Study on the Pathogenesis and Therapeutic Targets of Vitiligo Based on Network Pharmacology

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Abstract. Vitiligo is a skin disease characterized by acquired depigmentation, which is mainly manifested as white patches on the skin, mucosa or hair, affecting patients' mental health and quality of life. The pathogenesis of vitiligo is complex, easy to diagnose and difficult to treat. Single target is difficult to cure or control the disease, it is necessary to intervene from different targets. The rise of network pharmacology makes it possible to find the target of vitiligo from different levels. In this paper, the pathogenesis of vitiligo was summarized from different perspectives with neuroendocrine immunity as the main line, and the potential targets of vitiligo were screened and discussed under the guidance of network pharmacology, so as to provide new ideas for the basic research and treatment of vitiligo.

Introduction

Vitiligo is an acquired and progressive skin pigmentation disorder, without gender or ethnic differences. It is manifested as localized or generalized skin pigmentation lesions, with a incidence of 0.5\%-1\% [1]. The first-line treatment is mainly external glucocorticoid and UVB ultraviolet irradiation [2]. Network pharmacology can reveal the mechanism of the body's interaction with diseases from the perspective of system biology and biological network balance, and can be used for the construction of drugs, diseases and drug-disease network [3]. The skin is one of the main sites of neuro-endocrine- immune interaction, and the nervous system plays an important role in skin barrier function, skin inflammation and immunity. Based on the advantages of network pharmacology and the multiple factors in the pathogenesis of vitiligo, this paper focuses on the pathogenesis and network pharmacology to explore pathogenesis and potential therapeutic targets.

Pathogenesis

Genetic Susceptibility

Studies at home and abroad tend to prove that vitiligo is a complex skin disease, and its occurrence and development are mediated by both genetic and environmental factors [4-5]. Studies have shown that about 10\%-30\% of patients with vitiligo have a family genetic predisposition. Moreover, with the application of genome-wide association analysis, high-throughput genotyping technology, bioinformatics and other advanced research technologies, the fine localization of genetic susceptibility regions and susceptibility genes related to vitiligo has been emerging. Studies have shown that a region of about 200 KB on chromosome 6q27 in Chinese population is significantly correlated with the susceptibility to vitiligo. The fine localization of this vulnerable region indicates that RNASET2 gene is the related gene in the region of vitiligo 6q27 [6]. GZMB gene encodes granulocyte B, which plays an important role in inducing apoptosis of cytotoxic T cells. Based on the study of 3120 patients, GZMB gene is an important site of vitiligo in Han population [7]. In addition, genetic mutations of genes related to the genetic susceptibility of vitiligo, such as CAT manna-binding lectin 2 (MBL2), killer T cell lymphocyte-associated antigen 4 (ctla-4), can mediate the changes of vitiligo melanin [8].
Neuro-endocrine-immune Theory

Vitiligo patients had higher MAO in vivo than healthy people, suggesting that the patients' sympathetic excitability increased and their homeostasis was out of balance, leading to increased release of melatonin and decreased melanin synthesis. Neuropeptides (NPs) are major mediators of the nervous system acting on the endocrine and immune systems, have a variety of immunomodulatory properties. At the skin level, the interaction between neuroendocrine and immune systems mainly depends on the binding of NPs to the receptor and the activation of immune cells. NPs receptor is widely expressed in the skin and can regulate the functions of lymphocytes, keratinocytes and melanocytes, etc. [9]. Under stress conditions, corticotrophin-releasing hormone released from hypothalamus can promote the release of interleukin (IL-4), tumor necrosis factor-α (TNF-α), and aggravate the inflammatory reaction. Based on the changes in patients with vitiligo before and after treatment on indicators such as EP-β, IFN-γ the development and progression of vitiligo is a comprehensive effect process of neuroendocrine immune network, which is in line with the theory of vitiligo caused by the disorder of "kuwiti tabiy" in Chinese medicine [10].

Functional Melanocyte Deficiency

Lerner first proposed the theory of melanocyte self-destruction in 1971, believing that the accumulation of toxic precursor substances synthesized by melanocyte itself destroyed melanocyte [11]. Tyrosinase (TYR) plays a crucial role in the synthesis of melanocyte, and many drugs play a role by up-regulating the biosynthesis of this enzyme or re-modifying the molecular structure of this enzyme after translation to enhance its biological activity [12]. Melanocytes originate from the neural crest and enter the epidermis at the 7th week of embryonic development. Studies have shown that melanocytes may be stored in the hair follicle and may be located in the outer hair root sheath [13]. The results showed that in vitro cultured melanocytes transplantation was effective in the treatment of vitiligo, and the effect was better in patients with segmental-type vitiligo [14].

