

# Endoplasmic Reticulum Dysfunction: An Emerging Mechanism of Vitiligo Pathogenesis

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**Abstract:** The endoplasmic reticulum (ER) is the main site of protein synthesis, transport, and modification. Its abnormal status has now emerged as an established cause of many pathological processes, such as tumors and autoimmune diseases. Recent studies also demonstrated that the defective functions of ER may lead to pigmentary diseases. Vitiligo is a depigmenting ailment skin disorder whose pathogenesis is now found to be associated with ER. However, the detailed mechanism is still unclear. In this review, we try to link the association between ER with its inter- and intra-organellar interactions in vitiligo pathogenesis and focus on the function, mechanism, and clinical potential of ER with vitiligo. Expand ER is found in melanocytes of vitiligo and ER stress (ERS) might be a bridge between oxidative stress and innate and adaptive immunity. Meanwhile, the tight association between ER and mitochondria or melanosomes in organelles levels, as well as genes and cytokines, is the new paradigm in the pathogenesis of vitiligo. This undoubtedly adds a new aspect to the understanding of vitiligo, facilitating the design of targeted therapies for vitiligo.

**Keywords:** vitiligo, endoplasmic reticulum, organelles, cellular interactions, oxidative stress

## Introduction

Vitiligo is an acquired pigmentary disorder of the skin, resulting from severe melanocytes destruction. As the most frequent cause of depigmentation, vitiligo affects approximately 0.5–1% of people worldwide. Patients suffer from public misconceptions and negative social stigma, which continue to cause psychological devastation and even exacerbate the disease process.<sup>1,2</sup> Furthermore, vitiligo causes a substantial economic burden involving work absenteeism or psychotherapy fees.<sup>3</sup> Vitiligo is considered to be a multifactorial etiology disease, whose pathogenetic factors include neural theory, temporal sequence between oxidative stress and autoimmunity, genetic predisposition, and environmental stimuli.<sup>4</sup> Most of them acting in concert, rather than a single theory can account for.<sup>5,6</sup> The importance of oxidative stress in the pathogenesis of vitiligo has been highlighted in recent years.<sup>7–9</sup> Researchers have proposed that oxidative stress, serving as a significant instigating factor, may play a role in triggering the specific T cell immune response against melanocytes and subsequently causing cell damage.<sup>10–12</sup> However, the exact mechanism has yet to be fully understood.

The endoplasmic reticulum (ER) is an important organelle associated with the synthesis, folding, and transporting of proteins.<sup>13</sup> Now, it has become increasingly apparent that the ER plays an important role in immunity and immune-mediated diseases, and is extremely sensitive to oxidative stress.<sup>14,15</sup> Under physiological conditions, there are various mechanisms to make sure the correct modification of proteins in ER. Whereas, when cells encounter a stressful situation, disruption of ER homeostasis will result in the accumulation of unfolded or misfolded proteins, which is called ER stress (ERS), and subsequently activates the unfolded protein response (UPR).<sup>16</sup> It was reported that ERS has been associated with a variety of skin diseases, such as Darier's disease, rosacea, and melanoma.<sup>17</sup> Oxidative stress is considered to be an

important link in the pathogenesis of vitiligo, which suggests ER may also be indispensable in the vitiligo pathogenesis. In recent years, R E Boissy<sup>18</sup> revealed the presence of expanded ER in melanocytes of a vitiligo mouse model. Meanwhile, ER expansion and vacuolization were also found in vitiligo patients.<sup>19</sup> All of this evidence suggests and reinforces that ER is also involved in the pathogenesis of vitiligo.

Therefore, this review summarized the current progress of ER and its involvement in vitiligo, and also focused on its function and possible mechanisms in vitiligo pathogenesis from cellular level to organelle level. Moreover, we hope to provide new insight into its potential application in the diagnosis and treatment of vitiligo.

## ER

ER is one of the largest cellular organelles in eukaryotes, which was first described by Porter et al in 1945.<sup>20</sup> The structure of ER includes a nuclear envelope, smooth tubules, and rough lamellae. Different types of cells have a different ratio of lamellae to tubules, reflecting their different functions.<sup>21,22</sup> The rough ER (RER) structure is decorated with ribosomes and related to the synthesis of secreted proteins, while the surface of smooth ER (SER) is devoid of ribosomes.<sup>23,24</sup>

## The Function of ER

As one of the largest membrane-bound organelles, ER performs many critical cellular functions.<sup>25,26</sup> The functions of ER include 1) It can synthesize and secrete proteins. ER produces nearly 30% of the cellular proteome, including most secreted, membrane-bound, or integral membrane proteins. Newly synthesized proteins leave ER as vesicles to the Golgi, and then release to the endomembrane system or extracellular space; 2) It is also involved in metabolic processes, including gluconeogenesis, lipid and cholesterol synthesis;<sup>16,27–29</sup> 3) the ER is also an intracellular storage site for calcium ion (Ca<sup>2+</sup>).<sup>30</sup> As a vital and highly dynamic organelle, the importance of ER function in immune-mediated diseases has become increasingly evident.

