen, but this may not be the major role they play here in mitigating the onset or progression of uveal melanoma or AMD.

Paradoxically, it has been reported that solar radiation causes a decrease in the incidence of uveal melanoma (59). This is consistent with the dual effect of UV radiation on the occurrence of other malignant tumors. Recently, it has been reported that solar radiation reduces the risk and/or mortality of various systemic malignant tumors that are not exposed to sunlight, e.g. non- Hodgkin's lymphoma, and prostate, breast, colon and ovarian cancers. These beneficial effects occur because UV radiation increases vitamin D synthesis in the skin; vitamin D then converts to 1,25- dehydroxyvitamin D3, which inhibits growth and induces apoptosis in various malignant tumor cells both in vitro and in experimental animal models. Therefore, sunlight has dual effects on malignant tumors-a direct mutagenic effect on tissues exposed to the sunlight and an indirect protective effect on tissues not exposed to sunlight (59).

Cutaneous and conjunctival melanocytes are mainly exposed to solar radiation, and in their tissues the direct effect of UV radiation predominates and causes an increase in tumor incidence with decreasing latitude (increasing solar radiation). Uveal melanocytes, mainly the choroidal and ciliary body melanocytes, are not directly exposed to solar radiation, so no direct effect of solar radiation would be expected to occur in these locations. Therefore, the indirect protective effect of solar radiation causes a decrease in uveal melanoma (59).

The lower incidence of AMD in darkly pigmented eyes may be related to lower light intensity that is transmitted to the retina. This is because darkly pigmented indes (with more iridal melanin) will more efficiently attenuate the light that reaches the eye fundus. The spectrum of light transmitted by differently pigmented indes depends on the color of the indes. So if one hypothesizes that the actual damage that triggers the cellular processes leading to AMD is in the RPE, then melanin in the RPE can offer some protection against light-related phenomena. Indeed, there is a growing body of experimental evidence suggesting that AMD actually originates in the pathologic changes in the RPE (60).

The photo-screening effect of melanin can also play a role in melanoma of the iris. Iris melanoma is much rarer and less malignant than ciliary body and choroidal melanomas. The melanocytes of the iris are located in the eye's anterior surface and exposed to solar radiation. Iris melanoma tends to occur in the inferior sector of the iris, where exposure to sunlight is the greatest (61), indicating that its occurrence is related to exposure to UV radiation. The lower incidence of iridal melanoma in dark-colored eyes (61) might be related to the photo-screening effect provided by their more abundant iridal melanin.

Biophysical/biochemical protective effects

The choroid, located in the posterior segment of the eye, is highly vascularized and therefore is at elevated risk of experiencing significant oxidative stress. Choroidal melanin, an antioxidant and a weak free radical

scavenger, may deactivate ROS and protect the retina from oxidative damage (30,59). However, with age, the constant exposure of pigment cells to high levels of oxygen may diminish the antioxidant properties of melanin. In this case, melanin may even become a pro-oxidant, which may lead to the damage of photoreceptors and cause AMD (5,30,59). Uveal melanocytes in eyes with dark-colored irides contain a greater amount of melanin and therefore can resist ROS and protect the tissues until a later point in the aging process. This effect could explain the decrease in the incidence of AMD in the dark-colored eye.

Biochemical protective effects in the RPE may also play a role in the occurrence of AMD. Melanin in the RPE can act against ROS and protect the neural retina (62,63). With age, the constant exposure of the RPE to high levels of oxygen and light might diminish the antioxidant properties of melanin (64-67). Under these conditions melanin may become pro-oxidant, adding to the accumulation of the singlet-oxygen-producing pigment lipofuscin in the cytoplasm of aged RPE cells and ultimately leading to AMD (5,6,14,17-19,30,62,63,68). Uveal melanin, especially in the ciliary body and choroid, can also protect melanocytes from oxidative stress and reduce the malignant transformation of uveal melanocytes. Melanocytes in dark-colored eyes have a high quantity of melanin, which is more protective than that in light-colored eyes, consistent with the higher incidence of uveal melanoma in the light-colored eye (23,47,59).

BIOLOGIC AND PHOTOBIOLOGIC EFFECTS OF EUMELANIN COMPARED TO PHEOMELANIN

Several studies have compared the reactivity of eumelanin and pheomelanin and found that both melanins act as free radical scavengers and inhibit UV-induced lipid peroxidation (69-72). However, the antioxidant properties of melanin are related to the type of melanin-the greater the ratio of eumelanin to pheomelanin, the more antioxidative the pigment (69,70). Pheomelanin complexed with Fe (III) stimulates UV-induced lipid peroxidation, whereas eumelanin does not (71,72). Cultured melanocytes with high levels of eumelanin show a better survival rate after irradiation with UVB (73). UV irradiation of melanin also generates ROS, and this photosensitization is greater for pheomelanin than for eumelanin (72,73).

Takeuchi et al. (74) examined the induction of DNA lesions and apoptosis upon UV exposure of congenic mice with black, yellow and albino coats. UVB-induced cyclobutane dimerization and apoptosis measured by sunburn cells or keratinocytes containing active caspase- 3 was strain independent. Combining the results of measurements on TUNEL-positive cells with the concentration of pigments in different mice revealed that compared to eumelanin, the presence of pheomelanin induces a three-fold greater activity. This result strongly supports the conclusion that pheomelanin sensitizes apoptosis (via caspase-3 activation) in adjacent cells at a frequency greater than that induced by direct DNA absorption. Studies using free-electron laser photoelectron emission microscopy, femtosecond time-resolved absorption spectroscopy and electron spin resonance oximetry reveal that unlike eumelanosomes, pheomelanosomes exhibit a second threshold potential of 3.8 eV, corresponding to photons with wavelengths as long as 326 nm (75,76). The data suggest that pheomelanosomes may be more susceptible to adverse reactions induced by solar radiation.

Uveal melanin in dark-colored eyes contains more eumelanin than that in light-colored eyes (23). Because both melanins are protective and eumelanin is less photoreactive than pheomelanin, the high level of eumelanin in dark-colored eyes suggests that dark- colored eyes would have a lower incidence of uveal melanoma and AMD, consistent with the results of epidemiologic studies (43,47-52).

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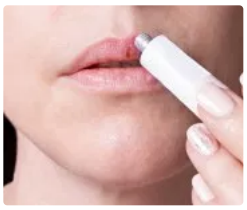

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