Role of ROS-mediated autophagy in melanoma (Review)

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Abstract. Melanoma is the most aggressive form of skin cancer with the poorest prognosis and its pathogenesis has yet to be fully elucidated. As key factors that regulate cellular homeostasis, both reactive oxygen species (ROS) and autophagy are involved in the development of melanoma, from melanomagenesis to progression and drug resistance. However, the interaction between ROS and autophagy in the etiology and treatment of melanoma is not well characterized. The present review examined the production of ROS and the role of oxidative stress in melanoma, and summarized the role of ROS-mediated autophagy in melanomagenesis and melanoma cell fate decision following treatment with various anticancer drugs. The present findings may lead to a better understanding of the pathogenesis and progression of melanoma, and suggest promising treatment options for this disease.

Contents

1. Introduction

Reactive oxygen species (ROS) mainly refer to superoxide anion ($\bullet O_2$-), hydroxyl radical (•OH), hydrogen peroxide (H_2O_2) and singlet oxygen, which are derived from the metabolism of O_2. These chemically reactive molecules are generated as metabolites of oxidative reactions in mitochondria, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and endoplasmic reticulum (ER) (1). In order to counteract ROS overproduction, multiple antioxidant enzymes exist to maintain redox homeostasis, including superoxide dismutase, catalase, and glutathione peroxidase (2). ROS are capable of reacting with proteins, lipids and nucleic acids, as well as regulate signaling pathways that are involved in various cellular processes (3). Thus, a state of equilibrium between oxidants and reductants is required for physiological processes, such as cell proliferation, differentiation and survival. However, the imbalance in ROS generation and removal causes excessive accumulation of ROS and thus oxidative stress, resulting in detrimental oxidative DNA damage, which is regarded as a major factor for carcinogenesis (4). Controlling ROS metabolism is beneficial for the prevention and treatment of cancer.

Autophagy is an evolutionarily conserved and lysosome-dependent catabolic process whereby cytoplasmic components, such as damaged organelles, protein aggregates and lipid droplets, are degraded and further recycled in autophagosomes for the maintenance of cellular homeostasis (5). In response to ROS-mediated oxidative damage, autophagy can be induced as an adaptive reaction to remove ROS and oxidative biomolecules and organelles, thus alleviating oxidative stress (6). The interaction between ROS and autophagy has been widely investigated in various cancer types, as it participates in tumorigenesis, metastasis and chemoresistance (7). As one of the most aggressive forms of cancer, melanoma is a type of skin cancer with a high metastasis potential and poor survival rate. In comparison with other solid tumors, ROS levels are particularly abundant in melanoma, which is considered a ROS-driven tumor (8). However, the crosstalk between ROS and autophagy in the development of melanoma remains elusive. During tumor progression or chemotherapy-induced stress, obsolete organelles and useless proteins are recycled by autophagy to foster cancer cell growth and chemoresistance. Understanding the role of autophagy in the development of melanoma is of great significance, and autophagy regulation represents a new potential therapeutic target in this disease. Chemotherapeutic agents both induce oxidative damage and autophagy via generation of amounts of ROS. However, cytoprotective autophagy limits the chemotherapy efficacy. Moreover, ROS-mediated autophagy is induced in diverse melanoma chemotherapies where it exerts double functions: i) Promoting cell survival, which is a mechanism of chemoresistance (9); and ii) triggering autophagic cell death, which improves antitumor efficacy (10). The aim of the present

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review was to emphasize the role of ROS-mediated autophagy in melanomagenesis and melanoma treatments, as well as discuss the therapeutic potential of combination chemotherapy with autophagy-regulating agents according to the functional status of ROS-induced autophagy in patients with melanoma.

In order to summarize the role of ROS-mediated autophagy in melanoma, a PubMed search was performed in April 2022. Articles containing the following key words were considered for inclusion: 'reactive oxygen species' (or 'ROS' or 'oxidative stress') AND 'autophagy' AND 'melanoma' (or 'melanomagenesis'). Relevant articles were also identified from a manual search of reference lists within those included. The abstracts of identified articles were screened and classified for inclusion in the review. A total of 60 original articles that have been published in a peer-reviewed journal and written in English were included.

