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Review Melanization and phagocytosis: Implications for age related macular degeneration

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Signaling pathways that upregulate melanization in the retinal pigment epithelium (RPE) may also be implicated in the downregulation of rod outer segment (ROS) phagocytosis by the RPE. Melanization activating pathways may also modulate oxygen consumption by the photoreceptors, apolipoprotein E4 levels, and the rate of photoisomerization events such that the net effect may be a reduction in drusen and/or lipofuscin accumulation. An increase in melanin at the apical microvilli of the RPE may shield ROS from light thereby contributing in part to the decrease in the rate of ROS phagocytosis. This decrease in ROS phagocytosis by the RPE may serve to maintain a balance between ingestion and degradation/recycling thereby avoiding an increase to its already substantial metabolic load. Several experimental drugs for age related macular degeneration (ARMD) coincidentally are also capable of decreasing the rate of ROS phagocytosis. This review attempts to identify the signaling pathways that may link the upregulation of melanization to the downregulation of ROS phagocytosis. Phagocytic pathways that are modulated by melanization need to be studied in isolation to determine what role, if any, they possess in ameliorating the onset and progression of ARMD. Many more empirical studies are needed to unravel specific pathways and mechanisms that seem to link melanization with ARMD.

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The retinal pigment epithilial (RPE) cells are responsible for the internalization and subsequent degradation of rod outer segments (ROS), which are shed daily from the distal ends of photoreceptors. The process of phagocytosis is complex and involves multiple steps involving recognition and attachment with various surface receptors [1-4], receptor-ligand interactions, and cytoskeletal rearrangement [5] with associated signaling and gene transduction mechanisms [6]. The process of degradation of internalized ROS is equally complex, involving lysosome-phagosome fusion [7], breakdown, or recycling of the fatty acids of the ROS by lysosomal hydrolases and the generation of free radicals and superoxides.

Circumstantial evidence indicates that perturbations in either the rate of phagocytosis [8,9] and/or the rate of internalized ROS degradation in the RPE [10,11] ultimately lead to metabolic impairment of the cell and to severe consequences for the photoreceptors whose survival depends on a healthy RPE. For example, a decrease in the rate of phagocytosis may cause oxidation of rod outer segment lipid constituents before RPE binding and/or internalization occurs. The RPE lysosomal system may be incapable of efficiently degrading such oxidized lipid constituents [12,13] in part because they may perturb the fusion of lysosomes with phagosomes [14] thereby causing a decrease in the rate of ROS degradation. The mechanisms underlying vision loss in AMD are multifactorial, complex, and incompletely understood [15,16]. The early nonexudative form of the disease shows a predilection for parafoveal loss of rods over cones [17,18]. The spatial distribution of lipofuscin generally matches the parafoveal loss of rods in early AMD [19]. Table 1 shows the possible permutations in the rate of phagocytosis (PR) or the rate of ROS degradation (RRD) along with the possible intracellular accumulation of lipofuscin. These permutations (in PR and RRD) are assumed to occur independently of each other, however, such may seldom be the case in vivo. An increase in the PR or/and a decrease in the RRD are factors that are most likely to cause

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an age related intracellular accumulation of lipofuscin [20].

Delayed or slower processing of internalized ROS has been associated in part with age related inactivation of lysosomal proteases [21-23]. Increases in intraphagosomal pH [24-26], lipofuscin accumulation [27], blocking phosphatidylinositol 3-kinase recruitment to the phagosomal membrane [14], increased susceptibility to oxidative processes [12], and decreases in antioxidant concentration have been proposed as some causative factors. Interestingly, vacuolar type H^+ ATPase inhibitors that can act nonspecifically to increase the pH of intracellular organelles like phagosomes and melanosomes can cause a slower processing of ROS with a simultaneous increase in melanization [28-30], respectively.

