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Unraveling Vitiligo: From Immune Mechanisms to Promising Therapeutic Strategies

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Abstract

Vitiligo is a dermatological condition affecting 1% of the global population, characterized by the loss of skin pigmentation. It appears in two main forms: nonsegmental (symmetrical depig-mentation) and segmental (localized depigmentation). Oxidative stress and mitochondrial dysfunc-tion in melanocytes cause vitiligo, while immune privilege protects hair follicle melanocytes, allow-ing for possible repigmentation. Genetic factors and associations with other autoimmune diseases, such as type 1 diabetes and thyroiditis, suggest a heritable autoimmune component. CD8+ T cells play a crucial role in vitiligo, targeting melanocytes and promoting apoptosis. These cells, along with IFN-γ signaling, contribute to disease progression. Therapies targeting these pathways, such as JAK inhibitors, have shown promise in repigmentation, particularly when combined with nar-rowband UVB phototherapy, a gold standard treatment. Surgical interventions, including punch grafting and suction blister grafting, show high efficiency but bring high risks of skin damage and hyperpigmentation. Vitiligo patients experience significant emotional suffering, requiring both a psychological and medical treatment approach. Dietary interventions, specifically those rich in anti-oxidants, may support disease treatment. Vitamin D, in particular, is a promising therapeutic agent by protecting melanocytes from oxidative stress via the WNT/β-catenin pathway. This review points out the need for more research on targeted therapies that combine immune regulation, photo-therapy, and dietary strategies for effective vitiligo treatment.

Keywords: vitiligo, interferon gamma, melanocyte, janus kinases.

Introduction

Vitiligo is a distinctive dermatological condition characterized by the loss of pigmentation in patch-es of skin. It affects approximately 1% of the global population regardless of sex, ethnicity, or geo-graphic region [1]. As illustrated in Figure 1, vitiligo can present in two main forms: nonsegmental and segmental.

Nonsegmental vitiligo, the more prevalent form, usually manifests symmetrically in acral areas. In contrast, segmental vitiligo is affects one region of the skin and often progresses more quickly, sometimes leading to early hair whitening [2, 3]. The entire epithelium of vitiligo patients is sub-jected to increased oxidative stress, which leads to significant metabolic disruptions, particularly within the mitochondria [2].

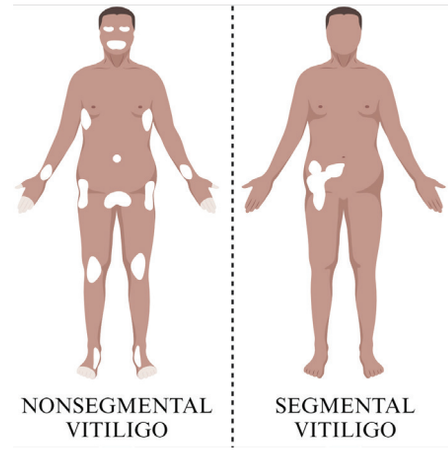

Figure 1 – Vitiligo types

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The disease is marked by its ability to reverse, distinguishing it from many other autoimmune disorders.

The primary targets of vitiligo are melanocytes, the cells re-sponsible for pigment production located in the interfollicular epidermis. However, melanocytes residing within the hair follicles often remain unaffected due to immune privilege at these sites. This immune protection is similar to the privileged melanocytes located in the brain, eyes, and inner ear [4]. Hair follicles contain melanocyte stem cells capable of repopulating the epidermis in vitili-go-affected areas. This process allows new, functional melanocytes to restore pigmentation in the skin. As a result, repigmentation typically occurs as small spots around hair follicles. Nonetheless, areas lacking hair or containing white hairs, where follicular melanocytes have not been protected from autoimmunity, do not repigment [4]. The statement that genetic factors play a significant role in vitiligo appears from observing a high incidence in certain families and an increased risk among individuals with first-degree relatives affected by the condition [5]. Moreover, the association of vitiligo with other autoimmune diseases, such as type 1 diabetes, autoimmune thyroiditis, and rheumatoid arthritis, points to a shared heritable risk for autoimmunity [5-7].

While a variety of treatment strategies are currently available for vitiligo, including topical agents, phototherapy, and surgical approaches, achieving consistent and sustained repigmentation remains a significant challenge [3]. This study aims to explore which existing therapies may dis-play synergy when combined, with a particular focus on enhancing repigmentation outcomes in treatment-resistant cases. Also underlining the gap in the knowledge about environmental factors of the vitiligo patients, such as psychological impact and vitamin D deficiency [8, 9], as it is important but rare discussed in traditional treatment strategies.