2. ROS generation in melanoma

Ultraviolet (UV) radiation is a major risk factor for melanoma development. UV can transduce its electromagnetic energy into chemical, hormonal, and neural signals upon absorption, thus regulating homeostatic activity, including activation of the central nervous system and endocrine glands through neural transmission or chemical messengers, which exerts systemic effects on patients with melanoma (11). The oncogenic effect of UV on skin is induced by ROS-mediated DNA damage (12). UV penetrates the epidermis and dermis of the skin and is absorbed by various biomolecules, which generates high levels of ROS in skin cells (13). By tracing the luminescence of singlet oxygen, high ROS levels can be detected during UV exposure both *in vitro* and *in vivo* (14). Photosensitizer molecules facilitate ROS production. Vitamins, well-known endogenous photosensitizers, whose chemical structure is altered upon absorption of UV radiation, are susceptible to producing ROS via photosensitized reactions (15). ROS oxidizes fatty acids in cell membranes, lipoproteins, and other lipid-containing molecules, and ultimately leads to impairment of cellular structures and functions. Oxidized fatty acids also produce ROS under UV irradiation and become strong photosensitizers under continuous UV irradiation (16). Photosensitizers such as flavins, urocanic acids, and cholesterols have been shown to produce ROS by absorbing the energy of UV radiation (17). ROS accumulation in the skin changes the absorption of those molecules, which in turn increase ROS production (18). Thus, an increase of ROS initiates a vicious cycle that amplifies the UV-mediated damaging effects on skin cells. Furthermore, UV radiation induces the activation of ROS-producing enzymes. Valencia and Kochevar revealed that UV activated NADPH oxidase (NOX)1 to generate ROS in human keratinocytes, which stimulates prostaglandin E2 synthesis and contributes to skin injury (19). Notably, UV radiation has been revealed to improve the expression of sestrin2 in melanocytes and melanoma cells, which inhibits the antioxidant response factor nuclear factor erythroid 2-related factor 2 (Nrf2) and further aggravates ROS production (20). Excessive ROS produced by UV radiation is considered to cause skin damage and ultimately tumorigenesis, mainly via oxidative stress-induced DNA damage (21).

Compared with those of keratinocytes and fibroblasts, both melanocytes and melanoma cells exhibit higher basal levels of ROS (22). Suppressing melanin synthesis in melanocytes by N phenylthiourea alleviates intracellular ROS (23). These findings indicate that the process of synthesis of melanin is an essential source of ROS. Further mechanistic investigations revealed that the melanosome and its melanin contents were associated with oxidative reactions, where superoxide anion and H_2O_2 were produced (24). Melanin has both photoprotective and phototoxic properties based on diverse conditions. The biosynthesis of melanin requires a series of oxidoreduction reactions and consumes oxygen, which generates cytotoxic intermediates, such as free radicals. Under physiological conditions, the process of melanin synthesis is limited within the boundaries of melanosomes, and plays a protective role against UV-induced carcinogenesis; however, this process can be dysregulated with cytotoxic intermediates leaking outside melanosomes under pathological conditions, thus contributing to the malignant transformation of melanocytes (25). Melanin exerts a double role in determining ROS levels: It absorbs UV radiation and thus mitigates UV-induced ROS production in melanocytes and keratinocytes; however, melanocytes are in a state of pro-oxidation during melanin synthesis, and become more predisposed to intracellular ROS accumulation and carcinogenesis (23). One explanation could be that the pro-oxidant activity is different between the two forms of melanin in the skin, namely the reddish-yellow pheomelanin and the brown-black eumelanin. L-tyrosine and L-dihydroxyphenylalanine serve as substrates for melanin pigmentation, which is regulated by transcriptional factors including tyrosinase and tyrosinase-related proteins, and signaling pathways involving cAMP and protein kinase C (26). In addition, metal cations such as Mn^{+2} and Cu^{+2} stimulate L-dihydroxyphenylalanine auto-oxidation to melanin (27). Melanocytes with high pheomelanin content become pro-oxidant and thus generate ROS upon exposure to UV radiation and metal ions (28,29), while this effect can be prevented by eumelanin, if present in sufficient quantity (30). Thus, the enhanced ratio of pheomelanin to eumelanin in isolated melanosomes leads to mutagenesis through enhanced ROS production (30). Furthermore, eumelanin expression is regulated by the melanocortin 1 receptor gene (MC1R) signaling, which is responsible for ROS scavenging and DNA repair (31). MC1R inactivation results in elevated ROS production and compromised DNA repair, thereby leading to increased risk of carcinogenesis (32). However, increased melanin pigmentation is associated with shorter overall survival and disease-free survival time in patients with melanoma, and inhibition of melanin synthesis improves the radiotherapeutic response (33). The forms of melanin that are responsible for the negative effect of melanin on melanoma therapy remain to be investigated.