Oxidative damage has been implicated in the etiology of age related macular degeneration [31-34]. Melanin may exert multiple effects against oxidative damage to RPE cells. It can scavenge free radicals [35-41]. The activities of lysosomal hydrolases are elevated in melanocytes engaged in melanin synthesis [42]. It can prevent inactivation of lysosomal proteases in part by neutralizing 4-hydroxy-2-nonenal (HNE) that is generated by oxidation of low density lipoprotein [43,44]. It prevents lipid peroxidation [45,46] and hence may prevent oxidized lipoprotein (oxLDL) mediated inhibition of lysosomal fusion with phagosomes. Levels of A2E oxiranes and probably A2E were found to be substantially lower in pigmented *abcr*$^{-/-}$ mice when compared to albino *abcr*$^{-/-}$ mice due to attenuation of retinal illuminance by melanin [47]. Lower levels of A2E may also prevent elevation of intraphagosomal pH [48,49] and the associated inactivation of lysosomal enzymes. By virtue of its metal chelating properties, it may prevent oxidative damage to the membranes of phagosomes and lysosomes and associated damage to the cytoskeleton myosin and actin fibers [50,51]. Melanin greatly reduces oxygen driven lipofuscin formation [52]. Transgenic albino mice containing three point mutations in the opsin gene were observed to undergo a greater extent of photoreceptor degeneration than their age matched counterparts even when reared in darkness after birth [53]. It therefore seems reasonable to assume that an increase in melanogenesis may simultaneously contribute to a decrease in PR and an increase in RRD, thereby reducing the rate of lipofuscin formation. For instance, although increased lipofuscin was found to correlate with photoreceptor loss, the accumulation of lipofuscin was not as strong a determinant of photoreceptor loss in blacks as it was in whites [54]. Because the melanization of the RPE cell confers it such a broad range of protection against oxidative damage and also decreases the rate of rod outer segment photo-oxidation, the melanized RPE cell may be able to decrease its rate of phagocytosis of rod photoreceptor outer segments (ROS) without significant undesirable consequences. This decrease in ROS phagocytosis may serve to maintain a balance between ingestion and degradation/recycling thereby avoiding an increase to its already substantial metabolic load.

This review attempts to identify the signaling pathways that may link the upregulation of melanization to the downregulation of ROS phagocytosis. Mechanisms by which melanization, by itself, may contribute to a decrease in phagocytosis are identified. In the process, evidence is sought for the proposition that a decrease in ROS phagocytosis coupled with an increase in RPE melanization may have amiliorative effects in the onset and progression of age related macular degeneration.

Table 1. Relationship between rate of phagocytosis (PR), rate of ROS degradation (RRD) and formation of lipofuscin

Rate of phagocytosis (PR)	Lipofuscin formation	Rate of ROS degradation (RRD)
Increase	Yes	Constant
Decrease	No	Constant
Constant	No	Increase
Constant	Yes	Decrease
Constant	No	Constant

The shedding, internalization and degradation of ROS is a continuous process, perturbations in which could result in increased formation (and consequent accumulation) of lipofuscin. The table describes most plausible conditions of PR and RRD (in the realm of normal physiological possibilities) that could affect lipofuscin formation. A constant PR in combination with constant/increased RRD will not, in theory, facilitate lipofuscin formation. In contrast, constant PR with decreased RRD or increased PR with constant RRD can facilitate lipofuscin formation, conditions which can account for the accumulation of lipofuscin in the etiology of ARMD.

PATHWAYS AND STIMULI THAT EXERT OPPOSITE EFFECTS ON MELANIZATION AND PHAGOCYTOSIS

cAMP, PKC, and A_2 adenosine receptors: Upregulation of cAMP, PKC, and A_2 adenosine receptors has been shown to both increase melanization and decrease rod outer segment ingestion [55-59]. The adenylyl cyclase activator, forskolin, has been shown to inhibit tyrosine phosphorylation of a about 280 KDa protein that is essential for melatonin mediated melanosome aggregation [60].

Rats fed an α-Linolenic acid restricted diet showed a decrease in retinal lysosomal enzyme activity and a lower rod outer segment turnover rate [61], probably as a response to conserve the store of the important retinal constituent, docosahexaenoic acid (DHA) [62,63]. Restricted intake of (n-3) fatty acids has also been reported to decrease the adenosine dependent melatonin release in cultured rat pineal gland [64] and the rate of rhodopsin regeneration after bleaching [65], suggesting that the decrease in phagocytosis and the slowing of the visual cycle could be attributed at least in part to increased melanosome dispersion toward the apical microvilli processes of the RPE. Melanin dispersion toward the apical microvilli of the RPE correlates positively with the intracellular level of cAMP [66].

cAMP mediated increase in melanization may also be responsible for a decrease in ROS uptake in RPE cells on corneal endothelial extracellular cell matrices [67]. Elevation of cAMP in macrophages has been shown to inhibit phagocyto-

sis of apoptotic cells [55]. Light has been shown to suppress cAMP synthesis in retinas of wild type mice [68]. Forskolin, an adenylate cyclase (cAMP) stimulator, and theophylline, a phosphodiesterase inhibitor, both increase melanization of RPE and decrease ROS uptake [69].

