

Review Article

Autophagy in non-neoplastic skin diseases

Dermatology and Venerology

Azza S. Amer¹, Rehab M. Samaka² and Nayera H. Mofteh³

¹ Dermatology and Venerology department, Desouk General Hospital, Egypt.

² Pathology Department, Faculty of Medicine, Menoufia University, Egypt.

³ Dermatology and Venerology Department, Faculty of Medicine for Girls, Al-Azhar University, Egypt.

ABSTRACT

Background: Autophagy is an essential cellular mechanism that plays the "housekeeping" role in normal physiological processes, including the removal of long-lived, harvested, and misfolded proteins, damaged organs. On the other hand, under conditions causing cellular stress, such as malnutrition, hypoxia, oxidative stress, pathogen infections, radiation or cancer medication, there is an increase in the degree of autophagy, which leads to adaptation and cell survival. With the current interest in autophagy, this process appears to affect every organ and modify growing list of disease processes. The skin acts as the first line of defense against different environmental stresses; However, only a few studies have investigated the effect of autophagy on the pathogenesis of skin diseases. The level of autophagy may reflect the degree of some diseases; Therefore, detecting the level of autophagy may be an indirect means to assess some diseases.

Objective: to provides an overview of recent findings relevant to the role of autophagy in non-neoplastic skin diseases.

Conclusion: Autophagy plays an important role in mitigating or exacerbating various skin diseases. Understanding the mechanisms of autophagy and their regulation in different tissues and cells under healthy and stressful conditions will help better understand the etiology of skin diseases and develop more effective therapeutic approaches.

JRAM; 2(2): 214-225

Abbreviation: Acne, atopic dermatitis, autophagy, psoriasis, skin diseases.

Submission Date: 5 October 2020

Acceptance Date: 30 November 2020

Corresponding author: Azza S. Amer, Dermatology and venerology department, Desouk general hospital. Egypt. **Tel:** 201011376182. **E-mail:** azaasamyamer@gmail.com

Please cite this article as: Amer SA, Samaka RM, Mofteh NH. Autophagy in non-neoplastic skin diseases. *JRAM; 2(2): 214-225.* DOI:10.21608/jram.2020.44972.1087

INTRODUCTION

Autophagy, truly meaning "self-eating" is an intracellular catabolic handle of conveying cytosol and/or its substance to the lysosomes for debasement^[1]. The term "autophagy" was named by Christian de Duve after he disclosed lysosomes in 1955^[2]. Autophagy is a basic cellular component that plays a "housekeeping" part in typical physiological forms counting evacuating of long lived, amassed and misfolded proteins, clearing harmed organelles, development direction and maturing. Autophagy is additionally included in an assortment of natural capacities like an improvement, cellular separation, defense against pathogens and starvation^[3].

On a common level, autophagy shows up basic to preserve both cellular homeostasis (through the expulsion of harmed protein and organelles) and giving a survival component for cells amid a push^[4]. Subsequently, autophagy is associated with different pathologies, such as cancer, neurodegenerative disease,

and inflammatory bowel disorders^[5]. The skin serves as the primary line of defense against numerous distinctive environmental insults; however, the impact of autophagy on the pathogenesis of skin disorders was not adequately studied^[6]. The level of autophagy may be used to evaluate the degree of some diseases^[7]. This review provides an overview of recent findings relevant to the role of autophagy in non-neoplastic skin diseases.

TYPES OF AUTOPHAGY

There are three sorts of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), which contrast basically according to the way that materials are conveyed to the lysosome^[8]. Macroautophagy: may be a non-specific way in which a double-membrane structure, named an autophagosome surrounds a part of cytosol then fuses with a lysosome whose enzymes degrade the cellular constituents sequestered in the autophagosome^[9]. Microautophagy:

organelles or protein are taken up inside an invagination of the lysosome for breakdown [10]. Chaperone-mediated autophagy (CMA): is a specific process that removes individual proteins that contain a specific peptide motif recognized by the chaperone protein 70. The chaperone - protein complex translocates to the lysosome where it ties to a specific lysosome-related protein for protein internalization and corruption [11]. Macroautophagy is the major sort of autophagy [6].

MOLECULAR MACHINERY OF AUTOPHAGY

The autophagy process is often divided into these main stages: initiation, vesicle nucleation, membrane elongation, closure, maturation and degradation, it begins with an isolation membrane, also called a phagophore, this phagophore expands to engulf the intracellular charge, such as aggregates of proteins, organelles and ribosomes, thereby sequestering the charge in a double membrane autophagosome [12].

The stacked autophagosome matures through combination with the lysosome, promoting the debasement of the autophagosomal substance by lysosomal corrosive proteases, lysosomal permeases and transporters export amino acids to the cytoplasm, where they will be re-used for building macromolecules and for digestion system [13].

Although 31 ATG genes have been reported, 18 genes are referred to as ‘core’ ATG genes, which encode the fundamental autophagy-related proteins (Atg) for the biogenesis of autophagy related membranes [14]. The main machinery of the autophagy is formed by four functional groups: the UNC-51-like kinase (ULK) complex; the class III phosphatidylinositol 3-kinase (PI3K) complex containing Beclin 1 (also known as ATG6); and two ubiquitin-like conjugation systems: the ATG5-ATG12 conjugation system and the microtubule-related protein 1 light chain 3 (LC3-ATG8) [2].

