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Could ER Stress Be A Major Link Between Oxidative Stress And Autoimmunity In Vitiligo?

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Abstract

Vitiligo is an acquired pigmentary disorder characterized by areas of depigmented skin resulting from loss of epidermal melanocytes. The cause of the destruction of epidermal melanocytes is complex and not yet fully understood. However, there are several hypotheses related to biochemical, neural and genetic aspects as well as oxidative stress and autoimmune mechanisms proposed to understand this disorder. Oxidative stress has a role in vitiligo onset, while autoimmunity contributes to disease progression. In this review, we discuss the mechanisms that link triggering factors with the disease progression. Oxidative stress causes disruption in redox potentials that extend to the Endoplasmic Reticulum (ER), causing accumulation of misfolded proteins, which activates the Unfolded Protein Response (UPR). Melanocytes at the periphery of vitiligo lesions show dilation of the ER. Following exposure to various triggers of vitiligo melanocytes produce cytokines that activate immune response. These studies expand our understanding of the underlying mechanisms of melanocyte loss in vitiligo highlighting the possible mechanisms linking ER stress to oxidative stress and autoimmunity.

Keywords: Vitiligo; Oxidative stress; ER stress; Unfolded protein response; Auto immunity; Inflammation

Abbreviations: ROS: Reactive Oxygen Species; LPO: Lipid Peroxidation; ER: Endoplasmic Reticulum; UPR: Unfolded Protein Response; IRE1: Inositol-Requiring Enzyme-1; PERK: Protein Kinase RNA (PKR)-like ER Kinase; ATF6: Activating Transcription Factor-6; ERAD: ER-Associated Protein Degradation; BiP: Binding immunoglobulin Protein; eIF2α: eukaryotic Initiation Factor 2 α; GPx: Glutathione Peroxidase; CHOP: CCAAT-Enhancer Binding Protein Homologous Protein; JNK: Janus Kinase; Hcy: Homocysteine; NSV: Non-Segmental Vitiligo

Introduction

Vitiligo is an acquired, hypomelanotic skin disease characterized by circumscribed depigmented macules on the skin due to melanocyte loss. The worldwide prevalence of vitiligo is ~0.5-1% [1]. Vitiligo starts at the age of 20 years, in almost 50% of the patients and both males and females are affected [2-4]. Affected persons suffer from social and family stigma and, girls in particular, are subjected to ostracization from the marital point of view [5-9]. Vitiligo has been found to be associated with a number of other autoimmune diseases [10,11]. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis [2,12-15]. In vitiligo patients, skin melanocytes are partially or completely lost, and several theories have been put forward to explain the etiology of the disease such as oxidative stress, autoimmune, neural and genetic hypotheses [2,12,16,17]. Melanocyte death may occur due to intrinsic and/or extrinsic factors (Figure 1). Histological investigations have demonstrated presence of inflammatory infiltrate of mononuclear cells in the upper dermis and at the dermal-epidermal junction of peri-lesional skin of Non-Segmental Vitiligo (NSV) patients [18]. The initiation mechanism of this microinflammatory reaction is still not clear, nevertheless local triggers are reported to signal the innate immune system of skin that trigger adaptive immune responses targeting melanocytes [19,20]. There is wide range of evidence that show vitiligo to be a systemic rather than a local disorder. Impairment of humoral and cell-mediated immunity has been recognized in vitiligo patients [17,21]. Moreover, increased local and systemic cytokine expression has also been observed in vitiligo patients [22-31]. Many studies have addressed the key role of oxidative stress in melanocyte death and anti-melanocyte immune responses; however, the relationship between them remains unclear. Recently, we have reported a positive correlation between increased Lipid Peroxidation (LPO) levels and presence of circulating anti-melanocyte antibodies in vitiligo patients [32]. Reactive Oxygen Species (ROS) are produced as byproducts of melanogenesis controlled by various antioxidant enzymes [33-35]. Oxidative stress is considered to be the initial triggering event in the pathogenesis of melanocyte destruction [36]. Vitiligo is accompanied by oxidative stress characterized by overproduction and accumulation of H_2O_2 and melanocyte destruction [37-39]. For the interconnection between, oxidative stress and autoimmunity it has been suggested that oxidative stress may have a role in vitiligo onset, while autoimmunity contributes towards the disease progression [32,40]. Furthermore, Toosi et al. [41] demonstrated accumulation of misfolded proteins and activation of Unfolded Protein Response (UPR) in the endoplasmic reticulum due to redox disruptions caused by oxidative stress. Protein misfolding in the ER has been reported to contribute to the pathogenesis of many human diseases (Table 1). Though unfolded proteins have the potential to bring about ER homeostasis restoration and cell survival by the activation of Inositol-Requiring Enzyme-1 (IRE1), Protein Kinase RNA (PKR)-like ER kinase (PERK) and Activating Transcription Factor-6 (ATF6) pathways, persistent stress conditions can on the other hand trigger apoptosis [42-45] (Figure 2). Furthermore, inhibited UPR can contribute to the activation of autoimmune response by way of generation of self-altered antigens during degradation of misfolded proteins, besides release of neo-antigens by apoptotic cells, and altered immune-tolerance mechanisms in cells with an anomalous UPR [46].

These findings tend to suggest the possibility of a crosstalk between

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Disease	Oxidative Stress	ER Stress	Autoimmunity
Vitiligo	Yes [32,40,60]	Yes [72,108]	Yes [32,40]
Type I Diabetes	Yes [256]	Yes [257]	Yes [258]
Type II Diabetes	Yes [259]	Yes [260,261]	No
Alzheimer's disease	Yes [262]	Yes [263,264]	No
Parkinson's Disease	Yes [265,266]	Yes [267,268]	No
Cancer	Yes [269]	Yes [270,271]	No
Arthrosclerosis	Yes [272]	Yes [273,274]	No
Myocardial Infarction	Yes [275,276]	Yes [277]	No
Heart Failure	Yes [278]	Yes [279]	No
Inflammatory Bowel Disease	Yes [280]	Yes [281]	Yes [282]

Table 1: Involvement of oxidative stress, ER stress and autoimmunity in human diseases.

oxidative stress, ER stress and autoimmunity leading to melanocyte destruction in vitiligo patients. We review here possible mechanisms that can link triggering factors (such as ER stress) with disease progression (oxidative stress and autoimmunity) (Figure 1).