The cellular ROS pool in melanocytes and melanoma cells can be also derived from NOX family enzymes. Among them, NOX1, NOX4, and NOX5 have been demonstrated to be expressed in the melanocytic lineage (34). ROS generation induced by these NOX isoforms is required for the proliferation and malignant transformation of melanoma cells. NOX1 was shown to be upregulated in melanoma cell lines and is activated to produce ROS by the mutation of N-RAS, an oncogene, which

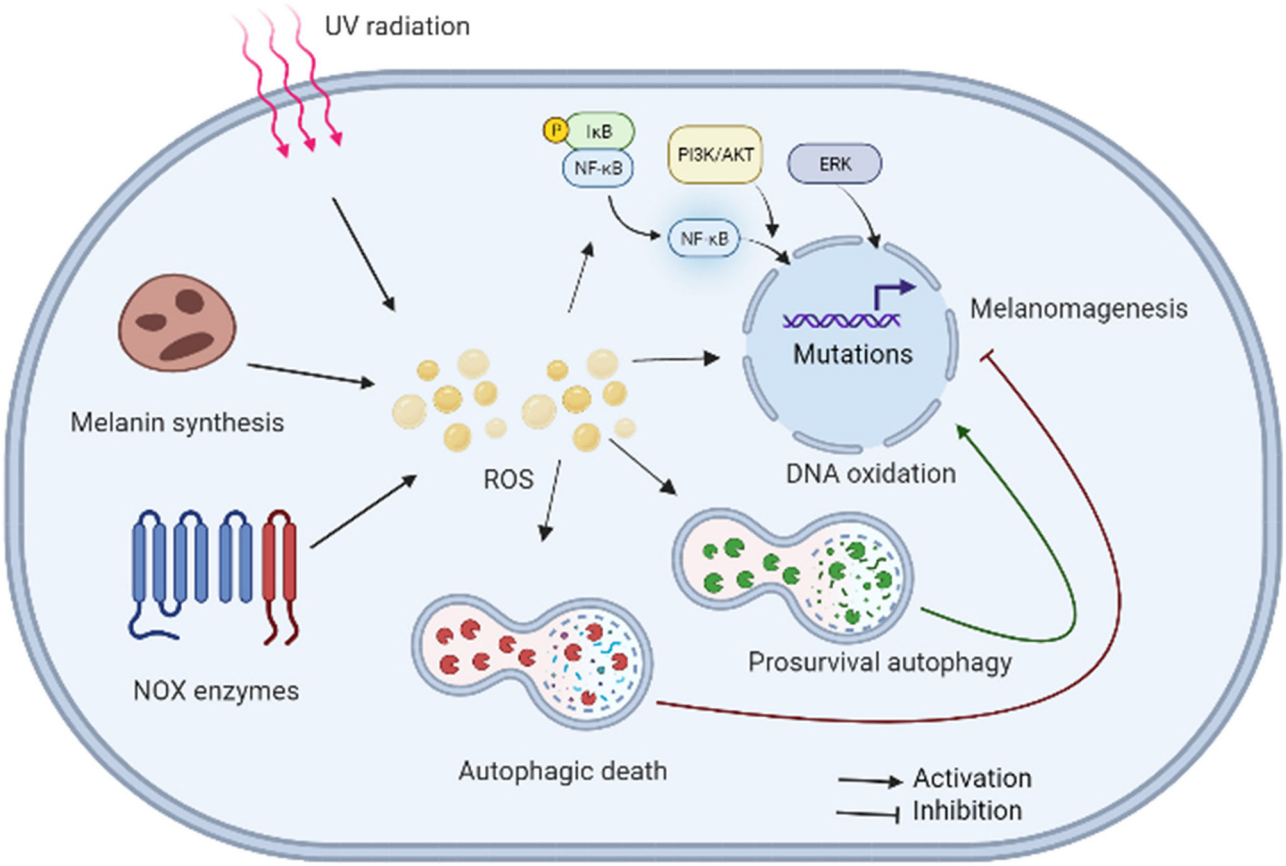

Figure 1. Role of ROS-induced autophagy in melanoma. Excessive ROS is produced through UV radiation, melanin synthesis and NADPH oxidase enzyme activation, which leads to oxidative DNA damage and genetic mutations via regulation of several signaling pathways, including NF-κB, PI3K/AKT and MAPK. Autophagy is activated by ROS and exerts dual functions: i) Providing metabolic demands for melanoma initiation and progression; and ii) inducing melanoma cell death to inhibit melanomagenesis. ROS, reactive oxygen species; UV, ultraviolet.

is involved in melanoma progression (35). NOX4 expression is significantly higher in melanoma tumors compared with that in primary tumors, indicating its oncogenic role in melanoma. Govindaraja *et al* (36) revealed that NOX4-generated ROS activated by AKT, a serine-threonine kinase highly expressed in melanoma, facilitated the transformation of radial growth to vertical growth that was required for the invasive and metastatic phenotype. In addition, ROS produced by NOX4 promote cell survival through activating the focal adhesion kinase pathway, maintaining cell adhesion and viability (37). Of note, in cultured melanoma cells under hypoxic conditions, NOX4 is involved in the generation of ROS and cell apoptosis mediated by α-melanocyte-stimulating hormone (α-MSH), an inducer of melanin (38). A possible explanation for this proapoptotic role of NOX4 is that NOX4-dependent ROS production sensitizes melanoma cells to TNF-related apoptosis-inducing ligand TRAIL-induced apoptosis via Bax phosphorylation (39). In addition, α-MSH activates its downstream signal transducer