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REVIEW

Update on Melasma—Part I: Pathogenesis

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ABSTRACT

Melasma is a multifactorial dyschromia that results from exposure to external factors (such as solar radiation) and hormonal factors (such as sex hormones and pregnancy), as well as skin inflammation (such as contact dermatitis and esthetic procedures), in genetically predisposed individuals. Beyond hyperfunctional melanocytes, skin with melasma exhibits a series of structural and functional alterations in the epidermis, basement membrane, and upper dermis that interact to elicit and sustain a focal hypermelanogenic phenotype. Evolution in the knowledge of the genetic basis of melasma and the cutaneous response to solar radiation, as well as the roles of endocrine factors, antioxidant system, endothelium proliferation, fibroblast senescence, mast cell degranulation, autophagy deficits of the melanocyte, and the paracrine regulation of melanogenesis, will lead to the development of new treatments and preventive strategies. This review presents current knowledge on these aspects of the pathogenesis of melasma and discusses the effects of specific treatments and future research on these issues.

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Key Summary Points

The incidence of melasma is increasing around the world, while curative treatments are not available.

The reasons for the persistence of focal hypermelanogenesis in skin with melasma are not fully understood.

Melasma results from the interaction of sun exposure, hormonal stimuli, altered oxidative status, and upper dermal abnormalities in genetically predisposed individuals.

The role of senescent fibroblast, melanocytes with impaired autophagy, mast cells, endothelium, keratinocytes, and upper dermal and basement membrane collagen degradation as a model for melasma pathogenesis is discussed.

INTRODUCTION

Melasma is a frequent chronic acquired focal hypermelanosis that affects photoexposed areas in adults, especially women of reproductive age. While skin pigmentation from sun tanning and postinflammatory hyperpigmentation fades spontaneously after the stimulus cessation; in melasma, this reduction usually does not occur. Melasma evolves from alterations in several skin layers and cell types to hyperfunctional melanocytes, which produce and transfer mature melanosomes to the whole epidermis [1].

This review aims to collate current findings on the pathogenesis of melasma. In the following sections, we reinforce the concept of melasma as a multifactorial disorder, and discuss multiple aspects that interact in its pathogenesis, regarding genetics, solar radiation, endocrine stimuli, oxidative status, as well as morphofunctional alterations. Finally, despite its incomplete understanding, we present a pathogenic model leading to the incorporation of all these elements. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

GENETICS

Melasma is a multifactorial disorder characterized by a cutaneous phenotype that results from exposure to external factors (such as solar exposure) and hormonal factors (such as sex hormones and pregnancy), as well as skin inflammation, in genetically predisposed individuals. The genetic basis of melasma is supported by its occurrence in first-degree relatives, as reported by 41–61% of patients in Brazil, including identical twin sisters, while the general expected prevalence in adults in the same region is 16–28%. Familial melasma is associated with prolonged duration and a reduced probability of induction by hormonal contraceptives [2–5].

Skin pigmentation follows a polygenic pattern of inheritance, which explains the phenotypic differences in mammalian species and human population groups. However, there are no animal models for melasma, although postinflammatory pigmentation can be induced in other species [6].

The evaluation of 67 Brazilian families with melasma, using a complex segregation model, demonstrated a genetic component (major gene) that follows autosomal dominant inheritance [7]. Some populations, including Middle Easterners, East Asians, Indians, African Americans, and Latin Americans, are more affected by melasma than others, such as North Europeans, Aboriginal Australians, Amerindians, and populations from Sub-Saharan Africa. A genomic ancestry study suggested that Brazilian women of mixed ancestry or with genes related to African ancestry are more affected by facial melasma [8].

A transcriptomic analysis comparing facial melasma and adjacent skin identified 279 differentially expressed genes. Genes related to melanogenesis (*TYR*, *TYRP1*, and *MLANA*) and the transfer of melanosomes (*Myosin5*a and *GDA*) are upregulated in melasma, as are those related to a subset of Wnt/β-catenin pathway modulators (*Wnt5a*, *sFRP2*, *LGR5*, and *WIF1*), prostaglandins (*PTGIS* and *PTGS1*), repair (*SERPINB3*), and angiogenesis (angiopoietin-like 1 and 2, heparanase, and *MMP2*). In contrast, genes related to lipid metabolism (*PPARα*, *ALOX15B*, *DGAT2L3*, and *PPARGC1A*) and *VEGFA* are downregulated [9].

Another transcriptomic analysis identified 334 differentially expressed genes. Genes related to the peroxisome proliferator-activated receptor (PPAR) pathway (*ADIPOQ*, *FABP4*, *PLIN1*, and *LPL*) are downregulated, but *GDA* and *INA*, associated with melanocyte dendricity, are upregulated, as are genes involved in the functions of the stratum corneum (*S100A8*, *SPRR2A*, *SPRR2B*, and *KLK6*) and those related to melanogenesis (*TYR*, *TYRP1*, and *sFRP2*), the suppression of tyrosine degradation (*NQO1*), and *PDZK1*, which can mediate estrogen-induced melanogenesis [10].

A comparison of facial melasma in retroauricular skin revealed downregulation of *H19*. Despite transcribing a noncoding RNA, mixed (melanocyte–keratinocyte) *H19*-gene-depleted cultures demonstrated increased melanogenesis and melanin transfer to keratinocytes, whereas melanocytes in monoculture did not, and estrogen-treated *H19*-depleted mixed cultures exhibited increased tyrosinase expression [11]. Moreover, lower expression of miR-675, an *H19* micro-RNA (miRNA) that targets *MITF*, is found in skin with melasma, and miR675 has been proven to target cadherin-11 (CDH11), whose expression in fibroblasts and keratinocytes induces damage in the basement membrane (BM) and melanogenesis [12]. There is also upregulation of the *PDZK1* gene in melasma. *PDZK1* is a member of the Na^+/H^+ exchanger regulatory factor and leads to increased melanogenesis and melanosome transfer to keratinocytes [13].

The most potent regulator of eumelanogenesis is the melanocortin type 1 receptor (MC1R), which is transcripted from a highly polymorphic gene responsible for multiple phenotypes of skin and hair color, as well as skin sensitivity to ultraviolet radiation [14]. In melasma, *MC1R* polymorphism, as characterized by substitution of guanosine for adenosine at codon 92 (Val92Met), is prevalent in Javanese women when compared with controls [15].

Primary cultures of fibroblasts from facial melasma and adjacent skin have revealed upregulation of the *WNT3A*, *EDN3*, *ESR2*, *PTG2*, *MMP1*, and *SOD2* genes and downregulation of *COL4A1*, *CSF2*, *DKK3*, *COL7A1*, *TIMP4*, *CCL2*, and *CDH11* in melasma. These genes are related to proinflammatory melanogenic factors and repair deficits, corresponding to a phenotype that can contribute to upper dermal damage and sustained melanogenesis [16].

All these findings support melasma as a multifactorial disorder that emerges in genetically susceptible individuals. Further studies should demonstrate the possibility of precise screening for such individuals to enable early detection and the implementation of rigorous preventive measures.

SOLAR RADIATION

As melasma only occurs in photoexposed skin, has late onset in darker phototypes, worsens following sun exposure, and is more prevalent in intertropical countries, sun exposure is considered to be the most significant environmental factor in its pathogenesis [4].

