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Perspectives of New Advances in the Pathogenesis of Vitiligo: From Oxidative Stress to Autoimmunity

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Vitiligo is an autoimmune cutaneous disease in which melanocytes are destroyed by $CD8^+$ T cells resulting in disfiguring white spots. From the very beginning of the disease, oxidative stress plays a significant role in promoting the onset of vitiligo, as noted by many studies. Multiple factors lead to the overproduction of reactive oxygen species (ROS), and collaboratively cause ROS accumulation in vulnerable melanocytes. However, ROS are responsible for melanocyte damage manifested by the level of molecules, organelles, and cells, and the generation of autoantigens, through different pathways related to the dysregulation of melanocytes. Recent studies have shown that presentation of autoantigens is mediated by innate immunity, which bridges the gap between oxidative stress and adaptive immunity. The recruitment of $CD8^+$ T cells induced by cytokines and chemokines guarantees the final destruction of epidermal melanocytes. Moreover, emerging concerns regarding regulatory T cells and resident memory T cells help explain the reinstatement and relapse of vitiligo. Here, we provide new perspectives in the advances in understanding of this disease pathogenesis and we attempt to find more interrelationships between oxidative stress and autoimmunity.

MeSH Keywords: Autoimmunity • Oxidative Stress • Vitiligo

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Background

Vitiligo is a common patchy depigmentation disease of the skin that is characterized by the destruction of epidermal melanocytes [1]. Oxidative stress may play an essential role in activating subsequent autoimmune responses related to vitiligo [2]. Reactive oxygen species (ROS) are induced by multifactors and as impaired antioxidant defenses, show the loss of melanocyte redox homeostasis, and therefore, the stressed melanocytes generate damage-associated molecular patterns (DAMPs) or autoantigens that then initiate innate immunity and adaptive immunity, leading to the dysfunction and death of melanocytes via an inflammatory cascade [3]. Ultimately, vitiligo occurs. Oxidative stress and autoimmunity with genetic susceptibility have been associated with the pathogenesis of vitiligo, how these 2 pathways precisely integrate with each other is not fully understood [4]. Here, we highlight the current opinions that illuminate how oxidative stress promotes autoimmunity activity in vitiligo.

Sources of ROS Overproduction in Vitiligo

Endogenous and exogenous stimuli

An observation that melanocytes from vitiligo patients were difficult to culture *ex vivo* in comparison to those from healthy donors suggests a vitiligo melanocyte-intrinsic defect, that is, an initial event of vitiligo, exist [5,6]. Furthermore, the pathogenic role of oxidative stress is supported by the evidence of elevated levels of ROS both in lesional and non-lesional skin [7]. Secretion of ROS can be interpreted as a way of coping with stressors for melanocytes [4].

From the inner stressor perspective, ROS can be attributed to a series of cellular metabolic processes which have an inherited incapacity to be resolved, such as melanogenesis, cellular proliferation/differentiation/apoptosis, and immune reactions [8]. Melanogenesis performed by melanocytes is an energy-consuming process, producing large quantities of pigment melanin [3], that can create a highly pro-oxidant environment in the epidermis [9,10]. The energy supplier, i.e., the mitochondria, is thought to be the key inducer of ROS, as suppressors of mitochondrial transition pores decrease ROS levels and cell death; in addition, alteration of mitochondrial transmembrane potential and respiratory chain complex, will result in marked increase of mitochondrial malate dehydrogenase and modification of membrane lipid components [11–13]. Several laboratory studies have suggested that damaged mitochondria may be the potential site of ROS production.

On the other hand, exogenous stimuli can also be of great importance in creating oxidative byproducts [3]. Exogenous stimuli include exposure to environment (e.g., ultraviolet irradiation, cytotoxic chemicals like monobenzone and other phenols, trauma), other diseases (malignancies, major infection, neural disorders, calcium imbalance), and medication application (e.g., certain drugs, hormones, vaccination) [2]. The role of monobenzone is well-known as the exclusive Food and Drug Administration (FDA)-approved therapy for perpetuating depigmentation [14], and induces the release of melanosomal related antigen-containing exosomes following overproduction of ROS from melanocytes [15].