melanocyte-inducing transcription factor to stimulate NOX4 gene expression and further drive ROS generation, ultimately suppressing melanin synthesis (40). Silencing of NOX4 expression in melanoma cells attenuates ROS production and thereby suppresses cell growth and tumorigenicity *in vivo* by regulating G2-M cell cycle progression, suggesting that NOX4-generated ROS elicit a transformation in the phenotype of melanoma cells (41). Furthermore, NOX5 is overexpressed in melanoma, and affects cell proliferation through the ROS-mediated hypoxia-inducible factor (HIF)-1α and p27Kip1 signaling pathways (42). Accordingly, these results indicate that NOX-induced ROS production is associated with melanomagenesis and melanoma progression. Differences in signals and resultant effects involving these ROS-producing NOX enzymes merit further investigation.

In summary, the main contributors to ROS generation in melanoma cells include UV radiation, melanin synthesis and NOX family enzymes (Fig. 1). Excessive ROS leads to oxidative stress, which enhances the melanomagenesis and progression of melanoma.

3. Oxidative stress and melanomagenesis

Excessive ROS causes oxidative stress, which is recognized as the initiator and promoter of melanoma. The main mechanism by which ROS overproduction promotes melanomagenesis has been well established, and involves the induction of oxidative DNA damage and mutagenesis. The by-products of DNA damage include 8-hydroxydeoxyguanosine (8-OHdG), cyclobutane pyrimidine dimers, pyrimidone adducts, DNA strand breaks, and DNA crosslinks, which result in genomic instability and transcriptional silencing (43). 8-OHdG, a major form of oxidative DNA damage, is regarded as a premutagenic DNA lesion and is highly expressed in melanocytes compared

with its levels in keratinocytes (44). Similarly, the expression level of 8-OHdG is lower in patients with melanoma, who have a significantly longer survival time (45). These findings indicate that ROS-mediated DNA oxidation exacerbates a malignant phenotype, and has been implicated in the poor prognosis of patients with melanoma.