Any radiation can interact with biological tissue, having effects that vary with the wavelength, intensity, skin penetration, exposure regimen, and individual susceptibility (such as skin phototype and body site). However, in melasma, the exact role of different wavelengths and the effect of their combination are not completely understood. Ultraviolet radiation (UVR) directly stimulates melanogenesis in melanocytes and affects keratinocytes, mast cells (MC), and fibroblasts, which paracrinally regulate melanogenesis. However, different effects are elicited in skin by radiation of various wavelengths [17].

UVB has fundamental effects on the epidermis and BM, while UVA extends to the upper dermis. Chronic UVR exposure leads to photoaging, oxidative stress, and inflammation that contribute to the sustained melanogenesis observed in melasma [18]. It also induces expression of p53 in keratinocytes, prompting synthesis of propiomelanocortins [such as adrenocorticotropic hormone (ACTH), melanocyte stimulating factor (MSH), and β-endorphin] and laminin-332 that paracrinally stimulate melanogenesis [19]. UVB increases the cytocrinic activity of melanocytes, leading to more effective melanosome transfer to keratinocytes [20]. It also contributes to the degradation of heparan sulfate chains in the BM, enhancing the transfer of melanogenic stimuli from the dermis to the epidermis [21]. Finally, UVB induces the release of inflammatory mediators, such as prostaglandins and vascular endothelial growth factor (VEGF), which stimulate endothelial proliferation. In addition, neuropeptides such as calcitonin gene-related peptide (CGRP), which also trigger melanogenesis and melanocyte dendricity, are induced by UVR [22].

Compared with UVB, UVA is far less erythemogenic, but it is more effective in inducing pigment darkening (immediate and persistent) and delayed tanning, especially in people with dark skin [17]. Unlike UVB, the effect of UVA on key skin biomolecules is not direct. The energy absorbed by chromophores is transformed to generate reactive species that lead to oxidative stress [23]. Beyond the skin, UVA exposure can also induce systemic oxidative stress [24].

UVR causes epidermal release of endothelin, nitric oxide, leukotrienes, and prostaglandins, which promote the increase of melanocyte dendrites and upregulation of the *TYR* gene [25, 26]. In the upper dermis, fibroblasts release several melanogenic soluble factors such as keratinocyte growth factor (KGF), interleukin (IL)-6, tumor necrosis factor (TNF)-α, stem cell factor (SCF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and granulocyte macrophage colony-stimulating factor (GM-CSF) and produce secreted frizzled-related protein 2 (sFRP2), regulating the Wnt/βcatenin pathway, which is involved in melanogenesis [27]. Chronic sun exposure also induces a senescent phenotype in fibroblasts, with active secretion of melanogenic and proinflammatory factors [28]. MCs degranulate under thermal, physical, and UVR stimuli, releasing bioactive mediators that induce melanogenesis and contribute to damage to the upper dermis and BM [29]. Compared with age- and phototype-matched healthy controls, women with melasma have lower erythematous dosage induced by UVB and UVA, indicating a UV-sensitive phenotype [30].

Visible light (VL) is nonionizing radiation that penetrates the deep dermis and subcutis. Pigmentation is found only in darker phototypes (III–VI) after high doses of VL exposure, and only shorter wavelengths (420–470 nm, blue and violet) can induce pigmentation through the activation of opsin 3 (OPN3) receptors in melanocytes [31]. While OPN3 is not overexpressed in skin with facial melasma compared with adjacent skin, use of tinted sunscreens (with iron oxides), which block short VL wavelengths, enhances the depigmenting effect of hydroquinone and hinders melasma pigmentation in summer [32, 33].

There are synergistic effects of long-wavelength UVA and VL on skin pigmentation and erythema [34]. In ordinary daily activities, UVA and VL are the types of solar radiation to which individuals are most exposed. Nonetheless, no available commercial sunscreen provides full protection within this range. Even sunscreens containing iron oxides demonstrate a drop in radiation absorption from 400 nm [33].

In facial skin explants subjected to minimal melanogenic doses of UVB, UVA, and VL, there is no difference in the increase in epidermal melanin density for each wavelength between melasma and adjacent skin. Nevertheless, coarser granulation of the epidermal melanin and greater density of the upper dermal melanin are evidenced in melasma skin after UVA irradiation [35].

The low-dose UVA, UVB, and blue–violet radiation experienced during ordinary indoor activities far from a window and illumination from interior lamps and electronic devices are irrelevant for skin pigmentation [35–37].

Infrared (IR) is nonionizing radiation that accounts for half of the solar spectrum and is perceived as heat [38]. Its ability to induce erythema and skin pigmentation is evidenced in erythema ab igne [39]. IR exposure has been indicated as a cause of matrix metalloproteinase 1 (MMP1) activation, vasodilatation, proinflammatory cytokine release, direct cytotoxicity, and increased oxidative stress and DNA damage, leading to photoaging. Notably, most studies on the effects of IR radiation in skin have been performed in vitro, using single exposures to artificial sources, dissimilar to the pattern of daily sun exposure in real life [17]. To date, no systematic investigation has examined the role of solar IR radiation in melasma. However, a recent survey revealed the association between disease severity and exposure to occupational heat [40].

The most important factor attributed to melasma development and aggravation is daily sun exposure, especially due to the failure to completely block all solar radiation involved in melanogenesis (UVB, UVA, and VL) owing to unsatisfactory use of sunscreens in real-life situations [41].

ENDOCRINE STIMULI

Female sex hormones are well-known risk factors for the development of melasma, and its preponderance in fertile women reinforces this hypothesis. Hormonal imbalances due to pregnancy, ovarian tumors, hormonal replacement therapy, and hormonal contraceptives stimulate melanogenesis [42]. However, the prevalence of melasma following hormonal stimuli varies: 14.5–56% of melasma cases occur in pregnant women, while 11–46% are associated with hormonal contraceptive use [2, 4, 5, 43, 44].

There is insufficient knowledge regarding the role of serum hormone levels in patients with melasma, and different studies have provided contradictory results. The serum levels of estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin in the early menstrual cycle are increased in Indian women with melasma compared with controls [45]. Similarly, estradiol levels in Pakistani women with melasma are higher than in controls [46]. However, lower serum levels of testosterone, LH, free triiodothyronine (fT4), thyroid stimulating hormone (TSH), estradiol, and progesterone have been found in Indian women with melasma than in controls, although no hormone levels have been correlated with melasma severity [47]. In Puerto Rico, a comparison of women with melasma versus controls evidenced lower estradiol but higher LH levels in women with melasma [48].

Beyond ovarian and placental hormones, pregnancy promotes the production of pituitary hormones, including LH, FSH, and MSH, which lead to transcription of tyrosinase and dopachrome tautomerase, increasing physiologic pigmentation and melasma, mainly during the third trimester [49].

Administration of hormones, including topical estrogens, has been reported to trigger melasma [50]. Hormone replacement therapy during the menopause has been associated with extrafacial melasma [51]. Nevertheless, a Brazilian study enrolling women with extrafacial melasma and controls revealed no association with menopause, oral contraceptive use, pregnancy, or hormone replacement therapy [52].

Melasma in men was first reported following hypogonadism, with high LH and FSH and low testosterone levels [53]. A young man developed facial melasma after ingestion of a gonadotropic stimulant, which increased LH levels [54]. Another young man presented melasma associated with the use of finasteride for androgenetic alopecia, which decreased dihydrotestosterone (DHT) levels but increased the testosterone available for peripheral transformation in estrogen [55].

