Autophagy in Skin Diseases

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Abstract

Autophagy, or self-eating, is an evolutionarily conserved process in which cytosol and organelles are sequestered within double-membrane vesicles that deliver the contents to the lysosome/vacuole for the degradation and recycling of cytoplasmic components in eukaryotes. It is well recognized that autophagy plays an important role in maintaining cellular homeostasis under physiological and pathophysiological conditions and the upregulation of autophagy may serve as an adaptive process to provide nutrients and energy when under stresses. Recently, studies have illustrated that autophagy is intricately related to skin diseases. This review provides a brief synopsis of the process of autophagy and aims to elucidate the roles of autophagy in different skin diseases and to highlight the need for increased research in the field.

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Introduction of Autophagy

Morphology

Autophagy is the cellular “housekeeping” process responsible for the degradation of damaged and dysfunctional cellular organelles and protein aggregates which is essential for normal cellular function, growth, and development [1]. There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (Fig. 1). Macroautophagy is the most common form which involves the formation of cytosolic double-membrane vesicles that sequester portions of the cytoplasm [2], and the sequestering vesicles, termed as autophagosomes, are not derived from the lysosome/vacuole membrane. Microautophagy is used to sequester cytoplasm by invagination and/or septation of the lysosomal/vacuolar membrane [3]. Chaperone-mediated autophagy is a secondary response to starvation and, unlike the other

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two processes, involves direct translocation of the targeted proteins with a consensus peptide sequence across the lysosomal membrane by specific chaperone complexes [3, 4]. The term “autophagy” we refer to usually indicates macroautophagy unless otherwise specified [5].

Process

Autophagy consists of several sequential steps: sequestration, transport to lysosomes, degradation, and utilization of degradation products [6]. The cytosolic double-membrane vesicles are first formed, termed as autophagosomes. Then fusion of the completed autophagosome with the lysosome or vacuole results in the delivery of an inner vesicle (autophagic body) into the lumen of the degradative compartment. Subsequent breakdown of the vesicle membrane allows the degradation of its cargo and eventual recycling of the amino acids, etc., generated [7] (Fig. 2). Each step seems to execute different functions in a variety of cellular contexts.

Functions

Autophagy not only eliminates the intracellular misfolded or long-lived proteins, redundant or damaged organelles, and invading microorganisms, but also is an adaptive response to provide nutrients and energy when under stresses [8]. To understand the various roles of au-

tophagy, it may be useful to subclassify macroautophagy into “basal autophagy” and “induced autophagy” [9]. The former is important for constitutive turnover of cytosolic components, while the latter is used to produce amino acids following starvation. Autophagy can act as an alternate energy source, and thus as a temporary survival mechanism under stressful conditions [6]. The presence of autophagosomes in dying cells raises the possibility that autophagy may also play an active role in cell death [10]. It is clearly demonstrated that autophagy has a greater variety of physiological and pathophysiological roles than expected, such as starvation adaptation, intracellular protein and organelle clearance, development, antiaging, elimination of microorganisms, cell death, tumor suppression, and antigen presentation [9].

Defective autophagy has been implicated in the pathogenesis of diverse disease states, such as myopathy [11], neuronal degeneration [12], microbial infection [13], inflammatory bowel disease [14, 15], aging [16], and cancer [17]. Besides its basal function, autophagy also plays a role in nutrient deprivation [18–21], metabolic stress [20, 22, 23], endoplasmic reticulum (ER) stress [24, 25] radiation [26], and anticancer drugs [27–30]. Therefore, it may be difficult to draw simplified connections between autophagy and skin diseases.

Autophagy in Skin Diseases

Autophagy in Infectious Skin Disease

Autophagy can protect against viral and other intracellular infection through degradation of viral/pathogen components (xenophagy), by promoting the survival or death of infected cells, through delivery of Toll-like receptor (TLR) ligands to endosomes to activate innate immunity [31], or by feeding antigens to major histocompatibility complex (MHC) class II compartments to activate adaptive immunity [32].