Oxidative stress also promotes the occurrence and development of melanoma via genotoxicity. On one hand, it causes oncogene activation. For example, mutations of the BRAF oncogene, occurring in ~50% of melanoma cases, are induced by oxidative stress (46). In addition, ROS stabilize the expression of HIF-1α, a transcriptional regulator of the hypoxic response, to activate the Met protooncogene, which drives the proliferation and metastasis of melanoma cells, and induces angiogenesis (47). Increased expression of HIF-1α can also originate from induction of melanogenesis in melanoma cells, and further regulates cellular metabolism and the behavior of cancer cells (48). Another oncogene, RAC1, which is associated with an increased risk of melanoma, can be activated by high levels of ROS to accelerate the migration and invasion of B16 melanoma cells; however, these effects are weakened by the suppression of ROS-mediated RAC1 activation (49). Notably, tumor suppressor genes compromised in melanoma aggravate oxidative stress. Jenkins *et al* (50) reported that depletion of p16 expression contributed to marked increases in ROS levels in cultured human melanocytes, which triggers oxidative DNA damage. Additionally, silencing large tumor suppressor kinase 1, a tumor suppressor in melanoma, was demonstrated to lead to enhanced oxidative stress, which is highly engaged in melanoma growth (51). Thus, the loss of tumor suppressor genes increases the susceptibility of melanocytes to oxidative stress and expedites carcinogenesis. On the other hand, oxidative stress mediates epigenetic modifications to induce melanomagenesis. Mologni *et al* (52) revealed that ROS increased DNA methyltrasferase 1 and DNA hypermethylation, which led to Ras activation and malignant transformation in melanoma via activation of the ERK signaling pathway.

Furthermore, oxidative stress favors the development of melanoma by the activation of specific signaling pathways. For instance, ROS-mediated oxidation of light chain 8 (LC8), a multifunctional protein of the dynein motor complex, activates the NF-κB signaling pathway due to the impaired ability of LC8 to bind to the NF-κB component I-κBα, suppressing its phosphorylation by IKK and ultimately leading to NF-κB activation (53). This effect facilitates melanoma progression by its antiapoptotic effects and creates an inflammatory microenvironment (54). Other signaling pathways, particularly the PI3K/AKT, MAPK/ERK and Nrf2 signaling pathways, are implicated in the initiation and progression of melanoma (35,43).

Melanogenesis is an essential process in melanoma cells. By interacting with hormones, neuropeptides and vitamin D, these cells participate in steroidogenesis and sex hormone conversion, which is required for the production of melanin (55). Local metabolites, such as HIF-1α, are upregulated during this process, and their accumulation can activate HIF-1-related pathways to affect the progression of melanoma (48). Melanosomes act as vital boundaries of the process of melanin synthesis, and restrict cytotoxic intermediates to leak into the surrounding environment, which influences the behavior of melanoma cells, triggering tumorigenesis (56). The induction of melanogenesis is associated with changes in glucose metabolism in melanoma cells (57). UV irradiation and UV-induced ROS also cause a persistent increase in glucose consumption, which is accompanied by increased glycolysis in these cells, and promotes the invasion of melanoma (58). In addition, intermediates of melanogenesis including quinones, semiquinones, quinonimines, and ROS produced during this process exert immunosuppressive functions in melanoma (59). The activity of T lymphocytes and cytokines, such as IL-1, IL-6, TNF-α, and IL-10, is suppressed during this process, and inhibition of melanogenesis increases the lymphocyte-mediated killing effect on melanoma cells (60). Mitochondrial ROS also promote inflammatory cytokines, including TGF-β and IL-13, which induce the activation and M2 polarization of macrophages, thus leading to an immunosuppressive microenvironment and metastatic behaviors in melanoma (61). Therefore, ROS-induced oxidative stress can facilitate melanoma progression through the promotion of glucose metabolism and immunosuppression.

ROS-mediated oxidative stress possibly leads to melanomagenesis through two potentially important effects: Genotoxicity and nongenotoxicity (Fig. 2). The genotoxic effect is induced by oxidative stress-mediated damage to DNA, which causes genetic and epigenetic changes in melanoma-related genes. The nongenotoxic effect is enhanced by the activation of specific signaling pathways that influence numerous cellular processes linked to carcinogenesis and melanoma progression. Moreover, oxidative stress triggers glucose metabolism and immunosuppression and further accelerates melanoma evasion.