## Structural and Functional Changes of ER

The ER forms a continuous network of tubules extending through the entire cell. It is crucial to understand the functional dependence of the ER on its structural organization for elucidating the cellular response to changes in the ER. It was reported that mutations in ER morphogens cause motor neuron diseases.<sup>31</sup> Similarly, vacuolation, granulation, and dilatation of the ER were also observed in vitiligo,<sup>19</sup> which might be an upstream event in vitiligo pathogenesis. In addition, one of the key functions of the ER is enabling Ca<sup>2+</sup> signaling. Rapid Ca<sup>2+</sup> release through a well-connected network of ER tubules,<sup>32</sup> which links the function of ER to its structure. Disruption of ER homeostasis disturbs Ca<sup>2+</sup> signaling, which in turn activates accumulation of unfolded or incompletely folded proteins in the ER lumen<sup>33</sup> (details shown in 1.3 and 1.4). These structural and functional alterations of the ER could be seen as stages in the initiation and progression of cell damages in vitiligo.

## ERS

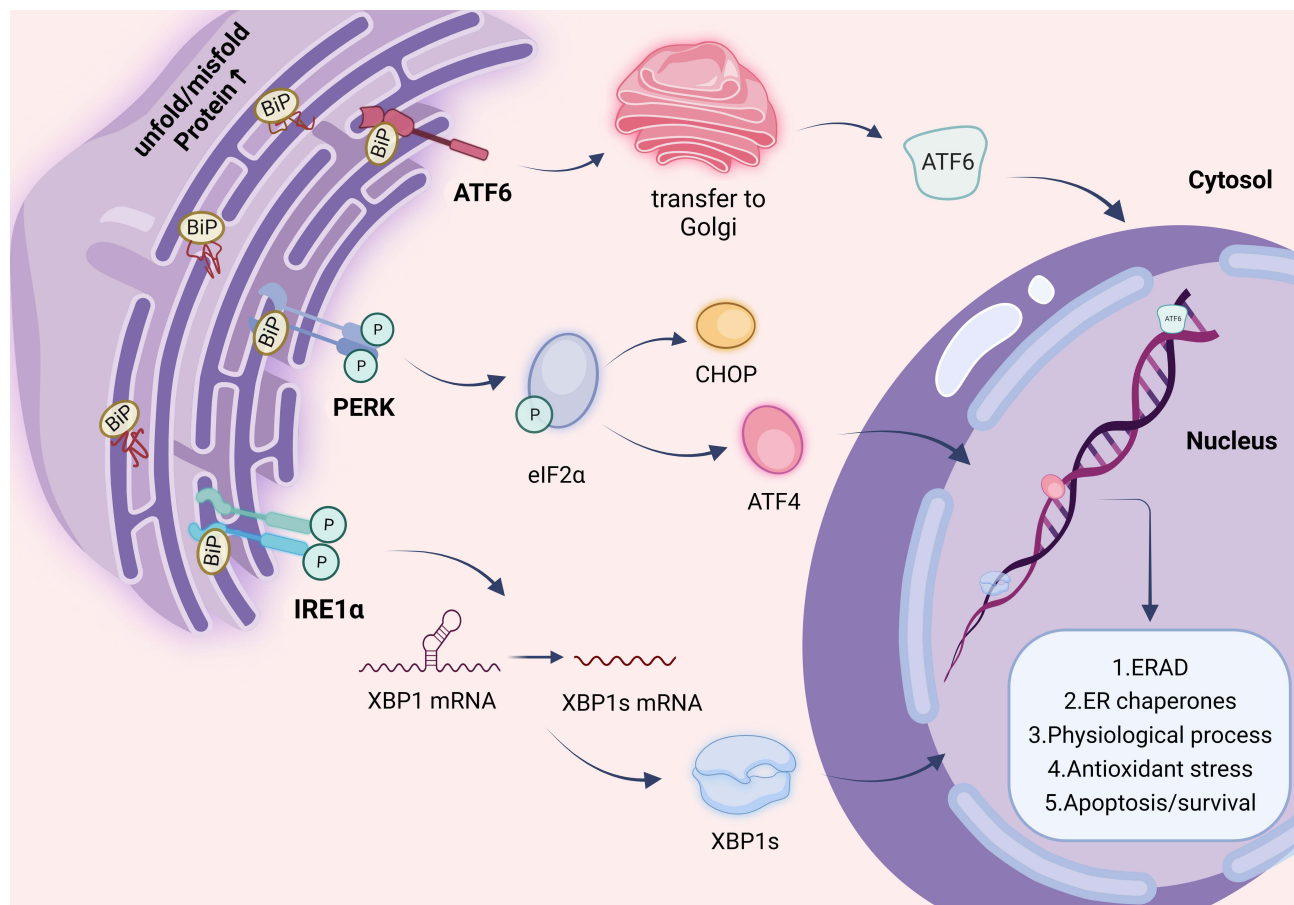
Newly synthesized polypeptides enter the ER to undergo the folding process. Proteins were modified by adding carbohydrate residues (n-strand glycosylation) or pairing with chaperones. One of the most abundant chaperones is immunoglobulin heavy chain binding protein/glucose regulated protein 78 (BiP/Grp 78).<sup>34,35</sup> ERS occurs when unfolded or incompletely folded proteins accumulate in the ER lumen. And then, it leads to the activation of the UPR, to maintain cellular homeostasis and normal ER function.<sup>36,37</sup> However, if ERS fails to be removed by UPR, persistent ERS will finally lead to cellular apoptosis and many diseases, such as cancer, metabolic disorders, and multiple neuronal disorders.<sup>24,38</sup>

