Review Article

Pathogenesis and the emerging Therapy of Vitiligo

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Abstract

Vitiligo is a common and a disfiguring autoimmune disease, which has a negative impact on patients' self-esteem and quality of life. Pathogenesis of Vitiligo involves the interaction between defects of natural and extrinsic melanocytes, immune innate to swelling and destruction of T-cell-mediated melanocyte. Vitiligo affects about 1% of the general population. The risk of the disease was 6% for siblings and 23% for identical twins treatment is not only intended to stop the disease, but also to support repigmentation through the regeneration, proliferation and migration of melanocytes. Treatment strategies for dealing with all aspects of pathogenesis and pigmentation can be very effective, and this strategy may require a combination. Current treatments generally do not imply objective autoimmunity, and emerging treatments may use more specific methods based on a deep understanding of the pathogenesis of the disease, which can provide a good safety profile with a higher effectiveness. However, as with most medical treatments, careful patient selection and monitoring should enable us to normalize the pathogenic response of vitiligo in order to achieve the internal balance of healthy individuals.

Keywords: Vitiligo; Disease; Pathogenesis; Melanocytes

Introduction

Vitiligo is a common and disfiguring autoimmune disease, which has a negative impact on patients' self-esteem and quality of life [1, 2]. The current treatment
of vitiligo is a common non-targeted immunosuppressive agent, which can only provide moderate efficacy. Developing safe and effective therapies requires a better understanding of the pathogenesis of the disease in order to identify new therapeutic targets [3]. Vitiligo is caused by a dynamic interaction between genetic and environmental risks, which can trigger an autoimmune attack on skin melanocytes.

Pathogenesis of vitiligo

Genetics
The wider observation of vitiligo in the immediate relatives of patients with vitiligo provides early evidence for its heredity. Vitiligo affects about 1% of the general population [4]. The risk of the disease was 6% for siblings and 23% for identical twins [5]. In addition, vitiligo patients and their relatives are at increased risk of other autoimmune diseases, including autoimmune thyroiditis, type 1 diabetes mellitus, pernicious anemia and Addison's disease, suggesting that vitiligo is also an autoimmune disease [6]. These early observations were later confirmed by genome-wide association (GWA) studies, which found that many common genetic variations in vitiligo patients encode congenital (NLRP1, IFIH1, casp7, c1qtnf6, trif) and adaptive immune system components (FOXP3, BACH2, CD80, CCR6, PTPN22, IL2R, alpha GZMB, HLA class I and II) [7-9].

Oxidative Stress
There is increasing evidence that melanocytes in vitiligo patients have inherent defects, which reduce their ability to cope with cellular stress [10]. Epidermal cells, including melanocytes, are often exposed to environmental pressures, such as ultraviolet radiation and various chemicals, which can increase the production of reactive oxygen species (ROS). Although healthy melanocytes can relieve these stresses, melanocytes from patients with vitiligo seem to be more vulnerable. For example, melanocytes from the skin of peripheral vitiligo exhibit dilated endoplasmic reticulum (ER) and abnormal structure of mitochondria and melanosomes, which are characteristics of increased cellular stress. High concentrations of epidermal H2O2 and decreased level of catalase (a key enzyme that protects cells from oxidative damage) were observed in the skin of vitiligo patients [11-17].

Environment
The earliest trigger for vitiligo is not entirely clear. Several studies have shown that the combination of defects in melanocytes and exposure to specific environmental factors may play a central role in the pathogenesis of diseases. This is evident in a group of factory workers who developed vitiligo in gloves after exposure to a single benzophenone, an organic chemical [18].

Later studies confirmed that the contact history of other phenolic and catecholic chemicals found in dyes (especially hair dyes), resins/adhesives and leather was related to vitiligo [19, 20]. Melanogenesis is a multistep process in which melanocytes produce melanin. Tyrosinase is a rate-limiting enzyme in this process, which controls melanin production by oxidizing amino acid tyrosine (a natural phenol) [21]. In vitro studies have shown that chemical phenols can act as tyrosine analogues in melanocytes, leading to high levels of cellular stress. This may include increased production of reactive oxygen species (ROS) and activation of unfolded protein response (UPR), which in turn activates congenital inflammation [22, 23].

