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Autophagy in psoriasis and vitiligo

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ABSTRACT

Autophagy is a primary catabolic process in eukaryotes which is responsible for degrading dysfunctional and redundant cellular organelles and proteins. The autophagy process plays several roles in maintaining cellular homeostasis, including an endogenous defence mechanism that might play an important role in the development and progression of skin diseases.

Psoriasis and vitiligo are common chronic inflammatory skin disorders. Psoriasis is characterized by well-demarcated, erythematous, thickened plaques with an overlying scale. Exact aetiology is complex and influenced by genetic and environmental factors but is not entirely explained. Defects of autophagy in psoriatic skin are likely involved in increased inflammation and disturbed keratinocyte differentiation. Research indicates that autophagy disorders may be associated with various pathways and molecules such as PI3K/AKT/mTOR or toll-like receptors. Vitiligo is characterized by the loss of functional melanocytes. Many hypotheses have been proposed for the pathogenesis of this disease. Autoimmunity and oxidative stress in melanocytes remain the most frequently mentioned. Deregulated autophagy in vitiligo melanocytes might disrupt the antioxidant defence system, which causes melanocytes to have oxidative insults.

Still, due to the complexity of this process, its precise role in immune-related inflammatory skin diseases such as psoriasis and vitiligo remains unclear. Objective results will enable the application of new therapeutic strategies.

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Key words: autophagy, vitiligo, psoriasis, skin barrier dysfunction

INTRODUCTION

Autophagy, literally meaning "self-eating", is a primary catabolic process in eukaryotes that allows cells to recycle and degrade cytoplasmic materials by the lysosome [1]. The autophagy process plays several roles in maintaining cellular homeostasis. Primarily, it removes old or damaged substances and pathogens from cells. Also, it supports an immune response or inflammatory processes and is an adaptive response to provide nutrients and energy during stressful conditions and starvation [2, 3]. Autophagy pathways include macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA); the main difference between them is the way of delivering materials to the lysosome [3, 4]. Macroautophagy is the major and the most common form of autophagy. This form involves the formation of the phagophore, and after elongating and closure, it forms the autophagosome, cytosolic double-membrane vesicle. Then autophagosomes fuse with lysosomes or vacuole and form autolysosomes, in which cytoplasmic components are degraded, and amino acids or other substances are eventually recycled. In microautophagy, lysosomes directly engulf the cytoplasm. Chaperone-mediated autophagy (CMA) also omits autophagosomes. Specific cytosolic proteins are transported into lysosomes by specific chaperone complexes, and individual proteins are removed [3, 5].

The autophagic process is regulated by a group of the autophagy-related gene (ATG), which initiates the formation of autophagosomes. Presently over 30 ATGs have been identified with 18 genes referred to as core ATG genes [1, 6]. In general, the functional core proteins consist of four groups: UNC-51-like kinase (ULK1) complex, the class III phosphatidylinositol 3-kinase (PI3K) complex containing Beclin 1 and two ubiquitin-like conjugation systems: the ATG5-ATG12 and the microtubule-associated protein 1 light chain 3 (LC3-ATG8) conjugation systems [4, 6]. Control of autophagy depends on many signalling complexes. The mammalian target of rapamycin (mTOR) is the critical upstream regulator of autophagy [7]. Energy depletion can activate AMP-activated protein kinase (AMPK) and activate the mTOR substrate complex, consisting of phosphorylated ULK1, ATG13, ATG101, and FIP200. Moreover, this pathway positively regulates the formation of autophagosomes. Envi-

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ronmental signals suppress autophagy by inhibiting mTOR. In addition, signalling of insulin and other growth factors activates PI3K-AKT class I, which inhibits autophagy by activating the mTOR signalling complex and inhibiting the Beclin 1 class III PI3K complex [8].

The skin is the body's largest organ and an integral interface between the organism and the external environment. It is the first barrier in the human body that protects against environmental dangers, including ultraviolet (UV) radiation, pathogens, allergens, mechanical stresses, oxidative stress, and toxic chemicals. The permeability barrier function is the most vital defensive function for terrestrial life [9]. Autophagy as a form of an endogenous defence mechanism that regulates skin homeostasis might play a vital role in the development and progression of skin diseases.

