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Research Progress on Pathogenesis of Melasma

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Abstract: Melasma is a common facial symmetrical pigmentation skin disease, which occurs in women of childbearing age and seriously affects the appearance and quality of life of female patients. At present, the etiology and pathogenesis of melasma have not been fully elucidated. In recent years, many studies have shown that ultraviolet radiation, hormone levels, genetic factors, inflammatory reactions, free radicals and skin microbial factors play an important role in the pathogenesis of melasma. This article reviews the research progress of the pathogenesis of melasma in order to better prevent and treat melasma in clinic.

1. Introduction

Melasma is an acquired hyperpigmentation and disfigurement skin disease. Usually its clinical manifestations are light brown or yellow brown, varying in size, irregular shape of the color spot, symmetrical distribution, can be sphenoid, often occur in the orbit, forehead and other places (see Figure 1). Melasma not only affects the face, but also brings serious troubles to the work and study of patients. The incidence of this disease is increasing year by year, and its etiology and pathogenesis are complex. Most scholars believe that it is closely related to ultraviolet radiation, hormone levels, genetic factors, inflammatory reactions, free radicals, skin microbial factors, impaired skin barrier function and abnormal content of trace elements, etc. The possible pathogenesis is described as follows.

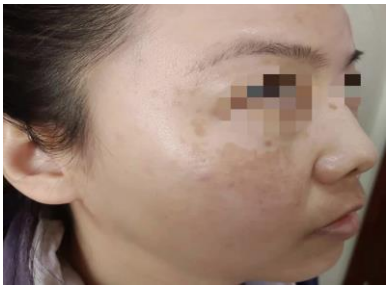

Figure 1: Brown pigmentation spots on the face with irregular shape and clear boundaries

2. Overview of the Pathogenesis of Melasma

2.1. Ultraviolet and Visible Light

As we all know, ultraviolet light is considered to be one of the important factors that induce the occurrence and aggravation of melasma [1]. Studies have found that UV irradiation can promote the release of histamine from skin mast cells, which has been shown to play a role in melanin production and can stimulate the proliferation and migration of melanocytes [2]. On the other hand, ultraviolet light can stimulate keratinocytes to produce a variety of cytokines, such as nerve growth factor, stem cell factor, alpha melanocytotropic hormone, vascular endothelial growth factor and basic fibroblast growth factor, which are involved in the occurrence and development of melasma. During the irradiation of ultraviolet light on the skin, human keratinocytes can secrete a melanocyte cytokine SCF, which acts on the c-Kit receptor on melanocytes, resulting in hyperpigmentation [3], as shown in Figure 2. In addition, repeated exposure to ultraviolet light can cause damage to the basement membrane zone, increase of mast cells and solar elastic degeneration in melasma lesions. Studies have shown that visible light is closely related to the onset of melasma. Visible light (blue-purple) can induce hyperpigmentation through specific sensors in melanocytes. Handel et al. [4] found that dentists, bakers and other professionals working under high-intensity light had a higher incidence of melasma than the general population, and the treatment was more difficult. These results suggest that ultraviolet radiation and visible light exposure are one of the important factors leading to the development and deterioration of melasma, and the research on photoprotection should be strengthened.