Innate Immunity
As mentioned earlier, GWA studies in vitiligo patients showed multiple susceptibility loci associated with genes that control innate immunity [7-9]. This may lead to congenital activation disorders in response to melanocyte stress by recruiting congenital populations such as natural killer cells (NK) and by producing and releasing high levels of pro-inflammatory proteins and cytokines, including heat shock proteins (HSP), IL-1beta, IL-6 and IL-8 [22-29]. Among the larger HSP molecules, inducible HSP70 (HSP70i) is unique because it can be secreted into chaperone peptides specific to the original host cells [30]. Recently, HSP70i has been shown to play an important role in the pathogenesis of vitiligo in mice by inducing inflammatory dendritic cells (DCs). These dendritic cells themselves may be cytotoxic or may carry melanocyte-specific antigens to T cells in lymphoid tissue [24,25]. This is considered to be a key interaction between innate immunity and adaptive immunity, leading to T cell mediated autoimmune destruction of melanocytes [31].

Adaptive immunity
Ultimately, cytotoxic CD8 + T cells lead to the destruction of melanocytes [32]. Cutaneous endocrine cytokines act as an early signal to help these self-activated T cells locate stress melanocytes. This may be important because the epidermis has no blood vessels, so active mechanisms are needed to help them locate melanocytes effectively [33]. Chemokines are small, secreted proteins that act as chemokines to guide T cell migration. IFN-gamma and IFN-gamma-induced chemokines (CXCL9 and CXCL10) are highly expressed in the skin and blood of vitiligo patients and in mouse models [34-36]. In addition, IFN-gamma and CXCL10 are essential for disease progression and maintenance of mouse models [34,37]. Recently, a separate study showed that serum CXCL10 levels in vitiligo patients were not only higher than those in healthy controls, but also correlated with disease activity and significantly decreased after successful treatment, suggesting that it could be used as a biomarker for monitoring disease activity and therapeutic response [39].

Emerging treatment
According to our current understanding of the pathogenesis of vitiligo, successful strategies for treating vitiligo should include three different approaches: reducing melanocyte stress, regulating autoimmune response and stimulating melanocyte regeneration. Existing therapies partly meet these needs, but emerging therapies may do so in a more targeted way, and combination therapies may produce better overall responses (Figure 1).
Figure 1: Current treatments, including local immunosuppressive agents, phototherapy and surgical methods, partially address these goals in a non-targeted manner.

The pathogenesis of vitiligo begins with the change of melanocyte, which shows the increase of cellular stress response. This can trigger autoimmunity, destroy melanocytes, and lead to local depigmentation. Pigment re-staining requires melanocyte growth and migration, usually from hair follicles. Therefore, there are three goals to consider in the treatment of vitiligo: 1) reducing melanocyte stress, 2) suppressing autoimmune targeting of melanocytes, and 3) Promote melanocyte regeneration.

Reducing melanocyte stress
The obvious decrease of catalase in epidermis of vitiligo patients and the increase of reactive oxygen species (ROS) level in diseased skin prompt people to assume that antioxidant therapy or ROS control may be an effective treatment strategy [38]. Pseudocatalase describes a treatment cream containing any amount of metal ions that converts a common reactive oxygen species, hydrogen peroxide, into water and oxygen. Early application of pseudocatalase combined with phototherapy for vitiligo seems promising [38-40]. However, they were either uncontrolled or not masked, and subsequent studies did not reproduce positive results [41-43]. It is not clear whether this strategy can be optimized or improved to develop future therapies.

Based on the antioxidant and anti-inflammatory properties of oral or local natural health products, vitamins and supplements, it has been suggested as a possible treatment [44-46]. It has been reported that the white matter polymer in plant extract improves the response of a small number of vitiligo patients to nbUVB compared with placebo [47]. A group of participants tested nbUVB with or without an "antioxidant pool" consisting of alpha-fatty acids, vitamin C, vitamin E and polyunsaturated fatty acids. They report that nbUVB combined with antioxidants is more effective for patients [48]. Greater controlled trials are needed to determine whether antioxidants are beneficial for patient management.

Regulation of autoimmunity
In the past decade, immunomodulators have made significant progress in the treatment of inflammatory skin diseases, including targeted treatment. Our latest understanding of the immune pathogenesis of vitiligo helps us identify new immune targets and develop and test new treatment methods for vitiligo.

