Volume 2, Issue 2, February 2024 ISSN (E): 2938-3765

SKIN HYPERPIGMENTATION: MODERN VIEWS ON ETIOLOGY AND PATHOGENESIS

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Abstract
A brief literature review of the etiology and pathogenesis of hyperpigmentation is presented based on modern scientific publications. The review focuses on the actively studied mechanisms of melanin synthesis in normal and pathological conditions, the physiology of pigment cells melanocytes, their interaction with other structures of the epidermis and dermis, as well as the mechanisms of regulation of melanogenesis. The main factors influencing the occurrence of hyperpigmentation are also covered.

Keywords: Hyperpigmentation, melasma, melanocyte, melanogenesis, melanin, melasma, lentigo.

Introduction

Melanin in the human body is primarily responsible for the color of the skin, hair and eyes. It is synthesized by melanocytes through a process called melanogenesis. However, abnormal accumulation of melanin melanin type hyperpigmentation leads to a number of dermatological problems such as solar lentigines age spots, melasma, ephelides freckles. These conditions, as well as post-traumatic hyperpigmentation, in some cases being a cosmetic defect, significantly reduce the patient's quality of life. Although various etiologies can lead to pigmentation disorders, to date no differences in the treatment of these disorders have been reported.

Thus, it can be assumed that common pathogenetic mechanisms may be involved in different types of skin hyperpigmentation. Melanocytes and melanin synthesis. In human skin, melanocytes are located at the dermal-epidermal junction, which is the border structure between the two main sections of the skin - the epidermis and dermis. Melanocytes in the basal layer of the epidermis produce varying amounts and different types of melanin eumelanin/pheomelanin, synthesized in organelles called melanosomes. Melanosomes move into melanocyte processes and are transferred to adjacent basal keratinocytes. As keratinocytes differentiate, melanosomes begin to degrade depending on the skin type, resulting in either fine melanosome remnants in light skin, or melanosomes remaining intact down to the outermost layers of the epidermis in black skin. The molecular and cellular mechanisms underlying the regulation and dysregulation of pigmentation are gradually becoming known. The process of melanin biosynthesis begins with the interaction of the amino acid L-tyrosine and the enzyme tyrosinase. Tyrosinase is a key enzyme in melanogenesis in melanocytes. It acts as a catalyst for two steps of melanogenesis - the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to DOPA-quinone. DOPA-quinone is converted into DOPA-chromium containing an indole ring, from which dihydroxyindolylcarboxylic acid (5,6-dihidroxyindole-2-carboxylic acid, DHICA) is synthesized with the participation of DOPA-chrome tautomerase in the presence of metal ions.

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The oxidation products of DHICA (enzymatic or non-enzymatic) polymerize, resulting in the formation of brown DHICA-melanin containing from 100 to 1000 DHICA monomers. DOPA-chromium can also be converted to 5,6-dihydroxyindole (DHI). The product of oxidative polymerization of DHI is black DHI-melanin. DHI and DHICA melanins are eumelanins. In addition, melanocytes synthesize sulfur-containing pigments - pheomelanins (yellow, red and brown), the precursor of which is 5-S-cysteinyl-DOPA (5-S-cysteinyldopa). The synthesis of pheomelanin pigments requires the presence of L-cysteine. Genes associated with tyrosinase (proteins TRP-1 and TRP-2) are involved in the synthesis of eumelanins. Tyrosinase, TRP-1 and TRP-2 genes are controlled by a transcription factor (Microphthalmia-associated Transcription Factor - MITF-M). Also important regulators of melanogenesis are derivatives of the peptide proopiomelanocortin (POMC), such as α-melanocyte-stimulating hormone (αMSH) and adrenocorticotropic hormone (ACTH). αMSH and ACTH were detected in the epidermis and dermis. They are produced by various types of cells such as keratinocytes, melanocytes, fibroblasts and endothelial cells (neuroendocrine system of the skin). Several factors such as ultraviolet radiation (UV), interleukin-1 (IL-1), cAMP (cyclic adenosine monophosphate) are known to activate POMC peptide. As a result, under the influence of aMSH, the Melanocortin 1 receptor protein (MC1R) initiates a complex signaling cascade through a paracrine, autocrine or intracrine pathway.

