

## REVIEW

## Melasma: Updates and perspectives

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## Abstract

Management of melasma is highly challenging due to inconsistent treatment results and frequent relapses. However, recent studies revealed that melasma may not only be a disease of melanocytes, but also a photoaging skin disorder. Herein, we attempt to validate that melasma is indeed a photoaging disorder by presenting the histopathologic findings of melasma: solar elastosis, altered basement membrane, increased vascularization and increased mast cell count. We also provide some therapeutic implications based on these findings and a discussion on the latest updates and perspectives regarding treatment.

## KEYWORDS

histopathology, melasma, photoaging, treatment

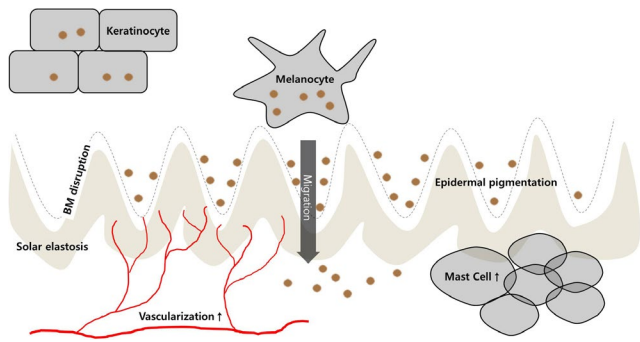
## 1 | INTRODUCTION

Melasma is an acquired hypermelanosis characterized by asymmetric, brown-coloured, irregular, reticulated macules on sun-exposed areas of the skin, especially the face. Asian women in their thirties and forties are especially vulnerable to developing melasma.<sup>[1]</sup> To date, the pathogenesis of melasma has not been fully elucidated; however, chronic ultraviolet (UV) exposure, female hormone stimulation and predisposed genetic background have all been proposed to play a role in the development of melasma.<sup>[2–4]</sup> Management of melasma is highly challenging, especially because it is prone to frequent relapse despite successful clearance.<sup>[5]</sup> The accumulated knowledge to date has revealed that melasma is a disease of melanocytes, which has features of photoaging.<sup>[6,7]</sup> Thus, conventional therapeutic modalities that target only melanosomes or melanocytes may not be successful in clearing melasmas, as the photoaged skin surrounding melanocytes would induce relapse. Herein, we validate that melasma is a photoaging disorder by presenting its histopathologic features. Based on these features, we also discuss its therapeutic implications. Moreover, we present the latest updates and perspectives regarding its treatment modalities.

## 2 | HISTOPATHOLOGIC CLUES OF MELASMA AS A PHOTOAGING DISORDER

The histopathologic features of melasma overlap with the hallmarks of photoaged skin, such as solar elastosis, altered basement membrane (BM), increased vascularization and increased mast cell count.<sup>[8]</sup> (Figure 1) Solar elastosis is an accumulation of abnormal elastic tissues in the dermis due to chronic sun exposure. About 83%–93% of melasma patients have variable degrees of solar elastosis.<sup>[9,10]</sup> The transcriptional analysis revealed that not only melanocytes but also the dermal components are involved in the development of melasma.<sup>[11]</sup> The Wnt signalling modulators secreted from fibroblasts were upregulated in lesional melasma skin compared with perilesional skin.<sup>[11]</sup> Reduced expression of Wnt inhibitory factor-1 (WIF-1)—either in the dermal fibroblasts or epidermal keratinocytes—stimulates melanogenesis and melanosome transfer through the upregulation of both canonical and non-canonical Wnt signalling pathway.<sup>[12]</sup> Overexpressed secreted frizzled-related protein 2 (sFRP2) induces the development of melasma through microphthalmia-associated transcription factor (MITF) or tyrosinase upregulation via  $\beta$ -catenin signalling.<sup>[13]</sup> Pleiotrophin expressed in melanocytes and fibroblasts

Kwon, Na are equally contributed to the work.



