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Melasma Update

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Abstract. Melasma is a common acquired hyperpigmentary disorder of the face. However, the pathogenesis of melasma remains largely unknown and the treatment is still challenging. This article discusses histology of melasma in view of melanin pigmentation with a more in depth question about number of melanocytes and melanophages in dermis of melasma. We also explore the current understanding of etiopathogenesis of melasma. We conclude the review with a discussion of important issues that should be addressed in future research to find effective treatment modality of melasma.

Key words: melasma, histology, pathogenesis, treatment.

ACTUALIZACIÓN EN MELASMA

Resumen. El melasma es un trastorno de la pigmentación facial, adquirido y frecuente. Sin embargo, se desconoce en gran medida su patogenia y el tratamiento continúa siendo un reto. En este artículo se discute la histología del melasma desde la perspectiva de la pigmentación melánica, profundizando más sobre el número de melanocitos y melanófagos en la dermis del melasma. También se comenta el conocimiento actual sobre la etiopatogenia del melasma. Concluimos la revisión con una discusión sobre aspectos importantes que se deben abordar en futuras investigaciones para encontrar un tratamiento eficaz del melasma.

Palabras clave: melasma, histología, etiopatogenia, tratamiento.

Introduction

Melasma is a common acquired hyperpigmentary disorders characterized by irregular light- to gray brown macules and patches involving sun-exposed areas of the face (i.e., cheek, forehead, nose, upper lip, and chin). The pathogenesis of melasma remains largely unknown and the treatment is still challenging.

Our review first addresses the histology of melasma in view of melanin pigmentation with a more in depth question about number of melanocytes and melanophages of melasma. We then explore the current understanding of its pathogenesis. Finally, we discuss several issues to be resolved for melasma treatment.

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Increased Epidermal Pigmentation is a Hallmark of Melasma

Histological examination of melasma consistently reported that lesional skin is characterized increased melanin deposition in the epidermis (fig. 1)[1-4]. Melanocytes within the affected skin are larger, intensely stained with prominent dendrites and contain more melanosomes than melanocytes of unaffected skin, suggesting that melanocytes may be hyperfunctional in melasma. The question is whether the number of melanocytes in lesional skin is increased. The answer is controversial, as NKI/beteb immunostaining showed that the number of melanocytes is increased, while Mel 5 staining did not confirm these findings[1,2]. In our preliminary studies, we found no significant differences in the mean number of MITF stained melanocytes in lesional skin compared with perilesional normal skin, but some patients showed an increased number of melanocytes in lesional skin.

In vivo reflectance confocal microscopy (RCM) is a new innovative tool to examine pigmentary disorders. RCM examination of melasma also supported the existence of epidermal hyperpigmentation in all melasma lesional skin. In addition, RCM showed activated melanocytes in some

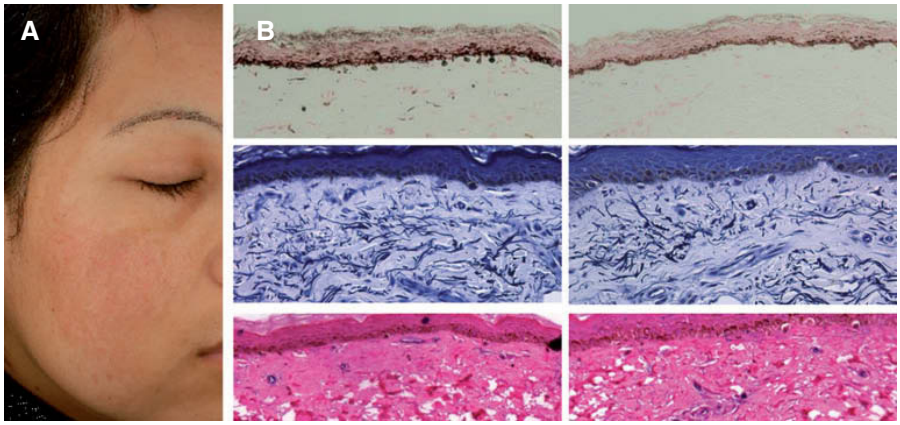

Figure 1. (A) Clinical photograph of melasma. (B) Histology of melasma. Fontana-Masson staining shows more pronounced epidermal hyperpigmentation in lesional compared with perilesional normal skin. Some patients show activated melanocytes and some melanophages in the lesion (×200). Lesional skin demonstrates abundant elastotic material compared with perilesional normal skin in the upper dermis (Verhoeff-van Gieson, ×200). CD31 immunostaining shows increased number of blood vessels in the upper dermis of the lesion compared with perilesional normal skin (×200).

patients (HY Kang et al unpublished data). These findings may suggest that there are individual characteristics among melasma patients. This fact has to be clarified but may explain the variable success rate of melasma treatment.

Another point in the histology of melasma concerns the melanophages of lesional skin. Histological studies of melasma showed that there is not a true dermal type of melasma but it showed there is a trend of increased melanophages in melasma[1,2]. Increased melanophages were also recognized in some melasma patients by RCM examination (HY Kang et al unpublished data). Interestingly, RCM examination showed that the topographic distribution of melanophages was very heterogeneous from one melasma region to another and even inside a given melasma region. This finding suggested that previous histological classification (epidermal, dermal, and mixed) according to pigment depth using single skin biopsy may be risky. A reliable classification should be based on the epidermal/dermal melanin ratio covering whole involved skin. It is still unclear whether the source of the dermal pigment comes from the epidermis. It is also unknown whether the dermal pigment can resolve spontaneously if it is not replenished from epidermis.