Higher LH and lower testosterone levels have been evidenced in Indian men with melasma in comparison with controls [56]. However, another comparative study found no differences in LH, FSH, TSH, testosterone, progesterone, estradiol, MSH, or dehydroepiandrosterone sulfate (DHEAS) levels [57].

Estrogen and progesterone have been associated with melasma because their effects on the skin are mediated by nuclear receptors, such as

estrogen receptors-α (ER1s) and β (ER2s) and progesterone receptors (PRs) [58]. In facial skin, ER2s are more widely distributed than ER1s, in contrast to the breast and abdomen [59]. Although both receptors have affinity for estradiol, they elicit different cellular responses regarding the epithelial-to-mesenchymal transition by genomic and nongenomic pathways [60].

Estradiol promotes epithelial proliferation through phosphorylation of Extracellular signal-regulated kinase (ERK)1-2/mitogen-activated protein (MAP) kinases and activation of the Wnt/β-catenin pathway in keratinocytes [61]. Furthermore, estrogens lead to increased epithelial production of KGF, which also stimulates melanogenesis [62].

Estradiol influences skin thickness by stimulating fibroblasts and collagen synthesis [63]. Estrogens directly mediate melanogenesis through ER2 activation in melanocytes. Human melanocytes cultured with estrogens show increased MC1R expression, promoting upregulation of *MITF*, *TRP1*, and *TRP2* through the blockade of protein kinase A (PKA). However, addition of ER2 antagonists inhibits melanogenesis [11].

In comparison with adjacent skin, melasma-affected skin presents increased expression of ER2 in the epidermis and fibroblasts in the upper dermis [16, 64].

The role of progesterone and PRs in melanogenesis and melanocyte proliferation is contradictory [65, 66]. In melasma skin, the epidermal PR expression is increased in comparison with adjacent skin [64]. However, progesterone exhibited no effect on tyrosinase activity and demonstrated, after UVR exposure, inhibitory effects of melanocyte proliferation and estrogen-mediated melanogenesis [66].

Regarding other endocrine alterations, thyroid abnormalities have been linked with melasma. However, the results of such studies are controversial, and none has been performed with an adequate methodology to support a reasonable hypothesis on these alterations in the pathogenesis of melasma.

The prevalence of thyroid disorders in Brazilian women with melasma is similar to that expected by age [2]. Among Indian patients with facial melasma, only 7.5% reported hypothyroidism while 0.9% reported polycystic ovary syndrome [40].

A comparison of Iranian women with melasma versus controls revealed no difference in TSH and thyroxine (T4) levels but a greater proportion of abnormalities in triiodothyronine (T3) levels in the melasma group [67]. Another investigation in Iran, comparing women with melasma and controls, found no difference in TSH or T4 levels, but abnormal levels of T3 and anti-thyroid peroxidase antibodies (TPO) were more frequently identified in the melasma group [68].

An assessment of Brazilian women with melasma demonstrated no abnormalities in thyroid hormones (TSH and fT4), prolactin, estradiol, FSH, or LH [69]. Nevertheless, a cross-sectional study in Turkey evaluating women with melasma and controls revealed higher levels of TSH, fT4, and anti-thyroglobulin antibodies, in melasma [70].

An Iranian study comparing women with melasma and controls found no differences in LH, FSH, DHEAS, prolactin, testosterone, or 17-hydroxyprogesterone, but a higher prevalence of ovarian cysts was observed in the melasma group [71].

These controversial results concerning hormonal stimuli may be attributable to the fact that most case series and cross-sectional studies have been conducted after the onset of melasma, when the endocrine imbalance that triggered the disease cannot be synchronously represented. Moreover, melasma can evolve from a focal hypersensitivity to induce hormonal effects, which are not the result of an endocrine disorder.

Endocrine stimuli, especially estrogens, are involved in the pathogenesis of melasma, and the pigmentary system is sensitive to several hormones. However, the role of local sensitivity versus endocrine alterations in melasma are not well established, although it is fundamental to the development of hormonal-based interventions in these patients.

OXIDATIVE STATUS

Exposure to oxidative stressors (such as UVR, air pollution, physical exercise, and sleep deprivation), even under normal conditions, can cause reactive oxygen species (ROS) to be produced in the skin. However, several physiological antioxidant mechanisms can neutralize their effects [72].

The lipid peroxidation of cell membranes is one of the main pathways of tissue damage caused by oxidative stress, and malondialdehyde (MDA) is the final product of this mechanism. However, some antioxidant substances can inhibit the oxidative damage caused by free radicals [73]. A strong negative correlation has been found between plasma glutathione (GSH) and the severity of melasma, suggesting that it represents a high-oxidative-stress condition, which leads to GSH depletion [74]. Plasma levels of superoxide dismutase (SOD) and GSH peroxidase activity are higher in patients with melasma than controls, but carbonyl levels are low [75]. Serum levels of MDA are also high among patients with melasma. In addition, there is a correlation between serum MDA levels and the clinical severity of melasma [76].

Inducible nitric oxide synthase (iNOS) is the primary source of nitric oxide (NO) in melasma and other inflammatory disorders. UVB stimulates the phosphatidylinositol 3-kinase/Akt pathway and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which induces iNOS expression in keratinocytes, leading to paracrine NO activation of tyrosinase in melanocytes. In melasma skin, iNOS is overexpressed in keratinocytes in the basal layer, in comparison with adjacent skin [77, 78].

Besides being a key regulator of the circadian rhythm and a potent scavenger of free radicals, melatonin is an indirect antioxidant. It stabilizes cell membranes, making them more resistant to oxidative damage by stimulating other antioxidant enzymes, such as SOD, glutathione peroxidase, and GSH reductase. Melatonin also inhibits UV-light-mediated synthesis of iNOS, and it can influence the metabolism of MSH, estrogen, and progesterone [79]. Serum levels of melatonin and catalase are lower among patients with melasma compared with controls, while serum levels of protein carbonyl and NO are higher [80]. Notably, a preliminary report has indicated promising results after topical and oral use of melatonin in melasma [81]. Finally, as sleep disturbances contribute to oxidative stress and melatonin dysregulation, the investigation of sleep disorders is warranted in melasma, and melatonin should be investigated as a potential adjuvant in the treatment of melasma [82].

The upper dermis of melasma-affected skin presents signs of oxidative stress, such as overexpression of p38, in comparison with adjacent skin [83]. Furthermore, melanin releases ROS after sun exposure, and melanogenesis is an intracellular oxidative process [84]. Several effective treatments for melasma are antioxidants, such as topical vitamin C, niacinamide, cysteamine, kojic acid, phytic acid, and oral pycnogenol [85]. These findings motivate the investigation of the mechanisms that drive the oxidative imbalance in melasma to explore therapeutic and preventive strategies.

Oxidative stress is the final consequence of several forms of damage and can also result from failure of the antioxidant system. In melasma, either local or systemic oxidative stress can be recognized and is associated with disease severity, but precise knowledge on the factors leading to (local and systemic) oxidative stress could lead to the development of effective interventions targeting the pathogenesis of this disease.

FUNCTIONAL ALTERATIONS

Skin with melasma exhibits several functional alterations that exceed those of photoaged skin and interfere with skin homeostasis. The melanin index, erythema index, and pH are higher in skin with melasma compared with adjacent photoexposed skin. However, no biophysical skin properties differ among so-called epidermal, dermal, and mixed melasma.

