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REVIEW ARTICLE

An updated review of melasma pathogenesis

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ABSTRACT

Melasma is a pigmentation disorder characterized by common clinical findings. However, the pathogenic mechanisms involved are heterogeneous in different individuals and ethnic groups. We have reviewed the pathophysiological mechanisms involved in melasma. Although the pathogenesis has not entirely been elucidated thus far, new findings are being identified by research groups. Epidemiologic studies may provide clues on the involvement of genetic factor(s), UV irradiation, or hormones in melasma. Some of the mechanisms of altered skin pigmentation, such as UV-induced pigmentation, may also be applicable to the pathogenesis of melasma. In fact, an increase in similar keratinocyte-derived melanogenic factors and their receptors occur in both UV-induced melanogenesis and melasma. Increased expression of female sex hormone receptors and the identification of the PDZ domain containing 1 (PDZK1) signaling mechanism provide insights to further our understanding of melasma. In addition to keratinocyte-derived paracrine factors, the role of paracrine factors from dermal fibroblasts, such as stem cell factor (SCF) and Wnt inhibitory factor-1 (WIF-1), is elucidated in melasma. Furthermore, the involvement of ion exchangers and microRNAs (miRNAs), such as H19 miRNA (miR-675), are also suggested.

Introduction

Melasma is one of the most commonly acquired hyperpigmentations that mainly affects the face. The disorder is much more common in women, particularly of reproductive age, and in darker skin types, such as Hispanics, Latinos, Asians, and African–Americans. Melasma has a deleterious impact on a patient's quality of life. The published review articles concerning melasma mostly focus on its treatment, however melasma remains therapeutically challenging. A thorough understanding of the etiology and pathogenesis is crucial to manage this condition.

The etiopathogenesis of melasma includes genetic influences, exposure to UV light, and hormonal activity. However, melasma is not the same skin hyperpigmentation as that induced by UV irradiation or inflammation. In addition, differences in susceptibility to melasma are identified between races and individuals. Nonetheless, most of the earlier studies examine mechanisms of skin hyperpigmentation induced by UV irradiation, hormones, growth factors, or cytokines.

Here, melasma is reviewed with the focus primarily on pathomechanisms with related clinical and microscopic findings.

Factors influencing melasma development

Genetic backgrounds, exposure to UV, and female sex hormones are implicated as the main causes of melasma.[1] Melanocytes undoubtedly play a critical role in melasma development and/or aggravation. However, increasing lines of evidence suggest that paracrine factors from neighboring keratinocytes or fibroblasts play a role in the pathogenesis of melasma.

Genetic factors involved in melasma

Racial and/or familial predisposition suggests that genetic factors contribute to the pathogenesis of melasma. However, to date, there have been no gene association studies with melasma. Pigmentary disorders including melasma are common in Hispanic and Asian racial groups with Fitzpatrick skin types III/V,[2] although a few epidemiologic reports are available in different ethnic groups.

Studies from different countries address the familial occurrence of the disorder. An epidemiologic study in a tertiary dermatological

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Table 1 Epidemiologic studies on familial occurrence of melasma.

References		Goh and Dlova[3]	Achar and Rathi[4]	Moin et al[5]	Tamega Ade et al[6]
Population		Singapore	India	Iran	Brazil
Participants	Total number	205	312	400	302
	Specific remark			Pregnant women	
	Skin phototype	III or IV in 90%			III in 34.4%; IV in 38.4%
Positive history, *n* (%)		21 (10.2)	104 (33.3)	(54.7)	(56.3)

referral center in Singapore showed that a positive family history was observed in 21 (10.2%) of 205 patients with melasma. Although 90% of the participants had skin phototype III or IV, the rate was not high.[3] A study with 312 patients with melasma in India reported that 104 patients (33.3%) had a positive family history.[4] A multicentric study across four regions in India also showed a similar overall rate, i.e., 31%, although a regional difference in the same country ranged from a low of 18.2% to a high of 38.5%. Positive family history, as high as 54.7%, was shown in a study on 400 pregnant women in Iran.[5] The high positive rate may have been due to the limited population of participant pregnant women. Racial preponderance may also reflect the high rate in this study.[5] However, without limitation of participants, familial occurrence is as high as 56.3% of 302 patients from Brazil.[6] Although the rate of occurrence from different countries and even from the same country shows a wide range of differences (Table 1),[3–6] family history is associated with melasma on epidemiologic study.

Role of UV irradiation in melasma

Sun exposure is generally believed to be one of the important causes of melasma. The location of the lesion and the development and/or aggravation of symptoms after sun exposure suggest a role for UV irradiation in melasma. Epidemiologic studies suggest that sun exposure alone[3,4,6] or sun exposure during pregnancy[7] may trigger or aggravate some patients with melasma (Table 2).[3–6] These results provide a rationale for the use of sunscreen in the management of melasma. However, these findings are not enough to conclude that an association between UV exposure and melasma development exists. In addition, no significant relation was shown between melasma and the use of sunscreens in an earlier study.[5]

The effect of UV irradiation on melanogenesis is well established. Repeated exposure to a suberythemal dose of UV radiation stimulates melanogenesis, increasing skin melanin content.[8] Excessive melanin deposition in the epidermis and dermis is also an outstanding microscopic finding of melasma, indicative of specific hyperfunctional melanocytes.[9] Microscopic findings may provide an insight into the role of UV exposure in melasma. However, as yet, there is no evidence for a direct association between melasma and UV irradiation.

