Endoplasmic reticulum stress-mediated pathways to both apoptosis and autophagy: Significance for melanoma treatment

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Abstract
Melanoma is the most aggressive form of skin cancer. Disrupted intracellular signaling pathways are responsible for melanoma's extraordinary resistance to current chemotherapeutic modalities. The pathophysiologic basis for resistance to both chemotherapeutic and radiation therapy is rooted in altered genetic and epigenetic mechanisms that, in turn, result in the impairing of cell death machinery and/or excessive activation of cell growth and survival-dependent pathways. Although most current melanoma therapies target mitochondrial dysregulation, there is increasing evidence that endoplasmic reticulum (ER) stress-associated pathways play a role in the potentiation, initiation and maintenance of cell death machinery and autophagy. This review focuses on the reliability of ER-associated pathways as therapeutic targets for melanoma treatment.

Key words: Melanoma; Endoplasmic reticulum; Apoptosis; Autophagy; Signaling pathways; Chemotherapy

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Core tip: This editorial describes the clinical validity of the endoplasmic reticulum (ER) as therapeutic target...
for melanoma treatment. In addition, we highlight in this review the mechanistic role of ER stress in the modulation of both apoptosis and autophagy-associated pathways. Drugs that perturb ER function may represent an alternative approach for melanoma treatment. This paper reviews the persisive and current published studies on the reliability of ER-associated pathways as therapeutic targets for melanoma.

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INTRODUCTION

Although melanoma accounts for less than 5% of all skin cancers, it exhibits the highest mortality rate of all cutaneous tumors and its incidence is rapidly increasing[6]. The high mortality rate is the result of the propensity of metastatic dissemination throughout the body[2], and the development of resistance mechanisms that permit melanoma to evade normal immune surveillance mechanisms and the anti-tumor effects of chemotherapy[3]. Early detection and surgical excision of early stage disease offers the best hope of cure in patients with primary melanoma[4]. Even with new targeted therapies, the prognosis for advanced metastatic malignant melanoma is poor[3]. The available options for patients with advanced malignant melanoma patients provide limited therapeutic benefit with successful treatments often being measured in months of increased survival rather than years[6-8]. The potential to develop resistance mechanisms that counteract drug-induced apoptosis and evade host immunological responses is particularly devastating[9]. Accordingly, the replacement of single agent chemotherapy with targeted therapies is revolutionizing systemic therapy[10]. Besides the mechanistic role of mitochondrial damage-dependent pathways in the modulation of anti-cancer agent-induced apoptosis of tumor cells, anti-cancer agents can also improve killing efficiency via endoplasmic reticulum (ER) stress-dependent pathways[11-13]. While autophagy-mediated tumor death in response to anti-cancers is clinically relevant, these anti-cancer agents can also induce autophagy-mediated cytoprotective mechanisms[12,13], a pattern of tumor resistance to chemotherapy.

Metastatic melanoma demonstrates particularly poor response rates to single chemotherapeutic agents[14,15]. For instance, dacarbazine (DTIC) demonstrates no impact on survival, though it is considered to be one of the most effective agents that is used as standard therapy for the treatment of metastatic melanoma[16,17]. Other anticancer agents such as cisplatin, carbustine and the vinca alkaloids (e.g., vindesine and vinblastine) fail to show any therapeutic advantage over DTIC[18], though several combination chemotherapy regimens demonstrate a modest increased response rate[19].

Melanoma’s resistance to therapy is the results of an upregulation in pro-survival factors, which potentiate tumor maintenance and progression[20]. One of these factors is the inducible transcription factor NF-κB that is responsible for the regulation of the expression of genes related to apoptosis[21]. It is also, central to the development of tumor resistance to alkylating agents such as DTIC[22-24]. Accordingly, the inhibition of NF-κB pathway may improve the cytotoxic efficacy of alkylating agent-based therapy. To that end, preclinical studies in vitro and in vivo using human melanoma tumor models revealed that the therapeutic efficiency of DTIC or temozolomide is enhanced with the addition of the proteasome inhibitor; bortezomib[25,26].

Traditional mono- or multi-chemotherapy regimens are also associated with the development of significant adverse effects[27,28]. The development of new tumor types in these patients is attributed to the molecular action of the anticancer agents leading to the induction and/or destruction of aberrant signaling pathways.

The molecular action of chemotherapy in tumor cells is commonly associated with phenotypic alterations including cell death and survival-dependent mechanisms including apoptosis and autophagy[12,13].