The skin barrier is compromised in melasma, as the stratum corneum (SC), although highly hydrated, is thinner than perilesional skin. The transepidermal water loss (TEWL) and the

amount of sebum do not differ between skin with melasma and adjacent skin. However, after skin injury caused by tape stripping, the TEWL was found to be increased in skin with melasma while the barrier recovery was delayed [86].

Thinning of the SC is a common finding in photoaged skin, and it correlates with delayed skin barrier recovery, as seen in melasma [87]. This finding is contrary to expectations in darker skin phototypes, which exhibit better barrier recovery, thicker SC, and lower pH than fair skin [88].

In general, total lipids, phosphatidic acid, phosphatidylserine, and ceramides are increased in melasma, possibly as a compensatory mechanism to preserve skin barrier function. Moreover, some key lipids have low expression with high melanocyte activation, suggesting that the repair of the damaged skin barrier may represent an effective additional treatment for melasma [89].

Human melanogenesis is a complex process mediated by paracrine, autocrine, and environmental stimuli, involving hundreds of genes and several signaling pathways that operate at transcriptional and posttranscriptional levels. However, these intricacies lie beyond the scope of this manuscript [90]. Regarding melasma, several melanogenic pathways sustaining skin pigmentation have been suggested (Fig. 1a).

MC1R, which is increased in melanocytes and keratinocytes in melasma, and its agonist α-melanocyte stimulating hormone (α-MSH) but not its antagonist agouti-signaling protein (ASIP), are secreted by the epidermis [83]. MC1R activation leads to transcription of several genes, including *MITF*, a major regulator of melanogenesis, which controls the expression of enzymes, such as tyrosinase, tyrosinase-related protein 1 (TYRP1), and TYRP2 [90]. Thus, classic treatments of melasma (such as hydroquinone and thiamidol) target tyrosinase inhibition, but melanogenesis represents the end of a complex underlying process, which can explain the frequent disease relapse [91].

Several growth factors with melanogenic activity are secreted by keratinocytes and fibroblasts in melasma. UVR stimulates fibroblasts to release HGF, NGFβ, SCF, and bFGF [92]. In vitro studies have found an accumulation of melanin in basal keratinocytes when epidermal tissue is incubated with UV-treated fibroblasts, suggesting a pigmentary role of fibroblasts in melasma [92]. SCF expression is increased in melasma dermis compared with nonlesional dermis; despite no difference in these epidermises, c-KIT is increased in the epidermis of melasma [26]. Moreover, KGF secreted by fibroblasts accumulates in the epidermis of melasma skin [93].

The Wnt/β-catenin pathway participates in melanoblast migration and proliferation, and the induction of pigmentation [94]. Wnt1 is its main activator through the frizzled receptor and promotes β-catenin accumulation and stabilization [95]. There is greater epidermal expression of Wnt1 in melasma skin than in adjacent healthy skin or photoprotected areas; additionally, Wnt1 correlates with the MC density in the upper dermis [1]. In addition, sFRP2 is overexpressed in the epidermis and around fibroblasts in melasma [27].

PAR2 is a member of the G protein-coupled receptor family and is activated by different stimuli, such as MC tryptase, KGF, α-MSH, factor VIIa, and factor Xa. The activation of a PAR2 receptor in keratinocytes mediates melanosome transfer and increases the production of SCF, which culminates in melanin synthesis [90].

Endothelins are potent vasoconstrictors produced by endothelial cells and keratinocytes after minimal UVB exposure [96]. They induce melanogenesis directly by binding to the endothelin B receptor (EDNRB), a specific receptor on melanocytes [97]. The expression of EDRNB and c-KIT in melanocytes is also induced by UVB [96]. Endothelin-1 (ET1), rather than other factors secreted by dermal endothelial cells, such as NO, leukotrienes, and VEGF, has been indicated as the mediator responsible for the activation of signaling pathways in melanogenesis. EDNRB triggers an enzymatic phosphorylation cascade of microphthalmia-associated transcription factor (MITF), causing upregulation of tyrosinase and dopachrome tautomerase via mitogen-activated protein kinases (MAPKs), ERK1/2, and p38 [97]. The role of endothelins and PAR2 activation in melasma has yet to be clarified, although tranexamic acid reduces ET1 in melasma.