Melanin synthesis is also regulated by intrinsic factors: inflammatory mediators, growth factors, neurotransmitters, neuropeptides and hormones (in particular, estrogens and glucocorticoids). Organized similarly to the hypothalamic-pituitary-adrenal axis, the cutaneous corticotropin-releasing factor (CRF)/urocortin-signaling system, including CRF, POMC, aMSH and ACTH, is capable of participating in the regulation of melanocyte homeostasis. Corticotropin-releasing factor (CRF)? acting through cognate receptors, it is able to increase levels of cAMP, inositol triphosphate (IP3)/Ca2+, as well as activate protein kinases A and C and, ultimately, stimulate proliferation, melanocyte differentiation and pigment synthesis. Other positive regulators of pigmentation are melanin precursors such as tyrosine and DOPA, which in addition to being major substrates of melanogenesis may also promote adequate organization and tyrosinase activity and influence melanosome formation and maturation.

Intercellular interaction in the regulation of pigmentation. In the skin, melanocytes are in close contact with neighboring keratinocytes. A large number of studies emphasize the role of keratinocytes in the control of skin pigmentation. For example, keratinocytes promote transient UV-induced melanogenesis (tanning) by paracrine secreting numerous growth factors such as aMSH, endothelin-1 (ET-1), stem cell factor (SCF), and various cytokines. However, there is growing evidence for the role of dermal components in the regulation of pigmentation. In the mid-1990s, extracellular matrix (ECM) proteins were shown to regulate melanocyte proliferation, resistance to apoptosis, and melanogenesis activity. Recent studies have demonstrated that dermal fibroblasts exert a regulatory role in pigmentation through the secretion of soluble factors. Close reciprocal interactions between the epidermal and mesenchymal compartments of the skin may also play a role in melanocytic homeostasis. Laminin 332, a major component of the epidermal basement membrane, has also recently been shown to promote melanin production. Growth factor/cytokine regulatory interaction also exists between epidermal and dermal structures and can influence the regulation of pigmentation. For example, cytokines produced by keratinocytes, such as interleukin 1α (IL-1α) or tumor necrosis factor α (TNFα), are able to stimulate fibroblasts, which

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in turn release melanocyte-stimulating factors such as hepatocyte growth factor (HGF) or stem cell factor (SCF). All these data, confirming and complementing each other, emphasize the role of dermal fibroblasts in the regulation of constitutional pigmentation and in the development of pigmentation disorders. It is hypothesized that physiological changes in fibroblasts over time, particularly as a result of photoaging, may influence skin pigmentation. Skin photoaging induced by chronic exposure to solar UV rays is associated with pigmentary changes and the formation of actinic keratosis (lentigo senile), which is a hallmark of photodamaged aged skin. Recently, an increase in the level of melanocytic cytokines in the upper dermis of lentigo senile skin has been described using immunoassays. Thus, it has been suggested that fibroblasts play a significant role in the formation of this hyperpigmentation. Studies have also been conducted on intercellular interactions in the formation of post-traumatic hyperpigmentation. Epidermal pigmentation after damage to the skin occurs due to the proliferation of melanocytes, their migration into the wound, the production of melanin, and the transfer of pigment to nearby keratinocytes.