Fig. 1. Three types of autophagy.

Fig. 2. Schematic diagram of autophagic process. Upon stimulation, the cytosolic double-membrane vesicles are formed, termed as autophagosomes. Then fusion of the completed autophagosome with the lysosome results in the delivery of an inner vesicle (au-

tophagic body) into the lumen of the degradative compartment. Subsequent breakdown of the vesicle membrane allows the degradation of its cargo and eventual recycling of the amino acids.

Autophagy in Viral Infectious Dermatoses

Epstein-Barr virus (EBV) is the type 4 of human herpes virus and is related to cutaneous lymphoma. EBV infection can also result in infectious mononucleosis, hemophagocytic syndrome, nasopharyngeal carcinoma and lymphoma, etc. CD4⁺ T cells recognize EBV nuclear antigen 1 (EBNA1, the dominant CD4⁺ T-cell antigen of latent EBV infection) by presentation on MHC class II molecules [33]. Casper's research found that using autophagy suppressor 3-methyladenine (3-MA) or silencing the autophagy-related gene (Atg) 12 (autophagy-associated gene) by siRNA can inhibit this process. Inhibition of autophagy decreased recognition by EBNA1-specific CD4⁺ T-cell clones. Thus, autophagy could eliminate virus via promoting CD4⁺ T cells to recognize antigens by MHC II [34].

Herpes simplex is caused by herpes simplex virus (HSV), including HSV-1 and HSV-2. The virus replicates at the portal of entry (mouth, genitals), and concurrently it is transported retrogradely to sensory neurons [35]. HSV-1 infection can induce herpes labialis, pharyngitis, keratitis, etc. [36], while HSV-2 can give rise to herpes proctogenitalis through damaged epidermis and mucosa [37]. Studies demonstrate HSV-1-encoded neurovirulence protein ICP34.5 binds to the mammalian autophagy protein beclin 1 and inhibits its autophagy function [38]. HSV-1 activates PP-1a by virulence factors ICP-34.5, dephosphorylating PKR-mediated eIF2a and eventually blocking the PKR signal pathway, thus inhibiting autophagy.

Human papillomaviruses (HPVs) are associated with a spectrum of diseases, from benign verrucae vulgares and condylomata acuminata to the malignancies of the cervix, vulva, anus, and penis. HPV-associated diseases can be divided into skin and mucosal lesions of the genital and extragenital regions. HPV is also related to skin tags, lichen sclerosus, seborrheic keratoses, actinic keratoses, epidermal cysts, psoriatic plaques, and plucked hairs [39]. HPV-16 can cause cervical carcinoma, and autophagy may be induced by the E7 protein of HPV-16, which can enhance the lipidation of LC3 and increase the number of LC3 puncta (autophagic vacuoles) in keratinocytes [40]. As keratinocytes expressing E7 are prone to cell death upon cell-to-cell contact or serum deprivation, autophagy induced by E7 may sensitize cells to death [41].

Varicella zoster virus (VZV) infection causes varicella or herpes zoster. Researches indicate VZV lacks ICP34.5 homologous protein. Western blot shows LC3B (an autophagosome-specific membrane marker) and p62/SQSTM1 protein (a ligand of autophagy) express in VZV-infected cultured cells. In addition, autophagosome (final

site of virion assembly) formation in infected cells closely resembled that seen after treatment of cells with tunicamycin, a potent initiator of ER stress. Meanwhile, a marked expansion of ER size, which is critical evidence of ER stress, emerges in both VZV-infected cells and cells transfected with the predominant VZV glycoprotein complex gE/gI. The above results suggested that autophagy was a common event in VZV-infected cells and that it was provoked at least in part by ER stress secondary to overly abundant VZV glycoprotein biosynthesis, which led to unfolded protein response activation in an attempt to maintain cellular homeostasis [42].