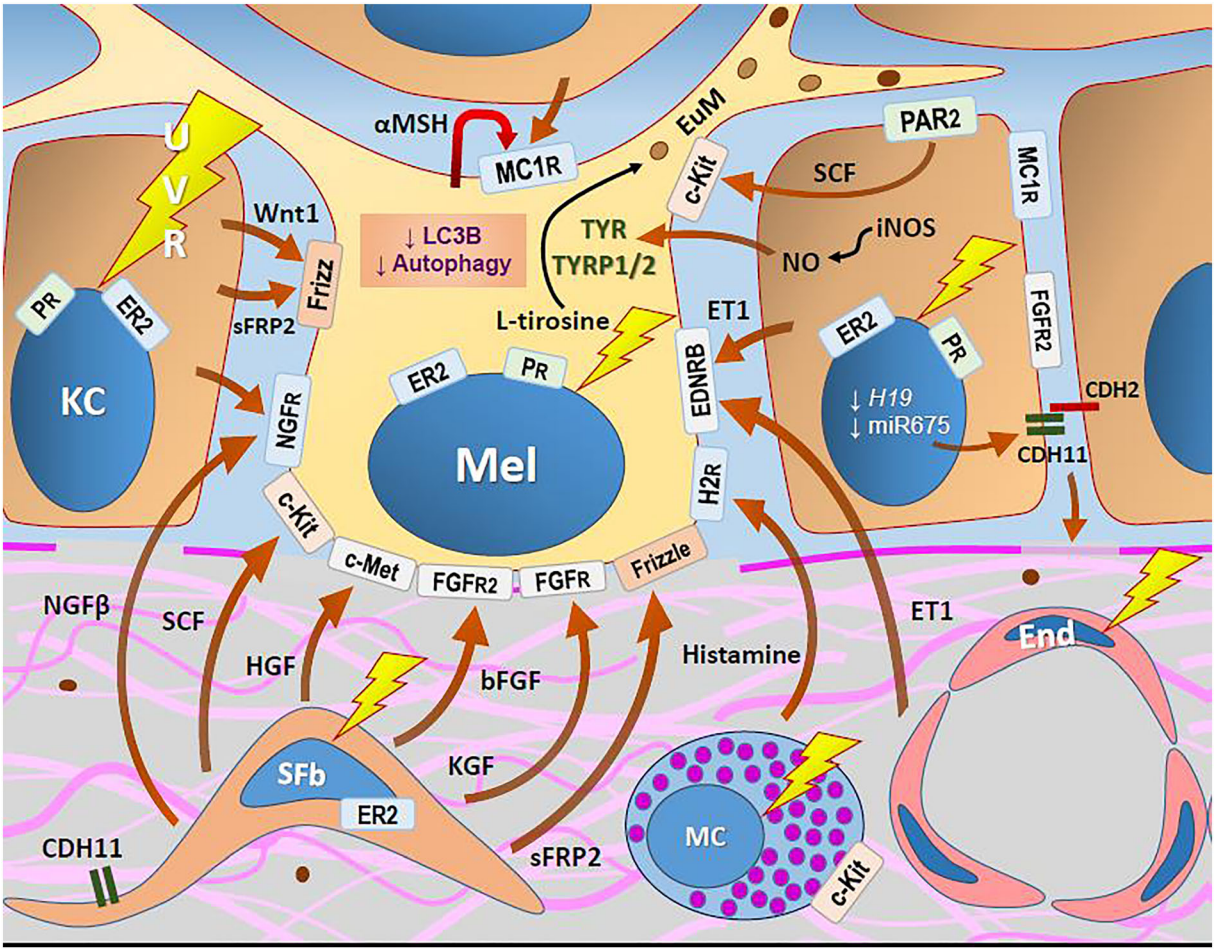

Fig. 1 Theoretic model of melanogenic pathways involved in melasma. Melanocytes (Mels) are hyperfunctional, promoting eumelanogenesis (Eum) due to paracrine and autocrine stimuli. UVR elicits melanogenic, oxidative, and inflammatory responses in the epidermis and upper dermis. Melanocortin (αMSH) and its receptor (MC1R) are increased in keratinocytes (KCs) and Mels. Hormonal stimuli mediate melanogenesis through the nuclear receptors of estrogen-β (ER2) and progesterone (PR). Several growth factors, which are also melanogenic, are actively released by senescent fibroblasts (SFbs), including nerve growth factor type β (NGFβ), SCF, HGF, bFGF, KGF, and sFRP2. Endothelin-1 (ET1) is secreted by the endothelium (End) and KCs after UVR exposure. Mast cells (MCs) release histamine under paracrine stimulation and UVR. Protease-activated receptor-2 (PAR2) stimulates melanocyte dendricity and melanosome phagocytosis by KCs and induces the release of SCF. In melasma, Mels present diminished autophagy (↓ LC3B–microtubule-associated proteins 1A/1B light chain 3B), which stimulates melanogenesis. In addition, the lower expression of miR-675, a MITF-targeted micro-RNA, is associated with greater expression of cadherin-11 (CDH11) in KCs and fibroblasts, which contributes to basement membrane and upper dermal damage. Nitric oxide (NO), produced by inducible nitrogen oxide synthase (iNOS) and Wnt1, is increased in the epidermis in melasma

UV-induced cyclooxygenase-2 (COX-2) expression prompts synthesis of PGE2 by keratinocytes, which mediates skin inflammation and cell proliferation. In vitro studies have indicated that COX-2 knockdown in melanocytes decreases the expression of tyrosinase, TRP-1, TRP-2, gp100, and MITF and reduces tyrosinase enzyme activity [98]. However, there is still no evidence to support the differential expression of PGE2 as a major pathogenic factor in melasma [83].

Autophagy is a catabolic cytoplasmic process that degrades abnormal proteins and damaged macromolecules [99]. It can be induced by starvation, hypoxia, oxidative stress, and UVR exposure [99]. The participation of autophagy in skin pigmentation is suggested by the evidence of impaired autophagy in premature skin aging [99]. Furthermore, there are differences in autophagic activity regarding ancestry, and keratinocytes from Caucasian individuals exhibit higher autophagic activity than those from African American individuals [100]. In cell cultures, autophagy-deficient melanocytes retain mature melanosomes and release chemokine ligands (CXCL1/2/10/12), which are associated with the induction of pigmentation and expression of MMP3 and 13 [101]. LC3 is a protein that participates in all phases of autophagy, and melanocytes from the basal layer in melasma have been found to present low expression of microtubule-associated proteins 1A/1B light chain 3B (LC3B), suggesting deficits in the autophagy process [102].

Fibroblast senescence is well documented in aged skin, especially following UVR exposure [103]. The dermis of melasma is prominent in senescent fibroblasts, which are less fusiform and have a lower mitotic rate; moreover, these cells present a proinflammatory and melanogenic secretory profile (e.g., SCF, HGF, and NGFβ) [16, 28]. Therefore, strategies that interfere with their secretory phenotype and eliminate senescent cells can reduce melasma recurrence and improve pigmentation [104].

Finally, a proteomic study of skin with melasma identified 29 differentially regulated proteins involved in energy metabolism, cell transport phenomena, control of melanogenesis, hemostasis, repair, and responses to oxidative stress [105].

All these functional alterations of the skin of melasma reinforce a localized phenotype that involves not only hypermelanogenesis but also changes in the whole epidermis and upper dermis, as discussed below.

MORPHOLOGIC ALTERATIONS

The epidermis in melasma presents morphologic alterations beyond hypermelanosis. The SC is more compact than in adjacent skin, and the granular layer is atrophic, with ridge flattening and epidermal thinning. Basal keratinocyte nuclei display larger sizes, polarization loss, irregular shapes, hyperpigmentation, and chromatin heterogeneity (Fig. 2a) compared with neighboring skin [1, 106]. Microneedling promotes early restoration of the epidermal thickness and increases Ki67 in patients with facial melasma [107].

The most important morphologic element in melasma is the increased epidermal density of eumelanin in all layers, including the SC (Fig. 2b), in which there is greater melanin degradation compared with adjacent skin [108].

Melanosomes transferred across the epidermis of melasma are larger, more mature, and more numerous than those in adjacent photoexposed skin. These alterations are independent of the skin phototype (Fig. 3) [109]. Low-fluence (laser toning) technologies target intraepidermal melanosome destruction with minimal thermal damage and accelerate the clinical results of conventional melasma treatments; however, they do not target the underlying alterations that maintain the stimuli-induced pigmentation [110].

The melanin density in the upper dermis is approximately 50–100 times lower than in the epidermis (Fig. 2b). Moreover, there is no difference in the amount of dermal melanin between melasma skin and adjacent photoexposed skin, but it is more intense than in photoprotected skin [1]. Upper dermal melanin increases with photodamage, and it is constitutively more prominent in darker phototypes.

The role of dermal melanin in melasma regarding clinical pigmentation and its role in treatment resistance is still a matter of discussion. Dermal melanin does not differ between epidermal and dermal melasma, as assessed by a Wood's lamp, highlighting that the differences observed in this clinical classification are not supported by histologic findings [111, 112]. In a study of 56 patients with melasma, only 7 (12%)

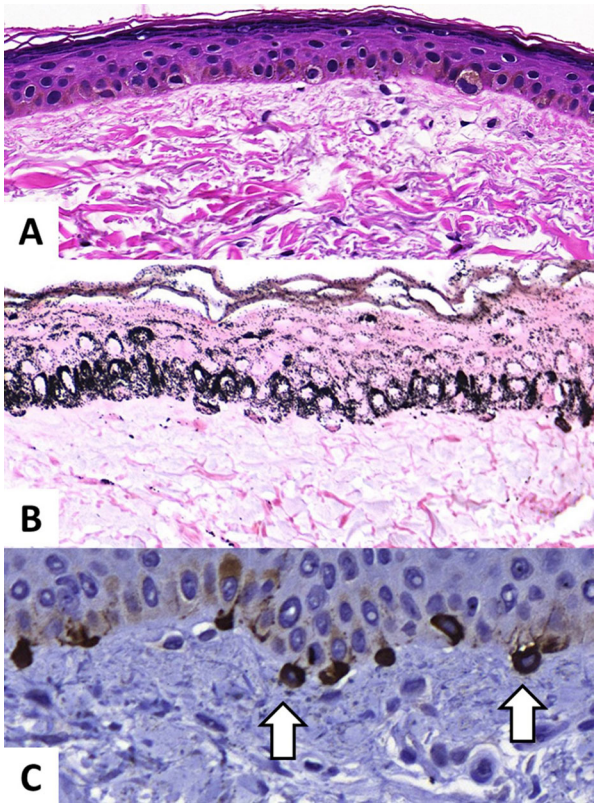

Fig. 2 Histologic images of facial melasma. **A** Atrophic epidermis with a thin stratum corneum, hypogranulosis, and polarization loss of the nuclei in the basal layer. Upper dermis revealing solar elastosis and overall unstructured collagen fibers (hematoxylin and eosin, 100×). **B** Dense and homogeneous melanin pigmentation with coarse melanosomes in all epidermal layers, including the stratum corneum, and extracellular melanin granules in the upper dermis (Fontana–Masson, 400×). **C** Atrophic epidermis with hypertrophic melanocytes (in brown) with prominent dendrites and melanocytes protruding into the dermis (pendulum melanocytes, arrows) and losing contact with the basal layer (Melan-A, 400×)