Vitiligo Pathogenesis

Patients with vitiligo have been found to have elevated serum levels of melanocyte-reactive anti-bodies, which have shown the capacity to damage melanocytes in vitro and in vivo models [10-12]. However, the role of these autoantibodies in disease pathogenesis is questionable, as the antibody-induced damage is relatively weak, and their titers do not correlate with disease activity [13, 14]. Histological examination of vitiligo lesions has revealed lymphocytic infiltrates, predominantly composed of CD8+ T cells, at the borders of depigmented areas, indicating active disease [15]. These CD8+ T cells have been found in increased numbers in both the skin of active lesions and in the peripheral blood of vitiligo patients, compared to healthy individuals [16-18]. CD8+ T cells specifically target melanocyte antigens, such as tyrosinase and Melan-A/MART-1 [19]. Remarka-bly, CD8+ T cells isolated from peri-lesional skin can induce melanocyte apoptosis in vitro, facili-tating the appearance of new depigmented patches. While the presence of antimelanocyte antibodies in vitiligo patients suggests an autoimmune component, the primary drivers of the disease appear to be CD8+ T cells. As shown in Figure 2 CD8+ T cells and their production of interferon-gamma (IFN-γ) orchestrates the disease's pathogenesis [1].

The recruitment of these pathogenic CD8+ T cells to the skin is mediated by a network of cyto-kines and chemokines, which are upregulated in the lesional skin of vitiligo patients. Gene expres-sion analyses have demonstrated an increased presence of IFN-γ and IFN-γ–dependent genes, such as the chemokine receptor CXCR3 and its ligands CXCL9, CXCL10,

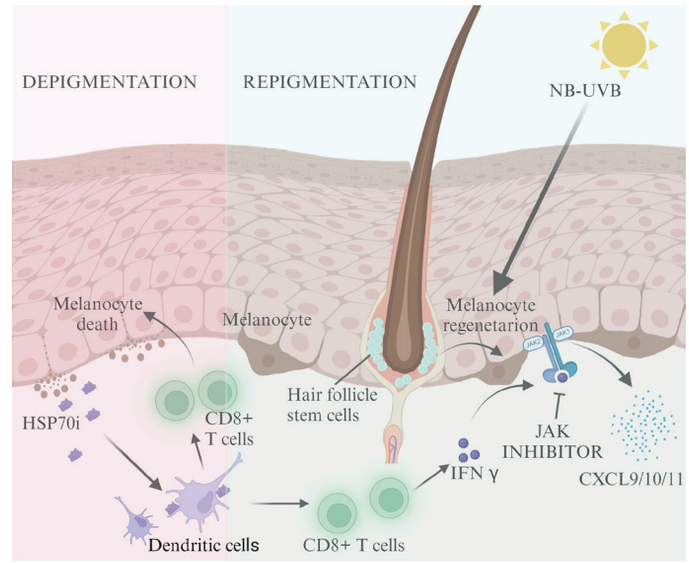

Figure 2 – Vitiligo pathogenesis and treatment approaches

Depigmentation is caused by stress-induced HSP70i, which recruits CD8+ T cells by activation of dendritic cells. CD8+ T cells produce IFN-γ, which induces release of chemokines CXCL9, CXCL10, CXCL11, further recruiting T cells to the affected area. JAK inhibitor therapy blocks the IFN-γ signaling pathway, thereby reducing chemokine production. At the same time NB-UVB therapy facilitates melanocyte regeneration from melanocyte stem cells preserved among hair fol-licle stem cells. IFN-γ: Interferon-gamma, NB-UVB: Narrowband ultraviolet B, JAK: Janus ki-nase, CXCL 9-11: C-X-C motif ligand 9-11. Created in BioRender.com

and CXCL11, which facili-tate the chemotaxis of T cells to the affected areas [20]. Recent research has shifted interest to keratinocytes as the primary producers of these chemokines. Disruption of IFN-γ signaling specifi-cally in keratinocytes has been shown to reduce depigmentation in mouse models. This suggests that topical targeting of IFN-γ signaling in these cells might offer a novel and effective treatment strategy for vitiligo [21]. This is supported by clinical evidence where blockade of the IFN-γ path-way using JAK inhibitors, such as tofacitinib or ruxolitinib, has led to rapid repigmentation in pa-tients with vitiligo. The decrease in serum CXCL10 levels post-treatment with JAK inhibitors fur-ther validates the mechanistic role of IFN-γ signaling in the disease [22-24]. Despite the effective-ness of treatments, vitiligo lesions frequently relapse after the cessation of therapy, with a 40% re-currence rate within the first year. This high relapse rate can be attenuated through periodic applica-tion of topical calcineurin inhibitors, indicating the presence of a long-lasting autoimmune memory within the lesional skin [25]. CD8+ resident memory T (Trm) cells are involved in the persistence of this memory. These cells are known for their key role in providing immunity against viral rein-fections. The potential targeting of Trm cells in vitiligo could lead to more long-lasting treatment outcomes, possibly even after discontinued treatment [26].

