Review article

Vitiligo: How do oxidative stress-induced autoantigens trigger autoimmunity?

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Vitiligo is a common depigmentation disorder characterized by a loss of functional melanocytes and melanin from epidermis, in which the autoantigens and subsequent autoimmunity caused by oxidative stress play significant roles according to hypotheses. Various factors lead to reactive oxygen species (ROS) overproduction in the melanocytes of vitiligo: the exogenous and endogenous stimuli that cause ROS production, low levels of enzymatic and non-enzymatic antioxidants, disturbed antioxidant pathways and polymorphisms of ROS-associated genes. These factors synergistically contribute to the accumulation of ROS in melanocytes, finally leading to melanocyte damage and the production of autoantigens through the following ways: apoptosis, accumulation of misfolded peptides and cytokines induced by endoplasmic reticulum stress as well as the sustained unfolded protein response, and an ‘eat me’ signal for phagocytic cells triggered by calreticulin. Subsequently, autoantigens presentation and dendritic cells maturation occurred mediated by the release of antigen-containing exosomes, adenosine triphosphate and melanosomal autoprophagy. With the involvement of inducible heat shock protein 70, cellular immunity targeting autoantigens takes the essential place in the destruction of melanocytes, which eventually results in vitiligo. Several treatments, such as narrow band ultraviolet, quercetin and α-melanophore-stimulating hormone, are reported to be able to lower ROS thereby achieving repigmentation in vitiligo. In therapies targeting autoimmunity, restore of regulatory T cells is absorbing attention, in which narrow band ultraviolet also plays a role.

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Abbreviations: ROS, reactive oxygen species; UV, ultraviolet; DMA, deoxyribonucleic acid; Nrf2, nuclear factor E2-related factor 2; ARE, antioxidant response element; HO-1, heme oxygenase-1; ER, endoplasmic reticulum; 8-OHdG, 8-hydroxy-2-deoxyguanosine; APE1, apurinic/apyrimidinic endonuclease 1; UPR, unfolded protein response; MART-1, melanoma antigen recognized by T cells-1; ATP, adenosine triphosphate; LCs, Langerhans cells; DCs, dendritic cells; CRT, calreticulin; HMC, major histocompatibility complex; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; IFN-γ, interferon-γ; CTL, cytotoxic T lymphocyte; TNF, tumour necrosis factor; CLA, cutaneous lymphocyte antigen; Th2, T-helper cells type 2; Treg, CD4+CD25+T regulatory cells.

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1. Introduction

Vitiligo is a common depigmented disorder characterized by a loss of functional melanocytes and melanin from epidermis [1]. Based on various hypotheses, the consensus has been reached that it is a result of complex interactions between oxidative stress and autoimmunity processes in patients with vulnerable genetic background [2–4]. The melanocytes of vitiligo, according to genome-wide association studies, acquire high susceptibility to damage or apoptosis under certain circumstances and final destruction resulted from the synergistical interactions between reactive oxygen species (ROS) and autoimmunity [2,3,5]. Specifically, both the abnormal generation of epidermal ROS and the compromised antioxidant defences indicate the loss of cellular redox equilibrium contributes to vitiligo [6]. The crucial role of autoimmunity in melanocyte destruction is supported by the markedly increased incidence of vitiligo in cases of immune dysfunction [3,4,7]. However, the specific interactions between ROS and autoimmunity in vitiligo still remains unclear. Here, by summarizing our current understanding, we try to shed light on ROS's role in the induction of autoimmune responses and melanocyte destruction.

2. The excessive production of ROS in vitiligo

The excessive ROS are caused by overproduction and inadequate antioxidants defences (Fig. 1).

Various exogenous and endogenous stimuli involved in the aetiopathogenesis of vitiligo are reported to be responsible for the overproduction of ROS, including ultraviolet (UV) irradiation, trauma, stress, major infection, malignancies, neural abnormalities, vaccination, pregnancy, calcium imbalance, certain drugs, hormones, and exposure to cytotoxic compounds [2,8]. However, for the shortage of evidence, the initiation of excessive ROS production in vitiligo still remains obscure. Mitochondrial dysfunction is doubted to be one of culprits. The membrane lipid defects of mitochondria, such as the altered transmembrane distribution of cardiolipin and cholesterol, was found to be responsible for the generation of ROS in peripheral blood mononuclear cells of vitiligo patients [9]. These stimuli, in our