Oxidative Stress in Vitiligo

Oxidative stress is a consequence of imbalance between pro and antioxidant activities in cells. Reactive intermediates formed by oxidative stress damage cellular macromolecules like proteins, carbohydrates, DNA and lipids [34,35]. The accumulation of H_2O_2 in vitiligo patients disrupts the recycling of (6*R*)-L-erythro-5,6,7,8-tetrahydrobiopterin ($6BH_4$) due to deactivation of 4a-OH-BH_4 dehydratase. The characteristic fluorescence of the affected skin under Wood's lamp (UVA 351 nm) is a property of 6- and 7-biopterin, H_2O_2 induced oxidation products. Rokos et al. [47] have reported accumulation of pterin-6-carboxylic acid (P-6-COOH) in the epidermis of vitiligo patients. They have also shown photo-oxidation of sepiapterin and 6-biopterin to P-6- COOH by UVA/UVB irradiation. Moreover, photolysis of sepiapterin and 6-biopterin produces H_2O_2 under aerobic conditions serving as an additional source for generation of H_2O_2 in vitiligo skin [47]. The aromatic amino acids L-phenylalanine, L-tyrosine and L-tryptophan are substrates for melanogenesis wherein $6BH_4$ is an essential electron donor in their hydroxylation. Apparently, $6BH_4$ is an essential component of the pigment generating system [48]. Elevated level of serum homocysteine reported in vitiligo patients [49] also seems interesting as oxidation of homocysteine can also generate ROS. Further, Reactive Nitrogen Species (RNS) also can be a contributing factor as inducible nitric oxide synthase activity in vitiligo epidermis is shown to be elevated, generating both H_2O_2 and peroxynitrite [50] (Figure 1). The activity of H_2O_2 metabolizing enzymes has been found to be altered both systemically and locally in vitiligo patients [33,51]. Furthermore, Methylene Tetrahydrofolate Reductase (MTHFR) which is involved in Hcy metabolism, affects ROS generation and the apoptosis process via downregulation of antioxidant enzymes such as glutathione peroxidase 1 (GPx1) [52,53]. Recently, Chen et al. [54] have suggested that an increased risk of vitiligo was associated with higher levels of total Homocysteine (tHcy) indicating the possible involvement of MTHFR and Hcy in pathogenesis of vitiligo [55]. SOD is a group of metallo-enzymes that scavenge and dismutate superoxide (O_2^-) anion in its detoxification process resulting in the formation of O_2^- and H_2O_2 [56]. Increased SOD levels have been reported in vitiliginous and non-vitiliginous skin from vitiligo patients [57]. Our recent study has also shown significantly higher activity of all three isoforms of SOD i.e. SOD1, SOD2 and SOD3 in vitiligo patients [58]. Other reports have also shown increased SOD activity in whole blood and serum [59,60] as well as peripheral mononuclear cells [61] from vitiligo patients. In addition, we have reported increased transcript levels of *SOD2* and *SOD3* in vitiligo patients suggestive of their increased activity in patients [58]. Another antioxidant enzyme GPx converts H_2O_2 and other peroxides into H_2O protecting important cellular proteins and membranes from the potential damaging effect of ROS and LPO [62]. Earlier studies had revealed decreased GPx activity in plasma and skin biopsy samples of vitiligo patients [51,63]. Hazneci et al. [64] have shown lower levels of GPx in the epidermis of lesional and non-lesional skin from vitiligo patients. Moreover, Maresca et al. [33] have reported higher levels of GPx during vitiligo progression indicating an imbalance of antioxidants in the epidermis of vitiligo patients. Our previous studies have shown decreased erythrocyte GPx activity in patients with vitiligo [60,65]. Recently, we have found positive genotype-phenotype correlations for the two exonic polymorphisms of *GPX1* with its decreased activity. Furthermore, we have also found decreased catalase and G6PD activities in vitiligo patients [12,60,65] resulting into increased H_2O_2 accumulation. Moreover, Hasse et al. [66] have reported that accumulation of millimolar concentrations of H_2O_2 can affect antioxidant enzymes as proved by low blood catalase and GPx activity in vitiligo patients. Increased SOD and decreased catalase and GPx activities could be responsible for the accumulation of H_2O_2 which undergoes Fenton and/or Haber -Weiss reaction to produce produces hydroxyl radicals leading to lipid, protein and DNA damage [56]. High levels of epidermal H_2O_2 as well as the methionine oxidation product- methionine sulfoxide, have been demonstrated *in vivo* in vitiligo patients [67,68]. LPO is one of the hallmarks of oxidative stress. MDA (malondialdehyde) is an end product of lipid peroxidation, and elevated serum levels of MDA have been documented in patients with vitiligo [56,60,69,70]. Recently, we have also demonstrated increased MDA levels in vitiligo patients [32]. Moreover, the increased MDA levels were characteristic of active cases and early stage of onset of vitiligo suggesting the crucial role of oxidative stress in progression as well as initiation of the disease [32]. Ultrastructural changes suggestive of lipid peroxidation have been demonstrated in melanocytes, keratinocytes and Langerhans cells from the skin of patients with vitiligo, both in affected and peri-lesional areas [71-74]. Various studies indicate the importance of FOXO3a as a transcription activator of *SOD2*, catalase (*CAT*), and peroxiredoxin 3 genes [75-77]. FOXO3a is a member of the forkhead class O (FOXO) transcription factors, and plays an important role in cell cycle regulation; apoptosis, oxidative stress, and DNA repair [78,79]. Olmos et al. [80] reported that FOXO3a can protect cells from oxidative stress by regulating *SOD2* and *CAT*. In addition, FOXO3a-deficient hematopoietic stem cells have shown reduced expression of ROS detoxification genes resulting in elevated levels of ROS [81]. Recently, Ozel Turkcu et al. [82] have shown decreased FOXO3a levels in vitiligo patients and its association with oxidative stress and active vitiligo suggesting its important role in oxidative stress mediated pathogenesis of vitiligo. Melanocytes are neural crest derived cells with an embryological link to the nervous system [83].