Apoptosis and autophagy occur in normal cells. These are essential physiological mechanisms required for the maintenance of organismal and cellular homeostasis[29]. Current information about autophagy in melanoma focuses on autophagosome formation and/or autolysosome degradation in response to a variety of therapeutic agents using melanoma derived cell lines[13,30,31]. Chemotherapy induction of autophagy serves to protect melanoma cells from intended chemotherapy-induced apoptosis. In fact, the induction of autophagy following the treatment of melanoma cells with bortezomib reduces bortezomib-induced apoptosis[13]. Similarly, the induction of autophagy by esomeprazole, a proton pump inhibitor, blocks melanoma cell death[32]. Based on these preclinical evidence, the modulation of autophagy-associated pathways offers a promising treatment strategy to increase treatment efficiency by overcoming melanoma resistance to chemotherapy.

The involvement of ER stress in the modulation of apoptotic mechanisms leading to melanoma cell death has been reported in several studies[12,13,33]. This may result from the induction of BH3 proteins such as Noxa and Puma leading to the inhibition of Bcl-2 localization at the ER membrane, alterations in the distribution of the calcium flux which produce ER stress[34,35].

Although ER stress and autophagy are capable of modulating each other in tumor tissues, their specific function is thought to be tumor type and stage-dependent[34-36]. The clinical potential of ER stress and/or autophagy-associated pathways as therapeutic
target for melanoma treatment has been reported in several studies[^37-39]. For example, BRAF wild type (wt) melanoma is more sensitive to ER stress-based therapies than melanoma with hyperactivating BRAF mutations[^40]. The frequency of BRAF mutation seems to be associated with elevated levels of autophagy in melanoma. Accordingly, ER stress-induced apoptosis of melanoma cells harboring oncogenic BRAF is lower than those observed in BRAF wt melanoma cells[^40-42]. Inhibition of autophagy is a good strategy to sensitize BRAF wt melanoma cells to ER stress-mediated apoptosis. In addition, the development of anti-cancer agents based on the enhancement or suppression of these processes may be relevant therapeutic strategies.

Tumor resistance or response to available therapeutic modalities depends on the balance between apoptosis and autophagy-associated mechanisms[^43,44]. Although the development of the most available therapeutic approaches focuses on the excessive activation of mitochondrial dysregulation-dependent pathways leading to apoptosis, there is increasing evidence that ER stress-associated pathways represent an important therapeutic target for melanoma[^13,47]. Thus, the development of anti-cancer agents with ability to trigger the intrinsic activation of ER stress/unfolded protein response (UPR)-associated pathways may offer a novel therapeutic strategy for tumor treatment. UPR is mediated in response to the enhancement of protein synthesis through the activation of mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) pathway that, in turn, induces cell proliferation, a mechanism that can block ER stress-induced apoptosis[^48]. Thus, ER stress-dependent pathways have been proposed to represent a new therapeutic target for melanoma treatment[^10,49]. Accordingly, the inhibition of oncogenic BRAF (V600E) and/or MEK-attenuated activation of inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) signaling of the UPR in melanoma cells may sensitize melanoma cells to apoptosis. Our work focuses on the reliability of ER stress-dependent pathways as a therapeutic target for melanoma treatment.

**FUNCTION OF ER IN NORMAL AND TUMOR CELLS**

ER is a network of tubules and flattened sacs comprising rough and smooth regions that differ in their structure and function[^50]. The rough ER is characterized by the existence of ribosomes attached to the cytoplasmic side of the membrane, whereas the smooth ER lacks these ribosomes[^50]. ER plays a crucial role in normal cellular functioning, by processing of post-translational modification and folding of secretory and membrane proteins. These secretory and membrane proteins are synthesized along the membrane of the rough ER and subsequently are passed onto the Golgi apparatus, where they undergo further post-translational modifications by the attachment of lipid and glucose moieties in a lipidation and glycosylation-dependent manner, respectively[^51]. The ability of ER to correctly fold nascent proteins depends on chaperone proteins that, under normal physiological condition, are in excess in the ER lumen[^52]. The function of most chaperone proteins is known to be Ca^{2+}-dependent[^53]. ER contains a high concentration of Ca^{2+} and is the only cellular organelle that plays an essential role in intracellular Ca^{2+} homeostasis[^54]. Thus, the escalation of intracellular calcium into the cytoplasm is a signal for pathophysiological alteration of the cells. This pathological phenomenon results from ER stress in response to externally physical or chemical stressors, such as radiation and toxins[^55].