ROS uptake of RPE cells grown on bovine corneal endothelial cell matrix (BCEM) and on tissue culture plastic with 44 mM $NaHCO_3$ (an adenylate cyclase stimulator) was significantly less than ROS uptake of RPE cells grown on tissue culture plastic alone. Reduced ROS uptake in the earlier two cases was accompanied by increased melanization.

The phagocytosis of fibronectin coated beads was increased by PKC inhibitors [70]. PKC inhibitors decrease melanization.

Phosphatidyl inositol-3 kinase pathway: Bovine ROS contain PI-3 kinase activity that is upregulated in light adapted retinas [71]. This suggests that a partial abrogation of photon counts reaching the distal ends of photoreceptors may serve to downregulate PI-3 kinase activity and consequently phagocytosis. An increased melanin concentration in the apical microvilli of the RPE may decrease the photointensity reaching the distal ends of the photoreceptor outer rod segments [72-74]. Inhibitors of PI-3 kinase cause a decrease in phagocytosis [75], thereby implicating this enzyme, at least in part, in the modulation of phagocytosis through the activation of its downstream target, myosin X [76]. Forskolin, a cAMP elevator, has been shown to exert its melanogenic activity at least in part through a downregulation of PI-3 kinase activity [77,78].

Nitric oxide pathway: Nitric oxide donors have been shown to induce melanogenesis in normal human epidermal keratinocytes [79]. Nitric oxide also has been shown to decrease phagocytosis of bovine outer segments by RPE cells in vitro consistent with its role in inhibiting actin polymerization and causing melanophore aggregation [80].

Cytoskeleton: Actin stress fiber formation has been shown to be controlled by the small GTP binding protein Rho [81]. Rho inactivation has been shown to enhance the cAMP stimulation of tyrosinase gene expression and melanogenesis, while its constitutive activation impaired these cAMP induced effects in B16 melanoma cells [82]. Rho has also been proposed to be an upstream regulator of both stress fiber formation and tyrosine phosphorylation of Focal Adhesion Kinase $p125^{FAK}$. FAK expression has been shown to promote phagocytosis of integrin (α-v-β-5) bound photoreceptors [83]. The inhibition of Rho can also be induced by α-MSH, which acts on the cAMP pathway. The parallel inhibition of FAK and the suppression of integrin expression leads to a decrease in phagocytosis with a simultaneous increase in pigmentation [84].

Apolipoprotein-E (apo-E): Persons carrying an apo-E4 allele show a decreased risk for AMD when compared with people homozygous for apo-E3 [85,86] and an increased risk for Alzheimer's disease [87]. Apo-E^- mice exhibit accumulation of electron lucent particles in Bruch's membrane at an earlier age and have more membrane bound material than controls [88,89]. The presence of apo-E in drusen and in basal laminar deposits has been demonstrated.

Although a direct effect of apo-E on pigmentation has not been reported, apo-E4 but not apo-E3, has been shown to activate an extracellular receptor kinase (ERK) cascade that results in activation of the cAMP responsive element binding protein (CREB) and an increase in the expression of downstream genes c-fos and Bcl-2 [90]. Upregulation of cAMP, c-fos, and ERK pathways is known to increase melanization and decrease ROS phagocytosis.