**FIGURE 1** Schematic view of histological changes in melasma. The amount of melanin is significantly increased in all epidermal layers. Basement membrane is disrupted and thinned, facilitating migration of melanocytes and melanin into the dermis. Melanocytes protruding into the dermis along with a disrupted basement membrane are a characteristic feature of melasma. Solar elastosis is prominent, and the number of mast cells is significantly increased in the dermis. The number of blood vessels, vessel size and vessel density are greater in lesional melasma skin than in perilesional skin

in the human skin inhibits pigmentation, probably through MITF degradation via Erk 1/2 activation in melanocytes.<sup>[14]</sup>

A disrupted BM was reported in 95% and 83% of melasma patients via periodic acid-Schiff-diastase (D-PAS) staining and anti-collagen type IV immunohistochemistry, respectively.<sup>[10]</sup> Then, pendulous melanocytes associated with BM abnormality were reported as a characteristic histologic finding in melasma.<sup>[15]</sup> Chronic UV exposure elevates the levels of matrix metalloproteinase (MMP)-2 and MMP-9, which degrade type IV and VI collagen in the skin.<sup>[16]</sup> Thus, disrupted BM promotes the descent of melanocytes and melanin into the dermis, which would appear as free melanin or melanophages in the dermis.<sup>[9,10]</sup>

The number of blood vessels, vessel size and vessel density are greater in lesional melasma skin than in perilesional skin.<sup>[17–19]</sup> Elevated levels of cytokines that could affect vascularization have been demonstrated in melasma skin, such as vascular endothelial growth factor (VEGF), stem cell factor (SCF) and inducible nitric oxide synthase (iNOS).<sup>[17,20,21]</sup> Endothelin-1 (ET-1) released from endothelial cells stimulates the pigmentation through endothelin receptor B activation at the surface of melanocytes.<sup>[22]</sup>

An increase in the number of mast cells has been observed more frequently in lesional melasma skin than in perilesional skin.<sup>[10,23,24]</sup> The role of mast cells in the development of melasma has not been fully understood to date; however, a release of histamine from mast cells in response to UV irradiation has been demonstrated to stimulate melanogenesis, which is mediated by H2 receptors via protein kinase A activation.<sup>[25–28]</sup> The growth-differentiation factor-15 (GDF-15), which is a member of the transforming growth factor- $\beta$  (TGF- $\beta$ ), was revealed to be involved in the histamine-induced melanogenesis.<sup>[29]</sup> The association between mast cells and histologic features of photoaging has further been demonstrated.<sup>[30,31]</sup> The release of mast cell tryptase was upregulated in response to repetitive UV irradiation, which is involved in dermal ECM degradation

**TABLE 1** A comparison of histological findings in melasma and SL

	Melasma	SL
Melanin	↑ in epidermis/dermis	↑ in epidermal basal layer
Number of melanocytes	↑ or no change	↑ (due to epidermal hyperplasia)
Rete ridge elongation or epidermal thickening	(–)	(+)
Solar elastosis	(+)	(+)
Dermal melanophage	(+)	Scant, but observed abundantly in some cases
BM disruption	(+)	(–)
Vascularization	↑	↑ (reported in one study)
Mast cell	↑	(–)

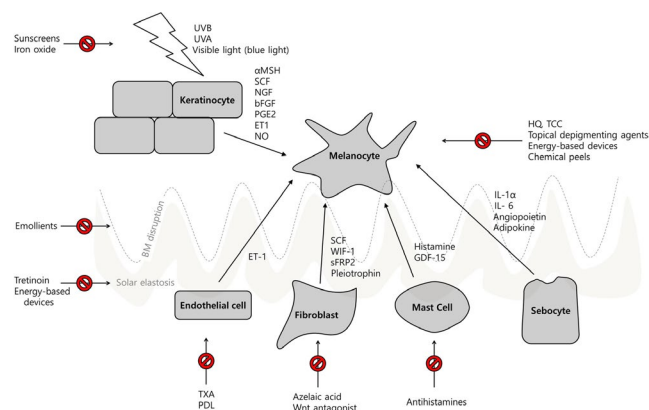
and BM disruption via proMMP.<sup>[32–35]</sup> Mast cell tryptase was shown to promote solar elastosis by inducing the production of elastin in fibroblasts.<sup>[36,37]</sup> Angiogenic factors released from mast cells, such as VEGF, FGF-2 and TGF- $\beta$ , induced vascular proliferation.<sup>[38]</sup> These findings suggest that mast cells are important regulators in the development of photoaging and hyperpigmentation.

In addition, sebocytes have been hypothesized to contribute to the development of melasma. When co-cultured with sebocyte cell line, human epidermal melanocytes showed dendrites formation and altered melanogenesis.<sup>[39]</sup> Several cytokines and growth factors, such as IL-1 $\alpha$ , IL-6, angiopoietin and adipokine, released from sebocytes have been demonstrated to exert paracrine effects on epidermal melanocytes.<sup>[7]</sup> The role of sebocytes with respect to the pathogenesis of melasma requires further investigation.