PSORIASIS

Psoriasis is a common, recurrent inflammatory chronic disease of the skin characterized by well-demarcated, erythematous, thickened, papulosquamous plaques with an overlying scale and possible comorbid arthritis or metabolic diseases. Plaques usually appear on the skin of the extensor aspects of elbows and knees, scalp and lumbosacral region, and umbilicus [10, 11]. Psoriasis affects 3% of the world's population. The prevalence of psoriasis appears highest in Northern Europe and lowest in East Asia. Studies suggest that psoriasis is a multifactorial or polygenetic disorder influenced by genetic and environmental factors [10]. Excessive activation of the adaptive immune system is thought to be central to the pathogenesis of psoriasis [12]. Traditionally, psoriasis is considered a T cell-controlled systemic inflammatory disease. The massive infiltration of lymphocytes, macrophages, and neutrophils into the skin is a hallmark of the psoriatic lesion [13].

It is known that several single nucleotide polymorphisms (SNPs) in ATG16L1 gene (rs10210302, rs12994971,rs2241880, rs2241879, and rs13005285) are linked susceptibility to psoriasis. ATG16L1 deficiency affects the autophagy machinery on signalling pathways that control cytokine production and result in the accumulation of toxic products of proteins and organelles, leading to cell death, tissue damage, and chronic inflammation [14]. The PI3K/AKT/mTOR pathway is an important upstream autophagy signal transduction pathway that regulates cell proliferation, apoptosis, survival, growth, and metabolism under physiological and pathological circumstances [15]. Activation of the PI3K/AKT/mTOR pathway and progressive inflammation in keratinocytes is often indicated as one of the possible disorders of autophagy in psoriasis. Varshney et. al [15] suggest that autophagy may be one of the mechanisms in regulating IL-17A-mediated inflammation in psoriasis. PI3K/AKT/mTOR activation in keratinocytes leads to autophagy inhibition by simultaneously inhibiting autophagosome formation and enhancing autophagy flux and increasing cholesterol during an IL-17A mediated inflammatory response. The activation of the PI3K/AKT/mTOR signalling pathway is also regulated by Aurora kinase A (AURKA). AURKA can aggravate the inflammatory response by blocking autophagy-mediated AIM2 inflammasome suppression. Results of one research showed that AURKA promoted inflammation in psoriasis skin by this mechanism [16]. Long non-coding RNA (lncRNA) maternally expressed gene 3 (MEG3) also controls PI3K/AKT/mTOR. Tang et al. [17] show that lncRNA MEG3 suppressed inflammation and facilitated autophagy in psoriasis by inhibiting PI3K/AKT/mTOR pathway. Psoriasis may also be connected with AMPK signalling pathway mediated autophagy and mitochondrial autophagy. Shen et al. [18] found that AMPK signalling was lowered in the skin tissues of psoriatic mice. Autophagy signals (ULK1 and ATG7) and mitochondrial autophagy signals (Pink1 and Parkin) were inhibited in the skin tissues of psoriasis mice, thereby aggravating the severity of psoriasis in mice. Up-regulation of AMPK signalling promoted autophagy and mitochondrial autophagy, thus playing a protective role in psoriatic mice. Their results demonstrate that inhibition of AMPK signalling affects the development of psoriasis by regulating autophagy and causes increased skin inflammation. In addition, Nada et al. [19] found that LC3, one of the most specific markers of autophagy monitoring, is reduced or absent in the epidermis of psoriasis patients, but there was no significant difference in LC3 expression compared to patients with different degrees of disease. Other observations were made by Wang et al. [20] they showed that the numbers of LC3 of autophagy markers and BECN1 and ATG5 were increased in the human psoriatic epidermis. They demonstrate that keratinocyte autophagy was positively correlated with psoriatic severity in patients. In another study, ULK1 has been suggested as a central node that integrates information from different signalling pathways such as AMPK or mTOR. It was found that ULK1 inhibition exerted an anti-psoriatic effect. However, psoriatic keratinocytes (KCs) already exhibited a lower level of ULK1 and phosphorylation at Ser556, implicating that a self-regulatory process exists to downregulate ULK1 in maintaining epidermal homeostasis in the context of psoriasis. Moreover, it was suggested that the communication of KCs and neutrophils might also be involved in the immunopathogenesis of psoriasis, so the inactivation of ULK1 could inhibit inflammation by targeting KCs and impairing their crosstalk with neutrophils [21].