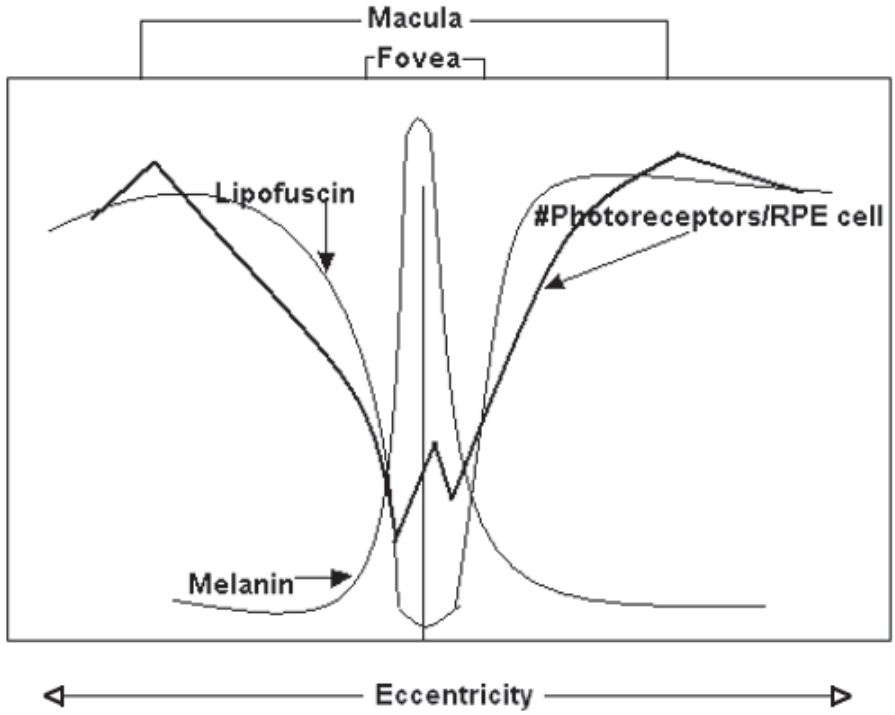

Figure 1. Correlation of melanization and metabolic load in the retina with the formation of lipofuscin. The metabolic load (ratio of photoreceptors to RPE cells) is lower at the fovea than at the macula. Increased melanization at the fovea (negatively correlated to the rate of phagocytosis) may also contribute toward decreasing the metabolic load at the fovea. Together, these effects may account in part toward the fovea sparing in AMD.

MECHANISMS BY WHICH MELANIZATION MAY DECREASE THE RATE OF PHAGOCYTOSIS

Alteration of zeta potential: Melanization in fungi is associated with an increased negative surface charge per cell [91] that in turn is responsible in part for protection against phagocytic attack by host macrophages [92,93]. ROS phagocytosis has been shown to be mediated by the interaction of the scavenger receptor CD36 on the RPE with anionic phospholipids present on the surface of ROS membranes [94]. Melanization of the RPE may decrease phagocytosis of rod outer segments due to increased electrostatic repulsion between these anionic lipids on the ROS membranes and the carboxy indole moieties, hydroquinone, or semiquinone sites on the melanin. Such a reduced rate of phagocytosis may enable the RPE cell to maintain the balance between ingestion and degradation/recycling so as to retard the formation of lipofuscin/drusen.

Reduction of photoisomerization events: The number of melanosomes in the apical processes surrounding adjacent photoreceptors of the mammalian RPE show a significant increase after light onset [95]. An increase in melanization in the apical region may reduce the number of photons incident on the rod outer segments, thereby reducing the number of phototransduction or photoisomerization events.

A reduction of the light intensity reaching the photoreceptor outer rod segments may also decrease the rate of phototransduction events. This is analogous to the slowing of rhodopsin regeneration by isotretinoin that has been shown to protect photoreceptors from light damage and bleaching possibly by competing with RPE65 binding [96,97]. Reducing the number of photoisomerization events may also be beneficial in some genetic retinal diseases including Stargardt macular degeneration [98]. Indeed, it has been shown that dark rearing of $Abcr^{-/-}$ mice prolongs rod cell survival by decreasing the retinoid turnover. A decrease of phototransduction events has also been shown to be beneficial in slowing down the visual cycle and preventing the formation of the major fluorophore of lipofuscin, A2E [97,99-101].

It is also reasonable to assume that the rate of phagocytosis may be controlled by phototransduction or photoisomerization events. Such a signaling mechanism may involve the cyclic nucleotide gated ion channels (CNG) on photoreceptor membranes that are modulated by cGMP. A phototransduction event leads to an activation cascade comprising rhodopsin, transducin, and cGMP-PDE. This phosphodiesterase breaks down cGMP, which causes the CNG channels to close and the photoreceptor cell to hyperpolarize, sending an electrical signal to the brain. Phosphodiesterase inhibitors such as theophylline, papaverine, and isobutylmethylxanthine have been shown to reduce ROS uptake and also simultaneously increase melanization, consistent with this hypothesis [69,102].