Therefore, it's critical to increase understanding of ERS and UPR in disease pathogenesis, which helps to find novel therapeutic targets. Three distinct mechanisms are then initiated to restore cell homeostasis, including inositol-requiring enzyme 1 $\alpha$  (IRE1 $\alpha$ ), protein kinase RNA (PKR)-like kinase (PERK), and activating transcription factor 6 (ATF6). Specifically, BiP dissociates from IRE1 $\alpha$  and binds to accumulated unfolded or misfolded proteins upon ER stress. Phosphorylation of IRE1 $\alpha$  activates its endoribonuclease activity to splice Xbp1 mRNA, generating spliced Xbp1 (Xbp1s) which encodes an active transcription factor that upregulates ER chaperones and genes encoding ER-associated degradation (ERAD) proteins. Meanwhile, PERK is one of three ERS sensors. BiP binds to misfolded

proteins and dissociates with PERK, which further promotes eIF2 $\alpha$  phosphorylation and halt general protein synthesis. Subsequently, ATF4 and CHOP could be selectively translated to promote apoptosis. In addition, under ER stress, ATF6 monomers traffics from the ER to the Golgi compartment and were cleaved by S1P and S2P proteases. Liberated ATF6 moves to nucleus and activation, resulting in reduction of levels of damaged proteins and ERS levels.<sup>39</sup> These ER stress sensors are activated to trigger a controlled response to eliminate or adapt to ERS. Failure of the UPR in reestablishing ER homeostasis will result in cell death and disease progression (Figure 1).<sup>40</sup> Nevertheless, how these misfolded protein sensors are activated is still unknown. Activation of the IRE1 $\alpha$ -XBP1 branch of the UPR has been reported to be closely related to immune cells and this point has not been explored for immune cells in vitiligo.

## ER Calcium Homeostasis

ER is a major Ca<sup>2+</sup> storage area. It is responsible for regulating Ca<sup>2+</sup> concentration by Ca<sup>2+</sup> channels, Ca<sup>2+</sup> transporters, Ca<sup>2+</sup> pumps, or Ca<sup>2+</sup>-binding proteins. Defected luminal Ca (2+) causes ERS and activates UPR, which could restore normal ER function or eliminate the cells by apoptosis pathways depending on the duration and severity of the stress.<sup>41,42</sup> ER calcium signaling is involved in many normal cellular functions, such as proliferation, and differentiation. In addition, severe Ca<sup>2+</sup> depletion induced by ER homeostasis alterations is also an upstream event in many disease



**Figure 1** Schematic overview of unfolded protein response (UPR). When faced with stress conditions, the level of misfold or unfold proteins increases in the endoplasmic reticulum (ER) lumen and promotes recruitment of BiP. And then, three ER stress sensor IRE1, PERK, and ATF6 are activated. Active IRE1 triggers XBP1u mRNA, the unconventional splicing, to produce active transcription factor sXBP1. Active PERK promotes phosphorylation of eIF2 $\alpha$  leading to translation of ATF4 and CHOP. Translocation of ATF6 to the Golgi and proteolytic cleavage result in transcriptionally active form. Activation of these pathways trigger downstream transcriptional machinery resulting in expression of target genes associated with lipid metabolism, immune, inflammatory response, and differentiation, as well as structural/ functional expansion of ER and ERAD to overcome the stress conditions. Otherwise, persistent or excessive ERS might changes Ca<sup>2+</sup> concentration inside mitochondria and mediate cell death pathway.