The association between melasma and UV irradiation is assumed based on the effects and mechanisms of action of UV irradiation on melanogenesis/melanosome transfer (Table 3).[10,11,13–15,18–25] UV-induced melanogenesis is mediated by direct effects of UV photons on DNA[10] and on melanocyte membranes. UV irradiation releases diacyl glycerol (DAG) and arachidonic acid from melanocyte membranes.[11] DAG is a representative endogenous factor of protein kinase C (PKC) activation, which is an important signal transduction pathway for the regulation of melanogenesis.[12] However, DNA damage or DAG/arachidonic acid pathways are undelineated in melasma. An increase in cell surface expression of receptors for keratinocyte-derived melanogenic factors is also involved in UV-induced melanogenesis. Basic fibroblast growth factor (bFGF), nerve growth factor (NGF), endothelin-1 (ET-1), and the proopiomelanocortin (POMC)-derived peptides, such as melanocyte stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), and beta-endorphin, are among the UV-induced paracrine melanogenic factors derived from keratinocytes.[13–15] Particularly, the melanogenic effect of POMC-derived peptides is mediated by binding to the specific receptor melanocortin-1 receptor (MC1R).[16] MC1R signal transduction is coupled to the activation of adenyl cyclase,[17] resulting in increased 3′,5′-cyclic adenosine monophosphate (cAMP) production. Similar findings on keratinocyte-derived melanogenic factors are observed in melasma skin. Increased expression of several factors is observed in hyperpigmented lesional skin compared to normally pigmented skin of melasma patients—these include NGF receptor with neural endopeptidase,[18] NGF,[19] alpha-MSH,[20] or alpha-MSH with MC1R.[21] Keratinocytes also secrete nitric oxide (NO) in response to UV radiation, playing an important role in UV-induced melanogenesis[22] through the cyclic guanosine 3′,5′-monophosphate pathway.[23] The role of NO in the pathogenesis of melasma is based on the observation of increased inducible NO synthase expression in the hyperpigmented lesional skin of melasma.[24] In addition, UV-B irradiation causes acute inflammation and elevation of histamine levels, leading to UV-B-induced pigmentation.[25] Although a role of mast cells in the pathogenesis is suggested,[26,27] histamine levels remain to be examined in melasma.

Chronic sun exposure results in numerous changes in the human skin such as wrinkling, elastosis, actinic keratosis, irregular pigmentation, telangiectasia, and skin cancer. More striking changes occur in the dermis by UV irradiation, showing massive elastosis, collagen degeneration and twisted dilated microvasculature as microscopic findings.[28] UV-induced degradation of dermal collagens could induce the wrinkling.[29] Elastase-like activity expressed by fibroblasts from sun-exposed skin is involved in the elastosis.[30] The microscopic finding of solar elastosis alone is considered a gold standard for assessing photodamage in skin, although there is no single method to quantify accurately the degenerative changes associated with photodamage.[31] Dermal changes on microscopic examination of melasma skin reveal more abundant elastotic material in hyperpigmented lesional compared to normally pigmented skin, as well as increased vascularity.[26,32,33] Similarities in the microscopic findings between skin with chronic UV exposure and melasma skin (Table 4)[26,28,29,31–33] may provide

Table 2 Epidemiologic studies on the effect of sun exposure in melasma.

References	Goh and Dlova[3]	Achar and Rathi[4]	Moin et al[5]	Tamega Ade et al[6]	Ortonne et al[7]
Population	Singapore	India	Iran	Brazil	France
Rate of association stated by participants (%)	26.8	55.1	9.8	27.2	27 with increasing outdoor activity during pregnancy
Effect of sunscreens stated by participants			No relation		

Table 3 Studies on melanogenic factors presented in UV-induced pigmentation versus melasma.

	UV-induced pigmentation	Melasma	Remarks
UV photons	Eller et al[10]; Carsberg et al[11]		
Keratinocyte-derived paracrine factors	bFGF[13]	NGF receptor[18]	In melasma, data came from immunohistochemistry
	NGF[13]	NGF[19]	
	ET-1[13,15]	alpha-MSH[20,21]	
	POMC-derived peptides (MSH, ACTH)[13,14]		
NO from keratinocytes	NO[22,23]	iNOS[24]	
Inflammation mediator	Histamine[25]		

ACTH = adrenocorticotropic hormone; bFGF = basic fibroblast growth factor; ET-1 = endothelin-1; iNOS = inducible nitric oxide synthase; MSH = melanocyte stimulating hormone; NGF = nerve growth factor; NO = nitric oxide; POMC = proopiomelanocortin.

morphological evidence for the role of cumulative sun exposure in the pathogenesis of melasma.