Fig. 1. ROS accumulation in the melanocytes of vitiligo. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Green: factors enhancing the production of ROS. Red: factors inhibiting the production of ROS. Various factors lead to ROS overproduction in the melanocytes of vitiligo patients: the exogenous and endogenous stimuli that cause ROS production, low levels of enzymatic and non-enzymatic antioxidants, disturbed antioxidant pathways, and polymorphisms of ROS-associated genes. These factors synergistically contribute to the accumulation of ROS in melanocytes, finally leading to melanocyte damage. The red text indicates pathways that may lead to excess ROS production; green text indicates antioxidant molecules or pathways that may alleviate oxidative stress in melanocytes. ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; UV, ultraviolet; GST, glutathione S-transferase; Nrf2, nuclear factor E2-related factor 2; ARE, antioxidant response element; HO-1, heme oxygenase-1.

supposition, may indirectly induce ROS overproduction through impairing mitochondria in their distinctive pathways.

ROS comprise a family of oxygen-based free radicals, including superoxide anions, hydroxyl radicals, hydrogen peroxide (H$_2$O$_2$), and singlet oxygen, which are produced during multiple cellular processes, such as cellular metabolism, proliferation, differentiation, apoptosis, and immune reactions [10,11]. Pollution, atmospheric gases, ionizing or UV radiation, microorganisms, viruses, and xenobiotics/drugs are proven environmental elicitors of excessive ROS that quickly prevail against tissue antioxidants and other oxidant-degrading pathways [10]. Meanwhile, melanocytes tend to own increased vulnerability to oxidative stress due to the reduction of catalase and glutathione peroxidase activity [7]. The gene polymorphisms of CAT, which are conventionally thought to be associated with vitiligo susceptibility, still lack sufficient evidence to support its pathogenicity according to a latest meta-analysis [12]. Some researchers speculated that given both catalase and glutathione peroxidase mainly function at low concentrations of peroxide, the dramatic growth of peroxide substrate may curb their activities instead [13]. Apart from the abnormal antioxidant enzyme, excessive ROS produced during melanin synthesis also pose remarkable damage to melanocytes under oxidative stress [6,11]. Although the presence of melanin in skin protects melanocytes and neighbouring keratinocytes through absorbing UV radiation, it also leads to higher levels of intracellular ROS during its synthesis, rendering melanocytes more susceptible to oxidative damage [6].

ROS overproduction caused by exogenous and endogenous stimuli in vitiligo has been illustrated by a host of studies [8]. Research in vivo and in vitro has demonstrated massive accumulations of H$_2$O$_2$ in vitiligo skin, coupled with impaired antioxidant activity [8]. Systemic oxidative stress, like mitochondrial alterations and oxidative DNA damage, has also been confirmed [3].

It is the enzymatic and non-enzymatic antioxidant levels and pathways altered in the melanocytes in vitiligo that exemplify the inadequate antioxidant defences [6]. The antioxidant system and oxidant degradation are the leading mediators of ROS clearance, whose dysfunction is partially responsible for ROS overproduction. The nuclear factor E2-related factor 2-antioxidant response element/heme oxygenase-1 (Nrf2-ARE/HO-1) pathway, one of the critical antioxidant systems, is functionally deficient in the disease-free epidermis of patients with vitiligo [14].

3. The damage of excessive ROS in vitiligo

As extremely active radicals, ROS potently damage most biological macromolecules (lipids, proteins, nucleic acids and carbohydrates) and are responsible for the formation of deoxyribonucleic acid (DNA)-protein cross-links, DNA breaks, lipid peroxidation, protein oxidation/fragmentation, and enzyme activation/inactivation [15]. ROS’s deleterious effects can lead to membrane peroxidation, decreased mitochondrial membrane potential, and vacuolization and apoptosis of both melanocytes and keratinocytes in vitiligo epidermis [16]. The mitochondrial alterations in apoptotic perilesional keratinocytes due to increased ROS production inhibit synthesis of stem cell factor, thereby altering the survival and proliferation of neighbouring melanocytes [17]. All the above changes lead to functional and structural damage in melanocytes, finally resulting in vitiligo. Additionally, impairments of antioxidant system, defective synthesis of membrane lipids, and impaired electron transport chain complex I activity render vitiligo melanocytes more vulnerable to the effects of ROS than normal melanocytes [9,14].