4. Autophagy as a response to alleviate oxidative stress

A complex interaction between ROS and autophagy exists. In response to various stimuli, ROS and autophagy can regulate each other through a variety of signaling pathways, thus determining cell fate, which is largely dependent on the quantity of ROS produced and the antioxidant ability of cells (62). Under hypoxic conditions, large amounts of ROS are accumulated in cancer cells, which subsequently stimulate autophagy (63). As the major species of ROS, H_2O_2 is generated in these starved tumor cells as a result of PI3K activation, which induces the formation of autophagosomes through oxidation of autophagy-related gene (ATG)4 (64). In addition, both O_2 and H_2O_2 trigger autophagy by AMP-activated protein kinase activation and subsequent mTOR inhibition, as well as through transcriptional regulation of ATGs such as p62 and Beclin 1 (BECN1) (65,66). Consequently, autophagy functions as an antioxidant defense mechanism to mitigate ROS damage to cells and maintains cellular homeostasis by engulfing oxidized substances (67). However, autophagy may provide nutrients and a favorable environment for tumor progression via the degradation of ROS-damaged organelles and proteins (62). In this context, ROS-mediated autophagy may play double roles in melanomagenesis and melanoma progression.

As aforementioned, UV radiation is a major resource for ROS generation in melanoma. Exposure to UV light increases the expression of p62 in an ROS-dependent manner, which involves Nrf2 activity to counteract oxidative stress (68).

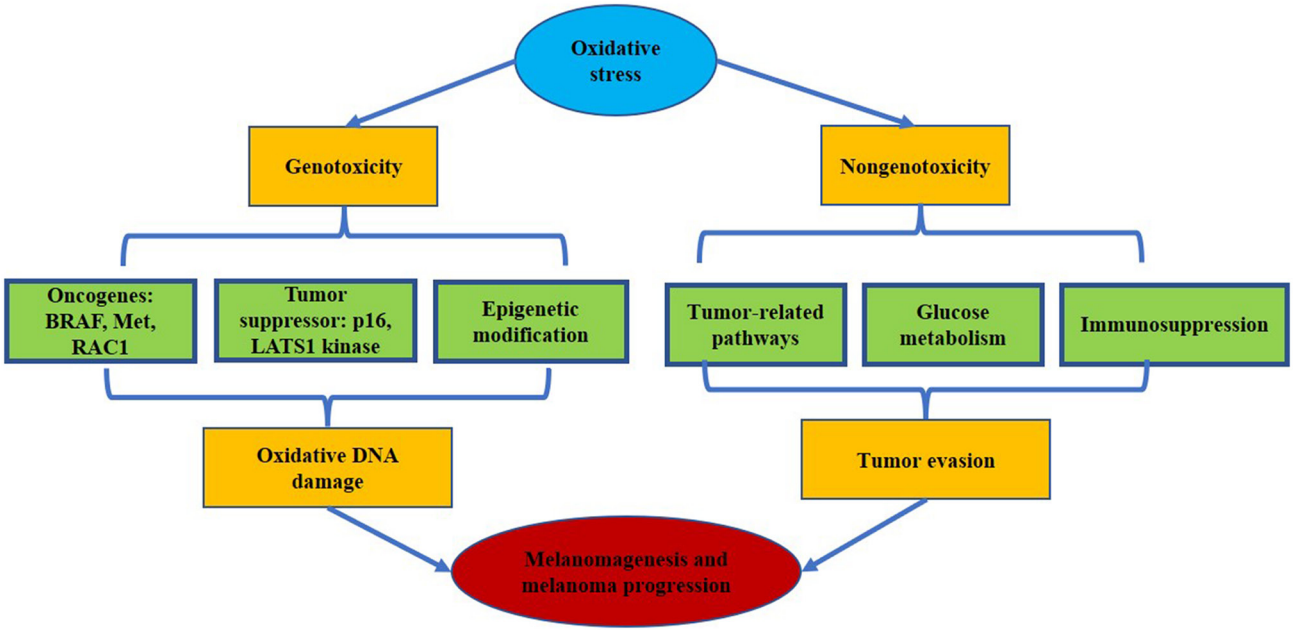

Figure 2. Role of oxidative stress on melanoma. Oxidative stress exerts a genotoxic effect via mediating DNA damage, which causes genetic and epigenetic alterations in melanoma-related genes. It also induces a nongenotoxic effect by the activation of specific signaling pathways that influence numerous cellular processes linked to carcinogenesis and melanoma progression. Moreover, oxidative stress triggers glucose metabolism and immunosuppression and further accelerates melanoma evasion.