ER function is critical for the regulation of many aspects of cell physiology, such as vesicle trafficking, lipid and membrane biogenesis as well as protein targeting and secretion. Normal and tumor cells react rapidly to ER stress via mechanisms mediated by a set of ER stress-associated pathways. The regulation of these pathways is thought to be the consequence of the perturbations in ER function, such as the accumulation of unfolded or misfolded proteins, as well as the accumulation of ER lipid, glycolipid imbalances, or alteration in the ionic or redox conditions in the lumen of ER[^56,57]. Three distinct signaling pathways have been identified as ER stress-dependent pathways, namely protein kinase RNA-like endoplasmic reticulum kinase (PERK), ATF6, and IRE1 pathways. The primary purpose of these pathways is implicated to promote cell survival by mechanisms mediated through the reduction of the misfolded protein[^58]. Figure 1 outlines the ER stress-associated pathways in normal and tumor cells.

**INDUCTION OF ER STRESS-ASSOCIATED PATHWAYS BY ANTI-CANCER AGENTS**

Dysregulation of ER homeostasis is a primary pathophysiological mechanism responsible for the initiation of an ER stress response that leads to the development of a number of human diseases including cancer[^59]. The induction of ER stress by anti-cancer agents and other stimuli has been reported in several studies. The anti-cancer agent’s bortezomib, vinblastine and taxol trigger ER stress in melanoma cells[^13,60,61]. Similarly, caffeic acid phenethyl ester, the BH3 mimetic obatoclax and the Abbott Compound ABT-737 have been reported to induce ER stress in melanoma[^33,62]. Interestingly, the induction of ER stress in melanoma cells by these agents is correlated with the deregulation of ER stress associated pathways including eukaryotic translation initiation factor 2α (eIF2α) and PERK.

ER stress induced activation of PERK leads to the phosphorylation of the eIF2α that inhibits the translation and subsequently triggers cell cycle arrest[^53]. CHOP (C/EBP homology protein) is downstream of PERK-
ER stress-induced activation of IRE1α is responsible for the regulation of the transcription factor XBP1. Once ER stress is initiated, the conversion of unspliced XBP1 mRNA to mature mRNA is mediated permitting the translation and further modification of this protein to operate as an active transcription factor. The activation of the transcription factor XBP1 is essential for the induction of the transcription of ER-related genes that, in turn, mediate the disposal of unfolded proteins. Although this panel of responses is mainly implicated in restoring ER homeostasis, sustained ER stress is essential for the promotion of apoptosis. More importantly, it has been demonstrated that ER-stress-associated pathways are involved in the modulation of the anti-cancer agent-induced apoptosis of tumor cells, particularly, in melanoma. In recent years, we and others uncovered the mechanistic role of ER stress-associated pathways such as PERK-ATF4-CHOP/Bim and IRE1α-ASK1-JNK-AP-1/HSF1-HSF70, in the modulation of anti-cancer agent-induced apoptosis of melanoma cells. More importantly, we demonstrated that Noxa-induced ER stress triggers apoptosis of melanoma cells via mechanism mediated by ASK1-JNK/p38 axis. Also, apoptosis related protein-2 (APR-2)-induced ER-stress drives apoptosis of melanoma cells via mechanism mediated by three parallel pathways, namely IRE1α/tumor necrosis factor receptor-associated factor 2 (TRAF2)-ASK1-JNK/Cytochrome c/caspase-9/caspase-3/PARP, Calpain-caspase-4/caspase-9/caspase-3/PARP, and PERK-ATF4-CHOP/Bim. Furthermore, bortezomib/vinblastine-induced ER stress in melanoma cells is essential for the induction of cell survival via autophagy-dependent pathways including, IRE1α-ASK1-JNK-AP-1/HSF1-
HSP70 axis. More importantly, in our laboratory, we demonstrated that the inhibition of IRE1α-ASK1-JNK-Ap-1/HSF1-HSP70 pathways synergistically enhance bortezomib or vinblastine-induced apoptosis of melanoma cells[12,13]. Accordingly, the knockdown of IRE1α or ATF6 sensitizes melanoma cells to ER stress-induced apoptosis[13]. To that end, the destruction of the IRE1α/XBP-1 pathway along ER stress is expected to overcome melanoma resistance to ER stress inducers. The involvement of IRE1α in the activation of PI3K/Akt pathway together with the induction of Mcl-1 expression has been suggested to play an essential role in the modulation ER stress-induced survival of melanoma cells[76,77]. ATF6 is involved in the transcriptional regulation of both GRP78 and XBP-1 and thereby plays an important role in melanoma resistance to ER stress-induced apoptosis[77]. In conclusion, the differential response of various tumor types to PERK activation seems to rest on cellular factors and/or cell growth and survival pathways-dependent activation. Although the importance of IRE1/XBP-1 axis in tumor growth and survival has been established[78,79], its mechanistic role in the promotion of the XBP1 splicing processes and the subsequent effect on the components of the downstream signaling pathway have not been well characterized. More importantly, the activation of IRE1 kinase has been reported to be essential for the activation of c-Jun-N-terminal kinase, JNK and NF-κB pathways besides its role in the modulation of the induced unfolded protein response[79,80]. Upon the induction of ER stress, IRE1 kinase becomes capable of recruiting TRAF2. This results in the activation of both JNK and NF-κB pathways[81]. The mechanisms, involved in the modulation of ER stress are outlined in Figure 1.

