

Advances in the Study of the Gut-brain-cortex Axis and Vitiligo

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Abstract: *Vitiligo is a chronic autoimmune disease with diverse etiology and complex pathogenesis, with common co-morbidities such as inflammatory bowel disease, rheumatoid arthritis, thyroiditis, diabetes, anxiety and depression. Recent studies have shown that intestinal flora and psychological stress have an important impact on vitiligo, and its possible realization of the “gut-brain-cortex axis” has become a research hotspot, providing a new direction for the treatment of vitiligo. In this paper, we summarize the progress of research on the link between the gut-brain-cortex axis and vitiligo.*

Keywords: Vitiligo, Gut-brain-cortex axis, Gut flora, Psychological stress, Immunity.

1. Introduction

Vitiligo is caused by the disappearance of melanin function or reduced number of cells in the skin, a kind of acquired limited or generalized skin pigmentation loss disease, clinically more common, and its main feature is the occurrence of white patches on the skin or mucous membrane area, which seriously affects the patient's appearance, and brings a greater psychological burden on the patient. According to statistics, the incidence of vitiligo in the world for 0.5%-2%, there are more than 20 million patients in China, and with the accelerated pace of life, and mental stress, the incidence of its incidence is rising year by year [1]. Modern medicine believes that it is closely related to immune function, oxidative stress, melanocyte self-destruction, heredity, neurochemical factors and other factors, but the specific pathogenesis is still unclear, easy to diagnose and difficult to treat, with a high rate of recurrence, which seriously affects the quality of life and mental health of patients. Vitiligo is also a systemic disease with an increased risk of multiple comorbidities. In recent years researchers have found that gut flora, psychological stress and the development of vitiligo may be realized through the gut-brain-skin axis. Therefore, it is important to understand the link between the gut-brain-cortex axis and vitiligo, which may provide new ideas for the treatment of vitiligo. In this paper, we will focus on an overview of the progress of research on the gut-brain-skin axis and vitiligo in recent years.

2. Relationship between Intestinal Flora and Vitiligo: The Gut-skin Axis

As the main interface between the human body and the external environment, the intestinal tract is closely related to the skin in terms of signal transduction mechanisms. The intestinal flora is the “largest micro-ecosystem” and the “second largest gene pool” of the human body, mainly located in the colon and the end of the ileum, with more than 1000 microbial species, which is more than 10 times the number of cells in the human body, with a total weight of about 1.5 kg, and the genes it carries are about 150 times larger than those in the human genome [2]. Although there are some differences in the structure of the intestinal flora between species and the

human body, the proportions of each species are usually relatively stable. The dynamic balance of the intestinal flora can be disrupted in various pathological states, thereby inducing an immune-inflammatory response in the body, leading to the development of disease. Thick-walled Bacteria, Anaplasma, Actinobacteria, Aspergillus, Micrococcus and Clostridium are the major bacterial groups in the human body [3]. A growing number of experimental results show that the structure of the intestinal flora is significantly altered and less diverse in patients with vitiligo compared to the healthy population. Our study pointed out that patients with vitiligo mainly showed a decrease in the abundance of *Mycobacterium anisopliae*, *Bifidobacterium bifidum*, *Clostridium difficile*, *Dolichobacterium*, *Brautobacterium*, *Alisonella*, *Igelziaceae*, *Hordmann-Moore*, *Bacillus vulgaris*, *Vibrio desulfuricans*, *Termitomyces peritrophic*, *Trueperella*, *Faecal-like monocytogenes*, *E. juvenile*, and *Brautobacterium*, and an increase in the abundance of *Candida-sugar* *Streptococcus*, *Barnesella* spp, *JAMSDA Mycobacterium* spp, and *Seatroutomonas* spp increased in abundance [4]. Foreign studies, on the other hand, have shown that patients with vitiligo have increased proportions of *Bacteroides* thickening and others in their intestinal tracts and decreased proportions of *Mycobacterium anisopliae*, *Bacteroides-like bacilli*, *Clostridium perfringens*, *E. faecalis*, and *Streptococcus thermophilus* and that patients with vitiligo with a course of more than 5 years have lower biodiversity than patients, with *Corynebacterium rods* 1, *Ruminal Staph* 2, *Salmonella* spp, and *Cryptobacillus thermophilus* being associated with the course of the disease and with serum IL-1 β levels [5]. Some of the inconsistencies in the results of domestic and international studies may be related to race, diet environmental factors, etc. However, certainly, the intestinal flora of patients with vitiligo changes significantly compared with that of healthy people, and this finding has an important impact on the pathogenesis of vitiligo. In addition, the proportion of common potential pathogenic bacteria such as *Streptococcus* spp, *Klebsiella* spp, *Escherichia-Shigella* spp and *Aspergillus* spp. in the intestinal flora of patients with vitiligo is significantly higher, which suggests that infections may be an important factor in the triggering or exacerbation of vitiligo [6]. Increased risk of cardiovascular disease in patients with vitiligo is also associated with gut microbial dysbiosis [7].