Decreasing subretinal Ca^{+2} concentration: Growth arrest specific (Gas6) protein is the ligand for the receptor protein tyrosine kinase, Mer [103]. Gas6 can specifically and selectively stimulate the phagocytosis of photoreceptor outer segments by normal cultured rat RPE cells [104]. Gas6 must bind to OS before the stimulation of OS ingestion can occur and this binding requires the presence of Ca^{+2} ions [105]. The level of subretinal Ca^{+2} concentration has been shown to be negatively correlated with the level of RPE pigmentation because RPE melanin has been shown to bind calcium in direct proportion to the level of hypopigmentation of individual mouse strains [106,107]. It may be that melanization reduces Gas6 mediated phagocytosis by modulating calcium ion concentration in the subretinal space.

Reduction of metabolic burden mechanisms by which a decrease in the rate of photoreceptor phagocytosis may ameliorate the progression of AMD: Spatial topography, age relationship, and racial distributions of lipofuscin exhibit remarkably similarity to patterns seen in AMD [108]. A positive correlation between the number of photoreceptors per RPE cell and elevated levels of lipofuscin has been observed [54]. Lipofuscin is lower at the fovea than in the nasal or temporal macula [109,110]. Accumulation of choroidal lipids with age appears to be greater in the central than in the peripheral region of the fundus [111]. Melanin is greatest at the fovea and decreases substantially from the fovea to about 5° eccentricity, exhibits a broad minimum between 5° and 20° and then increases slowly toward the equator [109,110]. The macular pigments lutein and zeaxanthein exhibit similar topographical concentrations, being highest at the center of the fovea and then diminishing with increasing eccentricity [112,113]. In addition to the beneficial antioxidant and free radical scavenging effects of these molecules at the fovea that may be partially responsible for its sparing in AMD, it has also been observed that the ratio of photoreceptors (rods and cones) to RPE cells was the lowest in the fovea and increased rapidly in the parafovea of the rhesus retina [114]. It has been suggested that this significantly smaller photoreceptor to RPE cell ratio in the fovea places less metabolic demand on the RPE cells at this location [114,115]. The fewer foveal (cone derived) phagosomes as compared to extrafoveal (rod derived) phagosomes in the RPE of Rhesus monkeys may be a manifestation of this reduced metabolic demand in the fovea [116]. This advantage may also contribute in part to the relative sparing of the foveal photoreceptors in aging and in some diseases of the retina [117-119]. As elucidated here, melanization appears to be negatively correlated with phagocytosis so that the increased melanization in the fovea may in part also contribute to lesser phagocytic burden on the RPE cells in this area. Figure 1 is a schematic depicting the concentration of melanin and lipofuscin and the ratio of number of photoreceptors per RPE cell plotted as a function of eccentricity.

Reduction of oxygen consumption: Photoreceptor cell phagocytosis by the RPE consumes oxygen [120]. It has been proposed that the high oxygen consumption of dark adapted rod cells is the driving force of inner retinal hypoxia [121,122]. Oxygen tensions in the dark adapted rod cells have been found to be around 25 mmHg lower than those of light adapted ones at a distance of 100 μm from the choroid [123,124]. Hypoxia has been shown to upregulate vascular epidermal growth factor [125,126], which in turn has been implicated in choroidal neovascularization [127].

It has also been observed that diabetic retinopathy induced retinal neovascularization rarely occurs in retinitis pigmentosa patients [121,128-130]. The clinical success of panretinal photocoagulation in inhibiting neovascularization may also be attributed to the destruction by this procedure of a large number of photoreceptor cells and the reduction of intraocular VEGF levels [131]. Ischemia induced neovascularization of the retina is abolished in a mouse strain with inherited photoreceptor cell degeneration [132]. Lipofuscin deposition was found to decrease significantly in retinal degenerate rats only after photoreceptors were lost [133].