Impaired self-defense against oxidative stress

Exogenous and endogenous stimuli drive the stressed melanocytes to generate intracellular ROS, constituted by oxygen-based free radicals such as hydrogen peroxide (H_2O_2), superoxide anions, hydroxyl radicals, and singlet oxygen. Nature has evolved 3 layers of antioxidant defenses to scavenge ROS, including small molecular antioxidants like vitamin C, vitamin E, and glutathione [16]. Damage-removing or repairing enzymes aid in biomolecule regeneration and recovery from oxidative damage [16]. Reduced levels and activity of antioxidant enzymes, such as catalase and glutathione peroxidase, as well as an imbalance in pro-oxidant/antioxidant equilibrium, serve as a detoxified intermediator, and are also responsible for the generation and accumulation of ROS, which helps explain the increased sensitivity of melanocytes to oxidative stress [6,16–18].

Apart from the enzymatic and non-enzymatic antioxidant role, there are other pathways that can protect melanocytes from oxidative damage. Several recent experiments illustrated the role of nuclear factor E2-related factor 2-antioxidant response element/heme oxygenase-1 (Nrf2-ARE/HO-1) pathway for protection [19,20]. For instance, dysfunctional autophagy was implicated by dysregulated and impaired Nrf2 pathway, and probably contributed to the vulnerability to oxidative stress for melanocytes [7]. Notably, aspirin, baicalein, and simvastatin have been shown to improve survival of vitiligo melanocytes through activating the Nrf2 pathway, as found in our previous study, and may be a promising therapeutic option for targeting vitiligo [21–23].

Consequences of Excessive ROS in Vitiligo

Biological macromolecules

The accumulation of ROS can cause DNA damage, protein oxidation/fragmentation, coupled with lipid peroxidation [24], thus dampening the function of these cellular biological macromolecules [11]. The significantly increased oxidized DNA base 8-oxoguanine or 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels, (a marker of oxidative DNA damage in the circulating immune

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complexes in systemic lupus erythematous patients) can be detected in the epidermal skin and plasma in association with upregulated apurinic/apyrimidinic endonuclease 1 (APE1) and DNA polymerase β levels [25,26]. ROS-induced DNA damage can be removed by base excision repair, in which APE1 plays a key role [27]. The genetic variations of APE1 (Asp148Glu) exacerbates oxidative status with higher level of 8-OHdG, causing genetic susceptibility to vitiligo, as suggested in by our previous study data [27].

The involvement of H_2O_2 can deactivate dihydropteridine reductase and thus result in modification of the active (binding) site and result in defective biopterin synthesis and recycling, which consequently disrupts melanin synthesis [28]. Deactivity and deregulation of acetylcholinesterase (AchE) due to H_2O_2-mediated oxidation further maintains epidermal oxidative stress [29]. The recovery of AchE proteins is in agreement with repigmentation of vitiligo patients. Calreticulin (CRT), a ubiquitous endoplasmic reticulum protein modulating intracellular Ca^+, translocates to the melanocytes surface from endoplasmic reticulum lumen under oxidative stress [30]. The overexpression of surface CRT enhances the predisposition of stressed melanocytes to immunogenic apoptosis through direct contact to dendritic cells. Besides, CRT also induces expression of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, correlating with immune responses [30]. Redox imbalance of membrane lipids may lead to a compromised functionality and altered structure, which could affect intracellular transduction mediated by membrane receptors, electron transport, and mitochondrial energy [12].

Stressed organelles

The overexpression of transient receptor potential cation channel subfamily M member 2 (TRPM2) driven by the involvement of H_2O_2, increases mitochondrial calcium influx and then facilitates mitochondria-dependent apoptosis of melanocytes [31]. Based on this process, it can be concluded that mitochondria, an essential organelle, interacts with oxidative stress and promotes the pathogenesis of vitiligo.

Observations from ultrastructural analysis also suggests augmented cellular stress from another intrinsic abnormality-related organelle, dilated endoplasmic reticulum profiles [3]. Vitiligo-prone patients have difficulty resolving oxidative stress. Accumulation of misfolded peptides activates the unfolded protein response (UPR) [2,32,33]. One of the crucial UPR components is transcription factor XBP1, the expression of which is elevated following the exposure to chemical triggers (e.g., phenols). It is accompanied by activation of production of immune mediators IL-6 and IL-8. IL-6, the most sensitive serum markers to distinguish progressive vitiligo [34], and halts the regulatory T cells (Tregs), with; IL-6 and IL-8 mutually augmenting the recruitment of immune cell populations [3].

Keratinocytes and chemokines

Little is known about effects of oxidative stress on other cells implicated in the aberrant microenvironment. Keratinocytes, for example, was recently studied by Li et al. [35]. CXCL16, a chemokine produced by stressed keratinocytes induced $CXCR6^+CD8^+$ T cells trafficking to the lesional sites and were shown to initiate adaptive immune events [35]. This was distinct from traditional cytokine stimuli like TNF-α, interferon γ (IFN-γ), and IL-1β, known for inducing the production of chemokines [36]. The Li et al. study provides a new insight into the chemokine-mediated link between ROS and autoimmunity [35].