Neural hypothesis suggests that various neurochemical mediators including acetylcholine secreted by the nerve endings to be toxic to melanocytes leading to their destruction. Decreased acetylcholine esterase (AChE) activity has been shown in vitiliginous skin during

depigmentation [84], suggesting that acetylcholine may aggravate the progression of vitiligo. In addition, decreased sweating in the depigmented epidermis of patients also suggests possible cholinergic involvement in vitiligo [85]. Moreover, Schallreuter et al. [86] have shown H_2O_2 mediated oxidation of AChE further emphasizing the role of oxidative stress in the precipitation of vitiligo. The inactivation of AChE has been proposed to be due to oxidation of Trp432, Trp435 and Met436 residues by H_2O_2 [86]. Acetylcholine has an inhibitory effect on melanocyte DOPA oxidase activity affecting melanin production [84]. Our previous studies have in fact shown decrease in blood AChE activity [87] and significant increase in lipid peroxidation levels in vitiligo patients [32,40,60,65,87]. These reports provide evidence for AChE inhibition in vitiligo patients to be due to high oxidative stress. Acetylcholine thus accumulated may lead to the destruction of melanocytes resulting in the precipitation of vitiligo.

The above literature review emphasizes the role of oxidative stress in the pathogenesis of vitiligo and indicates oxidative stress to be a more generalized course of action rather than a localized phenomenon. This could be one of the reasons for developing new lesions in vitiligo patients in the course of the disease [57]. Oxidative stress can also lead to the activation of stress signaling pathways and their transcription factors [88,89]. Even though the exact molecular mechanisms by which ROS activate these pathways are not understood, their activation can lead to different consequences, including growth arrest, senescence, upregulation of death proteins, and cell death by apoptosis or necrosis. Cells undergo apoptosis by cell surface, ER or mitochondrial pathways. In our earlier review, we had addressed the interplay between oxidative stress and immune system in vitiligo [40]. In the current review, we focus on structural and functional aberrations of ER linking oxidative stress with autoimmunity in vitiligo pathogenesis.

ER Stress in Vitiligo

In eukaryotic cells, the ER is crucial for synthesis, folding and maturation of proteins, lipid metabolism, and homeostasis of intracellular Ca^{2+} and redox potential. Previous studies of Schallreuter et al. [90,91] have shown perturbed calcium homeostasis in vitiliginous melanocyte and keratinocyte cell cultures, suggesting altered ER functions in vitiligo. Protein folding and modifications in the ER are highly sensitive to disturbances in ER homeostasis involving glycosylation, ER Ca^{2+} store, mRNA translation, oxidative stress, energy deprivation, metabolic challenge, and inflammatory stimuli. The accumulation of unfolded and misfolded proteins in the ER lumen, termed ER stress, activates intracellular signaling pathways to resolve the protein folding defect. This UPR tends to increase the capacity of ER protein folding and modification by reducing global protein synthesis, and activating ER-Associated Protein Degradation (ERAD). If ER stress is too severe or chronic, or the UPR is compromised and not able to restore the protein-folding homeostasis, numerous apoptotic signaling pathways get activated [92-94]. Preclinical and clinical studies in the past decade indicate ER stress and UPR to have a significant impact in the pathogenesis of multiple human disorders including vitiligo (Table 1). The ER stress response involves 3 distinct mechanisms: (i) translational attenuation of global protein synthesis (ii) transcriptional activation of chaperone and ERAD genes and (iii) ERAD mediated translocation of misfolded or aggregated ER proteins to the cytoplasm for proteasomal degradation [95] (Figure 2). The activation of UPR is mediated by three distinct ER stress sensors: PERK, ATF6 and IRE1 [45]. In non-stressed cells, these sensors are retained in the ER lumen by interaction with BiP/ glucose-related protein 78 (GRP78). During ER stress, these three sensors become free of BiP, leading to the induction of the three stress response mechanism [95]. The alteration in ER Ca^{2+} homeostasis can result in the activation of cytosolic calpains. They play a major role in ER mediated apoptosis by processing and activating caspase-12 and caspase-4 [96,97]. Severe and/or prolonged ER stress generally result in apoptotic cell death. The pro-apoptotic transcription factor CCAAT-enhancer binding protein homologous protein (CHOP) is strongly induced in response to ER stress [98] (Figure 2). Further, ROS cause protein damage leading to accumulation of misfolded proteins in the ER lumen. Many studies have shown H_2O_2 induced ER stress response factors cited above in different cells including human oral keratinocytes [99]. Apoptosis mediated by ER stress involves increased expression of CHOP, cleavage of calpastatin, and activation of calpain, caspase-4 and -12. Caspase-4 cleavage and up-regulation of CHOP were shown to be induced by peroxide radical in human oral keratinocytes [99]. Exact mechanism(s) regulating ER stress mediated apoptosis is (are) not fully understood. Several different pathways have been implicated including the