Effect of female sex hormones on melasma

Melasma occurs more commonly in females than males, although the epidemiological data for female to male ratios shows a country-dependent difference, such as 21:1 in Singapore[3] and 4:1 in India.[4] A female preponderance suggests a role for the female sex hormones in the pathogenesis of melasma. In fact, melasma is an undesirable cutaneous effect of oral contraceptives.[34] In addition, the advent of finasteride, an anti-androgen, may be related to an increase in male melasma patients.[35] In relation to pregnancy, melasma is generally considered as a common physiologic skin change due to hormonal alterations.[36] Epidemiologic studies also indicate pregnancy and oral contraceptive pills as important precipitating factors for melasma development and aggravation (Table 5).[3–6,37] A case–control study in 207 patients and 207 age-matched controls suggests a clear association with pregnancy (odd ratio = 3.59) and oral contraceptives (odd ratio = 1.23).[37] Although discrepancy in the prevalence is also observed in pregnancy and with oral contraceptive usage among different ethnic groups and skin phototypes, it is not as remarkable as compared to other factors, such as genetic factors and UV irradiation; 12.1% and 13.1% of melasma patients seen in a tertiary dermatological referral center in Singapore showed a causal relation to pregnancy and oral contraceptives, respectively.[3] A total of 56 (22.4%) patients and 46 (18.4%) patients considered pregnancy and oral contraceptives, respectively, as triggering factors in a study performed in India.[4] In a cross-sectional study in Iran, 14.5% and 11.3% of participants stated pregnancy and oral contraceptives as etiologic factors, respectively.[5] Pregnancy (36.4%) and contraceptive pills (16.2%) were also the most common triggering factors in a questionnaire study in Brazil.[6]

Estrogens have an important function in human skin with significant roles in both physiological and pathological skin conditions including pigmentation. Biological effects from estrogen and progesterone are mediated by their distinct receptors. In fact, the estrogen receptors estrogen receptor-alpha (ER-α) and ER-beta are expressed in human skin.[38] There has been a few findings on the expression of these receptors in melasma (Table 6),[33,39–41] and although the expression level of receptors may not coincide with the biological function, the reports are suggestive of a role for the female sex hormone in melasma pathogenesis. Immunohistochemical staining of melasma demonstrates increased expression of ERs in hyperpigmented lesions compared to normally pigmented skin of melasma patients.[39] An increase in expression of the progesterone receptor is also present in hyperpigmented lesional epidermis, whereas expression of ER is observed in the lesional dermis but not in the epidermis.[33,40] In addition, real-time polymerase chain reaction (PCR) shows higher expression of ER-alpha and/or ER-beta mRNA in the hyperpigmented skin than in the normal skin of melasma patients.[41]

The action mechanism of female sex hormones (estrogen and/or progesterone) involved in pigmentation has not being actively examined. A few studies suggest that estrogens increase the mRNA expression of tyrosinase, tyrosinase-related protein-1 (Trp-1), and Trp-2 and the activity of tyrosinase in cultured normal human melanocytes.[42,43] Activation of the cAMP–protein kinase A (PKA) pathway and upregulation of tyrosinase and microphthalmia-associated transcription factor (MITF) expression and activity is also a mechanism by which estrogen enhances melanin synthesis in melanoma cells.[44] Our recent study identifies a regulatory role for PDZ domain containing 1 (PDZK1) protein as a downstream mechanism of estrogens in melasma.[41] Expression of PDZK1 is upregulated in the hyperpigmented skin of melasma patients. Estrogens increase PDZK1 expression in both melanocytes and keratinocytes, and stimulate melanogenesis and melanosome transfer via ERs. PDZK1 is a member of the sodium–hydrogen exchanger regulatory factor (NHERF) family proteins, which mediate the most abundant protein–protein interactions, thus facilitating the estrogen action in melasma patients (Figure 1).

Table 4 Studies on common microscopic changes in the dermis from chronic sun exposure and melasma.

	Chronic sun exposure	Melasma
Massive elastosis	Gilchrest[28]	Hernández-Barrera et al[26]
	Baillie et al[31]	Kang et al[32]
Collagen degeneration	Gilchrest[28]	
	Nishimori et al[29]	
Dilated microvasculature	Gilchrest[28]	Jang et al[33]

Paracrine factors influencing melasma development/ aggravation

Cell-to-cell interactions play an important role in homeostasis of adult tissues. The crosstalk of resident cells is well documented between melanocytes and keratinocytes, as previously mentioned in UV-induced melanogenesis as well as in melasma. Increasing lines of evidence suggest that cell-to-cell interaction also occurs between melanocytes and dermal fibroblasts in physiological and pathological skin conditions (Table 7).[45–51] In topographic skin color difference, a role of dickkopf 1 (DKK1), an inhibitor of the canonical Wnt signaling pathway, which is secreted by dermal fibroblasts, is identified.[45] In addition, neuregulin-1 secreted by fibroblasts derived from dark skin increases the pigmentation of melanocytes, resulting in regulation of constitutive skin color.[46] Sublethal laser fluence stimulates fibroblasts, resulting in post-laser hyperpigmentation by production of melanogenic factors, such as stem cell factor (SCF), hepatocyte growth factor (HGF), and bFGF.[47] Increases in similar cytokines by persistently activated fibroblasts occurs in patients with familial progressive dyschromatosis disorder.[48] UV irradiation of fibroblasts also induces SCF secretion.[49]

Table 5 Epidemiologic studies on the effect of pregnancy/oral contraceptives on melasma.

References	Goh and Dlova[3]	Achar and Rathi[4]	Moin et al[5]	Tamega Ade et al[6]	Handel et al[37]
Population	Singapore	India	Iran	Brazil	Brazil
Association of pregnancy stated by participants	25 (12.1)	56 (22.4)	14.5	36.4	Odd ratio = 3.59
Association of oral contraceptives stated by participants	27 (13.1)	46 (18.4)	11.3	16.2	Odd ratio = 1.23

Data are presented as *n* or *n* (%).

Table 6 Studies on female sex hormone receptor expression in melasma.