Enhanced oxidative stress is associated with the severity of psoriasis [22]. Accumulation of superfluous reactive oxygen species (ROS) results in upregulating autophagy, which impairs mitochondria but also protects cells from further

damage under hypoxia. Hypoxia-inducible factor 1a (HIF-1a) induces autophagy in hypoxia. In psoriatic skin compared to normalskin noted that HIF-1a expression is clearly increased [3]. The Beclin1 protein is essential for the formation of autophagosomes. Nucleocytoplasmic topographic localization of Beclin1 was present only in psoriatic skin (either lesional or perilesional), with cytoplasmic localization being higher in the healthy epidermis [23]. Beclin1 is primarily localized in the cytoplasm and plasma membrane with a tiny part in the nucleus. Its nuclear localization is increased during extreme stressful conditions [5]. Psoriasis is speculated to upregulate HIF-1a, then promotes Beclin1 expression, and induces autophagy to clear the damaged mitochondria, suppressing mitochondrial-mediated apoptosis and promoting the proliferation of keratinocytes. Another research demonstrated that aryl hydrocarbon receptor (AHR) overexpression and activation may be involved in psoriasis pathogenesis. AHR activation by environmental stimuli inhibits autophagy, contributing to skin inflammation via the p65NF-κB/p38MAPK signalling pathway [24]. Laboratory studies also reported that AHR activation affects the proliferation and differentiation of Th17 cells, which have critical roles in psoriasis pathogenesis [25]. Toll-like receptors (TLRs) are a group of key recognition molecules in the immunity system, involved in the production of antimicrobial immune and pro-inflammatory mediators [7]. Inflammatory cytokine production is mediated by a disorder in keratinocyte autophagy. KCs detect the danger signals via the TLR system and initiate innate immune responses. Activation of TLR3 leads to an increase of pro-inflammatory cytokines related to psoriasis. Li et al. [26] indicate that activated autophagy attenuates TLR3, thus modulates cytokine production, and preserves keratinocyte homeostasis. The pathways controlling the activation of autophagy tightly control the expression of the p62/SQSTM1 scaffold adapter protein (p62). In another study, Lee et al. [27] show that keratinocyte autophagy negatively regulated p62 expression, which is essential for preventing excessive inflammation and the induction of cathelicidin in human KCs. It was reported that the level of cathelicidin and epidermal expression of p62 was higher in psoriatic skin lesions than in the skin of heal- thy people [3]. The classical treatments for psoriasis include retinoids, vitamin D analogues, and ultra-violet B therapy. These therapies may induce autophagy, suggesting that the- se drugs' benefits are connected to activation autophagy [4, 28]. It was also demonstrated that PSORI-CM02, an empirical Chinese medicine formula that inhibits the phosphorylation of the PI3K/AKT/mTOR pathway, treats psoriasis by inducing autophagy [28]. Autophagy plays a key role in modulating inflammatory responses in keratinocytes. Its regulation in different tissues and cells under healthy and stressful conditions will help better understand the aetiology of skin diseases and develop more effective therapeutic approaches.

VITILIGO

Vitiligo is a common skin pigmentary disorder. It is characterized by patchy loss of skin pigmentation. Approximately 1% of the world's population is affected by vitiligo [2]. This disease manifests itself by appearing in milky white, non-scaly macules with distinct margins on the skin. It can be divided into segmental and non-segmental types, where the second is the most common form. Non-segmental vitiligo (NSV) is characterized by symmetrical and bilateral white patches, and segmental vitiligo usually has a unilateral distribution [29]. Although vitiligo does not affect patients' survival, it can create social pressure and cause mental illness [30]. Studies suggest that triggering factors are genetic susceptibility, autoimmune response, oxidative stress, autocytotoxicity, melanocytorrhagy, and neural. However, autoimmunity and oxidative stress are mainly taken into consideration [31].

Many studies have shown the connection between the autophagy process and vitiligo. An analysis from Korea suggests a possible association of UVRAG polymorphisms (rs1458836,rs7933235) to NSV. It may be one of many genes that might play a role in polygenic susceptibility to NSV [32]. Sastry et al. [33] searched expressed genes (DEGs) in melanocytes modulated by H_2O_2-induced oxidative stress in a time- and dose-dependent manner. H_2O_2 also induced the expression of genes involved in autophagy. Their results suggest that autophagy in H_2O_2 -stressed melanocytes preferentially depends on GATA4 and ATG9B genes.