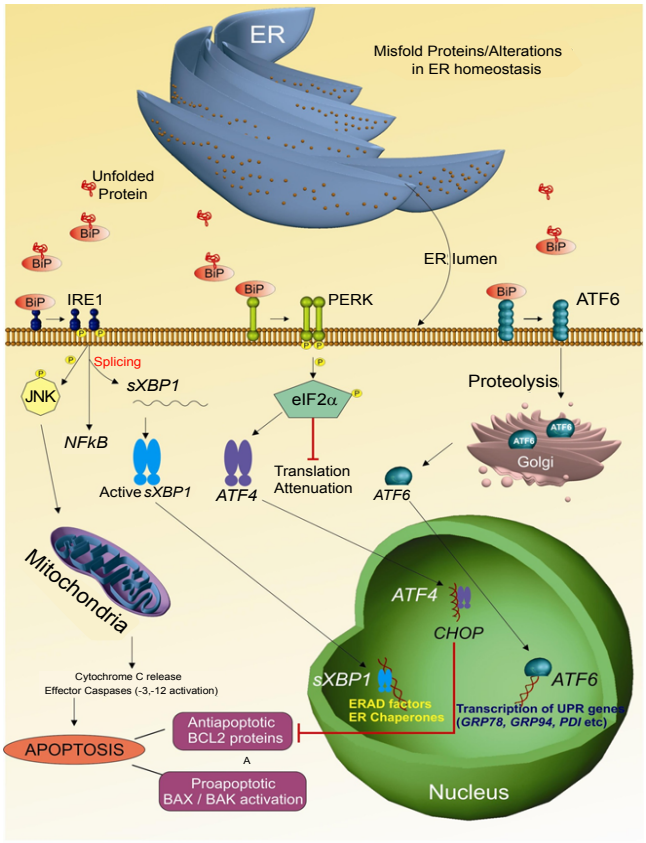

Figure 1: Overview of ER Stress Signaling Pathways: Activation of protective responses by UPR involves signal transduction through the IRE1, PERK and ATF pathways. PERK, IRE1, and ATF6 act as ER stress sensors by binding to the ER chaperone BiP, and by which they remain inactive under normal condition. Upon the accumulation of unfolded proteins, BiP preferentially binds to the unfolded proteins, which results in the release of PERK, IRE1, and ATF6. IRE1, once released from BiP, induces XBP1 by promoting the splicing of its mRNA. sXBP1 regulates chaperone induction and ERAD in response to ER stress. IRE1 also activates JNK which leads to cytochrome C release from mitochondria and activation of effector caspases leading to apoptosis. The released PERK phosphorylates eIF2α to suppress the overall transcription of mRNAs while selectively enhances the transcription of genes implicated in UPR such as the ATF4 mRNA. ATF4 thus formed initiates the transcription of UPR target genes like CHOP which represses antiapoptotic BCL2 proteins and activated proapoptotic Bax/Bak leading to apoptosis. The release of ATF6 from BiP results in the translocation of ATF6 to the Golgi apparatus, where ATF6 is cleaved and then translocates into the nucleus, and initiates the transcription of target genes.

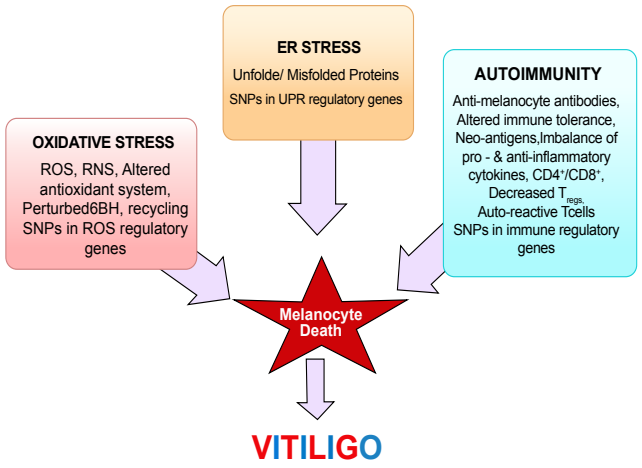

Figure 2: Multiple factors involved in melanocyte destruction leading to vitiligo: The factors such as ROS, RNS, UPR, auto-antibodies, auto-reactive T cells along with genetic susceptibility are involved in melanocyte destruction. A cumulative effect of oxidative stress, ER stress and autoimmune components is sought to be responsible for loss of melanocytes in vitiligo.

caspase-12/caspase-4, CHOP, or IRE1- JNK (Janus kinase) pathways [89]. Although caspases-12 and -4 have been implicated in ER stress-induced apoptosis, the events responsible for their activation remain ill defined. Pallepati and Averill-Bates [100] have shown H_2O_2 induced apoptosis in the ER of HeLa cells to be dependent on Ca^{2+}, calpain and caspase-7. The role of caspase-12 in ERmediated apoptosis though well understood in mice [96], its role in human cells is nevertheless unclear as human caspase-12 gene carries many inactivating mutations [101]. However, caspase-12 activation has been detected in several human cell lines, including HeLa cells [102,103].

Dilation of melanocyte ER has been reported by different groups in perilesional skin biopsies as well as melanocytes cultured from vitiligo patients [72,104,105]. Moreover, Moellmann et al. [106] and Galardi et al. [107] have also reported ER damage in surrounding keratinocytes as well. The defect in the perilesional melanocyte ER has been substantiated in both *in vivo* and *in vitro* conditions [72]. Manga et al. [108] have in fact shown caspase-12 mediated apoptosis in wild type melanocytes by thapsigargin induced ER stress. Tyrosinase which is a rate-limiting enzyme in melanogenesis, undergoes post-translational modifications, including N-linked glycosylation [109], and disulfide bond dependent folding [110] in the ER to attain a functional tertiary structure [111]. Such post-translational modifications require classical ER chaperones [110] in addition to melanocyte-specific factors [112]. Tyrosinase misfolding and retention can be a consequenece of either mutations in chaperone genes [tyrosinase-related protein 1 (TRP1) [113], oculocutaneous albinism type 2 gene (OCA2) [114] and OCA4 [115] or tyrosinase gene itself [116]. Toosi et al. [41] in their investigations involving early events associated with induction of vitiligo by 4-tertiary butyl phenol (4-TBP) and Monobenzyl Ether of Hydroquinone (MBEH) have shown ER stress in human melanocytes. They have also shown increased expression of *XBP1*, after exposure of melanocytes to phenols. Interestingly, they observed increased production of IL6 and IL8 upon XBP1 activation in their studies on induced vitiligo suggesting cytokine production by melanocytes linking to an activation of immune response. Ren et al. [117] have shown both increased expression of *XBP1* in the lesional skin of vitiligo patients and association of *XBP1* polymorphisms with increased risk of developing vitiligo. Oxidative stress induced ER dysfunction may involve non-functional thioredoxin domain containing 5 (TXNDC5) chaperone protein that has a protein disulphide isomerase-like domain to bring about protein folding. Three exonic SNPs of *TXNDC5* and their susceptible haplotypes were found to be significantly associated with vitiligo [118]. Earlier report indicates localization of both pro- and anti-apoptotic members of the BCL2 family in ER and together they regulate homeostasis and cell death in response to signals that impact ER function [119]. These proteins function at the potential point of integration between IRE1 and CHOP mediated apoptosis. Abdel-Aal et al. [120] have shown decreased *BCL2* expression in lesional, peri-lesional and nonlesional vitiliginous skin as well as increased expression of *p53* in the lesional skin from vitiligo patients. These findings emphasize increased susceptibility of melanocytes to apoptosis in the vitiliginous skin.