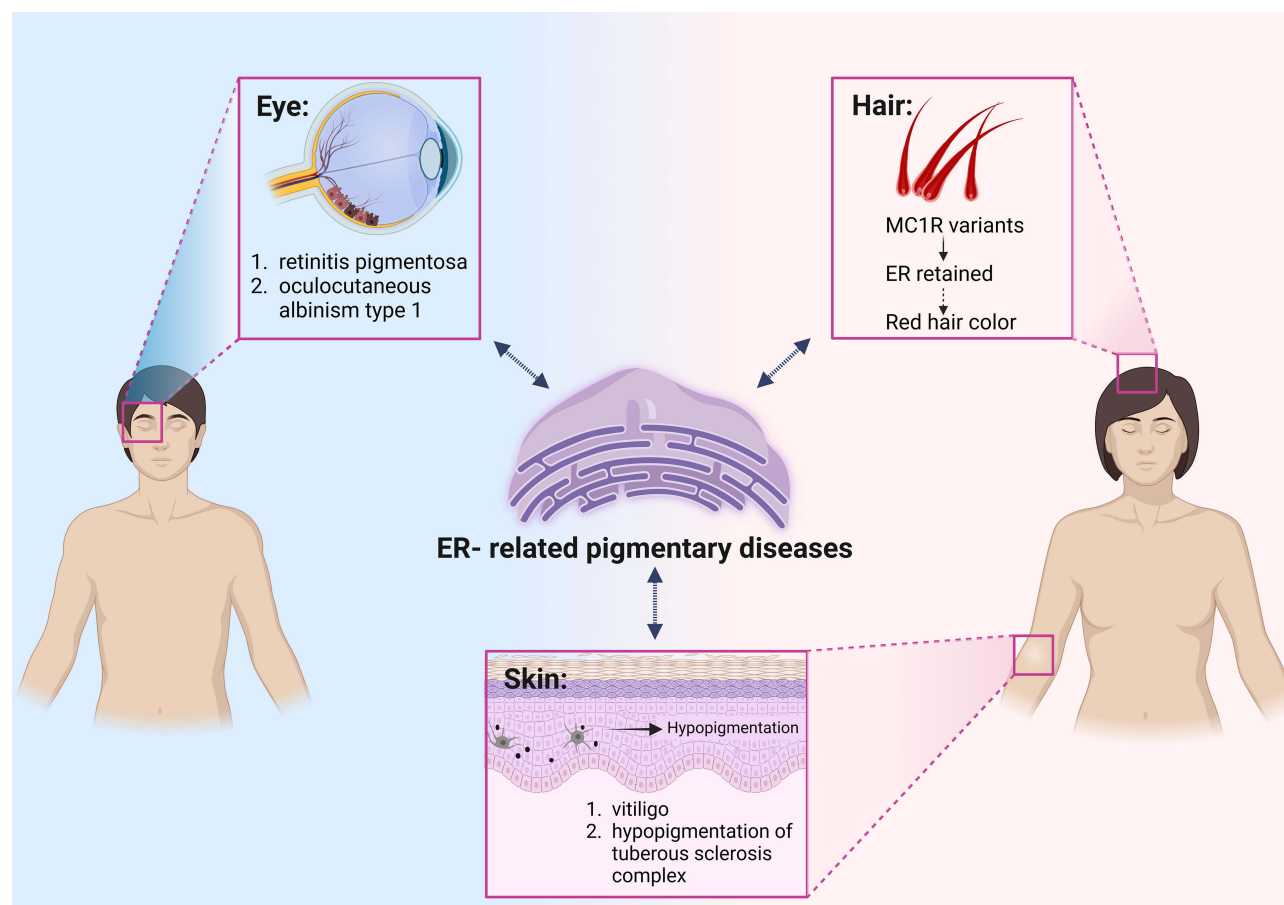
**Abbreviations:** BiP, binding immunoglobulin protein; IRE1, inositol-requiring enzyme; PERK, RNA-dependent protein kinase-like ER-resident kinase; ATF6, activating transcription factor 6; XBP1, X-box binding protein 1; eIF2 $\alpha$ , eukaryotic initiation factor $\alpha$ ; CHOP, CCAAT-enhancer-binding protein homologous protein; ERAD, ER-associated protein degradation.

pathogenesis. For instance,  $\text{Ca}^{2+}$  handling defects in the ER are related to the pancreatic  $\beta$  cell and might increase the risk of type I diabetes.<sup>43</sup> Therefore, disruption of  $\text{Ca}^{2+}$  homeostasis within the ER can affect a wide range of cellular processes and lead to a variety of diseases and pathological conditions. The regulation of ER  $\text{Ca}^{2+}$  homeostasis is critical for maintaining proper cellular function.

## ER and Pigmentary Diseases

ER dysfunction is associated with abnormal pigmented disorders in the skin, eyes, and hair, such as retinitis pigmentosa, vitiligo, hypopigmentation of tuberous sclerosis complex and red hair colour (Figure 2). The color of skin, eye, and hair are determined by melanin, while tyrosinase is a rate-limiting enzyme in melanogenesis. It was reported that the mechanism of oculocutaneous albinism type 1 was associated with tyrosinase retention in ER.<sup>44</sup> Similarly, retinitis pigmentosa is a degenerative blindness disease associated with genetic mutations in the rod visual pigment, rhodopsin.<sup>45</sup> It had been found that retinal mutations resulted in the inability of misfolded P23H rhodopsin to be further transported, causing abnormal proteins retained in the ER and photoreceptor cell death.<sup>45–48</sup> In addition, there are also many other abnormal misfolding proteins retained in ER that cause pigmentary diseases, such as piebaldism, hypopigmentation of tuberous sclerosis complex, and age-related macular degeneration.<sup>49–51</sup>

Abnormalities of the ER were found in all of the above diseases manifesting as hypopigmentation, suggesting that the ER is closely associated with pigmentary diseases. Vitiligo is the most common hypopigmented skin disease, whose etiopathogenesis includes oxidative stress, metabolic disorders, and autoimmune responses. Current studies have shown that vitiligo is also associated with ER dysfunction. ER is not isolated but forms contact sites with many other cytoplasmic organelles, including mitochondria, Golgi apparatus, peroxisomes, etc. Therefore, this suggests that the



**Figure 2** Pigmentary diseases related to ER homeostasis. Dysfunction of ER is associated with multiple diseases. Pigmentary disorders can manifest as abnormal pigmentation of the skin, eyes, and hair. These different kind of pigmentary diseases which are potentially relevant to ER dysfunction are listed.

involvement of ER in vitiligo pathogenesis may be related to intercellular and organelle connections. For example, interactions with mitochondria may affect cellular energy metabolism and stress responses. We summarize the advances between vitiligo and ER in inter- and intra-organellar interactions and also focus on the potential targeted therapies. Specific mechanisms need to be further explored and investigated.

