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Review Article

Current concepts in melasma - A review article

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ABSTRACT

Melasma is a common acquired hypermelanosis of the face, the treatment of which is challenging. The pathogenesis of melasma is complex and multifactorial. The classical triggering factors of melasma include positive family history, exposure to ultraviolet radiation, and hormonal factors. Apart from this, newer theories implicated in the pathogenesis of melasma include neural and vascular factors, impairment of barrier function, function of visible light, and other molecular pathways. Recent studies have also suggested the importance of cells other than the melanocytes such as keratinocytes, fibroblast, mast cells, and cutaneous vasculature in the pathogenesis of melasma. Identification of these factors will help in targeted treatment, which may have longer remission and reduced relapse rates.

Keywords: Etiopathogenesis, Melasma, Genetics, Hormonal, Vascular

INTRODUCTION

Melasma is an acquired, symmetrical, and circumscribed hypermelanosis presenting with light to dark brown macules on the face and occasionally on the neck and forearms. It is derived from the Greek word "melas" meaning black, which refers to its brownish clinical presentation. The prevalence of melasma is high in individuals of Asian, Latin American, and Hispanic origin and in Fitzpatrick skin types III–V.[1] For the patient, melasma is a cosmetic problem with severity ranging from mild pigmentation to severe disfiguring hypermelanosis which may have a considerable impact on the quality of life. For the dermatologist, the biggest concern is its therapeutic difficulty. Therefore, it is essential to understand the etiology and pathogenesis of melasma.

In this article, an attempt has been made to include all the newer theories in the pathogenesis of melasma. A PubMed search was carried out using the keywords "melasma," "pathogenesis," "recent," and "etiology."

ETIOPATHOGENESIS

Multiple factors have been incriminated in the causation of melasma which includes genetic factors, solar radiation, hormonal factors, drugs, and others.

Role of genetic factors

Evidence from various epidemiological studies have shown strong correlation between family history and racial factors in the pathogenesis of melasma.

Although there is a wide variation in the rate of positive family history in various studies, they still show a strong correlation. Positive family history rate as high as 61% has been reported.[2] High incidence of positive family history has also been reported in Indian studies.[3]

There is a high incidence of melasma in Latin Americans and Hispanics and in Asians with Fitzpatrick skin types III–V.[4,5]

The patients with melasma were found to have downregulation of the H19 gene in both hyperpigmented and normally pigmented skin. This leads to downstream effects which lead to stimulation of melanogenesis and increase in transfer of melanin to keratinocytes.[6]

Other genes concerned are those involved in melanin biosynthesis, especially the genes that encode tyrosinase (TYR), tyrosinase-related proteins TRP1 and TRP2, and microphthalmia-associated transcription factor (MITF), which is responsible for transcriptional regulation. There is upregulation of genes encoding TYR, MITF, and TRP1 in melasma skin.

Wnt pathway modulation genes, which have role in proliferation of melanocyte stem cells, genes involved in prostaglandin (PG) synthesis and genes in fatty acid metabolism are also implicated in melasma.[7]

There is a reduced expression of Wnt inhibitory factor-1 (WIF-1) in the hyperpigmented skin of melasma patients irrespective of ultraviolet irradiation. WIF-1 downregulation occurs in both epidermal keratinocytes and in dermal fibroblasts but not in melanocytes. It mediates its effect in melasma by stimulation of melanogenesis and melanosome transfer.[8]

Ultraviolet radiation (UVR) induces downregulation of genes involved in lipid metabolism such as peroxisome proliferator-activated receptor alpha (PPAR), arachidonate 15-lipoxygenase, and PPAR gamma coactivator-1 alpha.[9] The altered lipid metabolism in the lesional skin adversely affects the barrier function in melasma.

Role of sun exposure

Exposure to sunlight is undoubtedly the most important factor and both UVR and visible light stimulate melanogenesis. The mechanism involved is as follows:

i. Direct effect on melanocytes – By stimulating the formation of endogenous 1,2- diacylglycerol formation from melanocytes.[10] Nitric oxide production from keratinocytes is also stimulated which has got a paracrine effect on melanocytes and this leads to an increase in amount of both tyrosinase and tyrosinase-related protein 1.[11]
ii. Indirect effect on keratinocytes which release melanogenic factors – These melanogenic factors include basic fibroblast growth factor, nerve growth factor, endothelin 1, and Proopiomelanocortin-derived peptides such as melanocyte-stimulating hormone and adrenocorticotrophic hormone.[12]
iii. UV light induces production of reactive oxygen species (ROS) by activating inducible nitric oxide synthase which stimulates melanogenesis.[13] The level of oxidative stress is higher in patients with melasma.[14]
iv. Visible light is also able to induce pigmentation and it has been recognized that the visible light-induced pigmentation is more intense and stable compared to UV-A.[15] This highlights the importance of adding a physical sunscreen for better control of melasma.
v. UV and visible light-induced dermal inflammation lead to upregulation of stem cell factor (SCF) production by dermal fibroblast, which is a ligand for tyrosine kinase receptor (c-kit). This increased expression of SCF in dermis and c-kit in epidermis lead to stimulation of melanogenesis.[16]
vi. There is UV-induced synthesis of PG and upregulation of cyclooxygenase 2 which stimulates melanogenesis.[17] The emerging use of PG analogs in the treatment of vitiligo favors this theory.