The innate immune response also contributes to the pathogenesis of vitiligo. Stress-induced heat shock protein 70 (HSP70i) is released from the epidermis. It is capable of initiating autoimmunity by activating dermal dendritic cells (DCs), which in turn recruit T cells to propagate an autoimmune attack on melanocytes [27]. Additionally, a lowered regulatory T cells (Tregs) in the skin of vitiligo patients was observed [28].

Tregs, identified by the expression of the FOXP3 transcription factor, are essential in suppressing effector T cell activity and preventing autoimmunity. IPEX syndrome shows the critical role of Tregs, where patients lacking functional Tregs due to mutations in the FOXP3 gene suffer from a range of autoimmune disorders, including vitiligo [4]. Multifaceted mechanisms involving CD8+ T cells, IFN-γ signaling, Trm cells, and innate immune responses provide a complex picture of vitiligo pathogenesis. These findings give new directions for targeted therapies that may provide more effective and lasting treatments for patients suffering from vitiligo.

Current Therapeutic Approaches to Vitiligo

Treating vitiligo is often difficult. Various therapies are available for vitiligo, but they usually fail to meet patient expectations. General reasons for that are complicated methodology, time-consuming therapy strategy, and, most importantly, low efficacy and need for periodically repeated therapies [2].

Narrowband UVB (NB-UVB) is a gold standard therapy, largely due to its effectiveness and fa-vorable safety profile. Administered typically at a discrete erythematogenic dose, NB-UVB therapy is recommended 2 to 3 times weekly, which is more effective than its predecessor, PUVA therapy [29]. The advantages of NB-UVB include simplicity of administration and a reduced risk of side effects, leading to its classification as the preferred phototherapy option in vitiligo treatment guide-lines [30]. NB-UVB therapy is recommended for patients with both generalized vitiligo and those experiencing active, progressive disease, intending to stop disease activity and promote repigmenta-tion [31]. This form of phototherapy has been efficient in the repigmentation process, mainly when other therapies have not worked.

Recent findings have introduced the use of Janus kinase (JAK) inhibitors in treating vitiligo, providing a novel therapeutic approach. Early attempts to combine NB-UVB therapy with JAK inhibitors, such as tofacitinib and ruxolitinib, have shown promising results. The combination ther-apy has outperformed monotherapy with JAK inhibitors, especially in cases of facial vitiligo, sug-gesting a synergistic effect that enhances repigmentation outcomes [32]. JAK inhibitors have shown potential in interrupting the pathogenic mechanisms of vitiligo. In mouse models, the neu-tralization of IFN-γ antibodies has been demonstrated to prevent CD8+ T cell accumulation and subsequent lesion depigmentation [33]. By blocking IFN-γ signaling, JAK inhibitors, currently under clinical trials, such as tofacitinib, ruxolitinib, and baricitinib contribute to the repigmentation process, offering hope for patients with vitiligo [34-36]. However, the use of the top three market-ed JAK inhibitors—ruxolitinib, tofacitinib, and baricitinib—has been associated with an increasing number of reported adverse effects. These adverse events are primarily linked to overdosage and may include infectious complications, embolism, and thrombosis [37]. To effectively manage vitili-go, repeated and continuous therapeutic interventions are often necessary. This makes it crucial to explore combination treatment strategies that minimize side effects while maximizing efficacy. Alt-hough NB-UVB remains the gold standard for vitiligo therapy, the addition of JAK inhibitors into treatment strategy represents a significant advancement in the field.

Surgical Approaches to Vitiligo

Surgery is a practical option for patients with vitiligo, particularly those with stable disease. A cru-cial consideration for patient selection is the absence of the Koebner phenomenon, which could worsen the condition postoperatively [38]. The Koebner phenomenon is characterized by the ap-pearance of new vitiligo lesions at sites of skin depigmentation, which is particularly concerning in surgical intervention due to the potential for relapse or worsening of the disease. Before consider-ing surgical treatments, patients need to be fully informed about the risks, especially the possibility of relapse. Disease stability should be confirmed through detailed clinical follow-up to ensure the appropriateness of surgical intervention [39]. Several surgical techniques have been developed to treat vitiligo, each with its methodology and potential benefits. Punch grafting is a straightforward technique that involves transferring small biopsies of pigmented skin into depigmented lesions [38]. Suction blister grafting is another method that uses epidermal blisters created on pigmented skin, which are then transplanted onto areas lacking pigmentation. Non-cultured epidermal cellular grafting involves the application of epidermal cells, harvested from the skin, directly onto the depigmented dermis. Cultured epidermal cellular grafting grows cells in vitro before transplanta-tion, allowing for coverage of larger areas [40]. In addition to these surgical options, adjunctive treatments such as microneedling or ablative laser therapy, combined with NB-UVB phototherapy, enhanced repigmentation outcomes while minimizing adverse effects [41]. Nonetheless, it is essen-tial to note that while suction blister grafting and punch grafting may give the most promising re-sults regarding repigmentation, they also carry risks, such as scarring and hyperpigmentation that must be carefully weighed against the potential benefits [38]. The surgical management of vitiligo requires a personalized approach, considering the stability of the disease, the absence of the Koeb-ner phenomenon, and the patient's informed consent regarding the risks and benefits. With a range of techniques available, careful selection and use of the appropriate method can offer hope for sig-nificant repigmentation and improvement in the quality of life for vitiligo patients.