## The Link Between Abnormal ER and Melanocytes and Keratinocytes in Vitiligo

The epidermis is composed of two major cellular components, keratinocytes and melanocytes. Melanocytes connect with keratinocytes by transferring melanin containing melanosomes from the melanocytes to keratinocytes. It had been previously revealed that melanocytes and keratinocytes had intrinsic functional defects in vitiligo. But the detailed mechanism of melanocyte loss and keratinocyte defects in vitiligo are complex and incompletely defined. More and more studies point to oxidative stress and ER dysfunction in melanocytes and keratinocytes of vitiligo pathogenesis.

### ER-Melanocytes

The absence of functional melanocytes is the key process in vitiligo, which leads to pigmented lesions.<sup>52</sup> Previously, studies have found that melanocytes of vitiligo had intrinsic defects. However, there is still no precise explanation for the reason why melanocytes disappear. In 1991, R E Boissy found structural aberration of the RER in melanocytes from vitiligo patients.<sup>53</sup> Subsequently, S Im corroborated these results.<sup>54</sup> In addition, the dilation of the RER was also found in the vitiligo mouse model. Melanocytes still exhibited extensive ER expansion after hybridization, indicating a congenital defect.<sup>18</sup> However, there is still debate whether melanocytes death is related to defects in protein synthesis through the ER. Since the 21st century, studies have revealed once again that melanocytes from depigmented epidermal suction blister tissue and PIG3V, an immortalized human vitiligo melanocyte cell line, both existed dilated ER.<sup>19,55</sup> XBP1 is an essential regulator of UPR and ERS. During ERS, XBP1 is subjected to unconventional splicing and converted to an active form, which is critical for maintaining ER function. Recently, clinical trials revealed that the association of XBP1 polymorphisms and increased XBP1 expression has been observed in Gujarati and Chinese population,<sup>56,57</sup> further confirming its involvement in ER stress and the immune-mediated pathogenesis of vitiligo. In addition to XBP1, it was reported that receptor-interacting serine/threonine-protein kinase 1 (RIPK1), a protein serine/threonine kinase, could protect melanocytes from cell damage caused by ER stress by regulating the PI3K/AKT/mTOR and ER stress signaling pathways.<sup>58</sup> Therefore, more and more researchers have demonstrated the ER morphological and genetic abnormalities of melanocytes in vitiligo. Interestingly, ERS could not only induce melanocyte damage but also was reported to be associated with melanogenesis. Yuri Ahn revealed that particulate matter triggers melanin production through the activation of the IRE1 $\alpha$  signaling among UPR pathways.<sup>59</sup> The activation of IRE1 $\alpha$  pathway at an initial stage is crucial for cell protection against ER stress. These findings suggested that drug targeting IRE1 $\alpha$  might both protect melanocytes from damage and promote melanin synthesis, which may be a potential treatment for vitiligo.

### ER-Keratinocytes

In addition to melanocytes, numerous studies have focused on keratinocytes. This is because impaired keratinocytes might have a significant effect on melanocyte survival.<sup>4</sup> A previous study identified that keratinocytes can be targeted by oxidative stress, facilitating melanocyte loss in patients with vitiligo with complex crosstalk.<sup>60</sup> ER dilation in keratinocytes has also been observed in the lesions of vitiligo patients.<sup>11,61</sup> Meanwhile, it was revealed that stressed keratinocytes in patients with vitiligo could induce CXCL16 expression, which was associated with ERS and UPR activation.<sup>11</sup> Further studies are needed to demonstrate whether there are ER abnormalities in other kinds of cells, such as fibroblasts or immune cells in patients with vitiligo. Their precise link and exact role may have implications for vitiligo study.

## The Link Between ER and Other Organelles in Vitiligo

### ER-Mitochondria

Mitochondria produce ATP to maintain cellular bioenergetics and are fundamental for cellular metabolism and homeostasis. In addition to oxidative phosphorylation, mitochondria are also responsible for calcium regulation, the production



of reactive oxygen species (ROS), immune signaling. The role of mitochondria in ROS production and immunity makes it indispensable in vitiligo pathogenesis. As a membrane-bound most dynamic organelle, mitochondria do not stand in isolation. Similarly, it has been demonstrated that the ER is not isolated either. The forms of contact sites were found between ER and many other cytoplasmic organelles, while the organelle contact sites of ER and mitochondria (ER-mito) were the most well-characterized.<sup>25,26,62</sup> Contact sites are defined as regions where two membranes are closely apposed but do not fuse. The role of the ER-mito junction involves ion and lipid transfer, Ca<sup>2+</sup> signaling, mitochondrial membrane dynamics, and intracellular trafficking,<sup>63</sup> which might be related to the structural heterogeneity of ER-mito organelle contact sites. In other words, the existence of contact sites suggests that organelles can not only maintain their special identities but also aggregate factors located in two different organelles to cooperate with other functions in these special regions. In addition, the functions of ER-mito contacts in reactive oxygen species signaling also have been reported.<sup>64</sup> Under ER stress conditions, stress signals can be delivered to mitochondria via ER-mito contact sites.<sup>65</sup> It has been reported that mitochondria are vital in vitiligo. Mitochondrion enters an overactive state by melanocyte dysfunction leads to mitochondrial overactive state, which finally causes oxidative stress. And then, cytotoxic T-cell responses may lead to melanocyte death and vitiligo phenotype.<sup>66,67</sup> Considering ER and mitochondria interact directly within the cell through membrane contact sites, we propose the hypothesis that ROS can be transmitted between ER and mitochondria in vitiligo, and subsequently lead to the disease phenotype. However, this hypothesis needs to be verified experimentally. Therefore, future studies are needed to clarify whether such a delivery process in vitiligo. Besides, identifying the precise ER-mito contact proteins and blocking the delivery of ROS may be beneficial to vitiligo treatment.