Elevation of the Thick-walled phylum/Anthrobacterium ratio affects carbohydrate metabolism and leads to a significant decrease in the production of short-chain fatty acids (SCFAs) [8]. As one of the important metabolites of intestinal flora, SCFAs can maintain the integrity of the intestinal mucosal barrier, reduce intestinal inflammatory response, and promote the balance of Helper T Cells (Th)1, Th2, and Th17 regulatory cells, etc. Its important component butyric acid can provide energy for intestinal epithelial cells. Provide energy, through the inhibition of inflammatory cell proliferation, migration, adhesion and cytokine production to inhibit the immune response, there is a powerful anti-inflammatory effect on a variety of autoimmune diseases and inflammatory diseases have a certain therapeutic effect, such as inflammatory bowel disease (inflammatory bowel disease, IBD), irritable bowel syndrome, rheumatoid arthritis, depression, anxiety disorders etc. , which are recognized comorbidities of vitiligo [9-11]. It is noteworthy that the reduction of gut bacterial diversity in vitiligo patients is very similar to the pattern of ecological dysregulation that occurs in IBD, suggesting that vitiligo and IBD may intersect in pathogenic pathways, implying that alterations in the gut flora have an important impact on the pathomechanisms of vitiligo [12]. The mechanisms by which intestinal flora influence skin homeostasis may be related to the regulation of systemic immunity. The intestinal mucosa is the mucosal system with the largest area of contact with the outside world and is one of the organs with the largest number of immune cells in the body, and the immune cells in the mucosal tissues account for 80% of all immune cells, which have an important influence on both natural and adaptive immunity [13]. Intestinal flora promotes the development and maturation of intestinal immune tissues, regulates the differentiation of T cells to Treg cells, and induces the production of immunoglobulin A, which strengthens the host immunity barrier. Altered intestinal flora, on the other hand, reduces Treg differentiation and inhibition of Th17 cells, inducing or exacerbating immune-skin inflammatory responses, which directly leads to the disruption of the homeostasis of the intestinal immune system [14, 15]. Dysregulation of gut microbial composition and corresponding gene function and metabolism has been shown to potentially affect inflammatory and immune responses, vascular endothelial growth factor signaling pathways, and apoptosis leading to vitiligo [16]. Thick-walled bacterial phylum and fungal phylum have the role of producing butyrate, and it has been found that both are significantly reduced in the lesional skin of patients with vitiligo [17]. The reduction of butyrate will result in a lack of Treg cell numbers, causing melanocyte-specific T cell hyperfunction, which in turn kills the melanocytes, ultimately leading to the development of vitiligo. Another study pointed out that IL-23/Th17 signaling pathway plays a key role in inflammation in the intestine and skin, and SCFAs, which have the function of inducing the differentiation of Treg cells and IL-10-secreting T cells, inhibiting the differentiation of inflammatory cells Th17 and secreting the major cytokine IL-17, are significantly reduced in the intestinal tracts of patients with vitiligo, and so it is thought that they can be increased through the regulation of the intestinal bacterial flora to SCFAs, to achieve the purpose of the treatment of vitiligo [18, 19]. In addition to the effects on the intestinal immune system, new evidence exists that in the presence of an impaired intestinal barrier, the intestinal flora and its