Autoimmunity in Vitiligo

Case reports on inflammatory vitiligo furnished the first hint for the involvement of T cells in the pathogenesis of vitiligo [121-123]. Immune-mediated responses are consistently observed in progressive vitiligo at the periphery of depigmenting patches. Histopathological investigations of the peri-lesional skin suggest lymphocyte involvement in the depigmentation process. Immunohistochemical studies have also confirmed the presence of infiltrating T cells and their frequent opposition to peri-lesional melanocytes in skin biopsies from vitiligo patients [124,125]. Notably, similar *in situ* T cell infiltrates, primarily $CD8^+$ T cells, have also been detected in generalized vitiligo [126-131]. T cells are more prevalent in vitiligo peri-lesional skin than in surrounding non-lesional skin. The lymphocyte infilterate consists essentially of $CD8^+$ T cells with occasional $CD4^+$ T cells [124]. The prevalence of cytotoxic T cells and their co–localization with surviving melanocytes suggest T cell mediated cytotoxicity towards the melanocytes [132]. Various other studies including ours show decrease in systemic $CD4^+$ T-cells and an increase in $CD8^+$ T-cells with consequent decrease in $CD4^+/CD8^+$ ratio in vitiligo patients, suggesting role of $CD8^+$ cells in melanocyte death [133-136]. Recently, studies have shown a defective functionality and decreased frequency of regulatory T cells (Tregs) in vitiligo patients suggestive of the unchecked activation of $CD8^+$ cells [136,137]. Furthermore, Bertolotti et al. [131] have also reported the presence of IFNα secreting plasmacytoid dendritic cells (pDC) in the infilterate of progressive vitiligo. IFN*α* induces the expression of *MxA*, which encodes a guanosine triphosphate (GTP)-metabolizing protein. Association of MxA with the expression of chemokine (C-X-C motif) ligand 9 [*CXCL9*] correlates well with the recruitment of chemokine (C-X-C motif) receptor 3^+ [$CXCR3^+$] immune cells. Further, they also showed increased expression of *MxA* in peri-lesional skin in close opposition to surviving melanocytes within the T-cell infiltrate. In contrast, MxA was not evident in lesional skin, suggesting that IFN*α* production is an early event in the progression of the disease. Autoimmune aspect of vitiligo pathogenesis is strongly supported by the presence of auto-reactive T-cells [17,124,138].

They target melanocyte-specific antigens, such as melan-A/MART1, Gp100/Pmel 17 (a melanosomal matrix glycoprotein), tyrosinase [139-141], TRP1 and TRP2 [132,142] that are localized primarily on melanosomes [143-145]. In fact auto-antibodies against melanocyte antigens have been detected in the sera of vitiligo patients [10,32,146]. The transcription factors SOX9 and SOX10 have also been identified as melanocyte auto antigens [147]. Even auto antibodies against HLA Class I molecules have been detected in vitiligo [138]. A positive correlation has been seen between the level of melanocyte antibodies and disease progression in vitiligo [148]. This is further supported by the concentration of these antibodies in proportion to extent of skin lesion [149]. Overall, all these point to a new innate immune pathway

leading to the progression of vitiligo. Genes within class II region of the major histocompatibility complex (MHC) are associated with several autoimmune diseases [150]. This highly polymorphic region includes several genes involved in the processing and presentation of antigens to the immune system including low molecular weight polypeptide 2 and 7 (LMP2 and LMP7) and transporter associated with antigen processing 1and 2 (TAP1 and TAP2). Though *LMP/TAP* gene cluster is located on MHC class II region of chromosome 6, it is involved in antigen presenting function of MHC class I molecule. Different researchers have reported association of *LMP7* and *TAP1* with vitiligo susceptibility [151]. LMP2 and LMP7 are also involved in the degradation of ubiquitin tagged cytoplasmic proteins to peptides while, TAP1 and TAP2 are involved in transportation of peptides into the endoplasmic reticulum for exposure to nascent MHC class I molecules [150]. MHC-I molecules are crucial in the regulation of cytotoxic effector functions of Natural Killer (NK) cells and T cells. MHC-I molecules present antigens to cytotoxic T cells and are part of the recognition signals that regulate activation of NK cells [152]. Usually, antigenic peptides are generated by proteasomal degradation of cytosolic proteins and consequently translocated to ER by TAP. In the ER, assembly of MHC class I α chain, β2-microglobulin and peptides is guided by chaperones [150]. On the other hand antigenic peptides are associated with the chaperones GRP94, GP96, PDI and calreticulin [153-156]. Functional class I-peptide complexes are then transported to the cell surface. A necessary condition for the successful completion of this complex process is glycosylation and correct folding of MHC class 1 heavy chain in the ER. A failure in the above results in their slow or inefficient transport to the cell surface [157-161]. ER stress may result in decreased expression of MHC class I on the cell surface, thereby preventing the recognition of cells by the adaptive and innate immune system [162,163]. It has been reported that defects in the expression of different components of the MHC class I antigen processing machinery, such as the proteasomal subunits LMP2 and LMP7 and the peptide transporters TAP1 and TAP2, account for impaired MHC class I surface expression [151]. Further, an inappropriate expression or functioning of LMP7 might inhibit antigen processing and presentation, leading to a loss of peripheral tolerance to self-antigens and occurrence of several autoimmune diseases [151]. In this context, Ulianich et al. [152] have shown ER stress induced decrease in surface expression of MHC class I in thyroid cells. This effect was accompanied by activation of NK cells and their cytotoxicity to thyroid cells by increased IFNγ production. Together, these data indicate ER stress induced reduction in MHC class I expression and reduced NK-cells self-tolerance. It has been shown that IFNγ induces LMP and TAP subunits [151]. Our previous study found *IFNγ* mRNA and serum protein levels to be high in vitiligo patients [30]. Taken together these results suggest IFNγ induced expression of MHC-I, MHC-II and TAP on melanocytes. Recently, it has been shown that IFNγ induces senescence in melanocytes [164]. IFNγ signaling impedes maturation of melanosomes by concerted downregulation of some pigmentation genes that leads to IFNγ–mediated hypo- pigmentation of melanocytes [165]. IFNγ and TNFα induce the expression of ICAM1 on melanocytes [166]. We recently, reported increased levels of IFNγ, TNFα and TNFβ [29-31]. Levels of ICAM1 are found to be upregulated in melanocytes of peri-lesional of vitiligo patients [167]. Our recent study has also shown increased *ICAM1* transcript levels in vitiligo patients [30]. T cell melanocyte binding is enhanced by increased expression of ICAM1 on melanocytes [167]. A melanocyte is in close association with ~32 keratinocytes in the epidermal melanin unit. Keratinocytes synthesize cytokines, such as TNFα, IL1α, IL6, and transforming growth factor β (TGFβ), which are paracrine inhibitors of melanocyte proliferation and melanogenesis. In numerous cell types, TNFα plays an important role in apoptosis through activation of the receptor-mediated apoptotic pathway [168]. Moreover, TNFα can also inhibit melanocyte stem cell differentiation [169]. NACHT leucine-rich repeat protein 1 (NLRP1), known to be involved in inflammation and apoptosis [170,171], modulates the response of cells towards proinflammatory cytokines such as IL1β, IFNγ and TNFα. Recently, we have found increased expression of *NLRP1* in vitiligo patients [172]. Bassiouny et al. [173] have found increased level of IL17 and its positive correlation with disease pregression in both the lesional skin and sera of vitiligo patients. Zhao et al. [174] found decreased levels of anti-inflammatory cytokine IL10 in vitiligo patients. All the above studies indicate the significant role of immune mechanisms in the progression of vitiligo that finds support from the reported favourable response to immunosuppressive treatments [175].