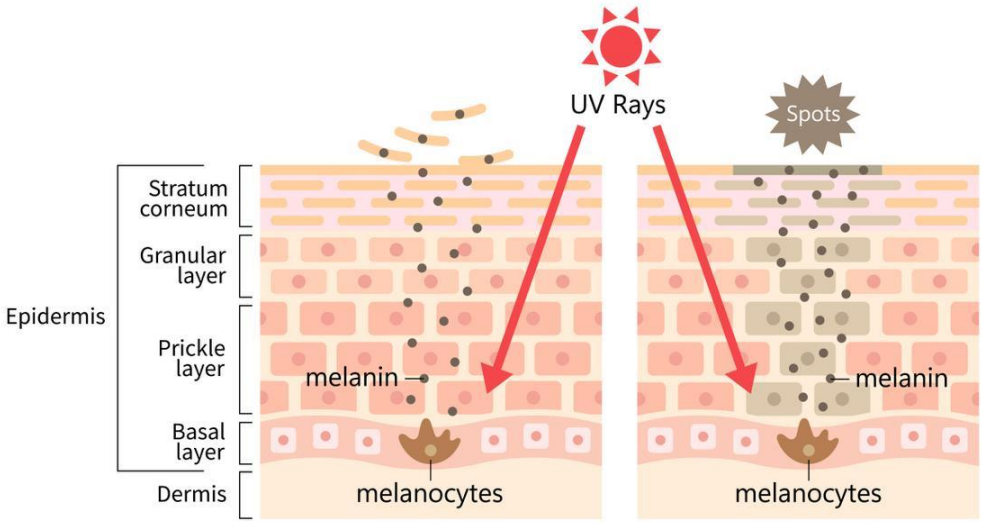

Figure 2: The Mechanism of Ultraviolet light on the skin to produce melanin

2.2. Genetic Susceptibility Factors

Clinical studies have shown that melasma is a dominant genetic disease with familial aggregation [5], and its occurrence has a certain degree of racial differences. Latin Americans, Hispanics and Asian Fitzpatrick iii-V skin types are prone to abnormal pigmentation changes, especially melasma and post-inflammatory pigmentation [6]. This suggests that the incidence of melasma in different races is significantly different, the incidence of yellow race and black race is

significantly higher than that of white race, and the incidence of melasma in female group is significantly higher than that of male group. Some scholars have investigated 200 male patients with melasma and found that the pathogenesis of endocrine disorders caused by diseases is roughly the same. In addition, male melasma is not only related to ultraviolet radiation, but also highly related to genetics [7]. Therefore, it can be considered that genetic factors are an important factor leading to the onset of melasma.

2.3. Hormone Levels

Melasma is more common in women over the age of 30, especially those who are pregnant and take oral contraceptives. The existence of this group suggests that its pathogenesis may be closely related to sex hormone levels, especially estrogen levels. Studies have shown that estrogen can improve the activity of tyrosinase under certain conditions, and bind to the estrogen receptor on the surface of melanocytes to promote the synthesis of melanin. Tyrosinase is a key enzyme in the synthesis of melanin in the organism. This enzyme oxidizes dopamine into dopa quinone in melanocytes and then oxidizes into some intermediates to synthesize melanin (see Figure 3), and its activity is positively correlated with the formation of melasma [8]. Thiohydrogroup (-SH) can bind to copper ions in tyrosinase, weakening the activity of the enzyme and reducing pigment formation [9]. Studies have found that the incidence of melasma in women after the age of 50 is significantly reduced, which may be related to the decrease of estrogen and progesterone levels and the decrease of the number and activity of active melanocytes in the skin [10]. Melasma affects not only women, but also men. Although the effect of estrogen on male patients has been excluded [11], changes in other hormone levels may also cause melasma. Studies have found that male melasma patients in India have lower serum testosterone levels and higher serum luteinizing hormone levels, suggesting that even in male populations, endocrine diseases may contribute to the occurrence of melasma to a certain extent.