While oxidative stress confers an explainable mechanism for how vitiligo is initiated, nonetheless, it cannot account for all of the disease process, since stressed melanocytes can still survive. A better understanding is required regarding how stressed melanocytes are ruined irreparably through immune responses functioning as downstream pathways [3].

Innate Immunity Bridges the Gap Between Oxidative Stress and Adaptive Immunity

Pattern recognition receptors (PRRs) and damage-associated molecular patterns (DAMPs)

After sensing stress signals induced by various stimuli, the downstream pathogenesis begins with the activation of innate immunity, which probably provides a better perspective for how stress signals are communicated, recognized, and translated into pro-inflammatory signals [37]. Innate immunity must be rapidly triggered via pattern recognition receptors (PRRs) and by other danger signals [3,37], contrary to antigen specificity recognition processed by adaptive immunity. Typical receptors embrace toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs), where in vitiligo, their activators of ligands are mainly referred to as DAMPs [4]. The generation and secretion of DAMPs by melanocytes are self-derived danger signals following cellular damage and sterile inflammation but are not related to pathogen-associated molecular patterns (PAMPs) [1,3].

The role of Hsp70i

For all these DAMPs, including mitochondrial DNA, HMGB1, and CRT, a star molecule, Hsp70i is necessary and its role in stimulating innate immunity should be underscored. In response to stress, intracellular inducible Hsp70i serves as a cytoprotector preventing apoptosis. The act and overexpression of Hsp70i in progressive depigmentation have been confirmed in some experimental animal models [38–40]. Hsp70i acts as molecular chaperone that binds melanocyte-specific melanosomal

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proteins/peptides that assist in protein folding, transporting, and potentially MHCI/II loading [41]. Its exposure boosts dendritic cells activation by processing and presentation antigens measured by expression of dendritic cells maturation markers such as CD80 and CD83 [42]. The enhanced uptake, processing, and presentation of Hsp70i-chaperoned proteins and peptides that are derived from cellular stress, promotes antigen-specific CTL-related immune responses [2,43]. Dendritic cells elevate the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and the Hsp70i receptors on its surface, for example CD91 induced by Hsp70i, helps explain the molecular mechanisms that Hsp70i uses to activate dendritic cells, and shows dendritic cell-mediated cytotoxicity through induced TRAIL receptors, which finally leads to the migration of skin homing T cells [42,44,45].

For the alteration on pro-inflammatory cytokines, elevated secretion of TNF-α, IL-1β, IL-6, and IL-12 from dendritic cells/macrophages/monocytes induced by Hsp70i have been shown to exert effects on dendritic cells maturation [46]. Moreover, Hsp70i not only elicits T cell cross-priming but prevents tolerance towards melanocytes in vitiligo [43].

Enhanced Hsp70i is upregulated by IFN-γ from perilesional cytotoxic T lymphocytes leading to a positive feedback identified as the Hsp70i-CTL-IFNγ-HSP70i loop. The loop amplifies the process and exacerbates the destruction of vitiligo melanocytes [2]. Furthermore, a recent study revealed that Hsp70i potentiated IFN-α generation by a subset of dendritic cells (pDCs) and subsequently IFN-α induced expression of CXCL9 and CXCL10 by keratinocytes, known importantly for the recruitment of $CXCR3^+CD8^+$ T cells, formulating an inflammatory cascade of Hsp70i-pDCs-IFN-α-CXCL9 and CXCL10-CTL axis [47].

It has been reported that macrophages and dendritic cells respectively induce Tregs and Th17 cell responses [48]. Hsp70i may downregulate macrophage activity rendering inhibition of Tregs and support Th17-mediated autoimmunity via the activation of dendritic cells [42].

A modified version of Hsp70i, $Hsp70i_{Q435A}$, a reversed depigmentation that was identified in Sinclair Swine recently, has also been observed in mice models, thus providing the rationale for study in human species. Mutant Hsp70i opens a door to potential new treatment for vitiligo patients [39].

