# Vitiligo Pathogenesis and Emerging Treatments

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**KEYWORDS**

• Vitiligo • Cellular stress • Autoimmunity • Chemokines • Targeted therapy • Melanogenesis

**KEY POINTS**

- Vitiligo results from the destruction of epidermal melanocytes by autoreactive cytotoxic T cells.
- Melanocyte-specific autoimmunity in vitiligo is a result of interplay among multiple factors, including genetic predisposition, environmental triggers, melanocyte stress, and innate and adaptive immune responses.
- An optimal treatment strategy in vitiligo would stabilize melanocytes, suppress the autoimmune response, and restore immune tolerance as well as stimulate melanocyte regeneration, proliferation, and migration to lesional skin.
- A better understanding of the key pathways involved in vitiligo onset and progression will enable developing treatments that have greater efficacy and a good safety profile.

## INTRODUCTION

Vitiligo is a common, disfiguring autoimmune disease that negatively affects patients' self-esteem and quality of life.[1,2] Existing vitiligo treatments, which are used off-label, are general, nontargeted immunosuppressants that provide only modest efficacy. Developing safe and effective treatments requires a better understanding of disease pathogenesis to identify new therapeutic targets.[3] Vitiligo is caused by a dynamic interplay between genetic and environmental risks that initiates an autoimmune attack on melanocytes in the skin.

## VITILIGO PATHOGENESIS

### *Genetics*

The observation that vitiligo was more prevalent in the immediate relatives of patients with vitiligo provided early evidence of its heritability. Although vitiligo affects approximately 1% of the general population,[4] the risk of a patient's sibling developing the disease is 6% and for an identical twin it is 23%.[5] In addition, patients with vitiligo and their relatives have an increased risk of developing other autoimmune diseases, including autoimmune thyroiditis, type 1 diabetes mellitus, pernicious anemia, and Addison disease, suggesting that vitiligo is also an autoimmune disease.[6] These early observations were later confirmed by genome-wide association studies, which identified numerous common genetic variants in vitiligo patients encoding for components of both the innate immune system (NLRP1, IFIH1, CASP7, C1QTNF6, and TRIF) and adaptive immune system (FOXP3, BACH2, CD80, CCR6, PTPN22, interleukin [IL]-2R, α-GZMB, and HLA classes I and II)[7–9] (see also Richard Spritz and Genevieve Andersen's article, "Genetics of Vitiligo," in this issue).

### *Oxidative Stress*

Accumulating evidence suggests that melanocytes from vitiligo patients have intrinsic defects that reduce their capacity to manage cellular stress (reviewed by Harris[10]). Epidermal cells,

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including melanocytes, are constantly exposed to environmental stressors, such as ultraviolet (UV) radiation and various chemicals, which can increase production of reactive oxygen species (ROS). Although healthy melanocytes are capable of mitigating these stressors, melanocytes from vitiligo patients seem more vulnerable. For example, melanocytes from perilesional vitiligo skin demonstrate a dilated endoplasmic reticulum and abnormalities in their mitochondria and melanosome structure, all of which are characteristic of elevated cellular stress. High concentrations of epidermal $H_2O_2$ level and a decreased level of catalase, a critical enzyme that protects cells from oxidative damage, have been observed in skin of patients with vitiligo.[11–17]

### Environment

The earliest triggering events that lead to vitiligo are not fully understood. Multiple studies suggest that a combination of melanocyte intrinsic defects and exposure to specific environmental factors may play a central role in disease onset. This was evident in a group of factory workers who developed vitiligo after exposure to monobenzone, an organic chemical phenol, in their gloves.[18] Later studies confirmed that a history of exposure to other phenolic and catecholic chemicals found in dyes (especially hair dyes), resins/adhesives, and leather was associated with vitiligo.[19,20]

Melanogenesis is a multistep process through which the melanocyte produces melanin. Tyrosinase is a rate-limiting enzyme in this process that controls the production of melanin through oxidation of the amino acid tyrosine, a naturally occurring phenol (reviewed by d'Ischia and colleagues[21] and discussed further by John E. Harris's article, "Chemical-Induced Vitiligo," in this issue). In vitro studies demonstrated that chemical phenols can act as tyrosine analogs within the melanocyte, precipitating high levels of cellular stress. This stress may include increased production of ROS and triggering of the unfolded protein response, which in turn activates innate inflammation.[22,23]

### Innate Immunity

As discussed previously, genome-wide association studies in vitiligo patients implicated multiple susceptibility loci related to the genes that control the innate immunity.[7–9] This likely causes dysregulated innate activation in response to melanocyte stress, demonstrated through recruitment of innate populations like natural killer cells and production and release of high levels of proinflammatory proteins and cytokines, including heat shock proteins (HSPs), IL-1β, IL-6, and IL-8[22–28] (reviewed in Refs.[10,29]). Among larger HSP molecules, inducible HSP70 (HSP70i) is unique, because it can be secreted to chaperone peptides specific to the originating host cells.[30] Recently, HSP70i has been shown to be important for vitiligo pathogenesis in a mouse model through induction of inflammatory dendritic cells, which themselves may be cytotoxic or carry and present melanocyte-specific antigens to T cells in lymphoid tissues.[24,25] This has been proposed to be a key cross-talk step between innate and adaptive immunity, leading to the T-cell–mediated autoimmune destruction of melanocytes.[31]

### Adaptive Immunity

Ultimately, cytotoxic $CD8^+$ T cells are responsible for the destruction of melanocytes.[32] Cytokines secreted within the skin act as an early signal to help these autoreactive T cells locate stressed melanocytes. This is probably important because the epidermis is not vascularized, so active mechanisms are required to help them efficiently locate melanocytes.[33] Chemokines are small, secreted proteins that act as chemoattractants to guide T-cell migration. Interferon (IFN)-γ and IFN-γ–induced chemokines (CXCL9 and C-X-C Motif Chemokine Ligand 10 [CXCL 10]) are highly expressed in the skin and blood of patients with vitiligo as well as in a mouse model.[34–36] In addition, IFN-γ and CXCL10 are required for both disease progression and maintenance in a mouse model of the disease.[34,37] Recently, a separate study demonstrated not only that serum CXCL10 was higher in patients with vitiligo compared with healthy controls but also that its level was associated with disease activity and significantly decreased after successful treatment, suggesting it may be used as a biomarker to monitor the disease activity and treatment response.[36]

## EMERGING TREATMENTS

Based on current understanding of vitiligo pathogenesis, a successful strategy to treat vitiligo should incorporate 3 distinct approaches: reducing melanocyte stress, regulating the autoimmune response, and stimulating melanocyte regeneration. Existing treatments partially address these needs; however, emerging therapies may do this in a more targeted way, and combination therapies may synergize to produce a better overall response (**Fig. 1**).

### Reducing Melanocyte Stress

The apparent reduction of catalase enzyme in the epidermis of vitiligo patients as well as elevated