## ER-Melanosome

Melanosome, known as melanocyte-specific organelle, is responsible for melanin synthesis and storage.<sup>68,69</sup> Melanosome development can be divided into four stages.<sup>70,71</sup> In stage I, it seems like melanosomes or premelanosomes develop from the ER.<sup>70,72</sup> In vitiligo, bizarre melanosomes were found near the extensive Golgi bodies and vesicles in melanocytes of vitiligo lesional epidermis through electron microscopy.<sup>19</sup> This evidence of spatial location demonstrated that the ER-melanosome was abnormal in vitiligo to some extent. Therefore, the link between these two components of vitiligo has attracted more and more attention.

On one hand, the link between ER and melanosome in vitiligo might be associated with calcium homeostasis. Premelanosome protein (PMEL) is synthesized in ER and ultimately transported to stage I and II melanosomes for fibril formation.<sup>73</sup> Fibrils may act as a sequester of highly reactive oxidative intermediates generated during melanin synthesis.<sup>74</sup> The PMEL processing is mediated by protease, which is highly dependent on calcium.<sup>75,76</sup> ER can transfer calcium to other organelles.<sup>77</sup> Therefore, as a result of cellular organelle interactions, calcium levels inside melanosomes can be affected, leading to improper maturation of PMEL fibrils, accumulation of oxidative stress, and defects in melanosomes. Then, vitiligo conditions may occur. Similarly, Hitaishi Kaushik have provided the hypothesis that mitochondria-melanosome interaction is also required for calcium homeostasis inside melanocytes in vitiligo.<sup>67</sup> On the other hand, abnormal accumulation of melanin-related proteins in ER might also be the key point of ER-melanosome in vitiligo. For instance, tyrosinase is responsible for the synthesis of melanin. Dysfunctional transport and abnormal accumulation of tyrosinase might cause vitiligo. It was demonstrated that excessive accumulation of tyrosinase proteins in ER was related to FBXO11, a gene involved in ER conformation.<sup>78</sup> Similarly, massive mutations in tyrosinase lead to its misfolding and ER retention, in which the melanin synthesis process is highly influenced.<sup>79</sup> The kinds of melanin-related proteins need more studies to identify in the future.

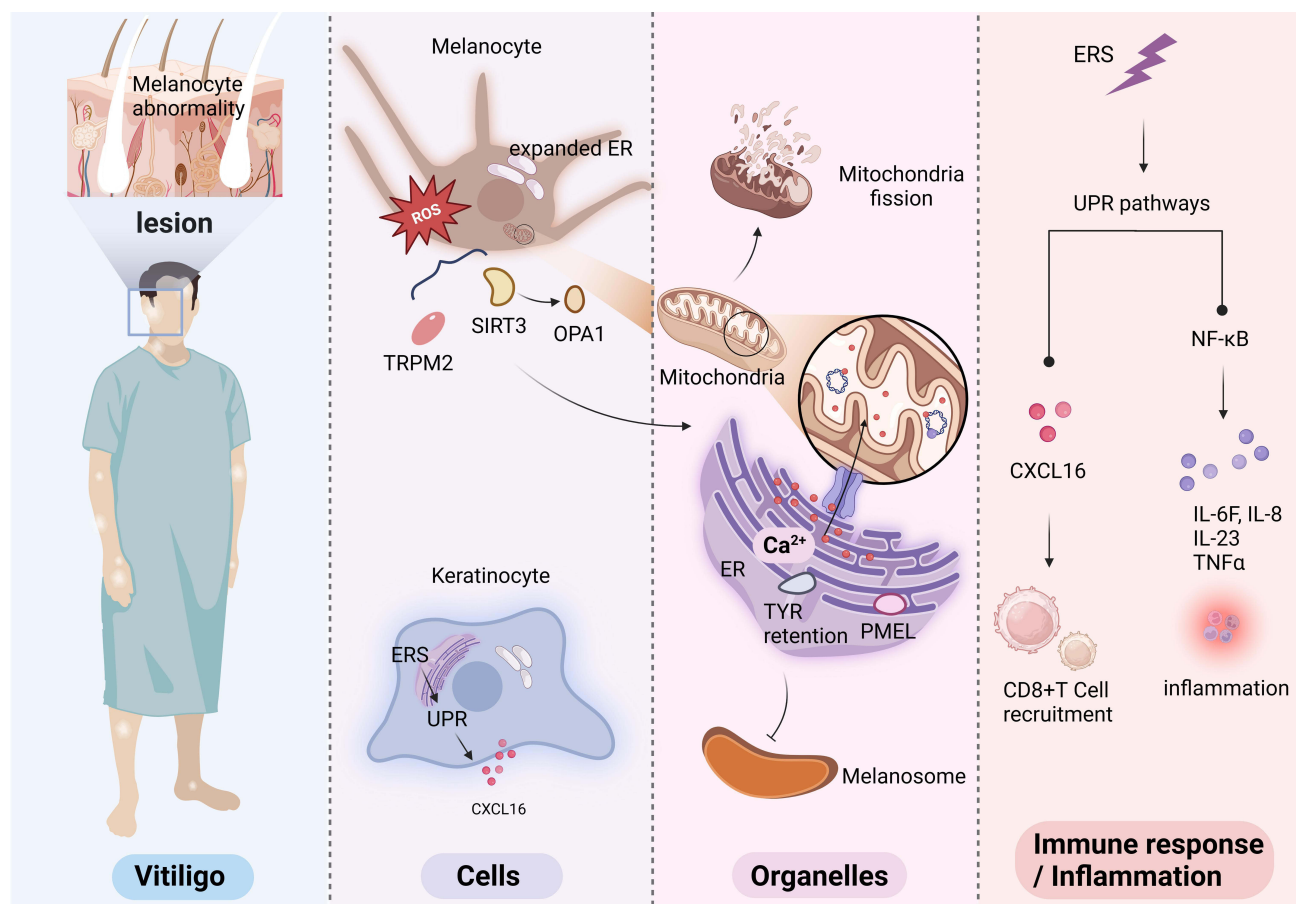
## The Link Between ER and Inflammation/Immune Response in Vitiligo