HSP70i - group reported the role of heat shock protein HSP70i in the pathogenesis of vitiligo, suggesting that heat shock protein HSP70i is released by stress melanocytes and causes congenital inflammation in the skin [49]. Then they found that the mutant protein reduced its immunogenicity and even induced tolerance when expressed in the skin of a mouse model to prevent disease. They propose future testing, a new treatment for vitiligo [25], although the transmission of a mutant protein in the skin of patients may take some time to develop and prove safety.

IFN - gamma / CXCL10 - axis is a key signaling pathway for the progression and maintenance of vitiligo. It is assumed that targeting the IFN-gamma / CXCL10 axis may be an effective therapeutic strategy [34,37]. Various antibodies and small molecule inhibitors have been developed to target components of this pathway (including IFN-gamma, CXCL10 and CXCL10 receptor CXCR3) and have been found safe in early clinical trials for the treatment of other autoimmune diseases, including psoriasis, Rheumatoid arthritis and Crohn's
disease. Most trials fail to reach the end point of efficacy, possibly because interferon-gamma is not the main driving factor for these diseases. However, recent findings in patient and mouse models suggest that vitiligo is the best disease to test these research drugs [3].

JAK-STAT signal - transduction. JAK-STAT signal is essential for the extracellular signal transduction of many cytokines including IFN-gamma to the nucleus. After ligation of cytokine receptor, Janus kinase (JAKs) phosphorylation signal transducer and transcription protein activator (STATs) are activated and target gene transcription is induced. JAK family has four members, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAK1 and JAK2 directly participate in IFN-gamma signal transduction and activate Stat1, which induces IFN-gamma-induced gene transcription including CXCL10 [50] (Figure 2).

Figure 2: The autoimmunity of vitiligo is driven by IFN-gamma-CXCL10 cytokine signaling pathway. Activated melanocyte-specific CD8+T cells secrete IFN-gamma and transmit signals through IFN-gamma receptor (IFN-gamma R) to activate JAK1/2 and STAT1. This induces the production of CXCL9 and CXCL10, which signal through receptor CXCR3 and recruit more autologous T cells to the epidermis, leading to extensive melanocyte destruction. Targeting this cytokine pathway is a new therapeutic strategy for vitiligo.

Some small molecular JAK inhibitors with unique selectivity have been tested in patients or are under development. Interestingly, a patient with generalized vitiligo has been reported to respond to oral tofacitinib, a JAK 1/3 inhibitor approved for the treatment of moderate to severe rheumatoid arthritis [51]. Ruxolitinib, another JAK inhibitor with JAK 1/2 selectivity, has been approved by FDA for the treatment of moderate or high risk myelofibrosis and polycythemia vera [52,53]. We report a case of leukoplakia with rapid pigmentation of the face and trunk after oral administration of ruxolitinib [54]. The treatment response of these inhibitors does not seem to last long because the patient loses re-pigmentation after discontinuation of treatment [55].

Like all other immunosuppressive drugs, tofacitinib and ruxotinib may have adverse effects, including opportunistic infections and rare malignant substances. In addition, ruxolitinib may income blood abnormalities.
including thrombocytopenia, anemia, and neutropenia [56]. Topical formulation of these drugs may provide therapeutic benefit without increasing the risk of adverse events [57]. Currently, an open label, phase 2, proof of concept clinical trial is recruiting participants to test the effectiveness of topical ruxotinib 1.5% in the treatment of vitiligo [58].

In addition to JAK inhibitors, STAT inhibitors may have similar effects. So far, seven members of the family have been identified, but only STAT1 as a homodimer participates in IFN-gamma signal transduction [50]. A previous in vitro study reported that statins inhibited STAT1 function by inhibiting HMG-CoA reductase to reduce cholesterol [59]. In addition, a vitiligo patient was reported to have improved after taking simvastatin [60]. A recent study tested systemic simvastatin in a white spot mouse model and found that it was effective in preventing and reversing disease [61]. However, we conducted a small pilot clinical trial to test that the efficacy of high dose simvastatin (80 mg per day) in patients with generalized vitiligo did not reach its primary therapeutic end point [62]. The adverse effects of limited simvastatin administration on human may be the cause of different outcomes between mice model and vitiligo patients. A study currently under way is recruiting patients to assess the benefits of Atorvastatin Combined with UVB in the treatment of active vitiligo [63]. Future studies could test local simvastatin as a method of increasing local concentration without toxicity.