metabolites can become translocated, inducing immune responses to occur and more directly disrupting skin homeostasis. Th17 cells are a key cell population in the pathogenesis of vitiligo and are also involved in the maintenance of the intestinal barrier and immune homeostasis. Overactivation of Th17 cells in patients with vitiligo as well as a decrease in SCFA, among others, can lead to impaired intestinal barrier function. Histamine is a metabolite of the genus *Arissonella*, which has the function of inhibiting intestinal microbial ectasia and promoting intestinal mucosal repair [20]. And it has been found that the abundance of this genus is significantly reduced in patients with vitiligo [4]. These are the key factors in the triggering or exacerbation of vitiligo. Existing studies have successfully isolated the DNA of enteric bacteria from the plasma of patients with vitiligo [12]. In addition, it has been found that the concentrations of all indicators affecting the intestinal barrier are altered in patients with vitiligo. Probiotic therapy may have a positive impact on the regulation of the intestinal flora and help to restore a state of balance among the intestinal flora in patients with vitiligo. These findings provide support for the influence of gut flora on skin homeostasis and confirm the existence of the gut-skin axis.

3. The Connection between Psychological Stress and Vitiligo: The Brain-cortex Axis

Surveys have shown that vitiligo patients suffer from a series of negative psychological stress reactions, such as depression, anxiety, negativity, and low self-esteem, due to the decline in the quality of life, economic burden, and social stigmatization. In recent years, several studies have confirmed the effects of vitiligo on the mental aspects of patients, especially on dark-skinned people [21]. Anxiety and depression, on the other hand, affect 1/4 of vitiligo patients and are positively related to the severity of the disease [22]. Several studies of psychological interventions for patients with vitiligo have found significant relief of clinical symptoms, especially in adolescents and dark-skinned people, further illustrating the important impact of psychological stress on vitiligo [23, 24]. Many immune cells associated with vitiligo, such as CD3+, CD4+, CD8+ cell percentages and CD4+/CD8+ cell ratios, are likewise released in emotional states such as depression, acute and chronic stress, and anxiety, leading to immune dysfunction in the body [25]. Conversely, the worsening of vitiligo can also now increase depression, anxiety and other adverse emotions. The interaction between psychological stress and vitiligo aggravates the immune imbalance and is one of the reasons why vitiligo is prolonged and difficult to cure.

In general, the skin can actively respond to various psychological stresses with the involvement of skin immune cells, hormones and neuromodulators [26]. The skin compensates for the nerves expresses a variety of hormones and their receptors, and originates from the same neural ectoderm as the central nervous system, suggesting that the skin has some connection with the neuroendocrine system. The skin has an independent peripheral hypothalamus-pituitary-adrenal gland (HPA) axis, which interacts with the central HAP axis to form the brain-cortex axis, and the HPA axis is an important part of the neuroendocrine system involved in controlling the stress