Oxidative Stress

The decline of the body's antioxidant capacity and the accumulation of reactive oxygen species (ROS) can lead to the occurrence of oxidative stress, stimulate the body to secrete a variety of cytokines, attack and kill melanocytes, and lead to the pathogenesis of vitiligo [15]. Reactive oxygen species (ROS), represented by hydrogen peroxide (H2O2), lead to the apoptosis of melanocytes by directly damaging the nucleus and mitochondria, and inhibit the production of melanocytes by inhibiting the activity of tyrosinase. It can also stimulate the autoimmune response of melanocytes to clear melanocytes and inhibit the production of melanocytes [16]. Studies have shown that in patients with vitiligo, the number of Nrf2 nuclei in the skin lesions was significantly reduced, and the polymorphism of Nrf2 promoter region -650 was associated with the occurrence and development of vitiligo. Abnormal MAPK, PKC and PI3K protein kinase pathways related to Nrf2 phosphorylation are all related to the pathogenesis of vitiligo [17]. In vitiligo patients, the expression of antioxidant enzymes CAT and GPX1 was inhibited, SOD and MDA activities were increased, and GSH-Px activity was decreased, which was statistically significant compared with healthy people [18].

Target Study of Vitiligo Based on Network Pharmacology

Network pharmacology can reveal the pathogenesis and potential therapeutic targets of vitiligo by using relevant technologies. Now the main targets related to vitiligo are represented in the form of Fig. 1 with the help of the research methods of network pharmacology.
**Gene Targets**

Studies have shown that vitiligo is a polygenic genetic predisposition to disease that does not comply with Mendelian laws of inheritance. A variety of genes, such as PTPN22, MITF, MC1R, MBL2 and CTLA4, are involved in the development of vitiligo. PTPN22 gene encodes lym photyrosine phosphatase, which plays a negative regulatory role in T cell signal transduction and is of great significance in maintaining the balance of the immune system. Previous studies have shown that PTPN22 (rs2476601) is related to non-segmental vitiligo [19]. Blocked or insufficient melanin synthesis is the direct cause of vitiligo, and increased expression of melanin biosynthesis genes (MC1R, MITF, TYR, TYRP1 and DCT) can increase melanin synthesis and alleviate or cure the disease [20]. Manna-binding lectin (MBL) plays an important role in innate immunity, contributing to the clearance of apoptotic cells and supplementary activation. MBL2 gene polymorphism affects MBL serum level and can increase the risk of infection. Studies have shown that genetic variation caused by the structure of MBL2 gene and promoter polymorphism are related to the increased risk of a variety of autoimmune diseases, including vitiligo [21].

**Neuro-endocrine-immune Targets**

Skin discoloration in patients with vitiligo is associated with increased T-cell lysis activity which against melanocytes, suggesting impaired autoimmune tolerance [22]. Increased sympathetic excitability may lead to increased release of melatonin and other neurotransmitters and decreased melanin synthesis. On the other hand, sympathetic excitation may lead to an increase in MAO activity, which in turn leads to the accumulation of hydrogen peroxide and the reduction of melanin synthesis. IL-2 and IL-4 are important cytokines secreted by T cells, which are involved in the immune response and immune regulation, and are important indicators to measure the immune function of the body. Appropriate amount of TNF-α is involved in the normal immune regulation of the body, and is an important mediator of immune protection in the body. Excessive secretion may lead to the occurrence of certain diseases [23]. The effective regulation of IL-2, IL-4 and TNF-α expression in vitiligo patients can interfere with the occurrence and development of the disease.

**Other Targets**

Studies have shown that low NRG1 expression may be involved in the loss of melanocytes in patients with vitiligo, which is a pathogenic factor, leading to the pathogenesis [24]. TYR is a key enzyme for melanin synthesis, which can be promoted by up-regulating the expression level of TYRmRNA or tyrosinase-related protein-1 (TRPp-1) mRNA [25]. Oxidative stress is the trigger event of the destruction of melanocytes, and the imbalance between oxidation and antioxidant in vivo, local oxidative stress and the damage of melanocytes to cause vitiligo are important pathogenesis theories of this disease [26]. In patients with genetic predisposition to vitiligo, mononucleotide polymorphism exists in exon 9 of CAT, which changes the structure of CAT in the epidermis and reduces its activity, and then causes excessive aggregation of H2O2 in the epidermis, leading to and aggravating oxidative stress. CAT is the main enzyme in melanocyte to remove H2O2, which can prevent the damage of free radicals from high reactive oxygen species to melanocyte, and can completely remove superoxide ions in coordination with SOD.
Discussion

Vitiligo pathogenesis is not clear, generally considered to be an individual with genetic quality, due to a variety of internal and external factors, the activation of immune function, neuropsychiatric and endocrine disorders, resulting in the inhibition of enzyme system or the destruction of melanocytes, or the formation, or make melanosome generation or blackening obstacle, cause pigment to be lost and cause. In the treatment of vitiligo, the treatment mode of "one disease, one target and one drug" has prominent limitations. The key to treating the disease is to "turn things around." Finding the locus of the disorder and intervening to get it back on track is an effective way. Through analysis, it was found that the target of vitiligo treatment from the perspective of network pharmacology was highly consistent with the pathogenesis of the disease, indicating that the target screened by network pharmacology could be the first choice for the treatment of the disease.

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