Deletion of ATG7 in a BRAFV600E/PTEN null model of melanoma was revealed to be associated with enhanced oxidative stress and senescence, which prevent melanoma tumorigenesis (69). These findings indicate that oxidative stress-induced autophagy exerts a tumor-promoting role. Autophagy is also essential for the survival of cancer cells under starvation, which further promotes melanoma metastasis (70). Moreover, in melanoma cells in response to hypoxia and reoxygenation treatment, the persisted accumulation of intracellular ROS is accompanied by increased autophagy (71). Suppression of autophagy markedly accelerates cell death induced by cycling hypoxia via increased ROS generation (72). Therefore, excessive ROS could induce autophagy to protect the survival of melanoma cell under stress conditions. In addition, BRAFV600E has been demonstrated to increase the ER stress response, which subsequently activates cytoprotective autophagy (73). Alterations in the oxidative environment of the ER cause the generation of ER stress-induced ROS (74). For example, NOX4, an essential ROS-producing NOX enzyme in melanoma, can be activated to generate ROS during the ER stress response (75). This process is responsible for high basal autophagy during melanomagenesis. Mechanistically, the JNK-mediated phosphorylation of Bcl-2 and Bcl-xl releases BECN1; meanwhile, tribbles homolog 3 inactivates mTOR signaling, triggering the autophagy process (76). Thus, melanoma cells employ autophagy as an adaptive mechanism to moderate oxidative stress.

In conclusion, autophagy plays a prominent regulatory role in tumor cell proliferation by counteracting ROS-mediated oxidative stress and maintaining cellular homeostasis. However, ROS overproduction prolongs the activation of autophagy and its excessive induction may culminate in autophagic cell death. In this regard, ROS could switch autophagic cell survival to death. Thus, clarification of the role of ROS-induced autophagy in melanoma progression may provide a promising therapeutic strategy for this disease.

5. Role of ROS-induced autophagy in melanoma treatment

Autophagy as a protective role to ameliorate ROS-induced apoptosis. Several studies have reported that various anticancer agents are employed to treat melanoma through ROS production and ROS-mediated apoptosis (77,78). Kalantuboside B, a natural bufadienolide derivative, has been demonstrated to enhance intracellular ROS levels, which induce apoptosis and autophagy; moreover, apoptosis was revealed to be potentiated by the autophagy inhibitors chloroquine and 3-methyladenine in A2058 melanoma cells and xenografts, suggesting that autophagy plays a protective role in melanoma (9). Further mechanistic evaluation revealed that this natural agent triggered ROS-induced autophagy via activating the ERK signaling pathway and downregulating the calcium-dependent p53 signaling (9). Dihydromyricetin, another natural compound, was also found to promote autophagy to alleviate cell apoptosis through the ROS-NF-κB signaling pathway in human melanoma cells (79). In fact, autophagy serves as a modulator of ROS generation and contributes to cell survival under stress. Esomeprazole, a proton pump inhibitor, was revealed to induce ROS accumulation and ROS-mediated cell death by mitochondrial dysfunction and involvement of NADPH oxidase, while it also elicited early autophagy to reduce its cytotoxicity against melanoma (80). Similarly, shikonin, a botanical anticancer drug, was demonstrated to facilitate ER stress-mediated apoptosis by increasing the generation of ROS, which was accompanied by prosurvival autophagy through activation of the p38 signaling pathway in A375 melanoma cells (81). These findings indicate that autophagy represents an adaptive survival response to overcome drug-induced cellular

stress and cytotoxicity. In addition, Zn(II) phthalocyanine photodynamic therapy, an emerging therapy for melanoma, causes ROS-mediated oxidative stress that further activates both apoptosis and autophagy; however, suppression of autophagy strengthens phototoxicity and prevents apoptotic cell death (82). Furthermore, combination of photodynamic therapy with the natural agent curcumin was shown to aggravate oxidative stress-mediated cell apoptosis and facilitate the formation of autophagosomes, which favor ROS-damaged melanoma cells to escape apoptosis (83). Therefore, these studies suggest that these anti-melanoma therapies induce a protective autophagy to eliminate ROS, which compromises ROS-mediated apoptosis.