Clinical observations in humans and animals suggest that melanocytes migrate from both wound edges and epidermal processes after wound epithelialization has occurred. The migration of melanocytic stem cells through the epithelialized wound is thought to be dependent on the melanocortin 1 receptor and the inflammatory response. Data have been obtained that show the close interaction of melanocytes with fibroblasts, which are involved in the joint regulation of skin repair. This epidermal-mesenchymal interaction may be particularly relevant to the study of slow-healing wounds, in which the immature basement membrane may allow the passage of paracrine mediators between the dermis and epidermis. The degree of pigmentation of a healing wound depends on the base skin tone, the depth of the wound and the time it takes to heal. Wounds that take a long time to heal often have abnormal pigmentation. Therefore, it is hypothesized that skin fibroblasts are capable of regulating the melanocytic response to cutaneous injury.

As the results of recent studies show, melanocytes are able to influence angiogenesis, inflammatory reactions and fibrosis after skin trauma. Excessive and prolonged inflammatory response after trauma to the skin contributes to the formation of hypertrophic scars and can lead to hyperpigmentation. Clinical observations have shown that the depth of injury can influence both the possible formation of scar pigmentation and the formation of a hypertrophic scar. Also, immunohistochemical studies with 24 facial skin biopsies with solar lentigo showed a significant increase in the density of the vascular network, accompanied by an increase in the expression of vascular endothelial growth factor. CD68 immunoreactivity a macrophage marker was significantly higher in affected skin, suggesting increased macrophage infiltration in solar lentigo skin. Thus, areas of skin with solar lentigo are characterized by increased blood flow and vasculature. These data suggest a possible influence of vascularization on the development of solar lentigo. Review of the main etiological factors of hyperpigmentation. The main causes of hyperpigmentation are traditionally considered to be genetic data, chronic exposure to ultraviolet UV radiation, and female sex hormones. Each of the above factors can simultaneously cause different nosological pigmentation disorders, such as pigmentation caused by chronic UV irradiation photoaging, pigmentation due to oral contraceptives or post-inflammatory hyperpigmentation. It is possible for different types of hyperpigmentation to coexist in the same patients, but their clinical characteristics will be different. Post-inflammatory hyperpigmentation develops at any age at the site of inflammation caused by physical or chemical trauma, skin irritation, contact dermatitis or various dermatoses. Thus, recently, many studies have begun to

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consider the role of inflammatory processes in the development of melasma. The data obtained indicate that melasma, in particular melasma, is characterized by the presence of chronic inflammation in the affected skin with its inherent cellular elements and mediators, which may explain its recurrent nature. Exposure to UV radiation. Pigmentation induced by chronic UV exposure may be accompanied by characteristic effects of photoaging, such as wrinkles, roughness, loss of skin elasticity and tone. The significant difference lies in the change in pigmentation in these pathological conditions - a tendency to restore the normal color of the skin, in contrast to melasma. The inflammatory response of the skin caused by UV radiation may play an important role in the formation of hyperpigmentation and recurrence of melasma by stimulating the production of melanogenic cytokines and growth factors.

There is also an increase in the lymphocytic infiltrate in affected skin (exposed to UV radiation), which is predominantly composed of CD4 lymphocytes, mast cells and macrophages. Levels of the cytokine IL-17 and the proinflammatory mediator cyclooxygenase (COX-2) were significantly increased in affected skin areas compared to healthy skin. According to the results of histological studies, similarities between the signs of melasma and solar elastosis were noted, such as dilatation of skin capillaries, partial destruction of the basement membrane with protrusion of melanocytes into the dermis. The similarities in microscopic features between chronically UV-exposed skin and melasma highlight the potential role of cutaneous photoaging and cumulative sun exposure in the pathogenesis of melasma. The disruption of the basement membrane structure is an important finding because it clearly shows the relationship between chronic exposure to UV radiation and melasma.