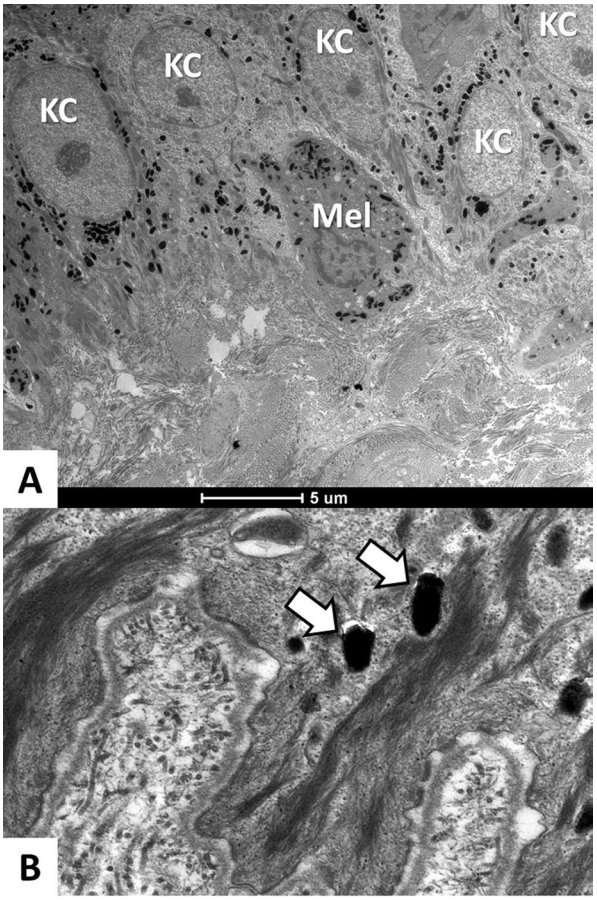

Fig. 3 Transmission electronic microscopy of facial melasma. **A** Intense distribution of mature melanosomes in the epidermis (KC, keratinocyte; Mel, Melanocyte). Sparse extracellular melanosomes in the upper dermis. **B** Mature and large melanosomes (type IV) in the cytoplasm of a keratinocyte from the basal layer (white arrows)

presented increased dermal melanin and melanophages compared with patients with perilesional skin [113]. Other controlled series have found no difference in dermal melanin between melasma skin and perilesional skin [109, 114]. However, an Indian series found that pigmentary incontinence and dermal melanophages are more frequent in melasma skin than adjacent skin. Notably, in that study, dermal melanin was evidenced in 77% of participants and classified as epidermal melasma, without differentiation between dermal and mixed [115]. Furthermore, despite the effective bleaching of melasma lesions after treatment with a triple combination, microneedling, or tranexamic acid, there is no difference in dermal melanin compared with pretreatment [116].

Melanocytes increase in volume and their dendrites are more prominent in the basal layer

of melasma skin (Fig. 2c) than in adjacent photoexposed skin. However, there is no evidence of a substantial increase in melanocyte density, as seen in solar lentigines [109, 113, 117].

Pendulum melanocytes protrude from the basal layer into the dermis (Figs. 2c, 3a) [118]. They are more frequent in melasma skin than in adjacent skin, and there is a correlation with the compaction of the SC, number of MCs, and solar elastosis [1]. However, they are not correlated with BM zone failures, suggesting that the presence of these cells is a result of chronic exposure to UVR (especially UVA1). However, as normal melanocytes do not survive in the dermis and pendulum melanocytes lose the connection to the epidermis, they are not involved in epidermal pigmentation or active dermal melanogenesis [119]. As some effective treatments for melasma (such as oral tranexamic acid) reduce the number of pendulum melanocytes, clarification of the role of these cells in the pathogenesis of melasma may be key to developing new therapeutic strategies [116].

Disruptions and gaps are more frequent in the BM in melasma skin than in adjacent healthy skin (Fig. 4). Moreover, the lamina densa is thinner, and there is a loss of anchoring fibrils from lamina lucida [120]. Structural damage to the BM facilitates the traffic of dermal cytokines to the epidermis. This may be promoted by increased activity of MMP2 and MMP9, causing degradation of collagen types IV and VII [120]. Keratinocyte expression of CDH11 has been associated with BM damage in melasma [12]. Microneedling promotes early restoration of BM damage in patients with facial melasma [107].

It has been suggested that the alterations in the upper dermis are responsible for the maintenance and recurrence of melasma. Dermal paracrine regulation of melanogenesis by mechanisms that are not completely known causes the permanent stimulation of epidermal pigmentation, which is a UVR-induced process related to the oxidative cell aging cycle (as senescent fibroblast) involving feedback by cytokines [96, 121].

Solar elastosis (SE) is more prominent in melasma skin (Fig. 5a) than in adjacent photoexposed skin. It largely results from the activation of metalloproteinases in the upper dermis due to UVR, MC activation, and the senescent fibroblast secretory phenotype [1, 113, 118]. SE is not considered a secondary epiphenomenon of photoaging but a condition characteristic of melasma development. The severity of SE is correlated with collagen heterogeneity after its fragmentation, superficial dermis cellularity, increase of MCs and dermal blood vessels, pendulum melanocytes,

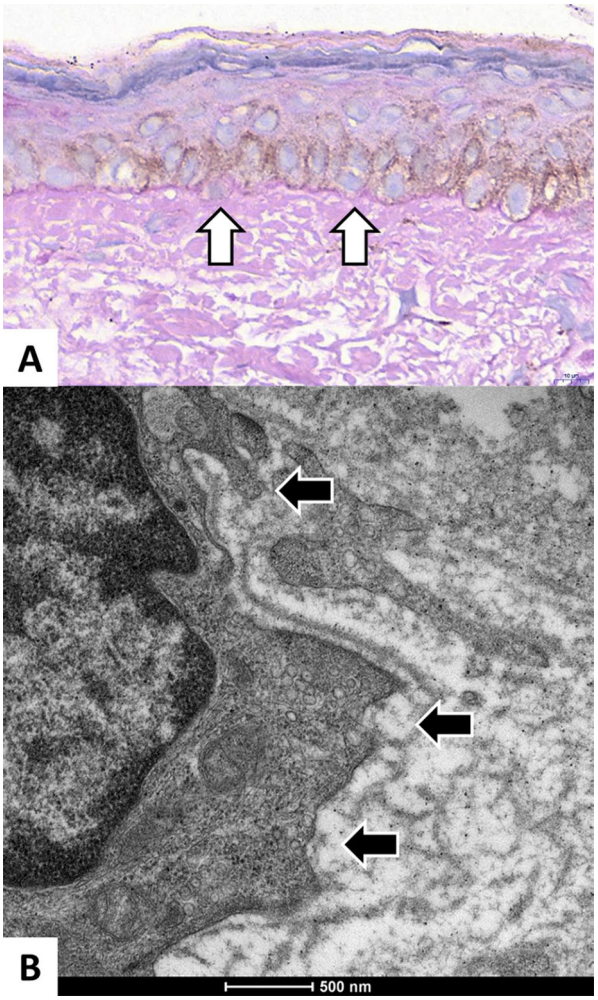

Fig. 4 Facial melasma. **A** Periodic acid–Schiff staining (400×) evidencing thinning and several discontinuities in the basement membrane (white arrows). **B** Transmission electronic microscopy of the dermoepidermal junction under a melanocyte revealing complete interruption of the lamina densa, structural damage, and loss of anchoring fibrils in the lamina lucida (black arrows)