ER stress-mediated pathways to apoptosis in melanoma

It is established that the primary function of ER stress is to restore normal ER homeostasis and to engage cytoprotective mechanisms to counteract or mediate both intra- and extracellular-induced alterations[71]. Therefore, if the induced ER stress is strong or persistent, the ER enhanced dysfunction becomes irreversible and consequently triggers cell death machinery to initiate apoptosis. Thus, the destruction of the ER stress-dependent pathways that are essential for the modulation of the cytoprotective machinery by small molecule-inhibitors would be expected to trigger apoptosis of tumor cells. In addition, the enhancement of key components leading to excessive activation of apoptotic pathways, such as the mammalian IRE1α, could impact the regulation of kinases such as ASK1[62]. The activation of the pro-apoptotic kinase ASK1, the upstream kinase of the JNK pathway, is essential for the regulation of ER stress-induced apoptosis of melanoma in response to chemotherapeutic agents such as vinblastine[12] as well as in response to pro-apoptotic proteins such as the BH- only proteins such as Noxa[70] and APR-2[58]. Unlike various tumor types, particularly, those undergoing prolonged ER stress, the ER stress-dependent pathways such as IRE1α and ATF6 are persistent in melanoma cells[72]. Thus, it is expected that constitutive activation of both IRE1α and ATF6 would be associated with the development of melanoma resistance to anti-cancer agents[72]. Accordingly, the destruction of IRE1α and/or ATF6 signaling pathways has been reported to trigger apoptosis via mechanism mediated by PERK pathway[72]. The role of the PERK pathway in the modulation of ER stress-induced apoptosis has been demonstrated in various tumor types including melanoma via mechanism mediated by the BH3-only protein Bim[58,73].

Although the UPR is established as a cyto- protective response, excessive and/or persistent activation of ER stress-associated pathways can also trigger apoptosis[74]. However, the mechanism whereby UPR switches from the cyto- protection to apoptosis is thought to be the consequence of the attenuation of IRE1α and/or ATF6 activities[72,75]. The resistance of melanoma cells to most anti-cancer therapies during the course of anti-cancer-induced ER stress is attributed to the fact that the melanoma cells have adapted to ER stress. Although the molecular mechanisms that describe the contribution of ER stress in melanoma survival has been established, several studies revealed that the resistance of melanoma cells to ER stress-induced apoptosis results from the prolonged activation of the IRE1α and ATF6 pathways that, in turn, lead to the attenuation of the PERK signaling pathway[72].
of Ataxia Telangiectasia mutated-dependent DNA damage response as well as the transactivation of the cyclin-dependent kinase inhibitor 1A[94]. Although its mechanistic role in tumor survival and resistance to treatment with chemo-and radiotherapy has been established, autophagy can also enhance the killing efficiency of chemotherapy-based treatments in various tumor types including melanoma[86]. In recent years, autophagic cell death, also known as type II apoptosis, gained more attention, as a potential therapeutic target for tumor treatment. Soares et al[87], demonstrated that the combination of Cl-IB-MECA inhibitor and paclitaxel can induce mTOR-dependent autophagic cell death, as well as caspase-dependent and/or independent apoptosis in melanoma cells. In addition, the potential of the micro-tubule poison, JG-03-14, to cause cytotoxic effects in melanoma cells both in vitro and in vivo via autophagy-dependent mechanism has been approved[88]. Thus, chemotherapeutic agents, whose cytotoxicity is mediated by autophagy-dependent mechanisms are considered to be suitable therapeutic approaches, particularly for tumors conferring resistance to anti-cancer agents-induced apoptosis. In addition, the identification of ER stress-associated pathways as a link between BRAF signaling and cytoprotective autophagy provides a potential therapeutic target for melanoma treatment[88]. Anti-cancer agents-induced autophagy is mostly resistant to several kinase inhibitors, particularly, those targeting the link between autophagic machinery and PI3K/AKT/mTOR pathway[89,90].