With chronic exposure to UV irradiation, the levels of matrix metalloproteinases (MMP-2 and MMP-9) increase and collagen types IV and VI are degraded, which leads to disruption of the organization of the basement membrane. The damaged basement membrane facilitates the penetration of melanocytes and melanin into the dermis. As a result, melasma tends to be resistant to treatment and has a high likelihood of recurrence. Also, based on recent studies, the role of the sFRP2 gene in the development of UV-induced hyperpigmentation has been suggested. It was found that sFRP2 stimulates melanin synthesis by modulating the Wnt signaling pathway, which is able to stimulate MITF-M, which regulates protein systems responsible for melanogenesis. The role of genetic factors. Genetic predisposition is considered one of the main reasons influencing the development of hyperpigmentation. Data from epidemiological studies show that there are differences in the occurrence of melasma among representatives of different races, and also note the influence of a family history of this type of pigmentary disorder. Susceptibility to pigmentation disorders, particularly melasma and post-inflammatory hyperpigmentation, has been described in all racial and ethnic groups, but is most common in individuals with darker skin types (Fitzpatrick type III-V) living in areas of intense UV radiation, especially in Latin America, Asia and Africa. Familial cases of melasma, according to some studies, ranged from the lowest rate (10.2%) in Singapore to the highest (61%) in Brazil. The highest percentage of familial inheritance was determined in a case-control study. Although family inheritance rates collected from different countries and even from the same country have shown a wide range of differences, based on epidemiological studies, there is a strong association between a strong family history and melasma. The role of age. Research in mice suggests that tyrosinase, TRP-1, and MITF gene activity may increase with age. These studies may be useful in elucidating the mechanisms of age-related pigmentation in human skin, such as melasma and solar lentigo. The role of female sex hormones.

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Melasma (chloasma) is a common physiological skin change during pregnancy. Melasma is also a side effect of taking oral contraceptives. Epidemiological data from different countries made it possible to diagnose melasma in 14.5-56% of pregnant women and 11.3-46% in women using oral contraceptives. Despite large differences in the prevalence of melasma between different ethnic groups and skin phototypes, the predominant development of melasma during the reproductive period of a woman's life and the association of melasma with oral contraceptive use suggest that female sex hormones (estrogen and progesterone) are another important precipitating factor for the development of melasma. and exacerbation of this disease.

The activities of estrogen and progesterone are mediated by specific receptors expressed in the skin, including estrogen receptors (ERS) ERα/ERβ and progesterone receptors (PRS), respectively. Immunohistochemical studies have shown increased ER expression in affected skin areas. Of note, significant ERβ receptor expression was present in the dermis of the lesions but not in the epidermis. Increased expression of the ER receptor suggests a potential role for estrogens in the pathogenesis of melasma. Estrogens have been shown to stimulate melanin synthesis in cultured human melanocytes by inducing the synthesis of tyrosinase, TRP-1 and TRP-2 proteins, and MITF. In addition, estrogen-induced melanogenesis may be associated with activation of the cAMP-PKA (protein kinase A) pathway, since estrogens are able to increase cAMP levels and activate tyrosinase and MITF. It should be noted that a number of studies have obtained conflicting results regarding the effect of these hormones, in particular progesterone, on melanogenesis.

Melasma has been reported as an adverse effect of taking contraceptives containing the synthetic progestin levonorgestrel, suggesting a role for progesterone in the development of melasma. In contrast, it has also been suggested that progesterone may inhibit melanocyte proliferation, thereby antagonizing the stimulatory effect of estrogen. This may have implications for the choice of progestogen in oral contraceptives to prevent the development of melasma. An increase in patients with melasma among men began to be noted in connection with the advent of a drug such as finasteride, which is an antiandrogen. These observations also suggest that increased progesterone levels are not associated with the development of melasma, since finasteride inhibits progesterone synthesis without changing estrogen concentrations. The role of microRNAs. MicroRNAs are small RNAs consisting of 20-24 nucleotides (a class of non-coding RNAs) that take part in the transcriptional and post-transcriptional regulation of gene expression. mRNAs are involved in a variety of signaling pathways and cellular processes. The connections between microRNA regulation disorders and a wide range of pathological conditions, such as malignant neoplasms, cardiovascular diseases, diabetes, liver and respiratory diseases, psychiatric, neurological, as well as inflammatory and autoimmune diseases, are being actively studied. Research into the role of microRNAs in pigmentation development is also continuously evolving. The role of microRNAs in skin pigmentation was revealed in studies on human melanocytes: microRNA-145 regulates melanin synthesis and melanosomal translocation in melanocytes under the influence of external stimuli. In addition, microRNA-125b has been identified as a regulator of melanogenesis in the absence of exposure to external stimuli. The potential role of miRNAs in the pathogenesis of melasma has also been highlighted through studies of the mechanism of action of H19 RNA. A decrease in the expression of RNA H19 and microRNA-675 in the skin of patients with melasma was detected. In addition, overexpression of miR-675 decreases the expression of tyrosinase, TRP-1, and TRP-2, while inactivation of miR-675 increases their expression. Although melanogenesis occurs in melanocytes, miR-675 is released from keratinocytes. MicroRNA-675 is contained in