Intrinsic abnormalities found in vitiligo possibly also render melanocytes more sensitive to ROS stress, such as dilated endoplasmic reticulum (ER) profiles, mitochondrial abnormalities, and abnormal melanosome compartmentalization [18].

Dysfunction of intracellular signalling induced by oxidative stress in vitiligo may perturb metabolism and alter cell survival in melanocytes and keratinocytes [16,19]. For example, long-term exposure to subcytotoxic oxidative stress has been suggested to cause chronic over-stimulation of the mitogen-activated protein kinase signalling cascade, Akt activation, and induction of both p16 and cyclin D1 expression in vitiligo melanocytes [16,20]. Disrupted signalling might lead to metabolic disturbances, cell cycle arrest, senescence, and cell death in melanocytes [16]. Additionally, the activation of p53-dependent signalling and the overexpression of RNASET2 under oxidative stress, both of which is able to alter cell survival, have been observed in both vitiligo melanocytes and keratinocytes [16,21].

In summary, redundant ROS may be the upstream pathogenic event that triggers melanocyte destruction through the above mechanisms.

4. Autoantigens from DNA damaged by excessive ROS

The significantly higher level of 8-hydroxy-2’-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage in the circulating immune complexes in patients of systemic lupus erythematosus, was detected in the skin and serum of patients with active vitiligo, implying DNA damage in vitiligo [22]. Apurinic/apyrimidinic endonuclease 1 (APE1) plays an important role in the base excision repair pathway, which mediates the removal of oxidatively damaged DNA [23]. Our group discovered that the APE1-Asp148Glu polymorphism aggravates oxidative stress in human melanocytes and contributes to the genetic predisposition to vitiligo [23]. Furthermore, serum 8-OHdG levels are elevated in APE1-148Glu allele carriers in an allele dose-dependent manner with a higher risk of vitiligo [23]. However, the autoantigens in vitiligo mainly originate from melanosomal proteins rather than damaged DNA, which means the autoantigens from damaged DNA may merely play an assistant role during the trigger of autoimmunity [24].

5. Autoantigens from melanosomal proteins caused by excessive ROS

The macromolecules and small molecules from melanocytes, whose structures were changed by oxidative stress, can act as neoantigens, inducing autoreactivities. Thanks mainly to the outburst of autoantigens from the target tissue, the amplified effect of neoantigens will result in the breakdown of self-tolerance [3,4,16].

ROS may eventually lead to apoptosis in melanocytes through a series of procedures. Owing to the immune responses activated by oxidative stress, melanocytes may undergo apoptosis, whose possible persistency will cause perpetuated death of melanocytes, resulting in progressive depigmentation. The autoantigens, which is induced by ROS and raises autoimmunity in vitiligo, mainly originate from melanosomal proteins [24]. The hypotheses of ROS stress contributing to autoimmunity in melanocyte destruction in vitiligo will be discussed next (Fig. 2).

Though direct experimental evidence for melanocyte loss in vitiligo is limited, some important concepts regarding the mechanisms of melanocyte loss concluded from in vitro data and animal models support apoptosis as the main cause of melanocyte loss [25]. A recent review proposed that a pro-oxidant state, increased sensitivity to oxidative stress, and a compromised antioxidant level may together induce melanocyte apoptosis after precipitating exposure [6]. A study of vitiliginous animal models has confirmed cell apoptosis in situ in the feathers of Smyth line

chickens [26]. These observations indicate apoptosis acts as the main cause of the melanocyte loss in vitiligo.

Oxidative stress may produce redox disruptions affecting ER, where oxidation/reduction reactions are critical for protein folding. The initiation of ER stress causes accumulations of immature proteins and mis-folded peptides, thus activating the unfolded protein response (UPR), which promotes restoration of ER homeostasis and cell survival as well as autoimmune responses via apoptotic cascades under sustained stress [27]. It has been discovered that UPR components such as the transcription factor X-box-binding protein 1 are induced following melanocyte exposure to the chemical triggers of vitiligo [28]. Individuals susceptible to vitiligo are unable to combat the oxidative stress, leading to sustained UPR activity, which causes melanocyte apoptosis and induces production of cytokines such as interleukin-6 (IL-6), IL-8, IL-11 and tumour necrosis factor (TNF) [28].