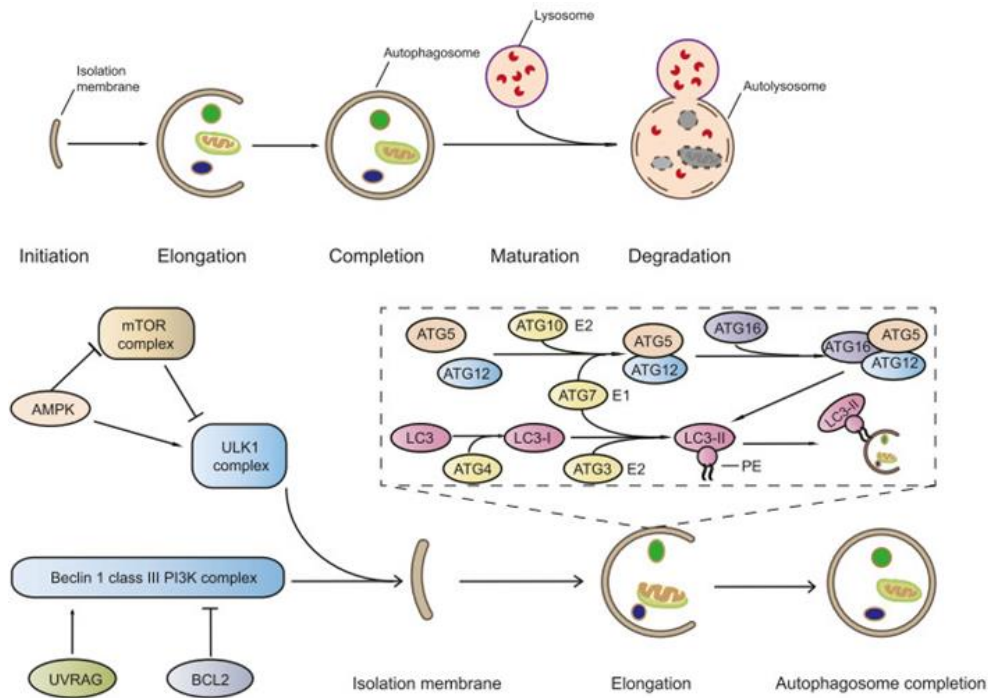


Figure (1): Molecular regulation of autophagy [6].

The key up-stream regulator of autophagy is the mammalian target of rapamycin (mTOR) which is classified into mTORC1 and mTORC2. In mammalian cells, mTORC1 suppresses the involvement of autophagy, but the role of mTORC2 in autophagy is not well characterized [15].

Adenosine monophosphate activated protein kinase (AMPK), regulated by adenosine monophosphate (AMP) levels, negatively controls mTORC1 and gives phosphorylates directly to the UNC-51-like kinase (ULK) complex. In response, it acts as a positive regulator of autophagy during lack of energy [16].

Autophagy is also controlled by autophagy related protein Beclin 1. Beclin 1 shapes a complex with a class III phosphatidylinositol 3-kinase (PI3KC3). Class III PI3K complexes are recruited at the assembly site to stimulate nucleation from activation of the ULK complex [17]. The elongation of the autophagosome double membrane requires 2 ubiquitin-like conjugation systems, both catalyzed by E1-like Atg7 [18]. In the first system, Atg12 binds to Atg5 via the help of Atg7 and Atg10, E1together with E2-like enzymes, respectively. The Atg5-Atg12 complex then interacts with the ATG16L1 in a non-covalent manner; the resulting complex could promote the second conjugation reaction [19].

The second conjugation system includes the binding of phosphatidylethanolamine (PE) to a microtubule-related ubiquitin-like protein of light chain 3 protein 1 (LC3-Atg8). Atg4 protease cleaves LC3 is at its C- end to generate the LC3-PE with the LC3-I form. The association of PE with LC3-I requires the sequential action of Atg7 (as E1) and Atg3 (as E2) activities. Membrane-associated LC3-II (the PE-conjugated form) is the most generally utilized marker for autophagy^[20]. Physically, autophagy is at a lower level. It is upgraded during hunger and in response to the accumulation of cellular components that are not needed to achieve the stabilization mission. To accomplish its homeostatic mission. However, pathologically autophagy is the cause of some diseases^[21].

AUTOPHAGY IN NON-NEOPLASTIC SKIN DISEASES

The level of autophagy may reflect disease development and may give a target for treatment. Typical levels of autophagy can secure cells from natural boosts; however, deviation from the normal level can lead to the development of the disease^[7].

▪ Autophagy and autoimmune skin disorders

Autophagy performs important roles in the immune reaction, such as antigen recognition and presentation. So, defective autophagy can lead to autoimmune disorders^[22].