response, and it is a key link in the perception of psychological stress, and it releases endocrine hormones related to the stress response, such as pro-adrenal hormone. Endocrine hormones related to stress response, such as adrenocorticotropin-releasing hormone (ARH), adrenocorticotrophic hormone (ACT), glucocorticoids, β -endorphin, α -MSH, and neuropeptides (NPs), such as substance P (SP), neuropeptide Y, and vasoactive intestinal peptide (VAP) [27, 28], and nerve fibers in the skin of the corresponding innervated areas can release NPs to regulate intrinsic and adaptive skin immunity [29]. It has been found that autonomic inhibition stimulates the release of neuropeptides in the skin, resulting in elevated levels of neuropeptide [30] and catecholamine [31] in patients with vitiligo. Altered levels of neuropeptides in the circulatory system modulate NKT cell activity, which is closely related to the activity of both limited and generalized vitiligo [32]. Also, the significant increase in catecholamine levels in patients suggests that stress stress-induced elevation of catecholamine levels is associated with the development of vitiligo. SP and NPY, which play a regulatory role in the maintenance of emotional homeostasis [33] and are highly expressed in vitiligo, stimulate the production of inflammatory factors by neutrophils and lymphocytes, including interleukin (IL)-1 β , IL-6, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α , leading to premature melanocyte stem cell failure and progressive hair pigmentation loss. High levels of SP expression were also observed in depressed patients [34]. This shows that psychological stress and vitiligo can interact with each other through the brain-cortex axis, and psychological interventions for vitiligo patients may be a new adjunctive treatment.

4. Connections of Vitiligo, Gut Flora, and Psychological Stress: The Gut-brain-cortex Axis

In the 1930s, some scholars found that inhibition, anxiety and other adverse emotions can change the composition of intestinal microbes, thus causing local or systemic inflammation, including skin inflammation, which speculated that there is a close link between the intestine, brain and skin, and put forward the theory of the unity of the intestines - brain - skin, but only until the 80 years up to the gradual attention received [35]. The discovery of the gut-brain-skin axis explains the correlation between the gut microbiota, emotional states, and systemic and cutaneous inflammation. The gut, known as the “belly of the brain,” is the body’s emotional organ and often exchanges information with the brain through the gut flora. It has been shown that the diversity and abundance of the intestinal flora of patients with depression and vitiligo are significantly reduced, and when the fecal flora of patients with depression is transplanted into rats by gavage, the rats can develop the characteristic behavior of depression, i.e., pleasure deficit [36, 37]. In addition, patients with vitiligo and depression showed hyperactivity of the HPA axis, and the gut flora of depressed patients was able to down-regulate the hippocampal STAT5a gene, which is involved in the regulation of the HPA axis [38], these studies further confirmed that disturbances in the gut flora may be a potential cause of psychological disorders. Irritable bowel syndrome is one of the common comorbidities in patients with vitiligo, whose altered intestinal flora structure is similar to

that of vitiligo patients, suggesting that intestinal flora may be an important link between vitiligo and psychological disorders [36-38]. Intestinal flora can influence the stability of the body’s internal environment through the immune system, the nervous system, the endocrine system and other pathways, such as two-way communication with neuromediators, inflammatory cells and so on. Therefore, the treatment of vitiligo from the perspective of the “gut-brain-cortex” axis is an innovative research direction for the future.

5. Summary

The human being is a multilevel and complete continuum; the health of the human body is inextricably linked to good psychological and social factors, while the recovery of human diseases also requires the support of psychological and social factors. It is a basic requirement of the modern medical model to conduct comprehensive analysis from the biological, psychological and social levels to recognize and evaluate human health and disease. Vitiligo is a common pigment disorder characterized by melanocyte loss and white spot formation. The proposed “gut-brain-skin” axis complements the pathogenesis of vitiligo that cannot be explained by currently known mechanisms examines the correlation between common gut microbial dysbiosis and psychological stress and the etiology of vitiligo, and then explores ways to the correlation between common gut microbial disorders and psychological stress and the etiology of vitiligo is explored. (1) Conventional treatments: a combination of antibiotics, probiotics, prebiotics, and probiotics. (2) Emerging therapeutic tools: application of special dietary therapies, microbial hybrids, fecal microbial transplantation (FMT), and targeted killing of characteristic pathogenic microbial species to treat vitiligo. Therefore, this paper reviews the relevant studies on the “gut-brain-skin” axis and vitiligo at home and abroad in recent years and provides a reference for exploring the new treatment direction of vitiligo.

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