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Review

Research progress of vitiligo repigmentation: from oxidative stress to autoimmunity

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Abstract

Vitiligo belongs to a frequent chronic autoimmune skin disease with the features of pigmented plaques on the diseased skin along with potential damage of melanocytes. There are many factors underlying the pathogenesis of vitiligo, among which oxidative stress is extensively regarded to be the critical factor leading to the loss of melanocytes. The changed redox state resulting from oxidative stress, containing ROS overproduction along with the reduced activity of the skin's antioxidant system, makes melanocytes less resistant to exogenous or endogenous stimuli, and ultimately pushes normal defense mechanisms, resulting in the loss of melanocytes. Given the crucial potential of innate together with adaptive immunity in vitiligo, there is growing evidence of a relation between oxidative stress and autoimmunity. Our review offers estimable insights into the possible properties of oxidative stress and autoimmunity in pathogenesis of vitiligo, as well as the potential role of antioxidant-based supportive therapy in vitiligo repigmentation, providing a hopeful value for further research and development of effective treatments.

Keywords: Autoimmune skin, Oxidative stress, Vitiligo repigmentation.

1. Introduction

As an autoimmune skin disease, vitiligo belongs to a relatively common acquired pigment disorder. It is featured by loss of skin pigment because of dysfunction of functional melanocytes, affecting about 1-2% of the global population. The main feature is obvious colorless pigment patches on the skin, reflecting the loss of epidermal melanocytes [1]. Lesions may appear locally or throughout the body and may aggregate to form large colorless areas. Due to the comparison between white areas and normal skin, vitiligo can have a profound impact on the quality of life of both children and adults, resulting in stigmatization, social isolation, and low self-esteem for those affected [2].

Many studies have shown that vitiligo is linked to insulin resistance, dyslipidemia along other metabolic disorders [3–5]. Various mechanisms targeting melanocyte destruction in vitiligo have been indicated, containing genetics, autoimmune response, oxidative stress, as well as the secretion of inflammatory mediators [6]. A variety of triggers, ranging from mechanical stimulation to chemical exposure, can be linked to the development of vitiligo, and these triggers are thought to trigger a stress response in keratinocytes as well as melanocytes, resulting in an imbalance between oxidative and antioxidant systems. Melanocytes together with keratinocytes affected by stress can secret more pro-inflammatory cytokines as well as chemokines, forming an abnormal epidermal microenvironment, while damaged melanocytes release autoantigens along with immune stimulation signals [7]. In response to reactive oxygen species (ROS) overproduction, the main factor of peroxidative stress, the stimulated antigen release is sensed and processed through antigen-presenting cells (APCs) containing local dendritic cells (DCs), eventually leading to elevated infiltration of melanocyte-specific T cells as well as antibodies against melanocytes' production around and in the vitiligo skin, activating an adaptive immune response in the vitiligo epidermis [8], leading to melanocyte dysfunction and death.

The therapy of vitiligo is not easy, it is on the basis of the spread along with location of the damage, and whether the condition is stable. In addition to traditional phototherapy, and local or systemic steroid therapy, years of research into etiology have resulted in the development of targeted treatments that are more efficient and have fewer side influences. The objective of this paper was to analyze the interaction between oxidative stress and autoimmunity underlying the pathogenesis of vitiligo through a narrative review of the literature, in order to provide insights on the

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treatment of vitiligo repigmentation from the blocking of oxidative stress and autoimmune-related pathways.

2. Oxidative stress in vitiligo

Although numerous theories have been proposed regarding the cause of vitiligo, there is no consensus on the accurate cause of how melanocytes are damaged and finally die. Oxidative stress has a crucial potential in the pathogenesis of vitiligo, resulting in the injury of melanocytes [9]. Oxidative stress induces a redox homeostatic imbalance, presented by overproduction along with inadequate clearance of ROS. ROS can be induced by both endogenous together with exogenous stimuli, ultimately resulting in the death of melanocytes. In the process of melanin production, excessive ROS production forms an oxygenophilic environment, making melanocytes vulnerable to oxidative stress [10].