Like melasma, solar lentigo (SL) (senile lentigo, ageing spot) is hyperpigmented macules that typically develop in chronically sun-exposed skin. Histologically, SL displays accumulation of melanin in epidermal basal layer together with elongated, club-shaped rete ridges. (Table 1) The increased length of basal layer rather than melanocyte hyperplasia is thought to contribute to the greater number of melanocytes observed in SL.<sup>[40]</sup> About half of the SL lesions have flattened epidermis, but epidermal thickening is consistently reported in the SL lesions.<sup>[40,41]</sup> Dermal change is rarely observed in SL except for age-related elastotic changes.<sup>[42]</sup> However, abundant melanophages in the papillary dermis was observed in 7.8% of the facial SL lesions. A recent study reported greater vascular density and increased macrophage infiltration in SL lesion compared with perilesional normal skin.<sup>[43]</sup>

### 3 | THERAPEUTIC IMPLICATIONS

Current therapeutic options target photoprotection, melanocytes activity, various dermal or epidermal cells which signal to



**FIGURE 2** Schematic view of pathogenesis and therapeutic options of melasma. Melanocytes, where melanogenesis and melanosome are transferred to keratinocytes, are under control of signals from various cells in the skin. Keratinocytes release cytokines and hormones to induce melanogenesis, especially in response to UVB exposure. Endothelial cells produce ET-1 to stimulate melanogenesis through endothelin receptor B activation of melanocyte. The Wnt signalling modulators secreted from fibroblasts regulates melanocytes activity. Dermal mast cells play a role in the histamine-induced melanogenesis in response to UV irradiation. Sebocytes produce cytokines and growth factors to exert paracrine effects on melanocytes. Chronic UV irradiation causes solar elastosis and disrupts BM, which are the hallmarks of photoaging. Disrupted BM induces a descent of melanocytes and melanin into the dermis, appearing as free melanin or melanophages in the dermis. Current therapeutic options target photoprotection, melanocytes activity, various dermal or epidermal cells which signal to melanocytes and abnormal tissue changes due to photoaging. (BM, basement membrane; HQ, hydroquinone; PDL, pulsed dye laser; TCC, triple combination cream; TXA, tranexamic acid; UV, ultraviolet)

melanocytes, and abnormal tissue changes due to photoaging. (Figure 2) Topical depigmenting agents are still used as the main modality of treatment for melasma. Hydroquinone (HQ), which inhibits the conversion of 1-3,4-dihydroxyphenylalanine to melanin by competitive inhibition of tyrosinase, is the most popular anti-melanogenic agent.<sup>[44,45]</sup> However, safety issues for HQ have been raised, including exogenous ochronosis, permanent depigmentation and potential carcinogenic risk.<sup>[46]</sup> The safety issue of HQ has motivated researchers to find other effective—yet safe—topical agents. To date, 4-n-butylresorcinol, niacinamide, ascorbic acid, resveratrol, azelaic acid and kojic acid are considered alternative topical agents that have been reported to exhibit depigmenting properties without severe adverse effects.<sup>[47–52]</sup> However, topical depigmenting agents alone cannot restore photoaged skin condition in melasma. Thus, anti-ageing approaches should be combined with topical depigmenting agents because melasma frequently relapses without the correction of other photoaging-related conditions that affect melanogenesis.

A triple combination cream (TCC) containing 4% HQ, 0.05% tretinoin and 0.01% flucinolone acetonide is the only HQ-containing drug approved by the United States Food and Drug Administration (FDA) to treat melasma.<sup>[53,54]</sup> Tretinoin exhibits not only a hypopigmentary

effect, but also an anti-ageing property.<sup>[55]</sup> Steroids inhibit the secretion of ET-1 and granulocyte macrophage colony-stimulating factor (GM-CSF) that act against mild inflammation associated with photodamage and melanogenesis.<sup>[56,57]</sup>

Azelaic acid, a well-known agent with anti-inflammatory and depigmenting properties, has been reported to reverse PUVA-induced senescence in human dermal fibroblasts.<sup>[58]</sup> By the activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), azelaic acid inhibits the secretion of MMP-1 and growth factors, such as hepatocyte growth factor (HGF) and SCF.<sup>[58,59]</sup>

Wnt antagonists, including cardamonin and FTY720 (fingolimod), have been demonstrated to suppress melanogenesis in vitro.<sup>[60,61]</sup> A recent study reported that andrographolide inhibited tyrosinase activity and melanin production via degradation of  $\beta$ -catenin in B16F10 melanoma cells and UVB-induced brown guinea pigs.<sup>[62]</sup>