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exosomes, which are small membrane vesicles of intracellular origin. Released in the extracellular environment, they contain unchanged and functioning microRNA-675, which is a means of communication between keratinocytes and melanocytes. MicroRNAs exert their effects through targets. MITF was identified as one of the targets for microRNA-675. When the expression of microRNA-675 decreases, the level of MITF increases in patients with melasma. It was found that individual miRNAs can target mRNA and cadherin 11 (CDH11), which is also a target for miR-675.

Although CDH11 expression was not detected in melanocytes, CDH11 in fibroblasts or keratinocytes was found to stimulate melanogenesis via the Wnt signaling pathway and protein kinase B in cultured melanocytes. The role of environmental pollution. Around the world, air pollution is a major health problem. Today, much scientific evidence has accumulated that air pollution plays an important role in the causes of external aging. It is also suggested that unfavorable environmental conditions may be a possible cause for the occurrence of melasma and other hyperpigmentation. Air pollution in the form of suspended solids and aromatic polycyclic hydrocarbons promotes their penetration through the skin in the form of nanoparticles. Subsequently, the process of generating quinones occurs, which participate in the reduction cycle and produce reactive oxygen species. Particulate matter increases the production of reactive oxygen species, which is a trigger for increased levels of metalloproteinases, leading to extrinsic aging, which includes skin hyperpigmentation.

Due to the growing interest in the problem of the influence of environmental factors on the occurrence of hyperpigmentation, some researchers have proposed a special term - “environmentally induced lentigo.” A role for activation of the aryl hydrocarbon receptor by UV radiation and environmental toxins has also been suggested to play an important role in initiating and maintaining disruption of intercellular communication between melanocytes, keratinocytes and fibroblasts leading to the development of environmentally induced lentigines and its resistance to treatment in human skin. . The role of thyroid diseases. Although little research has been done to date on the relationship between autoimmune thyroiditis and melasma, recent studies have shown that there is a significantly higher prevalence of thyroid dysfunction in women with melasma compared with controls. Thus, it has been suggested that there is a relationship between autoimmune thyroiditis and melasma. However, developing recommendations for screening for thyroid disease in patients with melasma requires additional research. Despite recent progress in understanding the pathogenesis of pigmentation disorders, the relationship between the appearance of hyperpigmentation and each etiological factor is only partially determined to date. It still remains unclear which factors play the main role in triggering the pathogenetic mechanism. In addition, not every patient with hyperpigmentation has similar clinical and histological features. It is assumed that the development of hyperpigmentation, in particular melasma, may include various etiological and pathogenetic factors. Thus, identifying the specific causes that trigger the pathological process of hyperpigmentation will help in the future to develop and implement more personalized therapy.

Conclusions:

In conclusion, we notethat the development of hyperpigmentation, in particular melasma, may include various etiological and pathogenetic factors. Thus, identifying the specific causes that

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trigger the pathological process of hyperpigmentation will help in the future to develop and implement more personalized therapy.

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