Psychological Impact and Dietary Considerations in Vitiligo Treatment.

Although the physical symptoms may seem straightforward, the condition often carries a signifi-cant psychological burden. Patients with vitiligo experience anxiety at rates comparable to those with other severe dermatological conditions, such as psoriasis or eczema [41]. Vitiligo patients per-ceive higher psychological stress, primarily related to the visibility of lesions, further leading to lowered self-confidence and social stigma [8, 42]. The psychosocial implications of vitiligo require a complete treatment approach that goes beyond skin depigmentation. Although the number of studies is limited, evidence supports the benefits of adjuvant care through group therapy, cognitive-behavioral therapy, and self-help programs [43].

Dietary factors, while not directly implicated in the etiology of vitiligo, have been considered in the context of disease treatment. The role of diet is primarily focused on the antioxidant properties of foods, their vitamin content, and the presence of micronutrients that may influence the pathophysi-ology of the condition. Specific dietary components, such as vegetable oils rich in omega-6 fatty acids, are thought to inflame vitiligo by promoting the production of reactive oxygen species (ROS) and pro-inflammatory cytokines [44]. Additionally, avoiding allergenic foods that could potentially trigger or develop vitiligo is recommended, as allergic reactions or irritation may worsen

the condition [45]. Recent advancements have shed light on the therapeutic potential of vitamin D in vitiligo treatment. Vitamin D analogs, mainly when used with UV light or corticosteroids, have been shown to enhance the repigmentation process [46]. The basic mechanisms of vitamin D's ac-tion in vitiligo, however, have mostly stayed unclear until recent studies started to reveal these complexities. Vitamin D was found to protect melanocytes from oxidative damage by activating the WNT/β-catenin signaling pathway. This pathway is key for vitamin D to control other important targets, such as Nrf2/ARE, MITF, and processes related to cell death, which are necessary for cell survival and pigmentation [47]. Furthermore, vitamin D insufficiency has been closely linked to the severity of oxidative stress in vitiligo patients, highlighting the importance of having normal vita-min D levels in disease treatment. Vitamin D positively influences β-catenin signaling at both the translational and posttranslational levels in melanocytes subjected to oxidative stress [47]. This is similar to the effects observed with WNT agonists, where vitamin D significantly reduced ROS accumulation and cell apoptosis in H2O2-treated melanocytes while promoting their proliferative and migratory activities. Notably, these protective effects were negated when β-catenin was si-lenced, further emphasizing the central role of β-catenin in the protective actions of vitamin D [46, 47]. Deficiency in β-catenin also inhibited the activation of Nrf2, MITF, and apoptosis, which are critical processes modulated by vitamin D in the context of vitiligo [47]. Dietary interventions, par-ticularly those emphasizing antioxidant-rich foods, may play a supportive role in managing the condition. Moreover, vitamin D is a promising agent in vitiligo therapy, with a newly explained mechanism involving the WNT/β-catenin pathway, providing a potential option for targeted treatment strategies. Future research should continue to examine the molecular interactions between vit-amin D and melanocyte biology to optimize therapeutic outcomes for vitiligo patients.

Conclusions

In conclusion, vitiligo is a complex autoimmune condition characterized by the loss of skin pig-mentation due to the destruction of melanocytes. While its pathogenesis involves a range of genetic, immunological, and environmental factors, CD8+ T cells, IFN-γ signaling, and oxidative stress play critical roles in disease progression. Advances in therapeutic approaches, including using JAK inhibitors, NB-UVB phototherapy, and surgical interventions, offer hope for improved outcomes, especially when tailored to individual patient needs. Despite these advancements, challenges re-main, such as the high relapse rate and the psychological impact of the disease. Addressing these issues requires a comprehensive approach, combining medical, psychological, and lifestyle inter-ventions, including dietary considerations and the potential role of vitamin D in promoting melano-cyte survival. Long-term efficacy studies are essential to determine the most effective combinations of therapies, especially in treatment-resistant cases. These studies should focus on evaluating the durability of repigmentation, minimizing adverse effects, and optimizing treatment protocols for sustained results. Continued research into the underlying mechanisms of vitiligo will be essential to develop more effective, long-lasting treatment options and to enhance the quality of life for those affected by this condition.

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