The common genetic alterations leading to the development of malignant melanoma are widely established to be the consequence of the activating mutations in NRAS and BRAF proto-oncogenes[90,91]. Also, genome-wide mutation detection in melanoma derived cell lines and primary tumors revealed significant alterations in the BRAF gene[92]. The most identified mutations were found to affect a single residue (V600E) that is located in the kinase activation domain of BRAF[94,95]. The importance of BRAF mutation is attributed to the potential role of RAF serine/threonine kinases, the most important key signaling components in the RAS pathways[96]. The clinical relevance of BRAF in melanoma is based on its mechanistic role in the activation of melanocyties in cAMP-dependent pathway in response to α-melanocyte-stimulating hormone-mediated activation of melanocortin receptor 1[97]. Accordingly, the mutation in the BRAF gene with its consequent impact on melanoma development and progression has gained increasing attention as a therapeutic target in melanoma. The development of a broad-spectrum of kinase inhibitors confirmed the clinical relevance of the inhibition of BRAF as an efficient therapeutic strategy for melanoma treatment. These kinase inhibitors have demonstrated the ability to inhibit BRAF, mutant BRAFV600E, and CRAF[98]. The most potent BRAF inhibitors, vemurafenib and dabrafenib, have demonstrated antitumor activity for advanced melanoma in phase III trials, particularly in patients with BRAF mutations[99]. Also, MEK inhibitors, such as trametinib, showed significant antitumor activity in melanoma patients with a V600 BRAF mutation[100]. Other MEK inhibitors, such as Binimetinib, exhibit antitumor activity in patients with advanced melanoma, who demonstrate NRAS mutation[101]. Most importantly, the combination of BRAF inhibitors such as dabrafenib with MEK inhibitors such as trametinib have enhanced therapeutic benefits when compared with the response rate to dabrafenib alone[102]. Despite the demonstration of therapeutic progress by both BRAF and MEK inhibitors, most patients with metastatic melanoma fail to achieve a clinical cure[103]. The development of more effective therapeutics for advanced metastatic melanoma requires a direct evaluation of novel and innovative therapies. The roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and the implications for sensitivity to treatment of melanoma are outlined in Figure 2.

While MAP kinase pathways modulate autophagy-associated cell death[104], accumulated evidence demonstrates that autophagy also plays a role in the promotion of tumor resistance and survival via MAP kinase pathway-dependent mechanisms[105-107]. Specifically, the induction of cytoprotective autophagy counteracts MAP kinase-mediated pathways to apoptosis in response to chemotherapy-based treatments[105,108]. The presence of autophagosomes in tumor cells undergoing apoptosis in response to the treatment with chemotherapy is evidence for the ability of tumor cells to evade the cytotoxicity via autophagy-dependent pathways[109]. Thus, the inhibition of autophagic machinery induced by chemotherapeutics, such as bortezomib, may prove to be an effective therapeutic strategy[110]. In addition, these pathways may play a role in ER stress suppression of the anti-tumor efficiency of vemurafenib, dabrafenib and trametinib in melanoma patients harboring activating NRAS or BRAF mutations (Figure 2).