Receptors		References
Estrogen receptor	Immunohistochemistry	Lieberman and Moy[39]
	Real-time PCR	Kim et al[41]
Progesterone receptor	Immunohistochemistry	Jang et al[33,40]

PCR = polymerase chain reaction.

Immunohistochemical staining of melasma skin samples suggests a role for increased SCF expression in the dermis in the hyperpigmentation of melasma.[50] However, the data for paracrine factors derived from dermal fibroblasts in relation to melasma may be preliminary. Wnt signals regulate skin pigmentation. Our study demonstrates a downregulation of Wnt inhibitory factor-1 (WIF-1), an inhibitor of both canonical and noncanonical Wnt signaling, in dermal fibroblasts as well as epidermal keratinocytes in melasma.[51] The decrease in WIF-1 either in fibroblasts or in keratinocytes is involved in melasma development by significant stimulation of melanogenesis and melanosome transfer.[51]

Other factors potentially involved in melasma

In addition to paracrine factors derived from dermal fibroblasts, abnormalities in dermal vasculature and factors regulating melanosome pH and ion transport in skin pigmentation may also be involved.

Microscopic examination showed that the number and size of dermal blood vessels increased with vascular endothelial growth factor (VEGF) expression in skin lesions of melasma patients, suggesting a pathogenic role of the altered vasculature.[52] The effect of tranexamic acid, a plasmin inhibitor, which reduced epidermal pigmentation along with vessel number,[53] supported the potential involvement of vascular factor(s) in melasma. However, the clinical effectiveness of copper bromide laser therapy showed discrepancies as improvement[54] and no changes.[55]

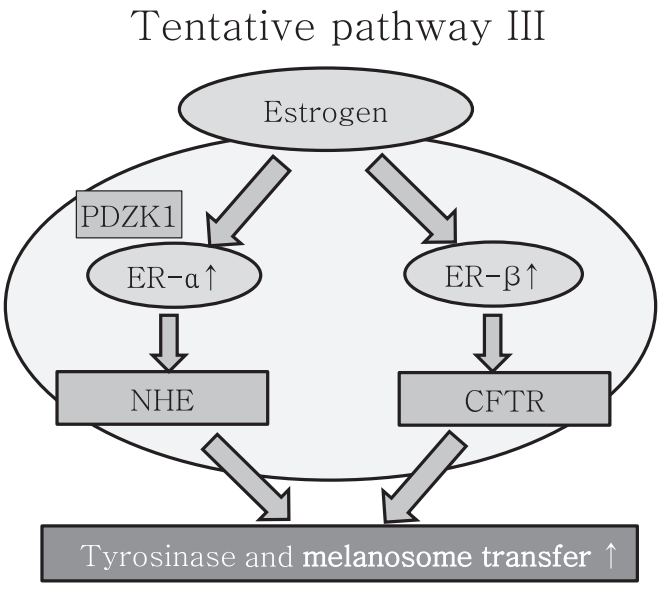

Figure 1 Schematic view of the role of PDZK1 in estrogen-induced hyperpigmentation in melasma. PDZK1 facilitates estrogen action via ERs, resulting in increased melanogenesis and melanosome transfer. CFTR = cystic fibrosis transmembrane conductance regulator; ER = estrogen receptor; NHE = sodium–hydrogen exchanger; PDZK1 = PDZ domain containing 1.

Tyrosinase is inactive in an acidic environment, and melanosomal pH regulates multiple stages of melanin production including late stages of eumelanogenesis.[56] Melanosomes of Caucasian melanocytes are acidic, whereas those of Black individuals are more neutral, resulting in suppression of melanin production in Caucasian melanocytes.[57,58] The adenosine triphosphate (ATP)-driven proton pump maintains a certain pH in melanosomes.[59] The pump transports anions to compensate for the charge of protons, thus acting as an ion exchanger. Mammalian Na^+/Ca^{2+} exchangers are ion exchangers involved in skin pigmentation. The Na^+/Ca^{2+} exchangers control Ca^{2+} flux across the plasma membrane of intracellular compartments, mainly extruding Ca^{2+} from the cytoplasm. The $Na^+/Ca^{2+}–K^+$ exchanger (NCKX; SLC24) comprises five members, and NCKX5 is expressed in the skin.[60] The putative cation exchanger SLC24A5 (NCKX5), which localizes to an intracellular membrane, such as the melanosomes, has a key role in human pigmentation. There is evidently an important role for ion exchange in the function of the melanosome.[61] In fact, regulation of natural skin color by NCKX5 is now known.[62] Melanosomal pH is also regulated by ion exchangers, such as SLC5A2.[63] In addition, alpha-MSH or forskolin activates the cAMP pathway and leads to an alkalinization of melanosomes by a concomitant regulation of ion transporters of the solute carrier family.[64] Although the effect of melanosomal pH on melasma is unknown, our recent study identifies the role of the ion exchangers Na^+/H^+ exchanger, cystic fibrosis transmembrane conductance regulator (CFTR), and SLC26A3 in melasma of specifically estrogen-related pigmentation downstream of PDZK1 signaling molecules.[41]

MicroRNAs (miRNAs) anneal to the 3′ untranslated region of mRNAs in a sequence-specific fashion and then either block translation or promote transcript degradation, thus playing a major role in posttranscriptional regulation of gene expression. Emerging evidence supports the association between miRNAs and a broad range of pathological conditions, such as cancer, cardiovascular diseases, diabetes, liver diseases, respiratory diseases, psychiatric diseases, neurological diseases, and inflammatory and autoimmune diseases. The role of miRNAs in skin pigmentation is also emerging. The involvement of miR-25 in alpaca coat color pigmentation involves targeting of MITF.[65] miR-429 is involved in the skin color

Table 7 Studies on dermal fibroblast-derived factors involved in pigmentation (physiologic or pathologic) versus melasma.