Systemic tranexamic acid (TXA), an antifibrinolytic agent, have been shown to inhibit UV-induced melanogenesis and neovascularization by hindering the plasminogen activator and plasmin activity.<sup>[63]</sup> Oral administration of TXA (250 mg) twice or three times per day for 2–3 months significantly decreased the melanin index and erythema index in melanin lesional skin.<sup>[23,64]</sup> A histologic analysis revealed significant improvement not only in the level of epidermal pigmentation, but also in the number of mast cells and vessels.<sup>[23]</sup> The expression of ET-1 was significantly decreased after TXA administration.<sup>[65]</sup> Although systemic TXA is well-tolerated with good safety profiles, topical TXA is formulated to avoid the theoretical thrombogenic potential. Topical TXA has been used in the treatment of melasma alone or in conjunction with other modalities, including microneedling, intradermal injection and fractional CO<sub>2</sub> laser, to increase uptake; however, the available data on the results are limited.<sup>[63,66–68]</sup>

Several studies investigating the efficacy of energy-based devices on melasma, including intense-pulsed light (IPL), fractional 1550-nm non-ablative laser, Q-switched neodymium-doped yttrium aluminium garnet laser (QSNYL), pulsed dye laser (PDL) and copper-bromide laser have shown positive results.<sup>[69–73]</sup> Laser toning technique using a collimated, low-fluence, 1064-nm QSNYL removes melanosomes and damages the dendrites of melanocytes without destructing the whole melanocytes by a process called “subcellular selective photothermolysis.”<sup>[74,75]</sup> However, the accumulation of energy by repeated laser toning often results in depigmented mottling lesions, which are scar-like conditions that hamper melanogenesis.<sup>[76,77]</sup> Recently, a picosecond laser, which produces higher peak powers at the same energy level with less heat transfer to the surrounding tissues compared with the conventional nanosecond lasers, was developed to treat melasma, although more evaluation is needed.<sup>[78–80]</sup>

High-intensity focused ultrasound (HIFU) with 1.5-mm transducer decreased UVB-induced hyperpigmentation on both animal and human skin.<sup>[81,82]</sup> Thermal coagulation lesions—created by ultrasound energy delivered beneath the dermo-epidermal junction and upper dermis—are thought to eliminate melanin and pigmented debris; however, thermally induced collagen denaturation and subsequent remodelling with HIFU application could further contribute to the improvement of photoaged condition in melasma patients.

The chemical peel is a well-known modality for treating melasma. It causes controlled epidermal dyscohesion and subsequent regeneration to remove epidermal melanin and suspend the transfer of melanosomes.<sup>[83]</sup> However, the result is unsatisfactory, especially in Asian patients with Fitzpatrick skin types III-IV due to high risk of post-inflammatory hyperpigmentation (PIH).

Photoprotection is critical in preventing relapse or exacerbation of melasma. In addition to the conventional UVA and UVB protection, visible light should be avoided in melasma patients since shorter wavelengths of visible light (blue light) promote hyperpigmentation through opsin 3 in melanocyte.<sup>[84]</sup> Sunscreens that contain iron oxide, which blocks shorter wavelength of visible light and broad-spectrum UVA/UVB filters, significantly lowered the relapse of melasma during summer when compared with broad-spectrum UVA/UVB protection alone.<sup>[85]</sup>

## 4 | PERSPECTIVES

The histopathologic features of melasma—solar elastosis, altered BM, increased vascularization and increased mast cell count—strongly suggest that melasma should be considered not only as a disease of melanocytes, but also as a photoaging skin disorder.

Although topical HQ is still the standard treatment modality for patients with melasma, we recommend combining it with anti-ageing therapeutic approaches to correct other photoage-related conditions. Anti-ageing therapies include topical tretinoin along with TCC, systemic TXA and laser treatment to reduce vascularization, as well as energy-based devices that promote collagen remodelling.

In the future, it is necessary to discover a more effective depigmenting agent with minimal side effects. Signalling pathways from keratinocytes, fibroblasts, sebocytes and endothelial cells need to be explored to regulate melanogenesis. Furthermore, therapeutic agents that restore the abnormal dermal matrix and disrupted BM are needed to reverse photoaging features. Considering these features, a laser or new energy-based devices need to be developed. We believe that by combining these methods, melasma can be treated more effectively and safely.

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## CONFLICT OF INTEREST

The authors have declared no conflicting interests.

## AUTHOR CONTRIBUTIONS

Park and Choi designed and performed the study. Kwon and Na wrote the paper. All of the authors (S.H.K., J.I.N., J.Y.C. and K.C.P.) have read and approved the final manuscript.

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