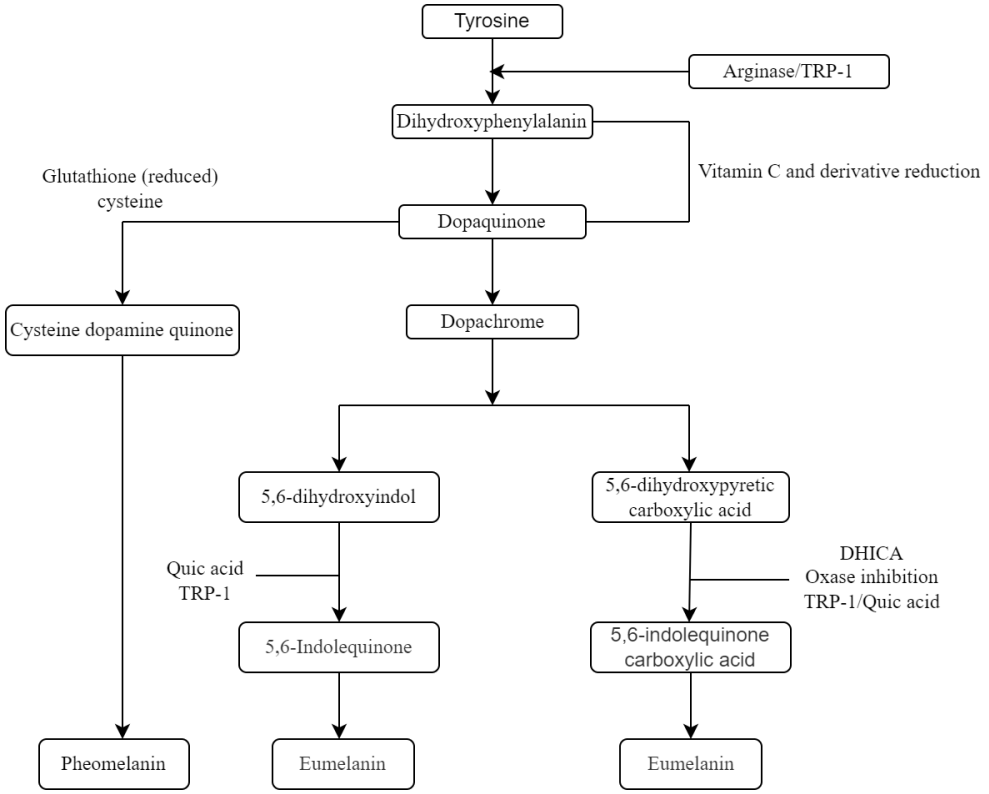

Figure 3: The inflammatory process of Proptobacillus acne

In recent years, with the continuous research on the pathogenesis of melasma, the abnormal thyroid hormone level in patients with melasma has attracted the attention of many experts and scholars. Foreign scholars compared the thyroid function of 70 patients with melasma and 70 healthy controls, and found that the probability of abnormal thyroid function was 18. 5% and 4. 3%, respectively, and the probability of positive anti-thyroid peroxidase antibody was 15. 7% and 5. 7%, respectively. The incidence of thyroid dysfunction in patients with melasma is significantly higher than that in the healthy control group (P=0. 008), suggesting that patients with melasma may be accompanied by thyroid dysfunction, and it is also suggested that patients with melasma should regularly test thyroid function [12].

2.4. Impaired Skin Barrier Function

Skin is the largest organ of the human body and the first protective barrier between the human body and the outside world. It has physiological functions such as barrier, secretion, absorption, excretion, immunity, metabolism, temperature regulation and sensation, among which barrier function is the most basic and important, including physical barrier, immune barrier, osmotic barrier, nerve barrier and pigment barrier. The skin barrier commonly referred to in clinical practice refers to the epidermal penetration barrier, which can participate in resisting the invasion of antigens, sunlight, microorganisms, etc. , and prevent the loss of nutrients and water in the body internally. Melasma is related to the breakdown of skin barrier, which can be divided into epidermal barrier, basal layer barrier and dermal barrier. The disturbance of epidermal lipid metabolism, the decrease of water content, the destruction of basal layer, dermal elastic fibrosis, local inflammation, vascular hyperplasia, etc. , all participate in the destruction of the epidermal basal layer and the dermal skin barrier (see Figure 4). Kang et al. [13] found that the expression of melanin synthesis gene increased in the lesion area of patients with melasma, while the expression of lipid metabolism gene decreased. Moreover, long-term ultraviolet radiation can also affect lipid metabolism, reduce lipid synthesis, produce excessive melanin, resulting in black pigmentation. Excessive ultraviolet radiation induces pathophysiological processes such as oxidative stress and inflammation, inhibits intracellular antioxidant enzymes, generates excessive oxygen free radicals, increases TEWL, and destroys the stability of skin barrier structure [14]. In addition, the stratum corneum is less hydrated, resulting in melanin cannot be transported evenly to the epidermis and pigmentation occurs. All these suggest that the skin barrier function of patients with melasma has been damaged to varying degrees.