Cross Talk between Oxidative Stress, ER stress and Immune System in Vitiligo

Vitiligo is believed to be a multifactorial, polygenic disorder and the exact underlying mechanisms and involvement of specific triggering factors are hitherto not well understood. Several hypotheses have been proposed for explaining the disappearance of melanocytes. We aim to link the plausible components identified in various hypotheses that may help detect the potential pathways participating in vitiligo pathogenesis and also understand the possible etiology of vitiligo. Numerous studies indicate possible cross talk between ER and oxidative stresses; however the mechanistic link is not fully understood [98]. Oxygen-utilizing metabolic processes such as oxidative phosphorylation in mitochondria generate ROS. ER provides a favorable oxidizing environment for protein folding and disulfide bond formation before transport to Golgi. Protein misfolding in the ER may lead to ROS generation through some possible mechanisms- (i) Binding of misfolded proteins to chaperones like BiP that consumes ATP can result in compensatory increase in oxidative phosphorylation in mitochondria and consequent generation of ROS and (ii) ROS may also be produced during disulfide bond formation and protein folding in the ER by way of transfer of electrons from thiol groups in folding substrates catalyzed by Protein Disulfide Isomerase (PDI) and ER Oxidoreductase 1 (ERO1) to molecular oxygen leading to the formation of H_2O_2 [176-178]. Protein misfolding in the ER lumen can cause escape of Ca^{2+} from the ER [179] that will be taken up by mitochondria wherein they can cause disruption in the electron transport chain. Oxidation of cysteine residues during disulfide bond formation in the ER may considerably contribute to oxidative stress [176,177]. Malhotra et al. [180] have shown that accumulation of unfolded proteins in the ER lumen is sufficient to produce ROS and that both ROS and unfolded proteins are required in concert to activate the UPR and apoptosis. These findings propose that unfolded proteins in the ER lumen signal ROS formation and they in turn can act as second messengers to activate UPR and induce apoptosis. Increasing evidence tends to suggest the expression of immunoglobulin heavy-chain binding protein (BiP)/ glucose-regulated protein 78 (GRP78), calnexin, calreticulin (CRT), GRP94 /gp96, oxygen regulated protein 150 (ORP150)/ GRP170, homocysteine-induced ER protein (Herp) and heat shock protein 47 (hsp47)/ SerpinH1 during ER stress, a few of which also present at the cell surface, can play pathophysiological roles as pro- or anti-inflammatory factors in autoimmune and inflammatory diseases [181,182]. GRP78 is a molecular chaperone, also known as BiP, initiates signaling cascades of UPR [183] (Figure 2). Various reports that show participation of GRP78 in antibody generation, T cell proliferation, and pro-inflammatory cytokine production can therefore serve as one of the potential factors in the precipitation of autoimmune diseases [184-186]. Xue et al. [187] have

demonstrated TNFα induction of UPR, including PERK-mediated eIF2α phosphorylation, and ATF6- and IRE1-mediated induction of sXBP1, by way of ROS-dependent pathways. Reported autoimmune mediated β-cell destruction in type 1 diabetes by ER stress [188,189] provides support to the above contention. Involvement of UPR in the pathogenesis of vitiligo is suggested by the presence of dilated ER in the peri-lesional skin of vitiligo patients [72]. It is well accepted that the presence of antimelanocyte antibodies can serve as a marker for the initiation and progression of autoimmunity in vitiligo [10,32,146]. Studies have shown IRE1 modulation of antibody producing B cell proliferation. Scarcity of IRE1is shown to hinder differentiation of pro-B cells into pre-B cells [190] while, XBP1 is essential for antibody production by mature B cells [191]. B-cell receptor (BCR) is reported to induce ubiquitin-mediated degradation of BCL-6, a repressor for B lymphocyte- induced maturation protein 1 (BLIMP1) [192]. BLIMP1 that downregulates the expression of B-cell lineage- specific activator protein (BSAP) [193] is suggested to function as a repressor for XBP1 [194]. Many studies have highlighted the importance of innate immunity in the pathogenesis of vitiligo [40,131] while, components of the UPR pathway are known to regulate innate immune response [174]. Various models support the notion that an inadequate UPR and aberrant protein folding may contribute to autoimmunity through four possible mechanisms: (i) recognition of misfolded proteins by autoreactive immune cells; (ii) release of neo-auto antigens and UPR-related auto antigens by cells that are dying from unrecoverable levels of ER stress, with subsequent provocation of autoimmunity; (iii) indirect contributions to autoimmunity through impairment of immune-tolerance mechanisms in cells with an abnormal UPR and (iv) conferring resistance to UPR mediated apoptosis or a survival advantage to autoreactive cells by upregulating ERAD-associated proteins [46].