Psoriasis is a long lasting immune mediated skin disease^[23], with around 0.51% to 3% prevalence^[24]. It has a complex pathogenesis^[23] however, its exact etiology isn't completely explained^[25]. It is characterized with cutaneous and systemic affection and significant negative impacts on quality of life. It has been related to various comorbidities, involving psoriatic arthritis, cardiovascular and psychiatric problems^[26]. The enhanced proliferation of keratinocytes is the main feature^[27]. The disease is related to combined genetic and environmental factors^[28]. Single nucleotide polymorphisms identified within the ATG16L1 gene has been connected to vulnerability to psoriasis development^[6]. Impaired autophagy can lead to IL-36 up-regulation in keratinocytes and results in skin inflammation^[29]. In addition, autophagy related to psoriasis is due to its association with apoptosis. The increased apoptosis observed in skin lesions is a protective mechanism that maintains uncontrolled proliferation^[30]. Autophagy is upregulated when overactive reactive oxygen species as mitochondrial damage, preventing further damage to cells under hypoxia^[31]. Hypoxia-inducing factor 1a is a major factor in inducing hypoxia autophagy, and expression of hypoxia-inducing factor 1a has been shown to be significantly increased in psoriatic lesions compared to normal skin. Therefore, it is hypothesized that psoriasis increases hypoxia-inducible factor 1a, then promotes expression of beclin1, induces autophagy to

eliminate damaged mitochondria, and suppresses mitochondrial-mediated apoptosis and promoting keratinocytes (KCs) proliferation^[32]. Another theory is that infection can trigger or exacerbate psoriasis, and that autophagy plays a crucial role in bacterial clearance. It is possible that impaired autophagy in psoriasis leads to altered clearance of and/or altered immune responses to bacteria. So, in this case compatible control of autophagy may represent a new strategy for treating psoriasis. In support of this concept, numerous first line drugs within the treatment of psoriasis such as vitamin D analogs, retinoids, sirolimus, and UVB therapy, can induce activation of autophagy, though these drugs might provide clinical benefits independent of autophagy activation^[6]. Inhibition of autophagy by activation of PI3K/AKT/mTOR has been suggested as a therapeutic approach to treat IL-17a-mediated psoriasis^[33]. Furthermore, other studies have demonstrated the autophagy therapeutic role in psoriasis by inhibiting the formation of IL-17a^[34]. Collectively, these findings suggest that autophagy may show therapeutic role in this disease. This evidence suggests that serious care must be taken if autophagy is to be used as a therapeutic target. Personal differences within the similar types of diseases should also be considered. The outcome might be totally different if autophagy inhibition is applied in two different types of patients. In this manner, advanced investigation is needed to clarify the control of autophagy in psoriasis, and future personalized treatment is strongly recommended^[35].

Systemic lupus erythematosus (SLE), also known as lupus, is a long-lasting autoimmune disorder caused by combined genetic and environmental factors and affects many important organs and systems such as the kidneys, heart, brain, and immune system. The skin is often affected^[32]. It is probably the most widely studied autoimmune disease in terms of its role in autophagy. There are many possible mechanisms by which autophagy can affect the pathogenesis of SLE, involving both adaptive and innate immunity. Because B cells represent a key player in SLE by acting on both antibody dependent and independent mechanisms, autophagy-mediated B cell modulation can directly affect the pathophysiology of SLE. It has been appeared that autophagy is increased in lupus B- and T-lymphocytes^[36]. Using LC3 conversion tests and electron microscopic experiments, Gros et al.^[37] found that the autophagy level is elevated in T lymphocytes of both mouse models and lupus patients compared with typical controls and non-lupus autoimmune diseases. Genome-wide association studies have shown that genetic mutations in or near ATG5 were involved in SLE pathogenesis, with evidence of Caucasian and Chinese populations^[38]. ATG5 is included in natural defense against attacking pathogens and natural stressors, such as bright (UV) irradiation. Together, these findings suggest that autophagy indicate a therapeutic role in SLE. Consistent

with this idea, hydroxychloroquine, a common treatment for SLE, may affect SLE via autophagy^[39]. Therefore, verified drugs that can impair autophagy are recommended for SLE as an innovative treatment^[40].

Vitiligo is an acquired pigmentation disorder affecting skin and mucous membranes and characterized by patchy loss of skin pigmentation due to the selective loss of melanocytes. The etiological hypotheses for vitiligo include autoimmune, oxidative stress, and genetic theories^[6]. A cohort study from Korea has linked non-segmental vitiligo to gene polymorphisms that are associated with UV resistance^[41]. Intramelanocytic oxidative stress is involved in vitiligo pathogenesis, while autophagy is involved in the redox homeostasis of melanocytes^[42]. Samaka et al^[43] reported that autophagy and beclin 1 play important roles in vitiligo pathogenesis by their effect on melanogenesis and melanosome corruption in keratinocytes. Also, it was reported that autophagy with its marker autophagy-related gene 7 (ATG7) plays a vital part within the pathogenesis of vitiligo through its impact on melanogenesis and melanocyte premature senescence^[44]. Thus, the intervention in autophagy provides a new therapeutic approach to vitiligo. With this theory, many commonly used anti-vitiligo drugs induce autophagy such as vitamin D analogs, sirolimus and UVB therapy^[41]. However, in ex vivo cultured human skin samples and in vitro human skin substitutes, melanin levels were significantly reduced by autophagy activators and increased via its inhibitors^[45]. In this way, it is reasonable to speculate that autophagy activators may be used to treat skin hyperpigmentation, such as melasma. Two studies suggest that activating autophagy may be an approach to treat hyperpigmentation disorders^[46].