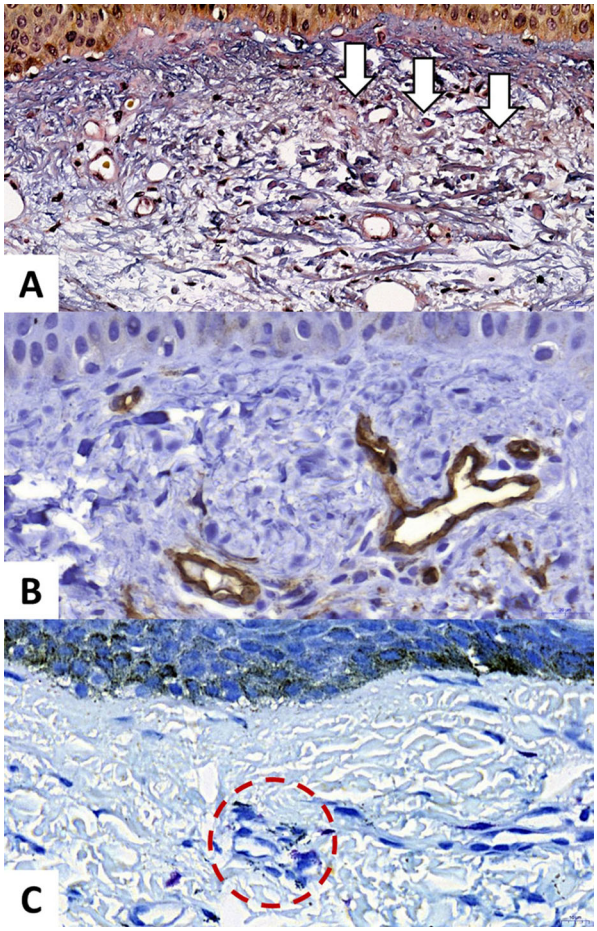

Fig. 5 Facial melasma. **A** Histologic image (Herovici, 200×) revealing upper dermis collagen fiber fragmentation with loss of structure and elastonization (solar elastosis, arrows). **B** Immunohistochemistry image of facial melasma (CD34, 400×) evidencing upper dermis endothelial proliferation (brown structures). **C** Histologic image (Toluidine Blue, 400×) evidencing mast cells in the upper dermis, especially in the perivascular areas (dashed circle)

SC compaction, and elastic fiber damage, suggesting the integration of various components in the pathogenesis of melasma [1, 122].

Skin with melasma presents an increased density of blood vessels (Fig. 5b) with an increased expression of VEGF, which is the likely angiogenic factor involved. The endothelial proliferation is also correlated with the intensity of melasma pigmentation [22, 97]. Pycnogenol, tranexamic acid, and vascular lasers improve melasma by reducing vascular proliferation [22, 123].

Perivascular MCs are increased in the upper dermis of melasma skin (Fig. 5c) in comparison with adjacent photoexposed skin, in which MCs are increased in contrast to retroauricular skin [1]. Patients with melasma treated with oral tranexamic acid have presented decreased MC counts in the upper dermis [124]. Moreover, women with melasma treated with oral ketotifen and famotidine have presented clinical and colorimetric improvement, superior to placebo, supporting the role of these cells in the pathogenesis of melasma [125].

MCs are not usual in normal photoprotected skin, as they are effector cells in allergic reactions and participate in tissue remodeling and repair. Their migration to the melasma dermis is mediated by SCF, secreted by senescent fibroblasts (Fig. 6) [26]. MC activity is influenced by environmental effects, and MCs degranulate with stimuli, such as heat, pressure, and UVR exposure. Inflammation and neurokinins also induce the release of a variety of biologically active mediators (such as heparin, bradykinin, serotonin, thromboxane, prostaglandins, and leukotrienes). The most relevant is histamine, which is a predominant component in cytosolic granules [29]. Histamine appears to play a central role in melanogenesis; human melanocytes treated with histamine undergo morphological changes and increased tyrosinase activity. These effects are completely inhibited by an H2 antagonist but not by an H1 antagonist [126].

In addition, MCs release enzymes that have a local tissue effect. The most important is tryptase, which contributes to the activation of MMPs and collagen degradation in the upper dermis. These active enzymes degrade type IV collagen and damage the BM [106].

MCs can induce vascular proliferation by secreting angiogenic factors, including VEGF, fibroblast growth factor-2, and transforming growth factor-β (TGF-β). These findings suggest that MCs are associated with UVR-induced chronic photoaging and promote SE, BM damage, and vascular proliferation, all of which are predominant features of melasma skin [106].

The role of sebocytes in melasma is still not established. Sebaceous glands are a well-known