As mentioned above, the involvement of ER in vitiligo may be related to its structural conformation. For instance, abnormal accumulation and aberrant transportation of tyrosinase and other related proteins in ER might cause melanin synthesis disorder. In addition to this, ERS may also contribute to vitiligo through release of the neo-autoantigens and UPR-related autoantigens to provoke autoimmunity subsequently, which link the oxidative stress and immune response in vitiligo pathogenesis. More and more studies provided evidence for this. Firstly, Li discovered that oxidative stress led to the induction of CXCL16 through two UPR pathways, PERK-eIF2 $\alpha$  and IRE1 $\alpha$ -XBP1.<sup>11</sup> CD8<sup>+</sup> T cells are essential autoimmune effectors in vitiligo melanocyte destruction. And they emphasized the importance of increased CXCL16 in

CD8<sup>+</sup> T-cell skin migration in vitiligo. In addition to CXCL16, which was involved in ERS and immunity response, there were other pro-inflammatory factors also participated.

ERS-induced UPR signaling can mediate proinflammatory transcriptional programs related to NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells). NF- $\kappa$ B encodes crucial inflammatory molecules including IL-6, IL-8, IL-1 $\beta$ , TNF- $\alpha$ , IL-23, etc.<sup>80,81</sup> Of these, IL6 is responsible for stimulating immune reactions as a key molecule.<sup>82</sup> Increased IL-6 and IL-8 have been carried out in vitiligo.<sup>83,84</sup> It had been reported by Toosi that phenols-induced vitiligo activates UPR in melanocytes and upregulates the expression of IL-6 and IL-8. Moreover, inhibition or activation of XBP1, an important component of UPR, could decrease or increase the expression of IL6 and IL8 correspondingly.<sup>85</sup> Thus, this direct evidence suggests that cytokines are involved in the pathogenesis of vitiligo through ERS. Furthermore, IL-23 and TNF- $\alpha$  are both indicated might be related to ERS in vitiligo.<sup>86,87</sup> This indirect evidence also suggests again that vitiligo pathogenesis could be mediated by ERS and subsequently cytokine signaling.

Taken together, vitiligo is characterized by the absence of melanocytes in white macules. At the cellular level, abnormal ER may be associated with various cells such as melanocytes and keratinocytes in vitiligo. Further, ER is not only linked to cells but also the organelles. It might also involved in the pathogenesis of vitiligo through inflammation and immune response (Figure 3). The relationship of other pro-inflammatory mediators to ERS in vitiligo needs further investigation.



**Figure 3** The cellular and intracellular interactions of ER in pathogenesis of vitiligo. The characteristic of vitiligo is melanocytes absence. Expanded ER can be seen in melanocytes and keratinocytes. The generation of ROS activates SIRT3-OPA1 and TRPM2, which cause Ca<sup>2+</sup> released from ER to mitochondria. Both conditions cause mitochondrial fission and ultimately lead to apoptosis of melanocytes. The link between ER and melanosome might be associated with PMEL and melanin-related proteins in ER, such as tyrosinase ER retention. PMEL is synthesized in ER and ultimately transported melanosomes for fibril formation. But affected by Ca<sup>2+</sup> homeostasis, improper maturation of PMEL fibrils and defected melanosome might also be involved in vitiligo. In addition, prolonged ERS could activate targeted genes and inflammatory reaction and increase the release of cytokines, which generates further ER stress and oxidative stress. CXCL16 could recruit CD8<sup>+</sup> T cell, resulting in an anti-melanocyte autoimmune response.