Factors	Pigmentation	Melasma
DKK1	Physiologic (Yamaguchi et al[45])	
Neuregulin-1	Physiologic (Choi et al[46])	
SCF	Pathologic (Poon et al[47]; Cardinali et al[48]; Shin et al[49])	Kang et al[50]
HGF	Pathologic (Poon et al[47]; Cardinali et al[48])	
bFGF	Pathologic (Poon et al[47]; Cardinali et al[48])	
WIF-1		Kim et al[51]

bFGF = basic fibroblast growth factor; DKK1 = Dickkopf 1; HGF = hepatocyte growth factor; SCF = stem cell factor; WIF-1 = Wnt inhibitory factor-1.

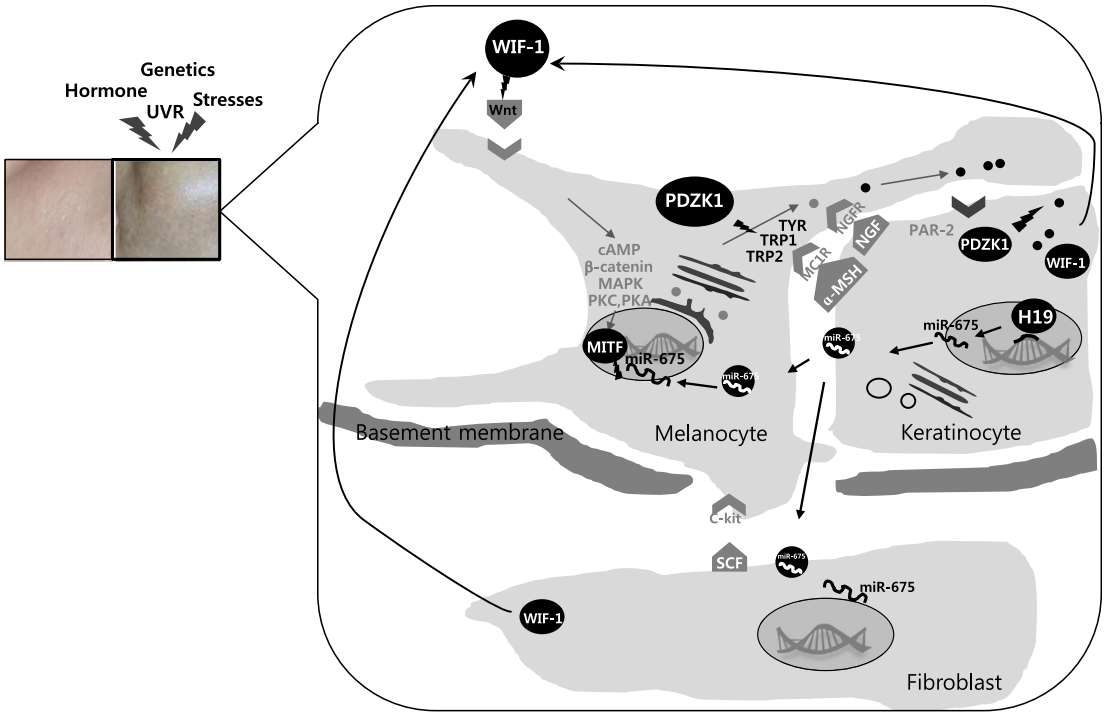

Figure 2 A schematic view of the role of triggering factors in melasma development: increased expression of NGF receptor with NGF and alpha-MSH with MC1R; PDZK1 upregulation in both melanocytes and keratinocytes; increased SCF from dermal fibroblasts; reduced WIF-1 in dermal fibroblasts as well as epidermal keratinocytes; reduced H19 in keratinocytes are involved in stimulation of melanogenesis and melanosome transfer in hyperpigmented lesional skin compared to normally pigmented skin of melasma patients. miR-675, a microRNA of H19 RNA, is released from keratinocytes as exosomes, and delivered to neighboring melanocytes or fibroblasts, regulating pigmentation via a direct target, such as MITF. miR-675 inhibits melanogenesis by targeting MITF. The melanogenic response of each skin cell type (melanocytes, keratinocytes, fibroblasts) and cell-to-cell interaction in response to UV exposure, female sex hormones, and stress could be different in different individuals. cAMP = 3′,5′-cyclic adenosine monophosphate; MAPK = mitogen-activated protein kinase; MC1R = melanocortin-1 receptor; MITF = microphthalmia-associated transcription factor; MSH = melanocyte stimulating hormone; NGF = nerve growth factor; PAR-2 = protease-activated receptor-2; PDZK1 = PDZ domain containing 1; PKA = protein kinase A; PKC = protein kinase C; SCF = stem cell factor; UVR = UV radiation; WIF-1 = Wnt inhibitory factor-1.