Recently, the vitiligo induced by the skin-depigmenting agent monobenzone was unveiled to share numerous similarities with vitiligo vulgaris in pathogenesis, especially the interplay between ROS and autoimmunity, therefore we speculated the monobenzone-induced vitiligo’s primarily explored mechanism may shed light on the obscure counterpart of vitiligo vulgaris [3,29]. One study focusing on depigmentation caused by monobenzone confirmed the release of antigen-containing exosomes from melanocytes following ROS over-production [30]. Oxidative stress, which was selectively induced by monobenzone in pigmented cells, promotes the release of tyrosinase- and Melan-A/MART-1 (melanoma antigen recognized by T cells-1)-containing exosomes and adenosine triphosphate (ATP) as well as melanosomal autophagy [30,31]. In addition, under oxidative stress, the melanosomal proteins-chaperoned inducible heat shock protein 70 (HSP70i), generated and secreted by genetically compromised melanocytes, activates Langerhans cells (LCs) as an alarm signal that drives the autoimmune responses in vitiligo [32,33].

Another culprit gaining attention recently is calreticulin (CRT), a ubiquitous ER protein regulating intracellular Ca²⁺, which conditionally localises to the surface of monocytes, macrophages, neutrophils, T cells and dendritic cells (DCs), mediating antigen presentation, complement activation and clearance of apoptotic cells and helps determine the immunogenicity of cancer cell death [34,35]. Our studies in vitiligo have discovered the redistribution of CRT from the ER lumen to the melanocyte surface under oxidative stress [34]. Surface CRT can then directly the contact of ROS-stressed melanocytes to DCs, followed by the activation of downstream immune responses leading to apoptosis [36]. Overexpression of CRT increases melanocyte susceptibility to DC-induced immunogenic apoptosis [34]. These apoptotic melanocytes supply abundant antigenic peptides to the downstream immune cells [3]. CRT also induces expression of pro-inflammatory cytokines like IL-6 and TNF-α, enhancing the immunogenic potential of the apoptotic melanocytes [34]. In addition, we discovered a positive relationship between CRT expression and vitiligo’s duration and lesion areas [34]. CRT-mediated melanocyte destruction may induce an immune response targeting apoptotic melanocytes under oxidative stress.

6. The initiation of autoimmunity

In monobenzone-exposed pigmented cells, DC activation upon uptake of exosomes induces a robust pigmented cell-reactive CD8⁺ T-cell response [30]. ATP released from exposed melanocyte activates the cryopyrin inflammasomes in local DCs, mediating DC maturation [29]. Moreover, ROS-provoking melanosomal autophagy targets melanosomal tyrosinase via lysosomal degradation to major histocompatibility complex (MHC) class-II compartments [30]. This reception of antigen input may enhance endogenous antigen presentation by MHC class-I molecules [37]. Thus, ROS-induced release of melanocyte antigen-containing exosomes and
Fig. 3. The cellular immune response against melanocytes in vitiligo. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Black arrows: processions. Green arrows: enhancement. Red arrows: prohibition or damage. ROS accumulation causes direct destruction of MC, leading to apoptosis. ROS could lead to CRT translocation from the ER lumen to the cell surface, HSP70i secretion, the UPR, autoantigen-containing exosomes release and expression of IL-6, IL-8, and TNF-α from stressed melanocytes. The binding of TRAIL on LCs to TRAILR on melanocytes also causes melanocyte apoptosis. LCs express the HSP70i receptors, CD91/14/40, and TLR 2/4, which could bind to the secreted HSP70i. Antigenic peptides from apoptotic melanocytes and peptides chaperoned by HSP70i (those originated from tyrosinase, Mart-1, and gp100) could be recognized by MHC-I molecules on epithelial LCs. These LCs undergo maturation during migration to draining lymph nodes, where peptide-carrying DCs activate CD8+ T cells through binding of peptide-MHC complex and TCR. CD8+ T cells migrate to the epithelium through help of cytokines, chemokines, and molecules of CLA and LFA-1. CTL damage the melanocytes through secretion of granzyme, perforin, IFN-γ, and TNF-α. KCs and fibroblasts (FBs) mediate damage through IL-1β, IL-6, and TNF-α. Treg cells secrete IL-10 and transforming growth factor-β, inhibiting CTL function.