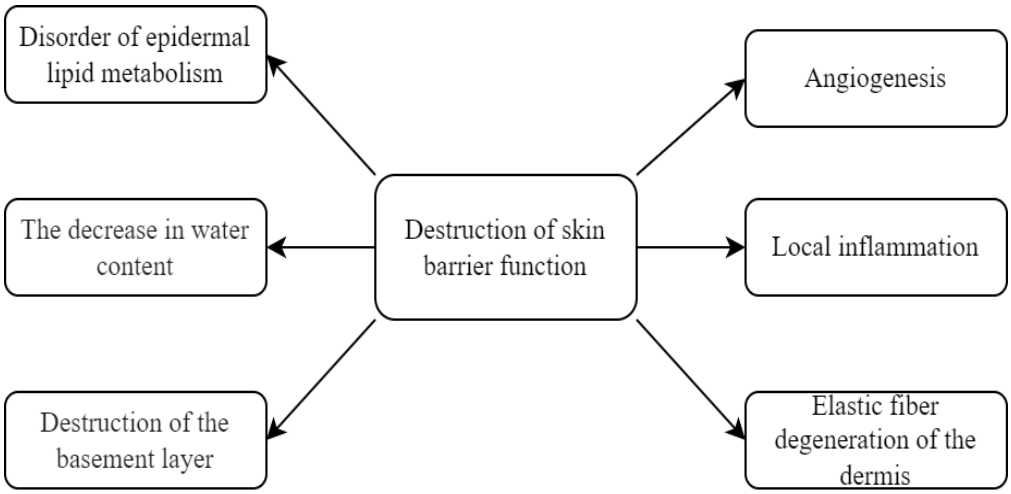

Figure 4: The inflammatory process of Proptobacillus acne

2.5. Inflammatory Response

Inflammation is closely related to the pathogenesis of melasma. Modern studies have found that fibroblasts and mast cells are related to skin pigmentation. After long-term ultraviolet irradiation, the number of mast cells increases, the level of melanocytes is upregulated, and leukocyte infiltration and blood vessel dilation are obvious [15-16]. In addition, the mrna expression of inflammatory receptors such as Toll-like receptor (TLR) 2 and TLR4 increased significantly. Wang Yinjuan et al. [17] collected peripheral blood from 40 patients with melasma and healthy controls, and collected skin tissues from 10 patients with melasma and 10 healthy controls for biopsy. The expression of TLR2 and 4mRNA in blood samples and skin lesions were detected by reverse transcription polymerase chain reaction (RT-PCR) and immunohistochemistry. Results of The mRNA levels of TLR2 and TLR4 in melasma lesions were significantly higher than those in healthy controls. The authors speculated that the incidence of melasma may be related to the local skin TLR-mediated inflammatory response. All these suggest that chronic inflammation is involved in the pathogenesis of melasma.

2.6. Vascular Factors

Melasma is a kind of pigmentation spot, which is mainly manifested as symmetrical brown spots on the face. In recent years, it has been found that the abnormality of blood vessels and hemorheology is considered a key factor in the occurrence of melasma. Kim et al. [18] conducted a comprehensive study on the capillaries in melasma lesions. They quantitatively measured the erythema severity of skin lesions and non-skin lesions in 50 female patients with melasma by colorimeter, and the results showed that the erythema severity of skin lesions was significantly higher than that of non-skin lesions, and the number of blood vessels increased and the diameter of the tube became larger, suggesting that the facial erythema of patients with melasma was caused by vascular proliferation and capillary dilatation at the same time. Kim et al. [18] further studied the capillaries in the lesions of melasma and found that the expression level of vascular endothelial growth factor (VEGF) was increased. VEGF can not only specifically induce the production of stroma, promote the growth of vascular endothelium, but also significantly increase the permeability of blood vessels. High expression of VEGF not only promotes the proliferation of blood vessels, but also activates arachidonic acid and phospholipase A2 through its receptors to accelerate the generation of melanin stains [19]. If the level of VEFG is reduced, the permeability of blood vessels will decrease accordingly, resulting in local microcirculation obstruction, oxygen free radical scavenger obstruction along with blood flow, resulting in dark spots [20]. In clinical studies, it was found that when the blood vessels of melasma hyperplasia were destroyed, the stain significantly subsided, which provided a theoretical basis for the treatment of melasma with pulsed dye laser (PDL), which reflected a unique and large advantage. In addition, oral tranexamic acid is one of the effective drugs for the treatment of melasma [21]. Endothelin-1 levels in patients with melasma were reduced after taking tranexamic acid for 12 weeks, suggesting that endothelin-1 may be associated with the onset of melasma [22].