Oral Lichen Planus (OLP): Lichen planus is a rare autoimmune process that affects the skin, mucous membranes, and skin adnexa. The oral presentation comprises white papules arranged in a linear or reticulated manner with atrophic or erosive forms are also presented. T cells are central participants in keratinocyte apoptosis^[47]. The ATG9 gene is associated with regulation of autophagy and suppression of innate immunity. Tan et al.^[48] found less expression of ATG9B in the OLP than in healthy controls. ATG9B also acts as an oxygen sensor and prevents apoptosis. Low expression of ATG9B causes oral epithelial apoptosis, which is a common occurrence. Several other genes, such as hepatocyte growth factor-regulated tyrosine kinase substrate (HGS), estrogen receptor 1 (ESR1) and synuclein alpha (SNCA), have been found to be downregulated in OLP T cells. The encoded proteins are responsible for lysosomal transport, vesicle recycling and metabolism of autophagosomes. In addition, autophagy inhibitors release SNCA protein into the extracellular space, leading to increased inflammation and cell damage, events associated with OLP^[48].

▪ **Autophagy and dermatitis**

Allergic contact dermatitis (ACD) is an inflammatory skin disease caused by type 4 hypersensitivity reactions to various low molecular weight compounds found in the environment^[49]. In the process of activating the immune system, numerous naive T cells differentiate to effector cells and play protective roles in the elimination of pathogens^[50]. The active immune system often causes excessive immune responses. Clinical features of ACD include vesicles, erythema and edema that are usually treated with cyclosporine A (CSA) and corticosteroids^[51]. However, most currently available immunosuppressants show poor selectivity for naive resting T cells and highly active T cells, leading to some adverse reactions^[52]. Wang et al.^[53] identified roseotoxin B, a natural cyclopeptide that improved allergic contact dermatitis via over activation of autophagy in active T lymphocytes through a specific anti-inflammatory mechanism. It effectively suppressed active T cell proliferation and production of pro-inflammatory cytokines with little naive T-cell toxicity. The impacts of roseotoxin B were restricted in LC3-knockout mice, demonstrating that roseotoxin B acts in an autophagy-dependent way in T cell mediated skin disease.

Atopic dermatitis (AD) is a chronic, long-lasting inflammatory skin disease. The hereditary or acquired skin barrier defect is the hallmark of AD^[54]. According to the model of AD pathogenesis “from the outside to the inside out”, inflammation is the result of a defect in the skin barrier, which also makes the skin susceptible to allergens and the penetration of microbes into the skin^[55]. The activation of the immune system also promotes the disruption of the skin barrier. The loss of filaggrin (FLG), a structural protein in the stratum corneum (SC), leads to decreased production of natural moisturizing factor (NMF) and SC hydration, as well as high skin pH, therefore activating several serine proteases in SC to cause inflammation by cleaving IL-1 cytokine precursors into their active form^[56]. Additionally, changes in SC lipids in AD skin may also contribute to skin barrier dysfunction. A decrease in the content of ceramides, in the length of the fatty acid chain of ceramides and in the proportion of certain classes of ceramides (ceramides 1 and 3) have been reported in both damaged and unaffected skin of patients with AD^[57]. Generous and frequent use of moisturizers is an important part of treatment, as they have been shown to improve clinical conditions, restore skin barrier function, and reduce the use of topical steroids in patients with AD^[58]. Autophagy plays a role in the pathogenesis of AD by regulating host defense mechanisms against invading pathogens, such as *Staphylococcus aureus*. Also, regulating inflammation and keratinocyte differentiation^[59]. Therefore, modulation of autophagic activity may be a pharmacological treatment option for AD. Kwon et al^[60] tried to evaluate the effectiveness of a moisturizer

containing pentasodium tetracarboxymethylpalmitoyl dipeptide-12 (PTPD-12), a synthesized peptide that can improve autophagic activity in the treatment of mild to moderate AD. The moisturizer containing PTPD-12 has been shown to be effective in treating patients with mild to moderate AD and provides a good therapeutic option for treating atopic dermatitis via restoration of the skin barrier and controlling the inflammation.

▪ Autophagy and skin Infections

The skin represents a physical barrier between the host and the pathogen. It is important to protect the skin from invading pathogens and maintain cell homeostasis. One of the key mechanisms of self-defense is autophagy, where autophagosomes can swallow various microorganisms and migrate to lysosomes for degradation. Therefore, upregulation of autophagy can help in the treatment of infectious skin disorders [6].

Viral skin infections

Human papillomavirus (HPV) is associated with a variety of diseases, from benign common warts and condyloma accuminatum to malignant tumors of the cervix, vulva, anus, and penis. Diseases associated with HPV can be divided into genital and extragenital skin and mucosal lesions. HPV is also associated with skin tags, lichen sclerosis, seborrheic keratosis, chemical linear keratosis, epidermoid cysts, psoriatic plaques, and plucked hair [61]. HPV-16 can cause cervical cancer and autophagy can be triggered by the E7 protein of HPV-16, which promotes lipidation of LC3 and increase LC3 puncta number (autophagic vacuoles) in keratinocytes [62]. E7-induced autophagy can make cells sensitive to death, because E7-expressing keratinocytes are prone to cell death through cell-cell contact or serum deficiency [63].