UPR is linked with inflammatory cytokines through various mechanisms including ROS, NFκB, and JNK. Excessive load of protein folding in ER may lead to oxidative stress [177]. The expression of ER stress-associated transcription factor, c-AMP responsive element binding protein H (CREBH),is stimulated by IL1β and IL6, which in turn govern the transcription of two critical factors implicated in innate immune response i.e., serum amyloid P-component and Creactive protein [190]. Furthermore, the differentiation of dendritic cells (DCs) is regulated by XBP1 [195]. Increased levels of *XBP1* mRNA splicing are found in DCs and, XBP1 deficient mice showed altered development of both conventional and plasmacytoid DCs. XBP1 deficient DCs are at risk to ER stress-induced apoptosis [195]. Additionally, IL23 secretion from DCs is regulated by CHOP. CHOP directly binds to *IL23* gene and regulate its transcription [196]. Vitiligo inducing phenols trigger UPR in melanocytes and upregulate the expression of IL6, and IL8. Co-treatment with XBP1 inhibitor reduces IL6 and IL8 production induced by phenols while, overexpression of XBP1 alone increases their expression [41]. Interestingly, increased expression of *XBP1* has been observed in lesional skin of vitiligo [117], emphasizing its involvement in ER stress and autoimmune mediated melanocyte destruction. Apart from IRE1, the PERK pathway of UPR is also associated with innate immune response. PERK signaling is reported to activate antioxidant pathway by promoting ATF4 and nuclear factor-erythroid-derived 2-related factor 2 (NRF2) [176,197] whereas, loss of PERK enhances ROS accumulation induced by toxic chemicals [176,198]. The IRE1 pathway can recruit IκB kinase (IKK), leading to the activation of NFκB, an important regulator of inflammation [199].

As a result, NFκB activation and TNFα production are reduced in cells lacking IRE1 [199]. Our previous study has shown increased TNFα levels in vitiligo patients [29] and TNFα has shown to induce UPR in an ROS-dependent manner [187]. In contrast to TNFα, oxidative stresses by H_2O_2 or arsenite only induces eIF 2α phosphorylation, but not activation of PERK- or IRE1-dependent pathways, indicating the specificity of downstream signaling induced by various oxidative stressors. Furthermore, the IRE1 pathway activates JNK, inducing the expression of inflammatory genes by activating activator protein 1 (AP1) [200]. ATF6 can also activate NFκB pathway [201].

Cytokines have been evidenced to activate the expression of inducible nitric oxide synthase (iNOS), leading to excessive Nitric Oxide (NO) production. Interestingly, cytokines are reported to induce ER stress via iNOS and JNK pathways. NO has also been suggested to be an important mediator of cell death. Inflammatory cytokines including IL1β, IFNγ and TNFα can induce iNOS expression which then produces copious amount of NO [202]. JNK pathway is activated by IL1β [203]. Activation of ER stress pathway is stimulated by IL1β and IFNγ leading to apoptosis via NO synthesis [204]. Our previous studies have shown increased expression levels of TNFA [29], IFNG [30] and IL1B [205] in patients with vitiligo. Increased level of NO induces DNA damage and results in apoptosis via p53 pathway or necrosis via poly (ADP-ribose) polymerase (PARP) pathway [206]. In addition, NO depletes ER Ca^{2+} storage by means of activating Ca^{2+} channels or inhibiting Ca^{2+} pumps [207,208]. Depleted ER Ca^{2+} levels leads to ER stress and apoptosis through induction of CHOP signaling [209]. Imbalance of various pro-inflammatory and anti-inflammatory cytokines has been reported in the microenvironment of vitiliginious skin. IL17 works to activate the production of other cytokines, including IL1 and IL6, and can potentiate other local inflammatory mediators like TNFα [173,210]. Keratinocyte dysfunction along with increased TNFα and IL6 production has been reported in vitiligo patients [211]. H_2O_2 is known to induce NFkB in nuclear extracts and increase phosphorylated p38 MAPK levels in cells. NFkB is present in the cytoplasm as an inactive NFkB complex. In response to various stimuli, the latent cytoplasmic NFkB/IkBa complex dissociates and activated NFkB translocates to the nucleus and induces the expression of relevant genes, including various cytokines genes [212]. The build-up of ROS causes protein misfolding in the ER which, may result in possible immune system defects precipitating inappropriate autoimmune response against melanocytes (Figure 3). Calreticulin (CRT) is a ubiquitous protein localized predominantly in the ER and plays a major role in intracellular Ca^{2+} homeostasis [213-216]. Cell surface localization of CRT has been reported on T cells, neutrophils, monocytes, macrophages and dendritic cells [217-220]. Localization of cell surface CRT reportedly affects antigen presentation, complement activation [221-223] and clearance of apoptotic cells [218]. Recently, Zhang et al. [224] have reported increased CRT expression in response to H_2O_2 in human melanocytes leading to apoptosis. In addition, CRT-treated peripheral blood mononuclear cells or stressed melanocytes show higher IL6 and TNFα levels. Higher CRT expression in vitiligo patients is positively correlated with lesion area and duration of disease. The exposure of CRT on the plasma membrane can precede anthracycline-induced apoptosis and is required for cell death to be perceived as immunogenic [225]. Several studies have found translocation of intracellular CRT to the cell surface in response to anthracycline and high doses of irradiation in a variety of human and rodent cancer cells, including melanoma [226-228]. Surface CRT then initiates an apoptotic signal [229] which is critical for the recognition and engulfment by DCs. In contrast, apoptotic cells have been suggested to be phagocytized because of their lack of CD47 expression and the coordinated upregulation of cell surface CRT in fibroblasts, neutrophils, and Jurkat T cells [218]. Interestingly, Zhang et al. [224]