2.7. Free Radical

Oxygen free radicals are a harmful chemical in the body associated with aging and chronic disease that can be removed by free radical scavengers. There are a variety of oxygen free radical scavengers in the human body, such as glutathione peroxidase (CSH-PX), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), etc. When lipid peroxidation (LPO) is enhanced or the level of free radicals is increased, there is a dynamic balance between oxidation and antioxidant in

the body due to the protective mechanism of gene regulation. Studies have shown that melasma is closely related to free radicals [23]. Abnormal accumulation of oxygen free radicals can lead to the imbalance of the antioxidant system, abnormal increase of lipid peroxide (LPO), enhanced activities of tyrosinase (TYR) and cyclic adenosine phosphate (cAMP), and decreased activity of superoxide dismutase (SOD), and ultimately increase the production of melanin [24-25], inducing the occurrence or exacerbation of melasma (see Figure 5). Clinical experiments have proved that the use of tea polyphenols can remove free radicals and prevent lipid peroxidation, thus reducing the occurrence of melasma [26].

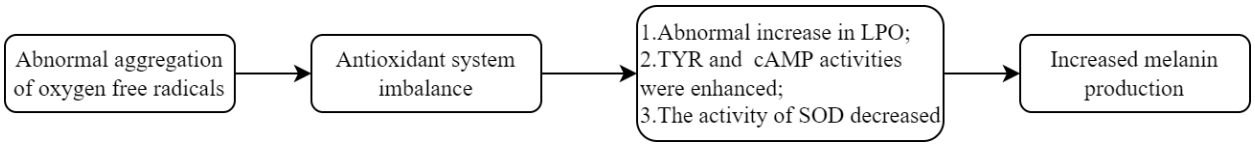

Figure 5: The process by which oxygen radicals produce melanin

2.8. Imbalance of Local Microbial Flora

Under normal circumstances, the skin surface is parasitic, staphylococcus (including Staphylococcus epidermidis, staphylococcus aureus), propionibacterium acnes, pseudomonas aeruginosa, non-radioactive mycobacterium, Escherichia coli and micrococcus and other a large number of microorganisms, according to their existence is divided into permanent bacteria and transient bacteria. There are symbiotic or antagonistic effects among the flora and participate in the formation of the epidermal lipid membranes, constituting a skin biological barriers, nourishing skin tissue, and participating in skin cell metabolism. The human body has the ability to maintain the stability of its own microbial flora, and if the normal flora is dysfunctional, it will easily lead to pathological changes such as skin pigmentation [27]. When Bai Jie et al. studied the facial microorganisms of college students, they found that the concentration of Propionibacterium acnes in the skin lesion area of patients with melasma decreased, and the number of Micrococcus pigmentococcus and gram-negative bacteria increased significantly compared with that of normal people in the same area. The decrease of the concentration of resident propionibacterium may lead to the decrease of the resistance of the skin to foreign bacteria, resulting in the proliferation of micrococcus. These bacteria can produce a large amount of brown pigment and orange pigment and exceed the self-purification ability of the skin, so that they are absorbed by the skin and deposited in the epidermis to form melasma.

2.9. Abnormal Content of Trace Elements

Studies have found that the occurrence of melasma has a certain relationship with the level of trace elements in the human body. For example, zinc, as a coenzyme of superoxide dismutase (SOD), catalyzes the disproportionation of superoxide ions. Low zinc content can reduce the activity of total SOD, enhance the activity of TYR, and increase the pigment. The formation of copper ion melanin is closely related, whether the copper content in the body is low or high, it can promote the production of oxygen free radicals and promote lipid peroxidation. In addition, studies have found that vitamin B and folic acid can promote oxidation and increase pigment.

3. Conclusion

As a chronic and refractory disease with multiple etiologies and complex pathogenesis, melasma faces many challenges in its treatment. Understanding the etiology and pathogenesis of melasma is

helpful to lay a solid theoretical foundation for the prevention and treatment of melasma and to reduce recurrence. At present, many experts and scholars have continuously discussed and studied its pathogenesis and made certain progress and found that it is closely related to ultraviolet and visible light, genetic susceptibility factors, impaired skin barrier function, inflammatory response, vascular factors, hormone levels, free radicals, microbial flora imbalance, abnormal trace element content and other factors. Although the etiology and pathogenesis of melasma at home and abroad have made some progress, there are still many problems, which need long-term research in the future.

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If any, should be placed before the references section without numbering.

Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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