Herpes simplex virus (HSV), a double-stranded DNA virus, usually causes skin and mucous membrane infections. There are two types of HSV, HSV-1 and HSV-2 [6]. HSV-1 infections can cause cold sores, sore throat, keratitis, and more [64]. HSV-2 can cause herpes proiesitialis through damaged epidermis and mucous membranes [65]. Autophagy induced during HSV-1 infection promotes the presentation of HSV-1 antigen on MHC class I molecules [66]. However, HSV-1 has developed a mechanism that interferes with the control of autophagy. For example, the HSV-1 neurovirulence protein ICP34.5 reacts with beclin 1 to inhibit autophagy [67]. In addition, Lee et al [68] reported that reversal of the ATG5 gene also suppresses the processing and presentation of HSV-2 antigens on MHC class II molecules, inducing susceptibility to HSV-2 infection in vivo.

Varicella zoster virus (VZV) infection causes chickenpox or herpes zoster. It has been suggested that autophagy is common in VZV-infected cells and that it

was caused, at least in part, by ER stress secondary to over-abundant VZV glycoprotein biosynthesis, which led to the activation of unfolded protein response in an attempt to maintain cellular homeostasis [69].

Bacterial skin infections

Group A Streptococcus (GAS) is found on the skin surface and may lead to cellulitis, impetigo, erysipelas, necrotizing fasciitis, scarlet fever, and Streptococcus toxic shock syndrome [70]. In 2004, Nakagawa et al. [71] showed the first evidence that autophagy is important in defending against bacterial pathogens (such as GAS) that invade cytosols. They showed that after endosomal escape, cytoplasmic GAS was enveloped by autophagosomes and killed upon fusion of autophagosomes and lysosomes.

Staphylococcus aureus (S. aureus) is a common bacterial skin infection. It has been reported that autophagic degradation was performed to remove the *S. aureus* [72].

Mycobacterium tuberculosis can affect the skin, causing tuberculosis cutis. It is a chronic inflammatory granulomatous disease with extensive damage leading to tissue destruction and necrosis [73]. Under normal circumstances *M. tuberculosis* enters host macrophages, where it resides in phagosomes that remain immature and do not acquire phago-lysosomal degradation characteristics [74]. Induction of autophagy by pharmacology (rapamycin) or physiology (amino acid starvation) overcomes the block of mycobacterial phagosome maturation and delivers tuberculous bacteria to the degradation compartment [75].

Fungal skin infections

Fungal skin infections are caused by fungi such as *Candida albicans* and dermatophytes. Autophagy plays an important role in controlling the spread of fungal infections and susceptibility to disease [76]. A 20-year-old study suggested that miconazole may inhibit the growth of one of the skin dermatophytes, *Trichophyton mentagrophytes*, by an autophagy-like pathway [77].

▪ Autophagy and skin aging

Skin decreases in protein breakdown with aging. The presence of undigested substances in lysosomes (residues or lipofuscin), such as those found in older fibroblasts, can lead to a defect in fusing and / or degrading the contents of autophagosomes. Studies have also suggested that defective structure of autophagosomes is involved in the aging process [81]. Interestingly, the autophagy pathway is disrupted in older dermal fibroblasts, resulting in decreased skin integrity and skin sensitivity [82]. Exposure to UV is a main factor that stimulates photoaging by elevating the level of oxidized lipid and metabolite aggregate levels. Much progress has been made in the fight against UV photoaging, while the role

of autophagy in resistance to photoaging is still clearing up. Autophagy plays an important role in UV-induced apoptosis, repair of DNA damage, removal of oxidized lipid, and the like. Therefore, autophagy can be considered a new way to avoid photoaging and skin cancer^[83]. Aging is an important area of interest for the cosmetics and skin care field. Clinically, skin aging is associated with health problems, including skin weakness, delayed wound healing, and increased incidence of skin cancer^[78]. Aging cells often show an accumulation of damaged proteins, reflecting an imbalance between the rate of protein loss and protein turnover^[79]. Autophagy is an important proteolytic system^[80] and therefore impaired autophagy affects aging by reducing the degradation of altered proteins and prolonging the "residence time" of the protein in the cell, increases the risk of posttranslational alterations^[79]. There is some evidence that a decrease in the ability of lysosomes to destroy intracellular components (a later stage in autophagy) may be the main reason for a

▪ Autophagy and acne

Acne vulgaris is a common skin disease, mainly affecting the skin regions with dense pilosebaceous units^[84]. While commonly occurs in early adolescence, adult acne is also an important health and cosmetic problem^[85]. In addition to pain, disfiguring lesions, and scarring, significant impact on life quality and negative effects on self-esteem on patients makes acne one of the highest life-burdening diseases. While various factors have been suggested to be involved in acne pathogenesis, including follicular hyperkeratosis, proliferation of *Cutibacterium acnes* (C acnes), and inflammation, excessive formation and secretion of sebum are considered as an initiating one^[86]. Recent research on the important role of autophagy signaling in sebaceous lipogenesis and epidermal differentiation suggests that autophagy activation in acne has potential benefits^[87]. Lee et al^[87] reported that autophagy activation may be an option in treating early forms of acne as topical application of autophagy-activating peptides improves skin barrier function and reduces acne-prone skin symptoms by reducing sebum production. Combining autophagy-activating peptides with other components may improve the clinical outcome or eliminate the adverse effects of topical formulation by reducing the concentration of potentially irritating formulations.