Melanocytes have been reported to suffer cumulative damage from ROS, which disrupts the structure and function of their DNA, lipids, as well as proteins [11]. Oxidative stress can result in vitiligo via a variety of mechanisms. For example, oxidative stress leads to decreased expression of GATA3 and affects SIRT3-mediated deacetylation of HMGB1, thus significantly inhibiting melanin secretion and expression of melanin-related proteins, leading to increased apoptosis [12]. In addition, results from another study show that SIRT3 expression and activity are significantly reduced in vitiligo melanocytes. Loss of SIRT3 induces mitochondrial dysfunction as well as the release of cytochrome C, leading to more apoptosis of melanocytes [13]. Zhou *et al.* [14] reported that the transitional accumulation of ROS destroyed the melanin synthesis process as well as caused the destruction of lipid stability in melanocytes, leading to the damage of the mitochondrial electron transport chain as well as the sharp increase of ROS production, resulting in a vicious cycle, resulting in a large number of melanocytes dying [14]. Many studies have confirmed that the increase of ROS belongs to a key factor in promoting the secretion of chemokines by keratinocytes, which guide $CD8^+$ T cells and result in migration to skin tissues, resulting in melanocyte death [15]. For example, the decreased expression of AQP3 in keratinocytes of vitiligo patients leads to increased oxidative stress of neighboring melanocytes, resulting in the death of melanocytes [16].

3. Role of ROS and immune system in vitiligo

It has been reported that oxidative stress as well as autoimmunity with genetic susceptibility are related to the pathogenesis of vitiligo [17]. Exogenous or endogenous stimuli cause melanocytes to stress and produce excessive ROS, which contributes to the secretion of damage-associated molecular patterns (DAMPs) as well as the secretion of melanosomal antigens that stimulate innate immunity.

3.1. Innate immunity

Reactive oxygen species regulate various immune together with inflammatory molecules. Followed by sensing oxidative stress signals, the innate immune system responds quickly to these signals. Innate immunity then converts stress signals into pro-inflammatory signals, providing a rapid response for better protection. Toll-like receptors and nucleotide oligomeric domain (NOD)-like receptors can be involved in pro-inflammatory signaling. Autoantigens are secreted by the body's cells, not by pathogen-linked molecules. They produce pro-inflammatory signals to promote an immune response.

Unfolded proteins form as well as accumulate when oxidative stress disturbs the redox potential. The unfolded protein response (UPR) is the steady-state recovery of cells against unfolded proteins together with inappropriate protein folding caused by ER dysfunction. UPR belongs to an initial pro-survival signaling in which translation is weakened and the cell cycle is stopped to hinder further translation loading of the ER [18].

Activated UPR consists of 3 major endoplasmic reticulum transmembrane receptors: eukaryotic initiation factor 2α kinase (PERK), activating transcription factor 6 (ATF6) along with inositol requiring 1 (IRE1α) [19, 20]. Chen *et al*. [21] reported that amino acid metabolite homocysteine up-regulates PERK expression by activating ROS, thus activating PERK-eIF2α-CHOP pathway to induce apoptosis of vitiligo melanocytes 21.

Another cytoprotective agent involved in progressive pigmentation loss is the 70-kDa heat shock protein (Hsp70). In response to stress, Hsp70 serves to be a chaperone, binding to melanocyte-specific melanosome proteins, promoting protein folding and transport, and major histocompatibility complex I/II load [22]. For instance, studies have displayed that HSP70 mRNA expression is significantly enhanced in diseased skin biopsies of vitiligo patients than in non-focal skin biopsies of vitiligo patients [23]. In addition, LBP can protect keratinocytes from oxidative stress through CXCL9/CXCL10 pathway by downregulating the expression of Hsp70 [24].

Additionally, exosomes also have a crucial role in the innate immunity of vitiligo. These exosomes create an inflammatory microenvironment, causing inflammation along with recruiting immune cells to clear stressed melanocytes. In their study, Zhang *et al*. [25] reported that the patient-derived exosome miR-21-5p inhibited melanin production in melanocytes by targeting SATB1 in vitiligo. In addition, the downregulation of keratinocyte-derived exosome miR-200c inhibits melanin production in vitiligo lesions [26].