Autophagy in Bacterial Infectious Dermatoses

Streptococcus-Related Dermatoses. Group A *Streptococcus* (GAS) species are responsible for a wide variety of human diseases that range from noninvasive, mild infections, such as pharyngitis, to life-threatening, invasive conditions, such as bacteremia, pneumonia, or necrotizing fasciitis [43]. In skin diseases, GAS is responsible for impetigo, acute rheumatic fever, erysipelas, psoriasis, etc. [44]. Nakagawa's research has found that autophagic machinery could effectively eliminate GAS within non-phagocytic cells [45]. In GAS-infected cells, LC3-II, which binds to autophagosomes [46, 47] and directly correlates with the number of autophagosomes, increased. After escaping from endosomes into the cytoplasm, GAS became enveloped by autophagosome-like compartments and were killed upon fusion of these compartments with lysosomes. In autophagy-deficient Atg5^{-/-} cells, GAS survived, multiplied, and were released from the cells. Thus, the autophagy is induced by GAS invasion and can act as an innate defense system against GAS.

Mycobacterium-Related Dermatoses. *Mycobacterium tuberculosis* or tubercle bacillus causes tuberculosis, one of the most prevalent infectious diseases worldwide [48]. Overall, one third of the world's population is currently infected with the tubercle bacillus [49]. Tuberculosis usually attacks the lungs but can also affect other parts of the body such as the skin, resulting in tuberculosis cutis. Tuberculosis cutis is a chronic granulomatous inflammatory disease of great damage. It causes tissue destruction and necrosis [50], which is balanced by healing and fibrosis, finally appearing as tiny white tubercles in the tissues. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. Studies demonstrate that autophagy has a complex interaction with mycobacteria: it influences both the direct antimycobacterial host defense mechanisms, as well as the inflammatory response to mycobacteria [51]. The intracellular *M. tuberculosis* can

be eliminated by the induction of autophagy. The induction of autophagy overcomes the mycobacterial phagosome maturation block and delivers the tubercle bacilli to degradative compartments where they are eliminated [52]. Under normal circumstances, *M. tuberculosis* enters the host macrophages where it resides in phagosomes that remain immature and do not acquire phagolysosomal degradative characteristics [53, 54] and survives in macrophages by inhibiting phagolysosome biogenesis. *M. tuberculosis* blocks phagolysosome formation by interfering with phosphatidylinositol-3-phosphate (a key membrane trafficking regulatory lipid required for phagosomal maturation) generation [55–60], whereas autophagy is a phosphatidylinositol-3-phosphate-dependent process that can overcome *M. tuberculosis* phagolysosome biogenesis arrest. Another connection between autophagy and immunity is the endogenous pathway of MHC II cytosolic antigen processing and presentation [34, 61]. Several bioactive lipids, such as S1P [62], ceramide [63], and vitamin D₃ [63–65], shown to have antimycobacterial activity play a role in autophagy. In addition, cytokines, such as interferon- γ [66], TNF- α [67], and interleukin (IL)-1 β [68], strongly correlating with protective immunity against tuberculosis, induce autophagy and bypass phagolysosome biogenesis arrest. Recent studies show that the tubercle bacillus is associated with polymorphisms in IRGM1, a gene essential for autophagy, and with a number of other genes that regulate the process of autophagy [51], such as Atg5, Atg8, and Atg12 [52]. The induction of autophagy by pharmacological (rapamycin) or physiological (amino acid starvation) means promotes elimination of intracellular *M. tuberculosis* in a wortmannin and 3-MA-sensitive manner [69].

Autophagy in Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease that affects approximately 2% of the population worldwide [70]. It is a multifactorial disorder, influenced by both genetic and environmental factors [71], and pathologically characterized by inflammation and epidermal proliferation.