▪ Autophagy and hair loss

Hair loss affects millions of people around the world and can occur due to aging, hormonal dysfunction, autoimmunity, or as a side effect of cancer treatments. Hair growth in mammals consists of cyclical repetitions of the telogen (rest), anagen (regeneration), and catagen (degeneration) phases of the hair follicle^[88]. It has recently been reported that low molecular weight autophagy activators such as alpha-ketoglutarate and alpha-ketobutyrate cause mice to switch from telogen

(resting phase of the hair cycle) to anagen (active hair growth phase)^[89]. Rapamycin and metformin also enhanced hair growth and their effect may be blocked via inhibition of autophagosome production^[89]. Studies in mouse and human alopecia are required to determine whether the pharmacological autophagy activation can treat hair loss^[90].

Alopecia areata (AA) is a common autoimmune disease with an abnormal interaction between the immune system and the hair follicle resulting in hair loss that usually begins with patches on the scalp but progressing to affect the whole scalp (alopecia totalis) and body (alopecia universalis)^[91]. The genetic basis of the disease demonstrated an increased risk of the disease among family members^[92]. Gene expression data and identification of classes of genes in alopecia areata including ATG4B revealed an etiological role for autophagy. This study implies an etiological role for autophagy in AA^[91].

▪ Autophagy and wound healing

When wounds heal following injury or an invasion of pathogens, the skin's immune responses stop the ongoing inflammation to initiate the healing process^[93]. In rats, autophagy heals the epithelium of a burnt hair follicle^[94]. An et al^[95] showed that the use of mesenchymal stem cells (MSCs) to repair the skin requires autophagy. Rapamycin-induced autophagy in MSCs induces vascular endothelial growth factor (VEGF) secretion and improves VEGF-mediated circulation, which in turn promotes skin wound healing and tissue regeneration^[95].

▪ Autophagy and genodermatoses

Autosomal recessive congenital ichthyosis is a rare heterogeneous epidermal keratinization disorder^[96]. Patients generally represent an infantile collodion phenotype accompanied by dehydration, heat loss, electrolyte imbalance, and sepsis^[97]. One of the proteins associated with the disease, protein 1 containing a patatin-like phospholipase domain (PNPLA1), plays a key role in the epidermal synthesis of Omega-O-acylceramide and is located on the surface of Lipid Droplets (LDs) which are specific organelles consists of neutral lipids as triacylglycerides (TG) and sterol esters^[99]. LD interacts with other intracellular components, including endoplasmic reticulum, mitochondria, and peroxisomes, through proteins on their surface, and plays a key role in maintaining energy balance by regulating lipid synthesis and degradation in cells^[98]. Selective degradation of LDs by macroautophagy is called lipophagy^[99]. Onal et al.^[99] reported that lipophagy impairment by PNPLA1 mutations resulting in disturbance in both autophagosome formation and fusion of autophagosomes with lysosomes has been shown to contribute to the accumulation of lipid droplets in primary fibroblasts of autosomal recessive ichthyosis patients.

The tuberous sclerosis complex (TSC) was first described about 150 years ago as an autosomal dominant disorder due to a mutation in the TSC1 or TSC2 gene [100]. Mutations in the TSC gene cause constitutive activation of the mammalian target rapamycin pathway (mTOR), leading to a wide range of symptoms [101]. Hypopigmented macules are the first sign. Topical treatment with rapamycin, an mTOR inhibitor, has been shown to protect patients with TSC from hypopigmentation, but the etiology of these lesions is poorly understood [102]. Yang et al. [102] demonstrated that melanocytes in TSC patients showed autophagic deregulation, which reduced pigmentation and served as the basis for the hypomelanotic macules.

▪ **Autophagy and malnutrition-associated dermatoses**

Diseases associated with malnutrition, involving necrolytic migratory erythema, hepatitis C viral infection, pellagra, and zinc deficiency related acrodromatitis enteropathica share many clinical and pathological features; especially upper epidermal necrolytic changes [103]. Hirai et al. [103] reported autophagy involvement in the development of necrolysis in three patients with malnutrition-related dermatoses through examining an autophagy-specific molecule, microtubule-associated protein light chain 3 (LC3), using a monoclonal antibody. LC3 is strongly expressed in the granular layer of the active lesion, observed with low intensity in the perilesional areas, and has little or no background levels in controlling skin diseases.

CONCLUSION

Autophagy plays an important role in mitigating or exacerbating various skin diseases. Understanding the mechanisms of autophagy and their regulation in different tissues and cells under healthy and stressful conditions will help better understand the etiology of skin diseases and develop more effective therapeutic approaches.

Conflict of interest: No conflict of interest has been declared by the author(s).

Financial support: This work not funded from any governmental or non-governmental agencies.