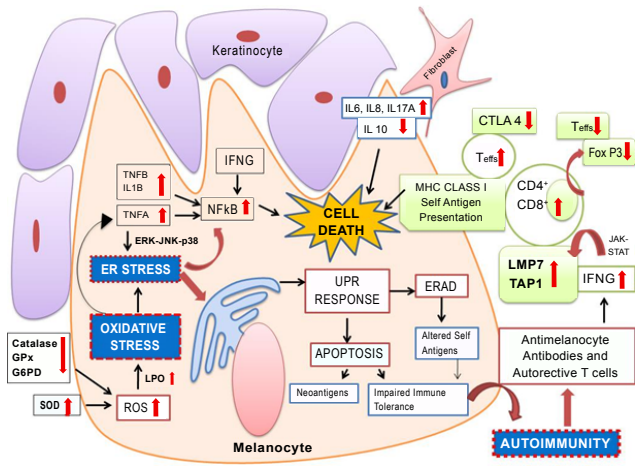

Figure 3: Cross talk between oxidative stress, ER stress and immune System in melanocyte death: Decrease in antioxidant enzymes leads to ROS formation, ultimately leading to oxidative stress. Oxidative stress induces ER stress leading to activation of Unfolded Protein Response (UPR) which in turn activates autoimmune response. [Abbreviations: GPx (Glutathione Peroxidase), G6PD (Glucose 6 Phosphate Dehydrogenase), SOD (Superoxide Dismutase), LPO (Lipid Peroxidation), ROS (Reactive Oxygen Species), TNFA (Tumor Necrosis Factor- alpha), TNFB (Tumor Necrosis Factor - beta), IL1B (Interleukin 1-beta), NFkB (Nuclear Factor kappa – beta), IFNG (Interferon -gamma), UPR (Unfolded Protein Response), ERAD (Endoplasmic Reticulum Associated Degradation), LMP7 (Low Molecular Weight Polypeptide 7), TAP1 (Transporter Associated With Antigen Processing 1), Treg (T regulatory Cells), Teff (T effector cells), (Interleukins - IL6, IL8, IL10, IL17A), CTLA4 (Cytotoxic T Lymphocyte Antigen 4)]

have shown increased surface levels of CRT in response to H_2O_2 and this correlates with decreased CD47 levels, suggesting increased susceptibility to H_2O_2 mediated oxidative stress induced apoptosis [230]. These findings demonstrate translocation of CRT to the cell surface, via H_2O_2 induced oxidative stress to play an essential role in melanocyte apoptosis suggesting a relationship between apoptosis and immune responses during melanocyte destruction. Nevertheless, the relationship between CRT and ROS-induced apoptosis in melanocytes is still not fully explored. However, the defective Ca^{2+} homeostasis in vitiligo patients [90,91] certainly proposes a crucial role of CRT and thus the ER stress in vitiligo pathogenesis.

Cells under stress halt typical protein synthesis in favor of heat-shock protein (HSP) and/ GRP synthesis [231,232]. In the ER, this can induce the UPR which upregulates HSPs [233]. Among larger HSPs, inducible HSP70 (HSP70i) is unique for its secretion from cells as a chaperokine [234]. The unique secretory property of HSP70i may be attributed at least in part to its cellular location, associated with melanosomes [235]. HSP70i is exported by cells through the endolysosomal pathway [236]. A rise in intracellular Ca^{2+} serves as a signal for exocytosis [237].

HSP70i can stimulate proliferation and cytotoxicity of NK cells [238], and enhances leukotriene secretion by mast cells [239]. Moreover, HSP70i has shown to induce maturation and type-1 polarizing cytokine production by DCs and stimulate cross-priming of T cells [241], breaking the tolerance and inducing autoimmune mediated tissue destruction in mice [241]. Mosenson et al. [242] reported that modified HSP70i prevents T cell–mediated depigmentation. In addition, they have also shown HSP70i induces an inflammatory DC phenotype in both vitiligo mouse models as well as in vitiligo patients, which is necessary for depigmentation [242,243]. Interestingly, mutant HSP70iQ435A has been shown to prevent and reverse the depigmentation in different mouse models prone to vitiligo. These findings indicate a vital role of HSP70 in precipitation of vitiligo and targeting HSP70i might be a promising approach towards the treatment of vitiligo [242-244].

Genetic and pathophysiological studies provide strong evidence for vitiligo to be a polygenic, multifactorial disorder. The genome-wide association studies provide a partial explaination for the heritability of vitiligo but polymorphism in various candidate genes may play a crucial role in the disease phenotype, such as progression or age of onset [245]. Most vitiligo susceptibility loci encode melanocyte components, and antioxidant and immune-regulatory proteins [40,246]. For example, associations have been established between vitiligo pathogenesis and polymorphisms in tyrosinase (*TYR*) [247], catalase (*CAT*) [65], glutathione peroxidase (*GPX*) [65], melanocortin 1 receptor (*MC1R*) [248], major histocompatibility complex *(MHC*) [249], NACHT leucine-rich repeat protein 1 *(NLRP1)* [172], tumor necrosis factor A (*TNFA*) [29], interferon-γ (*IFNG*) [30], intercellular adhesion molecule-1 (*ICAM1*) [30], tumor necrosis factor B (*TNFB*) [31], superoxide dismutase (*SOD*) [58], cytotoxic T lymphocyte associated antigen 4 (*CTLA4*) [250], interleukin 4 (*IL4*) [28], melanocyte proliferating gene (*MYG1*) [251], X-box binding protein 1 *(XBP1)* [117], and methylenetetrahydrofolate reductase *(MTHFR)* [252]. Both protective and susceptibility-increasing effects have been found in the case of different polymorphisms in these genes [253,254]. Interestingly, our recent study on skin miRNA profiling from non-segmental vitiligo have shown 38 differentially expressed miRNA signatures in patients [255]. In the light of the above studies, it can be proposed that ER stress could also result due to variations at genetic levels involving the genes participating in the specific pathways contributing to ER function in these patients.

Conclusions

The cross talk between oxidative stress, ER stress and autoimmunity appears crucial and may emerge as a critical aspect of vitiligo pathogenesis. The present article suggests that oxidative stress may be the initial triggering event to precipitate vitiligo, which is then exacerbated by contribution of ER and autoimmune factors together with oxidative stress. However, more detailed studies focusing on ER stress are required for underlying the major role of ER stress in oxidative stress and autoimmunity mediated pathogenesis of vitiligo. Further, delineation of the melanocyte-specific UPR would be of significance in developing and evaluating the efficacy of response modifying compounds that can be used to prevent melanocyte death in vitiligo.

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