Adaptive Immunity in Vitiligo

$CD8^+$ T cells: Role of progression

Melanocyte-specific, cytotoxic $CD8^+$ T cells have been strongly implicated in the destruction of melanocytes in multiple studies. $CD8^+$ T cell infiltration of the epidermis and dermis has been demonstrated histologically, in addition, higher numbers of cytotoxic $CD8^+$ T cells in the blood were found in patients with vitiligo compared to healthy controls [49]. The intensity of $CD8^+$ T-cell reaction has been found to correlate with disease severity and T cells were shown to be eradicated by melanocytes *in vitro* [50]. Biopsy results have shown that T cells separated from lesional skin were significantly enriched for recognizing specific melanocytes antigens, and when they migrated to the melanocytes in unaffected normal skin, they induced apoptosis of melanocytes [50]. However, perilesional T cells did not induce apoptosis in lesional skin, for loss of melanocytes, therefore suggesting melanocyte-specific cytotoxic activity of $CD8^+$ T cells [50]. By contrast, $CD8^+$ T cell-depleted perilesional T cells did not have the capacity to induce cytotoxicity and apoptosis of melanocytes [50]. $CD8^+$ T cells also express cutaneous lymphocyte antigen (CLA), a skin-homing marker [51]. CLA/HLA-DR/$CD8^+$ circulating T cells migrated to the perilesional skin and became activated (granzyme-B^+, $perforin^+$), inducing melanocytes apoptosis. Antigenic proteins derived from normal or stressed melanocytes involved in the melanin synthesis include gp100, Melan-A/MART-1, tyrosinase, and tyrosinase related proteins 1 and 2, which are carried by dendritic cells and specifically recognized by infiltrating T cells later on [2].

Several cytokines, such as TNF-α and IFN-γ that are primarily involved in melanocytes destruction, are produced by $CD8^+$ T cells [52]. Although functioning as a key inflammatory mediator, TNF-α was found to be moderately increased in the lesional skin and blood of vitiligo patients, however, the TNF-α inhibitors are not readily effective in vitiligo, which suggests it plays a minor role in adaptive immunity [53]. IFN-γ-induced CXC chemokines like CXCL9 and CXCL10 are also reported to be increased in the patient serum [54]. Serum CXCL10 may correlate with disease activity and severity, and be used as a novel specific biomarker in monitoring vitiligo activity [34,55]. CXCL10 drives the recruitment of melanocyte-specific $CD8^+$ T cells migrating to the epidermis by interact with the receptor CXCR3, which is expressed on the autoreacitve T cells both in the blood and lesional skin [56]. Functional studies in mice models have identified an essential role for IFN-γ-CXCL10-CXCR3 axis both in progression and maintenance of hypopigmentation in vitiligo [54]. Given the key driver of autoimmunity in vitiligo, IFN-γ, was monitored and found to be mainly produced by CTL, supports previous reports that IFN-γ-CXCL10-CXCR3 axis transforms into the positive feedback loop [57]. And more importantly, it has been reported that IFN-γ inhibited melanogenesis and directly induced melanocyte apoptosis [57]. Thereby, therapies that disrupt the pathway targeting IFN-γ, IFN-γ receptor, downstream signal JAK-STAT pathway, CXCL10, and its receptor CXCR3, are of interest. For instance, a recent study showed that in a mice model, CXCR3 depleting antibodies can decrease autoreactive T cell numbers, preventing and

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reversing vitiligo [56,58]. Moreover, 2 JAK inhibitors, tofacitinib and ruxolitinib, were reported to induce abundant repigmentation in 2 separate vitiligo patient cases [53,59,60].

Regulatory T cells (Tregs): Role of reinstatement

Aberrant functional Tregs from active vitiligo patients have been shown to compromise suppressive activities towards $CD8^+$ T cells in vitiligo [61,62]. Not surprisingly, uninhibited $CD8^+$ T cells can contribute to robust and lasting depigmentation. Tregs have been found to be relatively less abundantly infiltrating in vitiligo skin, suggesting an unfavorable ratio of Tregs/$CD8^+$ T cells [63]. Previous studies reported alterations in the number and/or function in Tregs from vitiligo patients [63,64]. Tregs showed lower expression of TGF-β in active vitiligo [62]. In addition, the transcription factor FoxP3 that can downregulate T cell activation and cytokine genes (e.g., encoding IL-2, IL-4) while upregulating immunosuppressive cell-surface molecules (e.g., CD25, CTLA-4), is the most reliable Treg marker and the number of Tregs expressing FoxP3 is reduced significantly in lesional skin [64]. With respect to the chemokines and their receptors attracting Tregs to the skin, the expression of homing receptor CCL22 was found to be remarkably reduced in vitiligo skin [65], and reversely, overexpression of CCL22 has been shown to reinstate the resident Treg population and suppress vitiligo [66]. New therapeutic strategies that may halt depigmentation include adoptive Tregs transfer, restoring expression of FoxP3 (i.e., vitamin D), enhancing Tregs abundance (i.e., rapamycin), and topical CCL22 [63,66].