Role of hormones

Estrogen

Melasma has been found to aggravate during pregnancy because of an increase in the placental, ovarian, and pituitary hormones.[18] Melasma is also common among women using estrogen-containing oral contraceptive pills and hormone replacement therapy and among men using estrogen derivatives in the treatment of prostatic cancer.[19]

This is due to the presence of estrogen receptors on melanocytes which stimulate the process of melanogenesis.[20,21] This is mediated by induction of synthesis of melanogenic enzymes such as tyrosinase, TRP1, TRP2, and MITF by estrogen through cyclic AMP-protein kinase A.[22]

Estrogen also mediates upregulation of PDZ domain protein kidney 1 (PDZK1) expression in the hyperpigmented skin of melasma patients. PDZK1 is a member of sodium-hydrogen exchanger regulatory factor family NHERF3. There occurs an increase in tyrosinase, cyclic AMP-responsive element binding protein, and MITF in melanocyte and also an increase in melanosome transfer.[20]

There is evidence of mild ovarian dysfunction associated with low serum estradiol and raised serum luteinizing hormone in patients with melasma.[23]

Thyroid autoimmunity

Several studies have shown association between melasma and thyroid disorders, especially hypothyroidism

and thyroid autoimmunity.[24] The exact mechanism is not clear. It is postulated that this may be due to the effect of these hormones on inducing the production of inflammatory cytokines. Higher circulating levels of pro-inflammatory cytokines have been seen in patients with hyperthyroidism.[25] It thus reinforces that melasma can be triggered by conditions associated with skin inflammation.

Role of vascular factors

UVR can induce secretion of vascular endothelial growth factor (VEGF) from keratinocytes. Melanocytes express functional receptors for VEGF and it enhances melanogenesis.[26] This is exemplified by the presence of prominent telangiectasia visualized on dermoscopy on lesional skin in melasma and also the therapeutic efficacy of tranexamic acid and vascular lasers in the treatment of melasma.

Role of neural factor

The presence of melasma along the distribution of trigeminal nerves suggests the role of neural involvement in the pathogenesis. Higher levels of neural endopeptidase in melasma lesions were detected which shows that neuroactive molecules, including nerve growth factor, may play a significant role in the pathogenesis of melasma.[27]

Role of drugs

Phenytoin has been implicated in the development of melasma like pigmentation which acts by directly causing dispersion of melanin granules and by inducing pigmentation of basal epidermis. This pigmentation is reversible following withdrawal of the drug.[28]

Other factors

Increased melanization

There is increased melanocytic activity with resultant increase in melanization and melanosome transfer to keratinocytes without actual increase in number of melanocytes. The size of melanosomes is also increased in the lesional skin.[9]

Damage of basement membrane

There is a significant damage to basement membrane in melasma which leads to dropping off or migration of melanin and melanocytes into the dermis. The presence of melanin in the dermis may be responsible for the persistent pigmentation in melasma.[29]

Impaired barrier function

Downregulation of genes involved in lipid metabolism contributes to the impaired barrier function in lesional skin in melasma. There is associated thinning of stratum corneum as evidenced by epidermal thinning and flattening of rete ridges seen on skin biopsy. Both of these factors lead to delayed barrier recovery rate and impaired stratum corneum integrity in melasma skin.[30]

Role of mast cells and solar elastosis

Solar elastosis is prominent in the lesional skin of melasma as photoaging can take place due to chronic sun exposure. Mast cells are also prominent in these elastotic areas of melasma skin.[31] Histamine produced by the mast cell induces melanogenesis by acting on H2 receptors and it is mediated by cyclic AMP-protein kinase A activation.[32] This histamine-mediated pigmentation is also implicated in post-inflammatory hyperpigmentation as well as in urticaria pigmentosa.

Role of fibroblast in dermis

a. Neuregulin-1 secreted by fibroblasts derived from dark skin has been found to increase melanogenesis and it also regulates the growth of melanocytes.[33]
b. There is increased secretion of SCF induced by UVR. Increased expression of SCF in dermis and c-kit in epidermis lead to stimulation of melanogenesis.

Role of pollution

ROS can be formed secondary to the presence of airborne particulate matter and polycyclic aromatic hydrocarbons (PAHs) present in the polluted environment. ROS trigger metalloproteinases which lead to extrinsic aging. Therefore, the incidence of melasma is high in geographic areas with heavy pollution.[34]

Role of microRNA (miRNA)

miRNAs are a family of small, 20–24 nucleotide, endogenously expressed non-coding RNAs which have a role in post-transcriptional regulation of gene expression either by blocking translation or by promoting transcript degradation.[35]

miRNA-125b is identified as a regulator of steady-state melanogenesis in the absence of external stimuli.[36]

miRNA has an important role in melanogenesis and melanosome transfer. Expression of an H19 RNA-derived miRNA, miR-675, is reduced in the hyperpigmented skin of melasma patients. Overexpression of miR-675 decreases the expression of tyrosinase, TRP-1, and TRP-2, whereas its knockdown increases their expression.[37]

CONCLUSION

Melasma is a condition with multifactorial etiopathogenetic mechanisms, understanding of which is essential for more efficacious treatment. The identification of newer pathogenic mechanisms and pathways is beneficial in paving the path for newer and more effective treatment for melasma.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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