Several pathogens, such as bacteria, viruses and even fungi, have been linked to psoriasis [72]. The strongest association occurs with tonsillar *Streptococcus pyogenes* infection, which has been linked to the development of guttate psoriasis and can persist as chronic plaque psoriasis [73]. As stated above, autophagy eliminates the bacte-

ria; thus, decreased autophagy in psoriasis leads to altered clearance of and/or altered immune responses to bacteria.

As an immune-mediated disease, T lymphocytes and related cytokines are the key to the pathogenesis of psoriasis. Mounting evidence indicated that T-helper (Th) 17 cells, inflammatory CD4⁺ T cells, play critical roles in the development of autoimmunity and allergic reactions by producing IL-17 [74] and present an increased level in psoriasis [75]. Studies showed that IL-17A-stimulated keratinocytes activated PI3K/AKT/mammalian target of rapamycin (mTOR) signaling and inhibited autophagy by simultaneously inhibiting autophagosome formation and enhancing autophagic flux [76], while regulatory T (Treg) cells, which release anti-inflammatory cytokines like IL-10 and transforming growth factor- β_1 , have an anti-inflammatory effect and maintain tolerance to self-components by contact-dependent suppression or releasing IL-10 and transforming growth factor- β [77]. A study showed that the ratios of Th17 to Treg cells were significantly higher in the patients with psoriasis than those in the normal controls, which demonstrated that the balance between Th17 and Treg plays an important role in the pathogenesis of psoriasis. A recent study shows that sRAGE (receptor for advanced glycation end-products, RAGE) overexpressing mesenchymal stem cells potentially inhibited Th1, Th17 cell differentiation and increased the level of CD4⁺FoxP3⁺ Treg cells. Meanwhile, mesenchymal stem cells that overexpressed sRAGE displayed enhanced migration activity and autophagy vesicle [78]. Another research demonstrated that intraperitoneal administration of metformin can ameliorate the clinical severity of acute graft-versus-host disease and lethality, which was associated with reductions in Th1 and Th17 and rises in Th2 and Treg cells. Furthermore, metformin-treated Th17 cells became converted into Treg cells via enhanced autophagy [79]. As stated above, autophagy was enhanced when Th17 decreased and Treg cells increased. The ratio of Th17 to Treg cells was elevated in patients with psoriasis; thus, decreased autophagy could affect psoriasis through Th17 and Treg cells.

CD147/basigin, a highly glycosylated transmembrane protein, belongs to the immunoglobulin superfamily, significantly responsible for the genesis and development of psoriasis. It is higher on neutrophils in psoriatic lesions than that of normal tissues [80]. Several studies demonstrated that CD147 played an important role in the inhibitory regulation of autophagy and autophagic cell death in tumor cells [81, 82]. Since CD147 contributes to the occurrence of psoriasis, and CD147 can modulate autophagy,

gy through the PI3K/Akt/mTOR pathway [83], we hypothesize that autophagy may affect psoriasis with CD147.

Several regions which regulate the innate and adaptive immune system in the genome, including the psoriasis susceptibility locus 1 (PSOR1), have been identified as conferring susceptibility to psoriasis [84]. Now that autophagy plays an important role in immune regulation including thymic selection, lymphocyte development and survival, antigen presentation, and tissue homeostasis [85], research found that polymorphisms in Atg16L1 gene (rs10210302, rs12994971, rs2241880, rs2241879, and rs13005285) contributes to the risk of psoriasis vulgaris [86]. Atg16L1 gene encodes the Atg16L1 protein, a key component of a large protein complex essential for autophagy [87]. Atg16L1 deficiency affects the autophagy machinery on signaling pathways that regulate cytokine production and result in accumulation of damaged proteins and organelles that are toxic, leading to cell death, tissue damage, and chronic inflammation.