Taken together, these observations support the hypothesis that oxygen consumption associated with rod cell metabolism or the rate of rod outer segment phagocytosis [134] by the RPE may represent a major driving force in ischemic retinal neovascularization. This proposition suggests that reducing the rate of ROS phagocytosis may play a role in decreasing choroidal neovascularization.

DRUGS MODULATING MELANIZATION AND PHAGOCYTOSIS

cAMP elevating agents [135,136], phosphodiesterase inhibitors, visual cycle slowing agents, cytoskeleton disruptors, lysomotropic agents [137], agents that affect cellular charge, certain prostaglandins may be reasonably expected to decrease the rate of ROS phagocytosis and increase melanization of RPE.

Although most approved or experimental drugs for ARMD target the vascular endothelial growth factor or are anti-angiogenic agents, there are several investigational drugs in preclinical or clinical trials that are capable of decreasing the rate of ROS phagocytosis by the RPE. Some examples are: (1) an α-5-β-1 integrin antibody fragment (Protein design labs, Fremont, CA,), (2) integrin antagonists (Jerini, Berlin, Germany), (3) bFGF-2 vaccine (Entremed, Rockville, MD), isotretinoin (UCLA, Los Angeles, CA) and (4) a phosphodiesterase-5 inhibitor (Pfizer, Groton, CT).

Several important questions need to be addressed to better understand the role of the rate of ROS phagocytosis on the onset and progression of AMD. The role that pigmentation plays in modulating the rate of ROS phagocytosis and therefore subsequent ROS degradation also needs further empirical analysis. In general the following may be worthy of further exploration:

1. Does increased melanogenesis decrease phagocytosis of rod outer segments?
2. Does increased melanization decrease the rate of intracellular degradation of rod outer segments?
3. Are RPE melanin levels elevated in macular degeneration relative to age matched controls?
4. Does increased melanin dispersion within the melanosome (i.e., more melanin present in the microvilli) decrease the rate of rod outer segment photo-oxidation and/or the rate of photoisomerization events?
5. Does decreasing the rate of ROS phagocytosis reduce lipofuscin formation and Drusen formation?

CONCLUSIONS

Several lines of evidence suggest that the pathways by which melanization and phagocytosis are activated are inextricably linked such that the overall effect seems to be that a downregulation of one causes an upregulation of the other. Such an effect may be reasonably anticipated since an increase in melanization in the apical RPE region contributes to an effective blocking and absorption of light reaching the rod outer segments (ROS). A reduction in light intensity is expected to decrease the photo-oxidation of the long chain fatty acids comprising the photoreceptor outer segment that may decrease the rate of phagocytosis.

Mammalian melanogenesis is regulated directly or indirectly by more than 95 distinct loci [138,139]. The melanization inducing gene Mitf also modulates expression levels of growth factors and intracellular proteins that cause a decrease in phagocytosis. In addition, cellular signals that modulate melanogenesis, phagocytosis and immune response share common receptors, genes or their transcription factors such as cfos, PI-3 kinase, MAP-K, cAMP, FAK, α-MSH, PKC, Punch, Pale, PPAR, CD36, Rho, and NF-kB. What factors could be responsible for packaging these different evolutionary traits (increased melanogenesis and decreased phagocytosis, for example) on the same genome? One possible explanation is that such packaging of dissimilar traits represents an evolutionary response to preventing increases in the already substantial ingestion rates of ROS by the RPE [140] in tropical regions or high photointense areas of the planet. Increased melanization may have constituted part of the response.

The above may also explain why these different genetic traits have partially overlapping signaling pathways so that activation of one gene results in the fortuitous modulation of the others. In this context, it is reasonably apparent that a decrease of photoreceptor phagocytosis by the RPE may be sustainable only when it is accompanied by a comparable decrease in photoreceptor photo-oxidation. Such a decrease in outer segment photo-oxidation can be attributed to increased melanization.

Rather than relegating melanization simply as a “marker” for a variety of pathophysiological disorders, its modulation by pharmacological agents can be used to constructively disrupt correlated phagocytic, angiogenic, and immune response signaling mechanisms as elucidated in this manuscript. In summary, the proposition that the onset and/or progression of AMD may be delayed by decreasing the rate of ROS phagocytosis may be worthy of further research. Many more empirical studies are needed to unravel specific pathways and mechanisms that seem to link pigmentation with other important ocular anabolic and metabolic processes.

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