Lesson from Global Survey

It has been generally believed that UV irradiation, sex hormone and genetics are the main causes of melasma. A recent large global survey with 324 melasma women confirmed that the combination of accepted triggers including pregnancy, hormonal birth control, family history and sun-exposure do affect onset of melasma[5]. The study showed that melasma is not always associated with pregnancy or history of contraceptive use. The most common time of onset was after pregnancy (42 %), with 29 % appearing before pregnancy and 26 % during pregnancy. In most patients, a combination of factors including UV exposure, family history and age are likely to play a role in the development of melasma.

Melasma Skin Show Alteration in Dermal Structures in Addition to Pigmentation Changes

UV exposure is a major triggering or aggravating factor for melasma development. The role of keratinocytes during UV exposure in melasma was suggested. UV irradiation is known to increase the synthesis of alpha-MSH and ACTH derived from POMC from keratinocytes[6]. These peptides lead to proliferation of melanocytes as well as an increase in melanin synthesis via stimulation of tyrosinase activity and TRP-1. When comparing biopsies of lesional skin and perilesional normal skin in melasma, lesional skin showed a statistically significant increase in alpha-MSH expresssion[7].

Recent histological and immunohistochemical studies have shown that melasma has an alteration in the dermal structures in addition to pigmentary changes, suggesting a role of the dermis for melasma development. Melasma dermal skin is different from perilesional normal skin and showed features of prominent solar damaged. Increased solar elastosis in lesional skin was shown[8]. The roles of fibroblast, or blood vessels in melasma development were suggested[9,10].

Overexpression of both stem cell factor from fibroblast and c-kit has been found in melasma[9]. The fibroblast derived cytokines stimulate proliferation and melanogenesis of melanocytes in culture[11]. Therefore, it is possible that the dermal inflammation induced by accumulation of UV irradiation may be associated with activation of fibroblasts, which result in up regulation of SCF in melasma dermis leading to increased melanogenesis.

Recently, it was shown that melasma is characterized by increased vasculature in the lesional skin both clinically and histologically[10]. The number of vessels had a positive rela-

tionship with epidermal pigmentation in melasma lesional skin. Expression of VEGF, a major angiogenic factor of UV irradiated skin, was up-regulated in melasma lesions compared to perilesional normal skin[10]. It has been reported that human melanocytes express functional VEGF receptors[12]. It was shown that nitric oxide expression is increased in lesional skin, providing hypothesis for the pathogenesis of increased vasculature in melasma[13]. However, the biological role of cutaneous blood vessels in the pathogenesis of melasma remains uncertain. It is unclear if prominent vasculature is a simple epiphenomenon of UV damage or a major melanogenetic factor in melasma.

Taken together, network of cellular interactions between keratinocyte, fibroblasts and perhaps vasculatures and melanocytes during chronic sun exposure may play an important role in development of melasma. They may work in conjunction to stimulate melanocytes resulting in epidermal hyperpigmentation.

Possible Mechanism for Melasma Associated with Sex Hormone

Melasma occurs in 10-15 % of pregnant women[14]. Also, 10-25 % of all women taking oral contraceptives develop melasma[15]. Elevated levels of estrogen, progesterone and MSH especially in the third trimester, have been found in association with melasma[16]. *In vitro* studies have shown that cultured human melanocytes express estrogen receptors[17]. Estradiol increased the level of melanogenic enzyme especially TRP-2 in normal human melanocytes[18]. Additional supporting evidences showed increased expression of estrogen receptors in lesional skin of melasma[19]. Therefore, it is speculated that melanocytes in melasma patients may be inherently more sensitive to increased concentration of estrogens and possibly to other sex hormones. It may be possible that these effects induced by sex hormones in patients may be needed additional synergistic events to prime melanocytes, for example, UV light.

Conclusion and Future Perspectives

The above discussion suggests that sun exposure and/or hormonal stimuli may trigger melanocytes in patients who have melanocytes with intrinsic sensitivity to those stimuli. Additionally, prolonged sun exposure could stimulate certain specific clones of keratinocytes, fibroblasts, or endothelial cells to produce melanogenic factors. These combined process may result in the epidermal hyperpigmentation of melasma. Some patients with strong or repetitive stimuli may have melanocytic proliferation, hyperactive melanocytes and/or melanophages (if melanophages come from the epidermis) in melasma.

Melasma continues to be a challenge for treatment. Resistance cases or recurrences often occur. Physical modalities like lasers sometimes yield rebound hyperpigmentation. Several important issues remain to be solved for melasma treatment. First, it is still unknown which changes in the dermis of melasma patients are simple epiphenomena of chronic sun exposure or primary event to stimulate melanocytes. If it is the main pathology in melasma, a treatment target would be the dermal as well as epidermal pigments. Large randomized, controlled clinical studies, for example vascular laser treatment for melasma, may be helpful to address this question. Second, as we mentioned before, it is still questionable the significance and fate of melanophages. It should be addressed whether the therapeutic outcome relies on melanophages. Rather, it may be possible that hyperactive melanocytes or increased melanocytes may affect the therapeutic outcome of melasma. RCM may be a useful tool to address this point as it allows repetitive examination. Finally, it may be very difficult to address intrinsic genetic alteration in melasma. However, future work is required to identify candidate genes responsible for the development of melasma.

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Conflict of interest
Authors have no conflicts of interest to declare.

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