Psoriasis is characterized by heavily scaled red plaques. The excessive epithelial keratinocyte (KC) proliferation and abnormal apoptosis are important features of psoriasis [88], and inhibition of the excessive proliferation of KCs is an effective treatment method [89]. Studies have recently shown that autophagy deficiency leads to inflammatory cytokine production and cell proliferation in KCs [90]. KC autophagy negatively regulates the scaffolding adaptor protein p62 (an autophagy receptor) expression, which is essential for the prevention of excessive inflammation and the induction of cathelicidin in human KCs. The pathway is activated by stimulation of TLR2/6 or TLR4 in KCs and p62 expression is upregulated through induction of NADPH oxidases 2 and 4 and the generation of reactive oxygen species. MyD88 and TNFR-associated factor 6, key signaling molecules that mediate TLR activation, are also important for the induction of autophagy and p62 expression. In addition, enhanced inflammatory responses and increased cell proliferation were observed in KCs treated with 3-MA and Baf-A1 which interfere with early and late autophagic processes or with siRNA targeted to genes essential for autophagy (hBeclin-1, hAtg5). While genetic knockdown of p62 resulted in a significant decrease in NF- κ B activation, inflammatory cytokine production, cathelicidin expression, and cell proliferation reduce the production of inflammatory cytokines and cell proliferation in KCs.

Moreover, autophagy links with psoriasis for its connection with apoptosis. The increasing apoptosis found in skin lesions is a feedback to uncontrolled proliferation and a protective mechanism to maintain cell dynamics

[91]. Autophagy is upregulated when superfluous reactive oxygen species accumulate resulting in mitochondria damage to prevent cells from further damage under hypoxia [92]. Hypoxia-inducible factor 1 α is the key factor to induce autophagy in hypoxia, and it is demonstrated that hypoxia-inducible factor 1 α expression is markedly increased in psoriatic lesions compared to normal skin. Therefore, we speculate psoriasis upregulates hypoxia-inducible factor 1 α , then promotes beclin-1 expression, and induces autophagy to clear the damaged mitochondria, hence suppressing mitochondrial-mediated apoptosis and promoting proliferation of KCs.

Autophagy in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE), also called lupus, is a chronic autoimmune disorder caused by both multiple genetic and environmental factors [93]. It affects multiple vital organs and systems such as the kidneys, heart, brain, and immune system [94]. The skin is also frequently affected.

Genome-wide association studies find that variants near or within the Atg5 locus, which is important for innate immune responses, are associated with SLE initiation and/or development [95]. Atg5 defends against invading pathogens and environmental stressors, such as ultraviolet irradiation, by delivering viral nucleic acids to endosomal compartments containing TLR7, which senses the viral nucleic acids and signals the induction of type 1 interferon production [96]. Atg5 mutant ascends the expression of microtubule-associated protein 1 light chain 3 (MAPLC3) mRNA in peripheral blood mononuclear cells and elevates beclin-1 expression [97]. It further supports that autophagy of peripheral blood mononuclear cells is involved in SLE.

Research found autophagy increased in T lymphocytes from both lupus-prone mouse models and human lupus patients compared with normal controls and on-lupus autoimmune diseases [98]. Meanwhile, a recent study suggests that autophagy is increased in murine and human lupus B cells and that autophagy is required for B-cell development [99]. It is further demonstrated that drugs modulating autophagy such as hydroxychloroquine [100], rapamycin [101] and the P140 peptide [102, 103] show beneficial effects on the development of the pathology in lupus-prone mouse models as well as in patients with SLE [104].

Autophagy in Skin Squamous Cell Carcinoma

Skin squamous cell carcinoma (SSCC) is a common form of skin cancer that develops in the thin, flat squamous cells which make up the outer layer of the skin. Recent researches investigated the role of autophagy in SSCC and the relationship with chemotherapy sensitivity.