determination of fish by the direct targeting of forkhead box D3 (FOXD3).[66] In humans, over 54 native miRNAs capable of silencing tyrosinase are identified for skin whitening and lightening, although data on miRNAs associated with pigmentation in humans are rare. Nonetheless, data on a specific miRNA, which shows a key role of miR-145 in regulating melanogenesis associated with forskolin treatment and UV irradiation,[67] together with data on Wnt signaling,[51] has been appraised to enhance the understanding of cutaneous pigmentation and point to targets in the development of novel therapeutic modalities.[68] miR-125b is also identified as a potent regulator of steady-state melanogenesis. As expected, data on miRNAs associated with melasma is quite rare. In another study, we identify that expression of H19 noncoding RNA is decreased in hyperpigmented lesional skin of melasma, resulting in stimulation of melanogenesis and melanosome transfer.[69] In the process of examining the potential role of a H19 RNA in melasma, we identify the involvement of miR-675, a H19 miRNA, in H19 RNA downregulation-induced melanogenesis. miR-675 is released from keratinocytes as exosomes to be delivered to neighboring melanocytes and/or fibroblasts without degradation. miR-675 inhibits melanogenesis by using MITF as a target.[70]

Conclusion

Most of the published studies are performed in skin pigmentation not restricted to melasma. Although melasma is different from skin pigmentation induced by UV irradiation or inflammation, common mechanisms may be involved among these pigmentation disorders. Endogenous and exogenous factors affect melanogenesis in melasma via intracellular machinery, particularly cAMP, PKC, or both, as in other types of skin pigmentation. Currently, it is unclear which causative and triggering factor(s) would be more important and what possible scenarios exist in the case of multiple factor involvement in melasma development. Here, the role of genetic factor(s), UV irradiation, and female sex hormones in the pathogenesis of melasma was reviewed together with their role in other skin pigmentations. The important role of ion exchangers and miRNAs in melasma as well as other skin pigmentations was described. The factors associated with melasma development are summarized in Figure 2. The pathogenetic mechanisms of melasma could be heterogeneous in different individuals and ethnic groups. A personalized approach towards characterizing the pathogenesis may provide insights into solving the therapeutic difficulties associated with melasma.

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References

1. Passeron T. Melasma pathogenesis and influencing factors – an overview of the latest research. *J Eur Acad Dermatol Venereol* 2013;**27**(Suppl. 1):5–6.
2. Halder RM, Nootheti PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003;**48**(Suppl. 6):S143–8.
3. Goh CL, Dlova CN. A retrospective study on the clinical presentation and treatment outcome of melasma in a tertiary dermatological referral centre in Singapore. *Singapore Med J* 1999;**40**:455–8.

4. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. *Indian J Dermatol* 2011;**56**:380–2.
5. Moin A, Jabery Z, Fallah N. Prevalence and awareness of melasma during pregnancy. *Int J Dermatol* 2006;**45**:285–8.
6. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. *J Eur Acad Dermatol Venereol* 2013;**27**:151–6.
7. Ortonne JP, Arellano I, Berneburg M, et al. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. *J Eur Acad Dermatol Venereol* 2009;**23**:1254–62.
8. Pathak MA, Fanselow DL. Photobiology of melanin pigmentation: dose/response of skin to sunlight and its contents. *J Am Acad Dermatol* 1983;**9**:724–33.
9. Grimes PE, Yamada N, Bhawan J. Light microscopic, immunohistochemical, and ultrastructural alterations in patients with melasma. *Am J Dermatopathol* 2005;**27**:96–101.
10. Eller MS, Ostrom K, Gilchrest BA. DNA damage enhances melanogenesis. *Proc Natl Acad Sci USA* 1996;**93**:1087–92.
11. Carsberg CJ, Ohanian J, Friedmann PS. Ultraviolet radiation stimulates a biphasic pattern of 1,2-diacylglycerol formation in cultured human melanocytes and keratinocytes by activation of phospholipases C and D. *Biochem J* 1995;**305**:471–7.
12. Park HY, Russakovsky V, Ohno S, Gilchrest BA. The beta isoform of protein kinase C stimulates human melanogenesis by activating tyrosinase in pigment cells. *J Biol Chem* 1993;**268**:11742–9.
13. Gilchrest BA, Park HY, Eller MS, Yaar M. Mechanisms of ultraviolet light-induced pigmentation. *Photochem Photobiol* 1996;**63**:1–10.
14. Pawelek JM, Chakraborty AK, Osber MP, et al. Molecular cascades in UV-induced melanogenesis: a central role for melanotropins? *Pigment Cell Res* 1992;**5**:348–56.
15. Imokawa G, Miyagishi M, Yada Y. Endothelin-1 as a new melanogen: coordinated expression of its gene and the tyrosinase gene in UVB-exposed human epidermis. *J Invest Dermatol* 1995;**105**:32–7.
16. Abdel-Malek Z, Suzuki I, Tada A, Im S, Akcali C. The melanocortin-1 receptor and human pigmentation. *Ann N Y Acad Sci* 1999;**885**:117–33.
17. Cone RD, Lu D, Koppula S, et al. The melanocortin receptors: agonists, antagonists, and the hormonal control of pigmentation. *Recent Prog Horm Res* 1996;**51**:287–318.
18. Bak H, Lee HJ, Chang SE, Choi JH, Kim MN, Kim BJ. Increased expression of nerve growth factor receptor and neural endopeptidase in the lesional skin of melasma. *Dermatol Surg* 2009;**35**:1244–50.
19. Kim JE, Chang SE, Yeo UC, Haw S, Kim IH. Histopathological study of the treatment of melasma lesions using a low-fluence Q-switched 1064-nm neodymium:yttrium-aluminium-garnet laser. *Clin Exp Dermatol* 2013;**38**:167–71.
20. Im S, Kim J, On WY, Kang WH. Increased expression of alpha-melanocyte-stimulating hormone in the lesional skin of melasma. *Br J Dermatol* 2002;**146**:165–7.
21. Miot LD, Miot HA, Polettini J, Silva MG, Marques ME. Morphologic changes and the expression of alpha-melanocyte stimulating hormone and melanocortin-1 receptor in melasma lesions: a comparative study. *Am J Dermatopathol* 2010;**32**:676–82.
22. Roméro-Graillet C, Aberdam E, Clément M, Ortonne JP, Ballotti R. Nitric oxide produced by ultraviolet-irradiated keratinocytes stimulates melanogenesis. *J Clin Invest* 1997;**99**:635–42.
23. Sasaki M, Horikoshi T, Uchiwa H, Miyachi Y. Up-regulation of tyrosinase gene by nitric oxide in human melanocytes. *Pigment Cell Res* 2000;**13**:248–52.
24. Jo HY, Kim CK, Suh IB, et al. Co-localization of inducible nitric oxide synthase and phosphorylated Akt in the lesional skins of patients with melasma. *J Dermatol* 2009;**36**:10–6.
25. Yoshida M, Hirotsu S, Nakahara M, Uchiwa H, Tomita Y. Histamine is involved in ultraviolet B-induced pigmentation of guinea pig skin. *J Invest Dermatol* 2002;**118**:255–60.
26. Hernández-Barrera R, Torres-Alvarez B, Castanedo-Cazares JP, Oros-Ovalle C, Moncada B. Solar elastosis and presence of mast cells as key features in the pathogenesis of melasma. *Clin Exp Dermatol* 2008;**33**:305–8.
27. Torres-Álvarez B, Mesa-Garza IG, Castanedo-Cázares JP, et al. Histochemical and immunohistochemical study in melasma: evidence of damage in the basal membrane. *Am J Dermatopathol* 2011;**33**:291–5.
28. Gilchrest BA. A review of skin ageing and its medical therapy. *Br J Dermatol* 1996;**135**:867–75.
29. Nishimori Y, Edwards C, Pearse A, Matsumoto K, Kawai M, Marks R. Degenerative alterations of dermal collagen fiber bundles in photodamaged human skin and UV-irradiated hairless mouse skin: possible effect on decreasing skin mechanical properties and appearance of wrinkles. *J Invest Dermatol* 2001;**117**:1458–63.
30. Cavarra E, Fimiani M, Lungarella G, et al. UVA light stimulates the production of cathepsin G and elastase-like enzymes by dermal fibroblasts: a possible contribution to the remodeling of elastotic areas in sun-damaged skin. *Biol Chem* 2002;**383**:199–206.
31. Baillie L, Askew D, Douglas N, Soyer HP. Strategies for assessing the degree of photodamage to skin: a systematic review of the literature. *Br J Dermatol* 2011;**165**:735–42.
32. Kang WH, Yoon KH, Lee ES, et al. Melasma: histopathological characteristics in 56 Korean patients. *Br J Dermatol* 2002;**146**:228–37.
33. Jang YH, Sim JH, Kang HY, Kim YC, Lee ES. The histopathological characteristics of male melasma: comparison with female melasma and lentigo. *J Am Acad Dermatol* 2012;**66**:642–9.
34. Foldes EG. Pharmaceutical effect of contraceptive pills on the skin. *Int J Clin Pharmacol Ther Toxicol* 1988;**26**:356–9.
35. Famenini S, Gharavi NM, Beynet DP. Finasteride associated melasma in a caucasian male. *J Drugs Dermatol* 2014;**13**:484–6.
36. Muallem MM, Rubeiz NG. Physiological and biological skin changes in pregnancy. *Clin Dermatol* 2006;**24**:80–3.
37. Handel AC, Lima PB, Tonolli VM, Miot LD, Miot HA. Risk factors for facial melasma in women: a case-control study. *Br J Dermatol* 2014;**171**:588–94.
38. Thornton MJ. The biological actions of estrogens on skin. *Exp Dermatol* 2002;**11**:487–502.
39. Lieberman R, Moy L. Estrogen receptor expression in melasma: results from facial skin of affected patients. *J Drugs Dermatol* 2008;**7**:463–5.
40. Jang YH, Lee JY, Kang HY, Lee ES, Kim YC. Oestrogen and progesterone receptor expression in melasma: an immunohistochemical analysis. *J Eur Acad Dermatol Venereol* 2010;**24**:1312–6.
41. Kim NH, Cheong KA, Lee TR, Lee AY. PDZK1 upregulation in estrogen-related hyperpigmentation in melasma. *J Invest Dermatol* 2012;**132**:2622–31.
42. McLeod SD, Ranson M, Mason RS. Effects of estrogens on human melanocytes *in vitro*. *J Steroid Biochem Mol Biol* 1994;**49**:9–14.
43. Kippenberger S, Loitsch S, Solano F, Bernd A, Kaufmann R. Quantification of tyrosinase, TRP-1, and Trp-2 transcripts in human melanocytes by reverse transcriptase-competitive multiplex PCR—regulation by steroid hormones. *J Invest Dermatol* 1998;**110**:364–7.
44. Jian D, Jiang D, Su J, et al. Diethylstilbestrol enhances melanogenesis via cAMP-PKA-mediating up-regulation of tyrosinase and MITF in mouse B16 melanoma cells. *Steroids* 2011;**76**:1297–304.
45. Yamaguchi Y, Itami S, Watabe H, et al. Mesenchymal-epithelial interactions in the skin: increased expression of dickkopf1 by palmoplantar fibroblasts inhibits melanocyte growth and differentiation. *J Cell Biol* 2004;**165**:275–85.
46. Choi W, Wolber R, Gerwat W, et al. The fibroblast-derived paracrine factor neuregulin-1 has a novel role in regulating the constitutive color and melanocyte function in human skin. *J Cell Sci* 2010;**123**:3102–11.
47. Poon VK, Huang L, Burd A. Biostimulation of dermal fibroblast by sublethal Q-switched Nd:YAG 532 nm laser: collagen remodeling and pigmentation. *J Photochem Photobiol B* 2005;**81**:1–8.
48. Cardinali G, Kovacs D, Giglio MD, et al. A kindred with familial progressive hyperpigmentation-like disorder: implication of fibroblast-derived growth factors in pigmentation. *Eur J Dermatol* 2009;**19**:469–73.
49. Shin J, Kim JH, Kim EK. Repeated exposure of human fibroblasts to UVR induces secretion of stem cell factor and senescence. *J Eur Acad Dermatol Venereol* 2012;**26**:1577–80.
50. Kang HY, Hwang JS, Lee JY, et al. The dermal stem cell factor and c-kit are overexpressed in melasma. *Br J Dermatol* 2006;**154**:1094–9.
51. Kim JY, Lee TR, Lee AY. Reduced WIF-1 expression stimulates skin hyperpigmentation in patients with melasma. *J Invest Dermatol* 2013;**133**:191–200.
52. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. *J Dermatol Sci* 2007;**46**:111–6.
53. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. *J Eur Acad Dermatol Venereol* 2013;**27**:1035–9.
54. Lee HI, Lim YY, Kim BJ, et al. Clinicopathologic efficacy of copper bromide plus/yellow laser (578 nm with 511 nm) for treatment of melasma in Asian patients. *Dermatol Surg* 2010;**36**:885–93.
55. Eimpunth S, Wanitphakdeedecha R, Triwongwaranat D, Varothai S, Manuskiatti W. Therapeutic outcome of melasma treatment by dual-wavelength (511 and 578 nm) laser in patients with skin phototypes III-V. *Clin Exp Dermatol* 2014;**39**:292–7.
56. Ito S, Suzuki N, Takebayashi S, Commo S, Wakamatsu K. Neutral pH and copper ions promote eumelanogenesis after the dopachrome stage. *Pigment Cell Melanoma Res* 2013;**26**:817–25.
57. Fuller BB, Spaulding DT, Smith DR. Regulation of the catalytic activity of preexisting tyrosinase in black and Caucasian human melanocyte cell cultures. *Exp Cell Res* 2001;**262**:197–208.
58. Ancans J, Tobin DJ, Hoogduijn MJ, Smit NP, Wakamatsu K, Thody AJ. Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells. *Exp Cell Res* 2001;**268**:26–35.
59. Brilliant MH. The mouse p (pink-eyed dilution) and human P genes, oculocutaneous albinism type 2 (OCA2), and melanosomal pH. *Pigment Cell Res* 2001;**14**:86–93.
60. Lytton J. Na^+/Ca^{2+} exchangers: three mammalian gene families control Ca^{2+} transport. *Biochem J* 2007;**406**:365–82.
61. Lamason RL, Mohideen MA, Mest JR, et al. SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science* 2005;**310**:1782–6.
62. Ginger RS, Askew SE, Ogborne RM, et al. SLC24A5 encodes a trans-Golgi network protein with potassium-dependent sodium-calcium exchange activity that regulates human epidermal melanogenesis. *J Biol Chem* 2008;**283**:5486–95.
63. Dooley CM, Schwarz H, Mueller KP, et al. Slc45a2 and V-ATPase are regulators of melanosomal pH homeostasis in zebrafish, providing a mechanism for