ROS, reactive oxygen species; MC, melanocytes; CRT, calreticulin; ER, endoplasmic reticulum; HSP70i, inducible heat shock protein 70; UPR, unfolded protein response; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; LCs, Langerhans cells; TRAILR, tumour necrosis factor-related apoptosis-inducing ligand receptor; TLR, Toll-like receptor; MHC-I, major histocompatibility complex-I; DCs, dendritic cells; TCR, T-cell receptor; CLA, cutaneous lymphocyte antigen; LFA-1, lymphocyte functional antigen-1; CTL, cytotoxic T lymphocytes; IFN-γ, interferon-γ; KC, keratinocytes; Th17, T-helper cells type 17; Treg, CD4+CD25+ T-regulatory cells; FB, fibroblast.

ATP, as well as melanosomal autophagy, facilitates the breaking of immune tolerance [29].

A likely link between ROS and cellular immunity in the pathomechanism of vitiligo is HSP70i [33]. Intracellular HSP70i localises with melanosomes, binds melanosomal proteins/peptides and assists in protein folding, trafficking and potentially MHC-I/Ii loading [38]. HSP70i exposure enhances uptake and presentation of antigens by epithelial LCs and the expression of LC activation markers [32]. LCs up-regulate HSP70 receptor expression (CD91, TLR-2, CD14/TLR-4, CCR5 and scavenger receptors) and the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) in response to HSP70i secretion, enabling LCs to kill melanocytes via up-regulation of TRAIL receptors [33]. HSP70i induces antigen-specific immunity by boosting uptake, processing and presentation of HSP70i-chaperoned proteins and peptides of LCs [33]. The activated LCs after a series of autoimmune processes may finally lead to the migration of skin homing T cells [2]. Moreover, HSP70i induces antigen-presenting cell maturation and production of the type-1 polarizing cytokines IL-1, IL-6, and TNF-α by DCs/monocytes/macrophages and stimulates T-cell cross-priming [39]. Additionally, interferon-γ (IFN-γ) from perilesional cytotoxic T lymphocytes (CTLs) enhances HSP70i release through a positive feedback mechanism [32]. This HSP70i-LCs-CTL-IFN-γ-HSP70i loop perpetuates melanocyte destruction in vitiligo [33].

HSP70i's necessary and sufficient role in inducing and accelerating depigmentation has been confirmed in vitiligo-prone mice. Le Poole et al. vaccinated HSP70i knockout mice, HSP70-2 knockout mice, and wild-type animals with optimized tyrosinase related protein-1, a highly immunogenic melanosomal target molecule, and failed to induce robust and lasting depigmentation only in the HSP70i knockout mice [32,40]. Additionally, mutant HSP70i does not induce depigmentation in melanocyte-antigen vaccinated mice and prevents depigmentation in vitiligo-prone mice, thus demonstrating the critical role of HSP70i in precipitating vitiligo and suggesting potent treatment opportunities [40].

Many studies have revealed the vital role of cellular immunity in the destruction of melanocytes in vitiligo. The research of lymphoid cells infiltrating depigmented areas of vitiligo revealed that early lesions are infiltrated mainly by DCs, whereas late lesions display significantly lower proportions of DCs and increased percentages of mature T cells [41]. Lesional borders of vitiligo are infiltrated mainly by CTLs reacting to melanocyte-specific antigens. Immunohistochemical staining has revealed a higher increase in the number of CD8+ T cells than CD4+ T cells’ in marginal skin in both stable and active vitiligo patients; furthermore, it was found that the number of CD8+ T cells was higher than the number of CD4+ T cells in the epidermis and dermal-epidermal junction (sites where melanocytes usually reside), with a resultant
significant decrease in the CD4+/CD8+ ratio in active cases in comparison to stable cases [42]. These results support cellular immunity as the main source of melanocyte destruction in vitiligo and are in accordance with several previous studies [4].

Cell-mediated autoimmunity in vitiligo targets melanocyte differentiation antigens [24]. Expressed in normal and transformed melanocytes, they are proteins involved in melanin synthesis, recognized and presented by LCs as antigens, like Melan-A/MART-1, tyrosinase and gp100 [3]. Of different cells activated after exposure to extrinsic or intrinsic stimuli in vitiligo, LCs are considered to participate in the early phase of immune reactions against melanocytes [41]. LCs move to the upper layer in the lesion site and become activated, which may be manifested by increases of their dendrite lengths and number, Birbeck granule formation, and LC-activated TNF-α and IL-6 levels [43].