The multifunctional glycoprotein cluster of differentiation CD147, as stated in psoriasis, is highly expressed on the cell surface of the majority of cancer cells and promotes tumor invasion, metastasis, and growth [105]. X-linked inhibitor of apoptosis, an important member of the inhibitor of apoptosis family that plays an essential role in suppressing apoptosis via inhibition of the caspase family, is the common mechanism of resistance to chemotherapy [106]. The silencing of CD147 reduced X-linked inhibitor of apoptosis expression and sensitized multi-drug-resistant SCC cells to 5-fluorouracil-mediated apoptosis [82]. The study demonstrated that CD147 inhibition and subsequent X-linked inhibitor of apoptosis depletion result in an antitumor effect by enhancing the susceptibility of cancer cells to apoptosis.

A study demonstrated the relation between autophagic activity and the aggressiveness of SSCC by tumor thickness and proliferative activity [107]. 75 cutaneous SCC of variable tumor thickness showed LC3A positivity by immunohistochemistry, representing in three patterns diffuse cytoplasmic, cytoplasmic/perinuclear, and “stone-like” structures (a large, rounded, densely stained amorphous material, 5 µm on average). Compared with the intermediate-thickness tumors (2.1–6 mm) and the <2-mm-thick tumors, >6-mm-thick SCC showed higher numbers of stone-like structures, which indicated that tumor aggressiveness was directly linked with stone-like structure counts and inversely with the cytoplasmic pattern.

Additionally, tumor suppressor WW domain-containing oxidoreductase was found dampening autophagy thereby rendering SCC cells susceptible to methotrexate-induced apoptosis by interacting with mTOR and down-regulating autophagy-related beclin-1, Atg12-Atg5 and LC3-II protein expression and autophagosome formation in SCC [108]. And the failure in inducing WW domain-containing oxidoreductase expression leads to chemotherapeutic drug resistance.

Another research suggests low MAPLC3 expression in SSCC [109] and a negative correlation with Bcl2 and survivin. The chemotherapy drug 5-fluorouracil increased the level of autophagy, thus resulting in drug resistance, and this process can be suppressed by the autophagy inhibitor 3-MA, time- and dose-dependently. When SSCC

cells were treated first with 3-MA and then with 5-fluorouracil, the inhibition of proliferation, migration, invasion, and apoptosis of SSCC cells was enhanced. And a recent report indicates that chloroquine, an autophagy inhibitor, can also enhance cell death induced by the flavonoid luteolin in metastatic SCC cells [110].

Autophagy in Melanoma

Melanoma originates from the melanocytes, the pigment-producing cells which reside at the base of the epidermis [111, 112]. Melanoma is the result of the interplay between the environment, such as ultraviolet light [113], and genetic components, including mutations in the CDKN2A, CDK4, RB1, MITF, KIT, NRAS and BRAF [114]. Those factors might stimulate malignant transformation of melanocytes. Melanoma is the most aggressive skin cancer and remains one of the most difficult human cancers to treat. It has been reported that during early stages of malignant transformation autophagy is decreased as compared to normal melanocytes, which is associated with downregulation of Atg5 [115]. However, in established melanoma, autophagy is enhanced enabling cancer cells to survive under high demands of metabolism and stressful microenvironment [116]. Meanwhile, a high level of autophagy in melanoma patient's tumors is related to a lower therapeutic response and a worse outcome [117].

In the early 1980s, pathologists described the presence of giant autophagic melanosome complexes in malignant melanoma [118]. Studies investigating the alterations in the autophagic status of the cells during melanomagenesis found that in benign nevi, autophagy was increased to support oncogene-induced senescence, such as driven by BRAFV600E [119]. However, during the early stages of malignant transformation, autophagy is decreased as compared to benign nevi [115] and melanocytes [120].

A research containing 12 cases of cutaneous malignant melanoma of the superficial spreading type, cells in florid melanoma in situ and invasive cells in the dermis exhibited autophagy through immunohistochemistry using the marker LC3B, and by electron microscopy [121]. It has been demonstrated that adaptation to ER stress is a driver of melanoma progression, while ER stress is known to trigger autophagy [25]. Therefore, autophagy is a protective mechanism for progressing melanoma when the ER is stressed by hypoxia and nutrient deprivation [122, 123].

