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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 | | |