REFERENCES

1. **Yang Z and Klionsky DJ.** Mammalian autophagy: Core molecular machinery and signaling regulation, *Current opinion in cell biology*, 2010; 22(2): 124-131.
2. **Mulakkal NC, Nagy P, Takats S, Tusco R, Juhász G, and Nezis IP.** Autophagy in Drosophila: From Historical Studies to Current Knowledge, *BioMed research international* 2014; 34(5):24.
3. **Ravanan P, Srikumar IF, and Talwar P.** 'Autophagy: The spotlight for cellular stress responses', *Life sciences*, 2017; 188: 53-67.

4. **Nussenzweig SC, Verma S, and Finkel T.** The Role of Autophagy in Vascular Biology, *Circulation research*, 2016; 116(3): 480–488.
5. **Samaka RM, Basha MA, and Mansour E.** Does the Autophagy Related Gene 7 (ATG7) Have a Role in Non-Melanoma Skin Cancer?, *Clinical, Cosmetic and Investigational Dermatology* 2020; 13, 49.
6. **Yu T, Zuber J, and Li J.** Targeting autophagy in skin diseases, *Journal of Molecular Medicine*, 2015; 93(1): 31–38.
7. **Xie F, Li L, and Chen LX.** Autophagy, a new target for disease treatment, *Science China Life Sciences*, 2013; 56(9): 856–860.
8. **Mizushima N, Levine B, Cuervo AM, and Klionsky DJ.** Autophagy fights disease through cellular self-digestion, *Nature*, 2008; 451(7182): 1069–1075.
9. **Mehrpour M, Esclatine A, Beau I, Codogno P.** Autophagy in health and disease, 1. Regulation and significance of autophagy: an overview. *American Journal of Physiology-Cell Physiology*, 2010; 298(4): 776-785.
10. **Yorimitsu T and Klionsky DJ.** Autophagy: molecular machinery for self-eating, *Cell death and differentiation*, 2005; 12(2): 1542-1552.
11. **Orenstein SJ and Cuervo AM.** Chaperone-mediated autophagy: molecular mechanisms and physiological relevance, *In Seminars in cell & developmental biology*, 2010; 21(7):719-726.
12. **Mizushima N.** Autophagy: process and function, *Genes & development*, 2007; 21(22): 2861–2873.
13. **Glick, D, Barth S, and Macleod KF.** Autophagy: cellular and molecular mechanisms, *The Journal of pathology*, 2010; 221(1): 3–12.
14. **Nakatogawa H, Suzuki K, Kamada Y, and Ohsumi Y.** Dynamics and diversity in autophagy mechanisms: lessons from yeast, *Nature Reviews Molecular Cell Biology*, 2009; 10(7): 458–467.
15. **Kim, J., Kundu M, Viollet B, and Guan KL.** AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nature cell biology*, 2011; 13(2): 132-141.
16. **Alers S, Löffler AS, Wesselborg S, and Stork B.** Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks, *Molecular and cellular biology*, 2012; 32(1): 2-11.
17. **Dupont N and Codogno P.** Autophagy plays a washing game, *The EMBO Journal*, 2013; 32(20): 2659–2660.
18. **Rossiter H, König U, Barresi C, Buchberger M, Ghannadan M, Zhang CF, et al.** Epidermal keratinocytes form a functional skin barrier in the absence of Atg7 dependent autophagy, *Journal of dermatological science*, 2013; 71(1): 67-75.
19. **Hanada T, Noda NN, Satomi Y, Ichimura Y, Fujioka Y, Takao T, et al.** The Atg12-Atg5 conjugate has a novel E3-like activity for protein