Emerging studies have shown that elevated frequency of Th17 cells together with higher level of IL17 is strongly correlated with disease activity, extent, and severity [67]. However, the caustic role still requires further investigation. So far, the role of other $CD4^+$ T cells in the pathogenesis of vitiligo is still controversial and not well defined.

Resident memory T cells: Role of reactivation

Depigmentation typically recurs at the same site after the termination of therapy, suggesting that autoimmune memory exists and may account for the disease reactivation [52]. Tissue-resident memory T (T_{RM}) cells have been widely identified in infectious and chronic inflammatory skin disease settings [52,68]. Very recently, T_{RM} were confirmed as being present in lesional skin from vitiligo patients [69]. T_{RM} do not circulate in the peripheral blood and have a long duration in epithelial barrier tissues; it proliferates locally and provides rapid on-site recall immune defense [70]. Moreover, a recent study found that T_{RM} cells and recirculating memory T cells (T_{CM}) collaborate to maintain lesions in mice [71]. It was reported that multiple skin infiltrating T_{RM} also expressed CXCR3 and were poised for release of IFN-γ and TNF-α, showing similarities with recruitment of cytotoxic $CD8^+$ T cells [52]. CD49a expression marks a subset of T_{RM} cells in defining the 2 autoimmune diseases, vitiligo and psoriasis. $CD8^+CD49a^+$ T_{RM} cells are poised for cytotoxic response with expression of effector molecules perforin and granzyme B and IL-15 stimulation [72]. A novel strategy through depleting T_{RM} by blockade of IL-15 signaling has been proposed [69]. Besides CD49a, several studies have identified CD122 (IL-15 receptor), CD103, and CD69 as T_{RM} phenotype [52,69]. Notably, a recent article reported that survival and function of T_{RM} cells relies on the uptake of exogenous lipid and oxidative metabolism, and this finding may introduce a refreshing link between oxidative stress and memory adaptive immunity [73].

Currently, the focus on T_{RM} cells may help explain the recurrence of previous vitiligo lesion in the same location, since T_{RM} cells provide rapid localized defense against recurrent pathogens. Nonetheless, in vitiligo, the question remains as to what are the "pathogens" that activate the function of T_{RM} cells. Recent studies have revealed the role of IL-15 in promoting the function of T_{RM} cells *in vitro*, but which cells produce and correlate with IL-15 remains unknown. The markers CD122, CD103, and CD69 require more laboratory studies to demonstrate their functions interacting with other cells and cytokines. Moreover, how oxidative stress and innate immunity exert effects on and connect with T_{RM} cells remains to be explained. Anyway, treatments targeting T_{RM} cells may be highly effective or even reverse vitiligo, and deserve more attention [71].

Conclusions

Oxidative stress and autoimmunity are both leading theories proposed for vitiligo. But we cannot understand these 2 causative mechanisms without convergence. In fact, the new insights into how these 2 pathways work together may be helpful for a better understanding of vitiligo pathogenesis. Taken together, this study synthesized the mechanism of vitiligo from ROS triggers to spreading of lesions. To begin with, both exogenous and endogenous stimuli promote melanocyte stress, leading to excessive ROS, which contribute to the production of DAMPs and the release of melanosomal antigens that activate innate immunity. The activation and maturation of dendritic cells via Hsp70i present the antigen, followed by reactive $CD8^+$ T cells that destroy the melanocytes. The cytokines and chemokines are secreted under oxidative stress, acting as the mediator that facilitates the recruitment of $CD8^+$ T cells and amplifies the inflammatory network. The growing attention of Tregs and T_{RM} also correlate with oxidative stress and play indispensable roles in the pathogenesis of vitiligo. Both IL-17 and CXCL10 have been correlated with the severity and activity of the disease may be a clue for defining the role of Th17 cells.

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It will be critical to identify, simultaneously, the significance of CXCL9, if any, when evaluating the role of CXCL10. This will make it clearer whether the alteration of CCL22 is related to oxidative stress. Recent advances have enriched the details of how initial oxidative events lead to the activation of immune systems, thus bringing new potential strategies to vitiligo treatments. These promising therapeutic options originate from targeting the pathways involved, including activating Nrf2 pathways, mutant Hsp70i, inhibiting adaptive immunity-related cytokines and chemokines, replenishing Treg abundance, and blocking T_{RM}, which may all represent a step forward in understanding and treating vitiligo.

Conflicts of interest

None.

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