After being processed by LCs, antigenic peptides from melanocytes are presented to CTLs at local skin-draining lymph nodes in the context of MHC class-I molecules [4]. These effector T-cells migrate to target melanocytes in the dermal-epidermal junction with other inflammatory infiltrates [23]. The remarkable elevation was found in melanocytic antigen-specific CTLs in the perilesional skin and peripheral blood of vitiligo patients [44]. These CTLs exhibit anti-melanocyte cytotoxicity and express cutaneous lymphocyte antigen (CLA), a skin-homing marker [45]. Notably, the cytotoxicity of infiltrating CTLs is indicated by their failure to inducing apoptosis in the lesional skin with the absence of melanocytes, showing its autoimmune cytotoxicity is melanocyte-specific [44].

After migrating to the damaged melanocytes, CLA/HLA-DR/CD8+ T cells at the perilesional skin become activated (CD69+, CD137+, granzyme-B+, perforin+, and CD107a+) and induce melanocyte apoptosis [44]. Fig. 3 illustrates the development of the cellular autoimmune responses in ROS-induced vitiligo.

The specific role of CD4+ T cells in vitiligo still remains ambiguous, which is, however, likely to result in dysregulated Treg cells, easing the development of autoimmunity [1].

7. Emerging treatments to vitiligo targeting excessive ROS and autoimmunity

Repigmentation of vitiligo has been achieved by reducing hydrogen peroxide, such as the narrow band UVB-activated pseudocatalase, which is found able to lower the level of epidermal H₂O₂. has showed remarkable effect of repigmentation on both segmental and nonsegmental vitiligo [6,46]. Several studies demonstrated that narrow band UVB therapy in combination with oral antioxidants will greatly raise glutathione peroxidase and reduce malonyldialdehyde, indicating antioxidant’s role of adjuvant, which, supported by the effect of ginkgo biloba on slowly spreading vitiligo, can also act as a monotherapy [47]. Quercetin, another antioxidant that protects melanocytes against H₂O₂, was reported to stop the appearance of ER dilation and the blockage of tyrosinase export from the ER [48]. Peroxiredoxin I belongs to a family of antioxidant proteins, playing a protective role against UVA-induced apoptotic and inflammatory signals by controlling ROS accumulation [49]. In addition, topical tacrolimus was documented to reduce systemic oxidative stress levels in vitiligo patients while pimecrolimus did not reveal this character [47].

α-melanophore-stimulating hormone (α-MSH) was found to activate the melanocortin 1 receptor to attenuate the UV-induced oxidative DNA damage, inducing phosphorylation of p53, which weakens the oxidative DNA damage of melanocytes. α-MSH also promotes expression of Trc7 by thereby regulating the amounts of several antioxidative enzymes [47].

When it comes to the novel treatments to autoimmunity, restore of Treg cells is absorbing attention. The narrow band UVB therapy, which was usually thought to function through inhibiting CD8+ T cells, may improve the development of Treg cells via downregulation of proinflammatory cytokines and upregulation of IL10 [47]. Moreover, the adoptive transfer of antigen-specific induced Treg cells have been applied in a vitiligo mouse model and disease remission has been observed [47].

Given the massive infiltration of T cells occurring in perilesional keratinocytes from vitiligo skin, in which Treg and Th2 cells account for decreased proportions while Th1 and Th17 cells take up rising percentages, some researchers tried to reverse the condition with low-dose cytokines IL-10, IL-4, β-endorphin and basic fibroblasts growth factor, resulting in a positive effect on redox dyshomeostasis and viability of perilesional keratinocytes without impairments on their cell cycle [50]. This may be an indirect treatment to vitiligo.

8. Conclusions

In this review, we present evidence to suggest excessive ROS production triggers vitiligo through melanocyte apoptosis, sustained UPR, release of exosomes, aberrant expression of ROS-induced HSF70 and CRT translocation, assisted with cellular immunity. The improved understanding of the role of ROS in vitiligo may provide new perspectives on promising remedies, such as curbing ROS overproduction, rising Treg cells, inhibitors of apoptosis, the analogues of antigenic peptides and antibodies against cytokines.

Conflict of interest

The authors have no conflict of interest to declare.

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