Research found that in metastatic melanoma, the autophagy capacity is re-established to support cancer cells'

		Skin diseases	Mechanism	Autophagy-related gene
Viral infectious	EBV	Cutaneous lymphoma	Promote CD4+ T cell recognize antigens by MHC II	Atg12
	HSV	Herpes simplex	Block the PKR signal pathway	PP-1a
	HPVs	Verrucae vulgares, condylomata acuminata	Enhance the lipidation of LC3	E7
	VZV	Varicella, herpes zoster	ER stress	Atg5
Bacterial infectious	<i>Streptococcus</i>	Impetigo, acute rheumatic fever, erysipelas, psoriasis	Prolong intracellular survival	Atg5
	<i>M. tuberculosis</i>	Tuberculosis cutis	Host defense mechanisms, inflammatory response	IRGM1, Atg5, Atg8, Atg12
Genetic and environmental factors		Psoriasis	Regulate the ratios of Th17 and Treg cells	sRAGE
			Cell death, tissue damage, chronic inflammation	Atg16L1
			Inflammatory cytokine NF- κ B activation	p62
			Mitochondrial-mediated apoptosis	HIF-1a
		Systemic lupus erythematosus	Increase B-cell development	Atg5
		Skin squamous cell carcinoma	Susceptible to MTX-induced apoptosis	WWOX
			Drug resistance	MAPLC3
		Melanoma	Support metabolic demands and survival	Beclin, Atg7

Fig. 3. The mechanisms and autophagy-related genes in skin diseases.

high metabolic demands [116] and survival in the face of the stressful tumor microenvironment. Pharmacological inhibition of autophagy or knockdown of key autophagy genes, such as Beclin1 and Atg7, induces spontaneous melanoma cell death and reduces the clonogenic expansion of metastatic melanoma cells [124, 125].

Besides, autophagy has been shown to be stimulated by various antimelanoma therapeutic regimens showing a predominantly cytoprotective function [126], thus suggesting that interfering with autophagy could ameliorate their therapeutic effects. For example, IL-2 therapy induces massive autophagy activation, which when inhibited with the lysosomotropic drug CQ improved therapeutic outcome. When treating with the mTORC1 inhibitor temsirolimus, it induced pro-survival autophagy and the combination of temsirolimus with CQ treatment significantly increased therapy response [127]. In addition, patients harboring wild-type BRAF following anticancer therapy may be ameliorated by the combination with an autophagy blocker. On the other hand, for patients who express the BRAFV600E mutant, autophagy blockers will only be effective when combined with a BRAFV600E inhibitor [128]. Those results suggest that therapies inhibiting autophagy were effective for the treatment of malig-

nant melanoma by depriving cells of an important energy source.

These studies stated above indicate that melanoma progression is coupled to alterations in the amount of autophagosomes as well as pro-autophagic proteins, supporting a dynamic role for autophagy in melanoma progression.

Conclusions

The mechanisms and functions of autophagy in skin diseases are intricate. It plays a double-edged sword role in skin cancer, as deficiency of autophagy promotes cancer progression in association with oxidative and ER stress, DNA damage accumulation, genomic instability and persistence of inflammation, while functional autophagy enables cancer cell survival under stress and likely contributes to treatment resistance. Thus, treatment targeting autophagy could ameliorate the outcome of skin diseases (summarized in Fig. 3). Understanding of autophagy mechanisms and their regulation in different tissues and cells under healthy and stressed conditions will help us better understand the pathogenesis of skin diseases and develop more effective therapeutic approaches.

Key Message

This review elucidates the roles of autophagy in infectious dermatoses, psoriasis, systemic lupus erythematosus, and skin cancer.

Disclosure Statement

The authors have no financial or nonfinancial competing interests to declare.

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