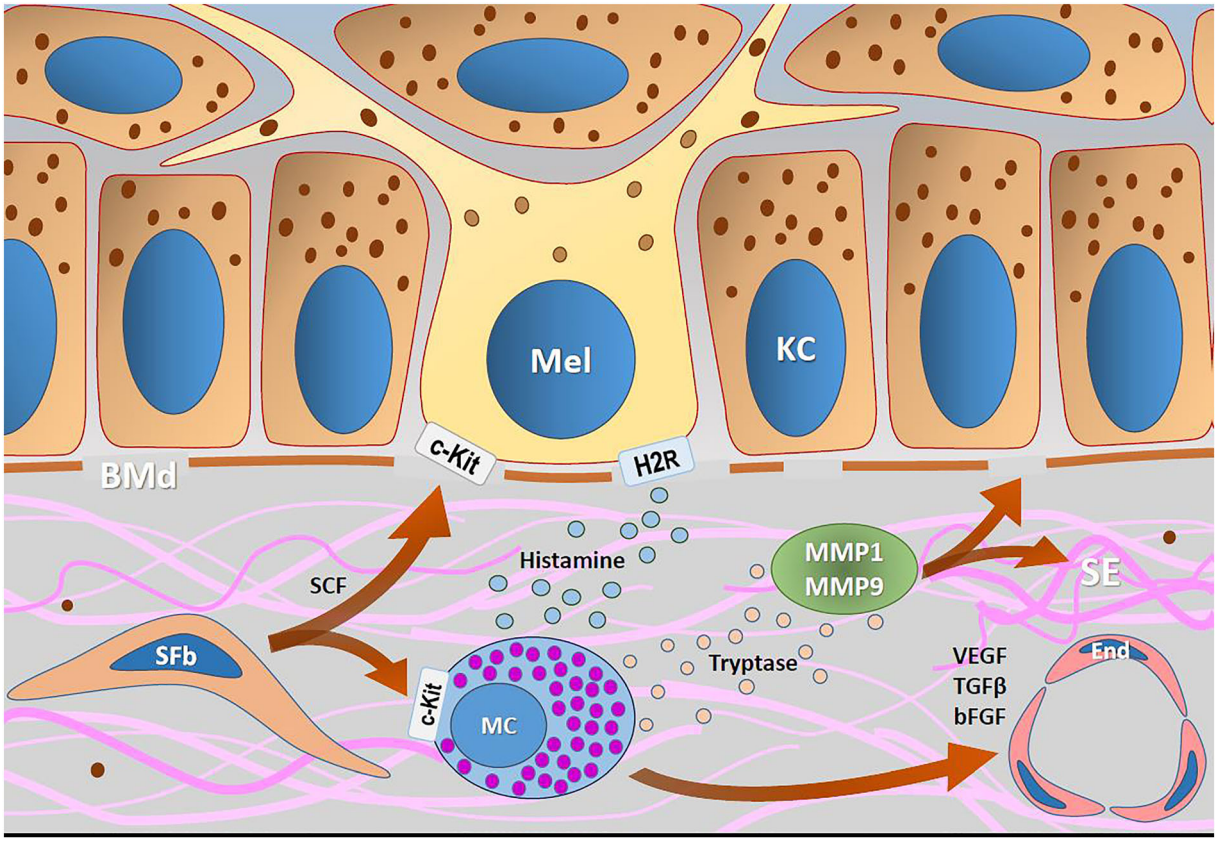

Fig. 6 Schematic representation of the interaction between senescent fibroblasts (SFbs) and mast cells (MCs) in melasma. Histamine stimulates melanogenesis directly through H2-receptors (H2Rs) in melanocytes (Mels). SCF is overexpressed in melasma, which influences MC survival, migration, and activation; it binds to the c-KIT receptor, inducing melanogenesis and the Mel cell cycle. Tryptase activates metalloproteinases (MMP1 and MMP9), which degrade type I and IV collagens, leading to extracellular matrix degradation (solar elastosis; SE) and basement membrane damage (BMd). MCs also induce endothelial (End) proliferation by secreting VEGF, bFGF, and TGF-β

source of VEGF, IL-1, and IL-6. Sebaceous gland cells exposed in vitro to UVA induced production of α-MSH, endothelin 1 (EDN1), b-FGF, SCF, and inflammatory cytokines and mediators. Furthermore, sebocyte-conditioned media increased pigmentation in melanocytes. In vitro, melanocytes cocultivated with sebocytes present greater dendricity and proliferation rates, suggesting that sebaceous glands may regulate melanin pigmentation [127, 128]. Although centrofacial melasma is more frequent, high-density sebaceous areas, such as the nose tip, glabella, and chin, are not involved in most cases.

Actually, damage in the basement membrane zone (BMZ), solar elastosis, and increased MC are also found in photoaged skin, and as melasma affects photoaged skin, it was suggested that melasma is a photoaging disorder [18, 129]. Nevertheless, in a comparison among melasma, adjacent photoexposed and retroauricular skin, despite the continuum between these findings at these sites, alterations in skin barrier, pendulum melanocytes, upper dermal collagen fragmentation, and the amount of CD34 cells were greater in melasma but did not differ between photoexposed and retroauricular skin, leading to the hypothesis of melasma as an

individualized phenotype that emerges from photoaged skin [1].

In addition, further studies on melasma pathogenesis should use adjacent photoaged skin, since the histological architecture, melanocyte density, melanophages, MC, hair follicles, and functional measures show major differences when comparing facial and extrafacial skin [130].

MISCELLANEOUS

Melasma has been associated with other triggers, such as drugs, esthetic treatments, contact dermatitis, and stressful events.

The role of topical drugs and cosmetics in melasma has been reported, but this hypothesis remains unconfirmed. In a study including patients with melasma who were patch tested, a cosmetic and fragrance series elicited positive reactions in 43%, but sunscreen series did not elicit any positive reaction. The high frequency of positivity suggests cosmetic contact sensitivity as a possible trigger for melasma [131]. In Northern India, mustard oil is commonly used on the face as an emollient and on the scalp for hair growth. It is a known photosensitizer that can act as a melasma trigger in predisposed individuals [57].

Acute stressful events have been associated with the development or worsening of melasma [132]. Notably, stress-related hormones, such as propiomelanocortins, are melanogenic through MC1R activation, as occurs in Addison's disease, although physiologic pituitary production has no effect on skin pigmentation. When compared with matched controls, a greater proportion of women with melasma uses antidepressant and anxiolytic drugs, and their scores of anxiety and depression are higher [5]. Other neuropsychological alterations in patients with melasma are low self-esteem, poor sleep quality, and higher accuracy in recognizing facial expressions of fear, suggesting differentiated brain processing of emotions [132, 133].

Melasma has been reported after peelings, intense pulsed light, and ablative treatments, which are all known to be triggers of postinflammatory hyperpigmentation. The association of these two conditions is well documented, and postinflammatory hyperpigmentation is 2.8 times more frequent in patients with melasma [134]. Melasma is also associated with lentigines and nevi, suggesting a predisposition to melanocytic proliferation in these patients [135].

Urban and industrialized societies are associated with greater exposure to air pollutants, leading to a significant health burden that includes dermatologic disorders [136]. The primary mediator of air pollution effects in the skin is the aryl hydrocarbon receptor (AhR), which is activated by aromatic hydrocarbons that are widely present in vehicular smoke. The AhR participates in the cell cycle and melanogenesis through upregulation of tyrosinase in the melanocytes. UVR exposure generates 6-formylindolo[3,2-*b*]carbazole, which is a high-affinity ligand and endogenous activator of the AhR transcription factor [137, 138]. Actually, the incidence of melasma seems to be increasing worldwide, especially in countries with greater indexes of air pollution [139].

Melanogenesis can be regulated by epigenetic factors, such as miRNAs, DNA methylation, and posttranscriptional controllers [140, 141]. Lower expression of miR-675 and miR-1299 has been demonstrated in skin with melasma compared with the adjacent area [142, 143].

Finally, ocular irradiation with UVR induces the central release of propiomelanocortins by hypophysis [144]. Though the pigmentary potential of this extracutaneous pathway has not been evidenced in humans, it is well defined in mice, in which UVB irradiation of the eye stimulates epidermal melanocytes and melanogenesis [145, 146].

All these factors that play a role in skin pigmentation need to be studied systematically in melasma, since the relapse of the disease after treatment and adequate sun protection can be promoted by several other factors.

CONCLUSIONS

Despite its high prevalence and the demand for dermatologic care, the mechanisms that lead to the sustained pigmentation in melasma are not completely understood. Beyond individual genetic susceptibility, several phenotypic alterations have been identified in the epidermis and upper dermis in melasma, especially related to the deficit of autophagy in melanocytes, and the senescence of fibroblasts. Moreover, the role of endocrine factors and oxidative stress are matters for future investigation regarding their systemic and local (in the skin microenvironment) actions, as well as how radiation of different wavelengths interferes with melanogenesis in melasma.

The pigmentary response in melasma is related to the interaction of multiple factors. As dermatologic science better understands the regulation of normal melanogenesis, photoaging, and the pathogenesis of melasma, new pathways will emerge as possible targets for effective treatment and preventive strategies.

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