**Stimulation of melanocyte regeneration**

**α-MSH** - Phototherapy is the first-line treatment for vitiligo, especially for patients with extensive diseases [1,2]. Phototherapy and combined therapy. Although the mechanism of its therapeutic effect is not fully understood, photochromism may be due to its ability to induce immunosuppression. Melanocyte stem cells can also be induced to differentiate and proliferate [70]. Alpha-melanocyte stimulating hormone (alpha-MSH) is a natural hormone that stimulates melanogenesis [71]. Alpha melanin peptide, a synthetic analogue of alpha-Melanocyte-stimulating hormone, has been approved by the European Drug Administration to alleviate photosensitivity of erythropoietic protoporphyria [72], which may also improve the efficacy of phototherapy for vitiligo [73]. Recently, we conducted a randomized, comparative multicenter trial to test the safety and efficacy of alpha-melanin tidal subcutaneous implants combined with NB-UVB in the treatment of generalized associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), etc. [64]. Interestingly, the response of melanoma patients to immunoassay site inhibitors is associated with the development of vitiligo [65]. It has been hypothesized that activation of these surface receptors can restore tolerance in vitiligo patients [66].

**Immune checkpoints** - The successful application of immunotherapy in the treatment of metastatic melanoma has attracted much attention in recent years by blocking inhibitory checkpoints. Immune checkpoints are molecules that regulate T cell responses to inflammation, including cytotoxic T lymphocyte
vitiligo in adults. Although side effects included nausea and excessive skin pigmentation, which led some subjects to withdraw from the trial, the combination therapy was slightly more tolerable. Compared with NB-UVB monotherapy, treatment results in faster and higher total pigmentation. This reaction is most evident in patients with dark skin [74]. It is not clear whether alpha melanopeptide has any benefit in the treatment of vitiligo.

**WNT signaling** - A recent study reported that the defective WNT signal of melanocytes in vitiligo patients is a way to promote the differentiation of skin melanocyte precursors. They hypothesized that this impaired signal transduction contributed to the pathogenesis of the disease, especially by inhibiting the regeneration and re-staining of melanocytes during treatment. Studies on human skin transplantation in vitro have shown that WNT activator can promote melanocyte differentiation [35]. Therapeutic WNT activation may therefore be an adjuvant therapy for vitiligo that supports melanocyte regeneration [75].

**Selective sunscreen** - Although it is currently the most effective treatment for vitiligo, phototherapy is still a challenge for patients. In order to receive treatment, patients usually go to a special clinic two or three times a week for a period of 1-2 years to obtain satisfactory treatment results. Although sunlight is an inexpensive alternative to phototherapy, it is difficult to monitor exposure, and non-therapeutic wavelengths of light may cause erythema and limit doses. Recently, a local formulation of 1% dimethicone has been reported to selectively block sunlight wavelengths below 300 nanometers, allowing therapeutic wavelengths to penetrate in the nbUVB range (~311-312 nanometers). A small double-blind placebo-controlled study found that the use of this cream under sunlight is safe and effective, and can induce pigmentation of skin lesions [76]. However, this needs to be confirmed in larger clinical trials, as the authors acknowledge that at certain times of the year, inadequate sunshine or physical inability to participate in public places limits their use. In addition, the cream does not block potentially harmful ultraviolet light, so this method may not be as safe as nbUVB phototherapy.

**Summary**

In order to better understand the pathogenesis of vitiligo, studies have shown that an optimal treatment strategy should consider three key aspects of the disease: 1) normalized melanocyte stress, 2) suppression of autoimmunity, and 3) promotion of melanocyte regeneration. Although current treatments, such as phototherapy, topical immunomodulators and surgical procedures, partially address these problems, they are carried out in a general, non-targeted manner, leading to suboptimal reactions and potential side effects.

New therapies seek to identify specific pathways through basic, transformational and clinical studies of vitiligo. To improve the efficacy and safety of patients (Figure 3). Although this is indeed a hopeful and exciting moment for vitiligo patients and their doctors, this excitement should be carefully balanced, especially as melanoma may use these same pathways to avoid immune surveillance or promote their growth. However, as with most medical treatments, careful patient selection and monitoring should enable us to normalize the pathogenic response of vitiligo in order to achieve the internal balance of healthy individuals.
Figure 3: Current and emerging treatments address 3 major goals in vitiligo treatment. Current treatments are listed in black, emerging treatments in red.

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Conflict of interest
The authors declare no conflict of interest.

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