**Anti-cancer agents affecting ER stress-associated pathways to apoptosis of melanoma**

There are a number of United States Food and Drug Administration-approved anti-cancer agents that influence key components of ER stress-dependent pathways. For example, the ruthenium-derived compounds trigger the expression of ER stress proteins such as, Bip, XBP1, PDI, and CHOP leading to tumor growth inhibition or cell death[100,111]. Also, the anti-cancer agent 2-Hydroxyoleic acid triggers ER stress and autophagy in various human glioma cell lines[112]. Furthermore, the inhibition of the proteasome system with bortezomib overcomes resistance in a variety of tumors via mechanisms mediated by the accumulation of misfolded proteins that overwhelm the ER-associated degradation pathway that produce ER stress[113]. This mechanism is well described in multiple myeloma (MM) cells that constitutively express ER stress-associated survival factors that are essential for propagation and maintenance of MM cells[114,115]. Thus, proteasome inhibitors induce apoptosis in MM because the UPR is
unable to mediate the degradation of the misfolded proteins\textsuperscript{[146].} In fact, compared to other cell lines, MM cells are the most sensitive to proteasome inhibitors-induced apoptosis via mechanism mediated by the activation of UPR-associated pathways including PERK and ATF4, and the pro-apoptotic target, CHOP\textsuperscript{[117]}. The involvement of ER stress in the modulation of melanoma cell death in response to the treatment with anti-cancer agents has been studied extensively. For example, Syed et al\textsuperscript{[118]}, demonstrated that fisetin-induced apoptosis of melanoma cells is mediated by ER stress-associated pathways such as IRE\textsubscript{1}, XBP\textsubscript{1s}, ATF\textsubscript{4} and GRP\textsubscript{78}\textsuperscript{[119]}. Also, the small molecule inhibitor honokiol, a potent anti-tumorigenic compound, has been shown to trigger apoptosis of melanoma cells via a mechanism mediated by the binding of honokiol to the unfolded ATPase domain of GRP\textsubscript{78} leading to the induction of ER stress and pro-apoptotic associated pathways. Beck et al\textsuperscript{[120]}, addressed an important role for ER stress-associated pathways in the modulation of the anti-cancer agents. For example, in patients with BRAF\textsubscript{V600E}-mutated melanoma vemurafenib-induced apoptosis is associated with increased levels of the spliced isoform of the transcription factor, XBP\textsubscript{1}, a marker for the induction of ER stress, and with increased phosphorylation of the translation initiation factor eIF\textsubscript{2}\textalpha. Also, ER stressors such as diallyl trisulfide play a role in the sensitization of melanoma cells to death receptor- induced apoptosis\textsuperscript{[121]}. Moreover, the role of ER stress-associated pathways in the modulation of the anti-tumor activity of the natural marine compound, 11-dehydroosinulariolide has been demonstrated\textsuperscript{[122]}. Interestingly, the 11-dehydroosinulariolide compound was found to trigger apoptosis of melanoma cells via mechanism-mediated by both PERK/eIF\textsubscript{2}\textalpha/ATF\textsubscript{4} and ATF\textsubscript{6}/CHOP-Bim\textsubscript{±} pathways\textsuperscript{[123]}. In another study, Hiscutt et al\textsuperscript{[124]}, demonstrated that knockdown of the X-linked inhibitor of apoptosis protein (XIAP) enhances both fenretinide and bortezomib-induced apoptosis of metastatic melanoma cells via ER stress-mediated pathways. Also, melanoma under ER stress shows more susceptibility to obatoclax-induced apoptosis\textsuperscript{[125]}. Moreover, the role of ER stress-associated signaling pathways, GRP\textsubscript{78}, ATF\textsubscript{6}, IRE\textsubscript{1}, and PERK/eIF\textsubscript{2}\textalpha has been reported to be essential for docetaxel-induced apoptosis of melanoma\textsuperscript{[126]}. More importantly, it has been suggested that the constitutively activated MEK/ERK pathway results in resistance of melanoma cells to ER stress-induced apoptosis. Accordingly, Jiang et al\textsuperscript{[49]}, demonstrated that the inhibition of MEK by U0126 inhibitor or by the knockdown of MEK1 by its specific siRNA sensitizes melanoma cells to tunicamycin- or thapsigargin-induced apoptosis. Also, the induction of ER stress by Tunicamycin can sensitize human melanoma cells to tumor necrosis factor-related apoptosis in response to ligand-induced apoptosis\textsuperscript{[126]}. CONCLUSION Although it has been demonstrated that ER stress-dependent pathways play a significant role in the regulation of tumor initiation and resistance, it is more difficult to confirm the hypothesis that ER is a valid therapeutic target for tumor treatment. The induction of UPR is a cellular mechanism that reduces or prevents the cytotoxic effect of anti-cancer treatment.
Accordingly, the destruction of key UPR components should provide an effective therapeutic strategy for melanoma treatment. Moreover, a functional analysis of UPR-mediated pathways, particularly those which are essential for cell survival or cell death, may help to identify key molecules of the aberrant pathways whose excessive activation and/or inhibition may overcome melanoma resistance to standard treatments. In addition, gaining an understanding of the molecular mechanisms of UPR may provide insight into the development of therapeutic strategies such as the development of small molecule inhibitors to control melanoma through the modulation of UPR signaling. Just as most current melanoma therapies were developed following a functional analysis of their ability to trigger mitochondrial dysregulation, ER stress-dependent pathways could provide new therapeutic targets designed to effect key components of aberrant signaling pathways.

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