3.2. Adaptive immunity

The concept that innate immunity can mediate the presentation of autoantigens to induce autoimmunity fills the gap between oxidative stress and adaptive immunity [17]. Studies have shown that melanocyte-specific $CD8^+$ T cells mediate the damage of melanocytes in vitiligo [27]. Antigen proteins from stress melanocytes are carried by DC and are specifically identified by infiltrated T cells. At the front of vitiligo decolorization, T cells appear patchy infiltration. The frequency of serum $CD8^+$ T cells in vitiligo patients presents higher relative to healthy controls and the frequency is correlated with disease severity. $CD8^+$ T cells secret several cytokines, containing TNF-α as well as IFN-γ, which are mainly implicated in the damage of melanocytes. After IFN-γ pro-inflammatory cytokines bind to their receptors, the Janus kinase signal transduction and transcriptional activator pathway can be stimulated and promotes the transcription of the chemokine ligands CXCL9 along with CXCL10 [28]. Clinically, serum CXCL10 represents a specific biomarker for monitoring the activity and severity of vitiligo [29]. CXCL9/10 modulates recruitment of melanocyte-specific CD8+ T cell

migration via binding to CXCR3.

4. Vitiligo repigmentation

Current therapies for vitiligo repigmentation contain phototherapy, local and systemic immunosuppressants, as well as surgery, which require long-time follow-up to evaluate the effectiveness of treatment. However, with these non-targeted treatment options, there are no effective therapies that can stimulate complete repigmentation, so more therapeutic approaches are needed to treat vitiligo.

4.1. Antioxidant therapy for vitiligo

Antioxidants are compounds that can greatly reduce or block the detrimental impacts of free radicals on human tissues [30]. Antioxidant-based supportive treatments have been proposed as therapies to prevent skin aging [31], skin cancer [32], and skin autoimmune diseases [33]. To date, many drugs including antioxidant-like substances have been studied to support or replace standard therapies for vitiligo.

Vitamin C reduces oxidative stress through oxidizing ascorbic acid to monodehydroascorbic acid and dehydroascorbic acid. Vitamin C together with its derivatives suppresses tyrosinase activity along with melanin content through a dose-dependent way [34]. The results of a randomized controlled trial showed that oral vitamin C reduced the serum stress oxidation index in patients with vitiligo [35]. However, another systematic review and meta-analysis of vitamin C failed to show reproducible results [36].

Vitamin E belongs to a photoprotective antioxidant absorbing certain wavelengths along with preventing lipid peroxidation [37]. Vitamin E can prevent oxidative stress caused by UV-A phototherapy, but does not affect the clinical improvement of vitiligo lesions [38]. Nevertheless, the combination of narrow-spectrum UVB and oral vitamin E may improve the therapeutic effect [39].

Selenium is identified to be a crucial trace element regulating oxidative stress [40]. A meta-analysis by Dai *et al*. [40] revealed reduced selenium levels in Asian vitiligo patients, while this finding was not observed in Caucasian patients. Zinc can protect melanocytes via its anti-apoptotic as well as antioxidant roles. It can also modulate melanin production via releasing alpha-melanocyte stimulants and precipitation of zinc-α2-glycoproteins in tissues. Also, zinc belongs to a kind of non-specific elements that help regulate cell-mediated immunity as well as control gene expression [41]. One study evaluated changes in serum zinc levels in a group of Iranian patients with vitiligo. The results suggested that disturbances in serum zinc levels were associated with vitiligo and may have a crucial potential in the development of the disease in Iranian patients [42]. The main role of copper is that it promotes the production of melanin and participates in destroying free radicals by forming superoxide dismutase, thus providing physiological protection against oxidative stress [43].

Ginkgo biloba is a traditional Chinese herb. *G. biloba* extract prevents apoptosis induced by oxidative damage of melanocytes through repressing H_2O_2 and inhibits the autoimmune response of melanocytes through repressing the secretion of Hsp70 [44]. Studies have demonstrated the efficacy of oral administration of *G. biloba* in the treatment of localized, slow-spreading vitiligo [45]. In addition, *G. biloba* extract EGb761 prevents human melanocytes from H_2O_2-stimulated oxidative stress via inducing Nrf2 [46].