**Abbreviations:** PMEL, premelanosome protein; TYR, tyrosinase.

# Clinical Treatments

According to the newly published International Vitiligo Working Group Position Statement,<sup>88</sup> topical steroids/topical immunomodulators and phototherapy are still important treatments in vitiligo. JAK Inhibitors Small-molecule therapies have emerged as efficacious treatment options in vitiligo. Ruxolitinib cream, a topical JAK inhibitor, have been approved by the FDA. Meanwhile, the oral JAK inhibitors in vitiligo are currently in Phase II trials as well. In addition, recent data shed light on some new targets, such as targeting IL-15 or its receptor CD122 as well as innate immune targets, HP70i. These new options are exciting development. Given the important role of ER in the pathogenesis of vitiligo, explorations targeting ERS will continue to pave the way for the future as well. Drugs targeted to ERS have been explored widely and it may be a potential avenue for novel therapeutic in many kinds of diseases, such as cancer, neurodegenerative diseases, brain damage, and gestational diabetes. These kinds of drugs include 4-phenylbutyrate (4-PBA), tauro-ursodeoxycholic acid (TUDCA), and many natural ingredients. It was reported that 4-PBA could alleviate hyperoxia-induced acute lung injury<sup>89</sup> and rescue hyperoxaluria-induced nephrolithiasis by modulating urinary glycoproteins.<sup>90</sup> In addition, TUDCA and 4-PBA have crucial effects on selenium distribution in diabetic mice<sup>91</sup> and they also block ER stress in post-ischemic kidneys.<sup>92</sup> Moreover, a study of gut microbial dysbiosis and plasma metabolic in vitiligo detected an abnormal level of TCDCA, an upstream metabolite of TUDCA.<sup>93</sup> It indicates that TCDCA might be suppressive in the progression of ERS-induced vitiligo. Therefore, this evidence indicated that drugs targeting ERS have great potential for clinical applications. Whereas, it has not been studied in vitiligo clinical research. Considering that ER is currently important in the development of vitiligo, studies have attempted to treat vitiligo through this novel and potential target. Quercetin is a natural flavonoid with antitumor activity and anti-inflammatory properties, and it can regulate a variety of signaling pathways, including NF-κB, MEK-ERK, and PI3K-Akt-mTOR.<sup>94</sup> The study found that quercetin attenuated H2O2-induced ER dilation and functional tyrosinase exportation in melanocytes, elucidating the potential effects of quercetin on melanocyte ultrastructure.<sup>95</sup> Bilobalide, the pharmacologically active component in *G. biloba*, also inhibited H2O2-induced ERS and protected melanocytes.<sup>96</sup> In other disease models, ginsenoside Rb1 inhibited ROS generation and overactivated ERS, and decreased cytoplasmic Ca2+ release to ameliorate renal fibrosis.<sup>97</sup> In addition, narrow-band ultraviolet B phototherapy is effective in treating vitiligo.<sup>98</sup> The current study found that combined NB-UVB and adipose-derived stem cell transplantation was beneficial to MBZ-induced vitiligo mice. The possible mechanism is related to the inhibition of ERS and regulation of ER Ca2+ homeostasis through Nrf2/HO-1 signaling.<sup>99</sup> These studies and action mechanisms are summarized in Table 1. It indicated that some classical therapy might combine with other emerging approaches, which could achieve therapeutic effects far beyond themselves by targeting ER. Overall, basic experimental and clinical research focused on targeted ER might have a promising future.

**Table 1** Potential Therapeutic Drugs Targeted to ER in Diseases

Therapies	Potential Mechanism of Action	Consequences	Diseases
4-PBA <sup>86</sup>	Claudin-4 expression ↑, NF-κB activation, ER stress↓, oxidative stress↓, apoptosis↓	Prolonged the survival of mice, decreased lung edema	Acute lung injury
4-PBA <sup>87</sup>	Tamm Horsfall Protein, Osteopontin, and Calnexin↓	Rescued the disrupted ER-Mitochondrial functioning, and calcium homeostasis	Nephrolithiasis
TUDCA and 4-PBA <sup>89</sup>	Glucose, glycated serum protein↓	Normalize the selenium distribution	Type I Diabetes
TUDCA and 4-PBA <sup>90</sup>	UPR molecules↓, apoptosis, inflammation and autophagy↓	Blocked ERS	Renal ischemia-reperfusion injury
Quercetin <sup>93</sup>	ER dilation↓, tyrosinase retended in ER↓	Protect melanocytes	Vitiligo
NB-UVB and adipose-derived stem cell transplantation <sup>96</sup>	Regulation of ER Ca2+ homeostasis through Nrf2/HO-1 signaling	Oxidative stress and Ca2+ unbalancing were improved in mice model	Vitiligo



## Further Prospects and Conclusions

Recently, the link between ER and vitiligo has attracted a great deal of attention. Studies indicated that ER may serve as a bridge to link oxidative stress and inflammatory/immunoregulatory response. However, the specific mechanisms are not fully explored. In this review, we summarized ER interaction with melanocytes, keratinocytes, and intracellular organelles as well as some important cytokines and genes in vitiligo pathogenesis in order to increase the understanding of ER and vitiligo. But there are still some problems need to be solved: 1) the other kinds of cells involved in vitiligo through ER; 2) specific molecular mechanisms and processes of ER in vitiligo; 3) whether the immune microenvironment has effects on ER. More importantly, new insights into the pathogenesis of vitiligo with ER might help to identify molecular targets and may develop new treatments in vitiligo in the future.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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