human pigment evolution and disease. *Pigment Cell Melanoma Res* 2013;**26**:205–17.
64. Cheli Y, Luciani F, Khaled M, et al. {alpha}MSH and cyclic AMP elevating agents control melanosome pH through a protein kinase A-independent mechanism. *J Biol Chem* 2009;**284**:18699–706.
65. Zhu Z, He J, Jia X, et al. MicroRNA-25 functions in regulation of pigmentation by targeting the transcription factor MITF in Alpaca (*Lama pacos*) skin melanocytes. *Domest Anim Endocrinol* 2010;**38**:200–9.
66. Yan B, Liu B, Zhu CD, et al. microRNA regulation of skin pigmentation in fish. *J Cell Sci* 2013;**126**:3401–8.
67. Dynoodt P, Mestdagh P, Van Peer G, et al. Identification of miR-145 as a key regulator of the pigmentary process. *J Invest Dermatol* 2013;**133**:201–9.
68. Yaar M. Cutaneous pigmentation in health and disease: novel and well-established players. *J Invest Dermatol* 2013;**133**:11–3.
69. Kim NH, Lee CH, Lee AY. H19 RNA downregulation stimulated melanogenesis in melasma. *Pigment Cell Melanoma Res* 2010;**23**:84–92.
70. Kim NH, Choi SH, Kim CH, Lee CH, Lee TR, Lee AY. Reduced MiR-675 in exosome in H19 RNA-related melanogenesis via MITF as a direct target. *J Invest Dermatol* 2014;**134**:1075–82.