Coenzyme Q10 belongs to a universal vitamin-like compound that acts as an electron transporter in the mitochondrial respiratory chain, which has a crucial potential in the metabolism of fatty acids, pyrimidines, as well as lysosomes, and modulates some genes' expression, containing those implicated in inflammation [47]. In a randomized trial conducted in Iraq, researchers discovered an apparent decrease in the vitiligo regional score index followed by 8 weeks of topical use of CoQ10 gel [48]. α-lipoic acid reacts with ROS together with active nitrogen in the form of reduced dihydrolipoate and protects cell membranes via disturbing vitamin C and E pathways [49]. A randomized clinical trial demonstrated no significant benefit of oral alpha-lipoic acid and UV-A phototherapy in the treatment of vitiligo [50]. However, another clinical study demonstrated that the combination of oral alpha-lipoic acid, betamethasone injection and UV-A phototherapy is effective and safe for non-segmentary progressive vitiligo [51].

Emblica possesses a high antioxidant ability because of its high purity of polyphenol compounds together with vitamin C. Fruit extracts are adopted as antioxidants, which repress lipid peroxidation as well as remove free radicals containing superoxide anion, hydrogen free radical, hydrogen peroxide, as well as nitric oxide free radical [52]. In a clinical study, an oral supplement of emblica fruit extract can effectively improve vitiligo [53].

4.2. Immunotherapy for vitiligo

As part of vitiligo management, there is an urgent need to stop abnormal innate immunity, and unfortunately, there are few new strategies to achieve this. Mosenson *et al*. [54] found that the application of HSP70iQ435A coding DNA several months previous to spontaneous pigmentation loss hindered vitiligo in mice expressing the transgenic melanocyte reactive T cell receptor. They successfully offset depigmentation in mice with spontaneous vitiligo. In 2018, Henning *et al*. [55] obtained similar results in pigs. As for drug treatment, topical application of vitamin D has been documented to decrease the number of DC in vitiligo skin [56].

Immunosuppressive therapy has always been the mainstream of vitiligo therapy, and the far-reaching effects of immune abnormalities on the destruction of melanocytes are also echoed. Currently, recommended immunosuppressive interventions contain topical steroids, calcineurin inhibitors (tacrolimus and pimeclimus), along with oral impact steroids. However, the above interventions are only moderately effective.

As previously documented, the IFN-gamma-CXCL9/CXCL10-CXCR3 signaling is integral in $CD8^+$ T cell killing of melanocytes, and disruption of this axis is effective in preventing vitiligo progression and promoting hyperpigmentation [57]. Richmond *et al*. [58] successfully cleared TRM from vitiligo-affected skin by long-term administration of anti-CD122 antibodies. CD122 belongs to a subunit of the heterotrimer IL-15 receptor, so blocking CD122 may repress TRM residency in the skin via eliminating IL-15 support [58].

5. Conclusion and prospect

Oxidative stress as well as autoimmunity is the main theories of vitiligo. But without convergence, we cannot comprehend these two mechanisms of disease. In fact, novel insights into how these two pathways work together

may help to better understand the pathogenesis underlying vitiligo. In summary, this study reviewed the potential of oxidative stress and autoimmunity in vitiligo. First, both exogenous and endogenous stimuli enhance melanocyte stress, resulting in an excess of ROS, which promotes the production of DAMPs along with the release of melanosomal antigens that stimulate innate immunity. In addition, this study reviewed the latest progress in treating vitiligo from the viewpoint of inhibiting oxidative stress as well as autoimmunity. However, the role of oxidative stress as well as autoimmunity in vitiligo needs to be better understood to develop more promising treatments.

Informed consent
The authors report no conflict of interest.

Availability of data and material
We declared that we embedded all data in the manuscript.

Authors' contributions
YT conducted the experiments and wrote the paper; WY analyzed and organized the data; LZ conceived, designed the study and revised the manuscript.

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