Autophagic cell death exacerbates ROS-induced death. A variety of anticancer drugs mediate autophagic melanoma cell death by increasing the production of ROS. Liang *et al* (84) revealed that squalene synthase (SQS) III, a derivative of *Schima crenata* Korth. with antitumor activities, induced apoptosis and autophagic cell death in the human melanoma cell line A375. These effects were reversed by the ROS scavenger *N*-acetylcysteine, indicating that SQS III-induced autophagic cell death resulted from ROS generation, which was further demonstrated to be a messenger to inhibit the AKT/mTOR signaling pathway, which is a negative regulator of the autophagy process (84). These findings demonstrated that drug-mediated ROS caused melanoma cell death by regulating autophagy-related signaling pathways. A previous study has reported that dimethylacrylshikonin, isolated from the roots of Boraginaceae, triggered the loss of mitochondrial membrane potential and thus ROS accumulation in melanoma cells, leading to autophagic cell death by mitochondrial dysfunction (85). A similar study revealed that inhibition of dihydrolipoyl dehydrogenase, a mitochondrial oxidoreductase enzyme, contributed to ROS overproduction and alteration of mitochondrial energy metabolism, and thus triggered autophagic melanoma cell death (86). Therefore, ROS generation attributed to mitochondrial dysfunction appears to be a major contributor of autophagic cell death. Additionally, berberine-photodynamic therapy activated ER stress, which contributed to a marked increase in ROS, and thus enhanced autophagy to facilitate apoptosis in human melanoma cells (87). Photodynamic therapy-induced ROS accumulation was sufficient to elicit oxidative stress, which further mediated autophagy and consequently inhibited cell proliferation in B16F10 melanoma cells (10). Furthermore, the bis(phenylidenebenzeneamine)-1-disulfide (88), graveoline (89) and terfenadine (90) have been found to induce autophagic cell death in melanoma cells through increasing ROS production.

Collectively, ROS-induced autophagy elicited by anticancer agents exerts double functions in the treatment of melanoma, either via autophagic cell survival or death (Fig. 1). It has been reported that low doses of nitrogen-doped titanium dioxide, a photodynamic therapy for melanoma, stimulate a protective autophagy flux response, whereas therapeutic doses impair autophagy and induce necroptosis via ROS production (91). A possible explanation is that the functional effects of ROS-induced autophagy on cancer cell death are dependent on the type of oxidative stress, as well as the quantity and location of the ROS produced (92). It should be noted that anticancer drug-induced ROS also inhibit cytoprotective autophagy to promote apoptosis, and that blocking autophagy fails to affect ROS generation (78,89), suggesting that ROS serve as messengers to modulate autophagy and thus determine the cell fate. In this context, further clarifying the role of anticancer drug-induced ROS and the resultant autophagy is essential for melanoma treatment.

6. Future directions

As a ROS-driven tumor, melanoma is susceptible to ROS production and thus to oxidative stress. The main resources of ROS in melanocytes comprises UV radiation, melanin synthesis and activation of NOX. Excessive ROS generation causes oxidative damage to melanocytes, including oxidative DNA damage, which is responsible for gene mutations and epigenetic alterations, as well as aberrant activation of signaling pathways that are involved in cell proliferation and differentiation, ultimately leading to melanomagenesis and melanoma progression. Autophagy is elicited as an adaptive response to remove ROS and oxidative components, which maintains genetic stability and inhibits carcinogenesis; however, once a tumor is formed, autophagy is induced to provide metabolic demands and nutrients for tumor progression. Furthermore, the sustained activation of autophagy may contribute to cell death, which is also known as autophagic cell death (Fig. 1).

The crosstalk between ROS and autophagy in melanomagenesis remains unclear. Understanding the mechanism of ROS-regulated autophagy in melanoma will provide new therapeutic strategies for this disease. In addition, it is essential to investigate whether anticancer drug-induced autophagy promotes cell survival or facilitates cell death. Agents that are cytoprotective autophagy-inducing drugs combined with autophagy inhibitors and autophagic cell death-mediating agents combined with autophagy activators are both effective therapeutic strategies for melanoma. Therefore, clarification of the functional status of ROS-induced autophagy is crucial in melanoma treatment. Of note, prolonged autophagy causes the removal of excessive ROS and the degradation of dysfunctional mitochondria, which leads to reductive stress. This novel reductive stress mechanism of cell death offers a novel approach for cancer therapy, including transfer-hydrogenation catalysts (93-95). Further studies on the role of reductive stress in melanoma may provide insights into the treatment of this disease.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

XZ performed the literature search. XZ, HL and CL wrote the manuscript. XY planned and supervised the writing of the present review article. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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