Yu et al. [34] found increased expression of the autophagy marker LC3II/I and decreased expression of p62 protein in lesional altered skin of active and stable vitiligo compared to control skin, as well as increased expression of autophagy--related ATG5 protein and decreased expression of mTOR protein in lesional skin of vitiligo patients. Skin with lesions from patients with stable vitiligo showed more autophagy activation than skin with active vitiligo skin lesions. On the contrary, He et al. [35] observed that both LC3-II and the ratio of LC3-II/I were relatively lower in the vitiligo melanocyte cell line exposed to H_2O_2 than in primary normal human melanocyte (MC) and the human melanocyte cell line. Naguib and Rashed [36] also showed that the level of LC3 in the affected skin of vitiligo was significantly lower than in normal controls. Also, another study found that the LC3-I, LC3-II, Beclin 1, and superoxide dismutase (SOD) levels were significantly lower in lesional skin than in nonlesional skin of patients as well as both lesional and nonlesional skin of patients than in controls which suggest downregulated autophagy [37]. Depleting the ULK1 protein, which is the link between the nutrient-sensing mTORC1 complex and the initiation of autophagosome formation, may cause an increase in melanin levels, suggesting an inhibitory function for this protein in melanogenesis. Furthermore, this increase was

accompanied by increased transcription of microphthalmia-associated transcription factor (MITF) and tyrosinase and by elevated tyrosinase protein levels, the rate-limiting factor in melanin biogenesis. The authors likewise show that the ULK1 function in this context is independent of the canonical ULK1 autophagy partners, ATG13, FIP200, and also mTORC1 inhibition [38].

The skin is a primary target of oxidative stress, principally due to ROS originating from the environment and skin metabolism. Reactive oxygen species (ROS) oxidizes components of cells, leading to melanocyte destruction and creating depigmented macules [31]. Autophagy is involved in response to oxidative stress and has implications for melanocyte dysfunction and manifestations of skin pigmentary disorders. Chronic restraint stress could cause vitiligo-like symptoms in mice, accompanied by an increase of IL-17 and IL-1b in serum. These results suggest that ROS autophagy--associated cell apoptosis induced IL-17 stressing melanocytes and an inflammatory microenvironment provoked by cytokines released from KCs. IL-17–mediated mitochondrial dysfunction inhibits melanogenesis; consequently, stress exposure induces vitiligo-like symptoms in mice [39]. It was suggested that dysregulated autophagy owing to the impairment of the Nrf2-p62 pathway increases the sensitivity of vitiligo melanocytes to oxidative stress, thus promoting the development of vitiligo [35]. ATG7-dependant autophagy is involved in oxidative stress homeostasis by regulating ROS production, the Nrf2 antioxidant signalling pathway, and the activity of several antioxidant enzymes [40]. Zhang et al. [41] suggest that deletion of the ATG7 autophagy gene specifically in MC successfully suppressed the key autophagy step, lipidation of LC3 in MC, and induced slight epidermal hypopigmentation in mice. Disruption of melanocyte autophagy does not prevent melanogenesis, although it leads to a slight but significant decrease in melanin and also has the effect of reducing proliferative capacity, premature ageing of melanocytes, and cellular redox dysregulation.

Autophagy determines skin colour by regulating the degradation of melanosomes in keratinocytes. In one study, Murase et al. [42] found that autophagy had a role in regulating melanosome degradation in keratinocytes and skin colour determination through siRNA-driven gene knockdown of ATG7 or ATG13 in human cultured keratinocytes, which suppressed cellular melanin content in melanocytes. Also, the synthetic inducer of PTPD-12 autophagy led to the degradation of melanosomes through the increased autophagic flow without affecting the expression of MITF [43]. Autophagy occurs in MC and skin fibroblasts without lesions of vitiligo patients. The level of autophagic activity correlates with defects in mitochondrial metabolism and the phenotype of senescent melanocytes and vitiligo fibroblasts. The authors suggest that induction of autophagy plays a protective role against intrinsic metabolic stress and increases the survival rate of the skin of vitiligo, in which melanocytes and fibroblasts are already prone to premature ageing, despite its normal appearance [44].

CONCLUSIONS

Autophagy has a significant impact on the immune system as it plays an important role in regulating inflammation, cytokine secretion, lymphocyte survival, and differentiation in skin diseases. Further studies are warranted to understand better the molecular mechanisms. A detailed comprehension of the function of autophagy can lead to the development of new treatment therapies for the treatment of psoriasis and vitiligo.

Conflict of interest

The authors declare no conflict of interest.

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