- lipidation in autophagy. *Journal of Biological Chemistry*, 2007; 282(52): 37298-37302.
20. Mizushima N, Yoshimori T, and Levine B. *Methods in Mammalian Autophagy Research* Noboru, Cell, 2010; 140(3): 313–326.
 21. Komatsu M, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, et al. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. *Journal of Cell Biology* 2005; 169(3): 425-434.
 22. Rinflerch AR, De Luca DA, Miretti MM, and Galimberti RL. Autophagy: Eating Myself as a Requirement for the Skin Health, *Journal of Investigative Dermatology*, 2017; 5(1):7
 23. Fotiadou C, Lazaridou E, Sotiriou E, and Ioannides D. Targeting IL-23 in psoriasis: current perspectives, *Psoriasis: Targets and Therapy*, 2018 ; 8: 1.
 24. Borska L, Kremlacek J, Andrys C, Krejsek J, Hamakova K, Borsky P, et al. Systemic inflammation, oxidative damage to nucleic acids, and metabolic syndrome in the pathogenesis of psoriasis. *International journal of molecular sciences*, 2017; 18(11): 2238.
 25. Bai F, Zheng W, Dong Y, Wang J, Garstka MA, Li R, et al. Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. *Oncotarget*, 2018; 9(1):1266-1278.
 26. Greb JE, Goldminz AM, and Elder JT. 'psoriasis'. *Natural Reviews Disease Primers*, 2016; 16082(2): 1-17.
 27. Lebowhl M. Psoriasis, *Lancet* 2003; 361(9364): 1197–1204
 28. Douroudis K, Kingo K, Traks T, Reimann E, Raud K, Ratsep R, et al. Polymorphisms in the ATG16L1 gene are associated with psoriasis vulgaris, *Acta Derm Venereol*, 2012; 92(1):85–87
 29. Mahil SK, Capon F, Barker JN. Update on psoriasis immunopathogenesis and targeted immunotherapy, *Seminars in immunopathology*, 2016; 38(1): 11-27.
 30. Takahashi H, Manabe A, Ishida-Yamamoto A, Hashimoto Y, Iizuka H. Aberrant expression of apoptosis-related molecules in psoriatic epidermis. *Journal of dermatological science*, 2002; 28(3): 187-197.
 31. Kongara S and Karantza V. The interplay between autophagy and ROS in tumorigenesis, *Frontiers in oncology*, 2012; 2: 171.
 32. Guo Y, Zhang X, Wu T, Hu X, Su J, and Chen X. Autophagy in skin diseases. *Dermatology*, 2019; 235(5): 380-389.
 33. Varshney P and Saini N. PI3K/AKT/mTOR activation and autophagy inhibition plays a key role in increased cholesterol during IL-17A mediated inflammatory response in psoriasis, *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 2018; 1864(5): 1795-1803.
 34. Peral de Castro C, Jones SA, Ni Cheallaigh C, Hearnden CA, Williams L, Winter J, et al. Autophagy Regulates IL-23 Secretion and Innate T Cell Responses through Effects on IL-1 Secretion, *The Journal of Immunology*, 2012; 189(8): 4144–4153.
 35. Yin H, Wu H, Chen Y, Zhang J, Zheng M, Chen G, et al. The therapeutic and pathogenic role of autophagy in autoimmune diseases. *Frontiers in immunology*, 2018; 9:1512.
 36. Wu DJ and Adamopoulos IE. Autophagy and autoimmunity, *Clinical Immunology*, 2017; 176(9): 55-62.
 37. Gros F, Arnold J, Page N, Décossas M, Korganow AS, Martin T, et al. Macroautophagy is deregulated in murine and human lupus T lymphocytes, *Autophagy*, 2012; 8 (7): 1113-1123.
 38. Ramos PS, Brown EE, Kimberly RP, and Langefeld CD. Genetic factors predisposing to systemic lupus erythematosus and lupus nephritis, *Seminars in nephrology*, 2010; 30(2): 164-176.
 39. Van Loosdregt J, Spreafico R, Rossetti M, Prakken BJ, Lotz M, and Albani S. Hydroxychloroquine preferentially induces apoptosis of CD45RO+ effector T cells by inhibiting autophagy: a possible mechanism for therapeutic modulation of T cells, *Journal of Allergy and Clinical Immunology*, 2013; 131(5): 1443-1446.
 40. Gros F and Muller S. Pharmacological regulators of autophagy and their link with modulators of lupus disease. *British journal of pharmacology*, 2014; 171 (19): 4337-4359.
 41. Jeong TJ, Shin MK, Uhm YK, Kim HJ, Chung JH, and Lee MH. Association of UVRAG polymorphisms with susceptibility to non-segmental vitiligo in a Korean sample. *Experimental dermatology*, 2010; 19(8): 323-325.
 42. Ralf Paus L, Schallreuter KU, Bahadoran P, Picardo M, Slominski A, Elaissiutye YE, et al. Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? *Experimental dermatology*, 2008; 17(2): 139-140.
 43. Samaka RM, Basha MA, and Zahran AM. Role of beclin 1 and autophagy in vitiligo, *Menoufia Medical Journal*, 2018; 31(3): 822-825.
 44. Hamed SM, Samaka RM, and Basha MA. Role of autophagy-related gene 7 in the skin of vitiligo patients, *Egyptian Journal of Dermatology and Venerology*, 2019; 39(1): 1-14.
 45. Murase D, Hachiya A, Takano K, Hicks R, Visscher MO, Kitahara T, et al. Autophagy has a significant role in determining skin color by regulating melanosome degradation in keratinocytes, *Journal of Investigative Dermatology*, 2013; 133(10): 2416-2424.

46. Kim ES, Chang H, Choi H, Shin JH, Park SJ, Jo YK et al. Autophagy induced by resveratrol suppresses α -MSH-induced melanogenesis. *Experimental Dermatology*, 2014; 23(3): 204-206.
47. Bascones-Ilundain C, González Moles MA, Carrillo de Albornoz A, and Bascones-Martínez A. Oral lichen planus (I). Clinical, etiopathogenic and epidemiological aspects. *Av. Odontostomatol*, 2006; 22: 11-19.
48. Tan YQ, Zhang J, Du GF, Lu R, Chen GY, and Zhou G. Altered autophagy-associated genes expression in T cells of oral lichen planus correlated with clinical features. *Mediators of Inflammation*, 2016.
49. Chong SZ, Tan KW, Wong FH, Chua YL, Tang Y, Ng LG, et al. CD8 T Cells Regulate Allergic Contact Dermatitis by Modulating CCR2-Dependent TNF/iNOS-Expressing Ly6C+ CD11b+ Monocytic Cells. *Journal of Investigative Dermatology*, 2014; 134(3): 666-676.
50. Mueller SN, Gebhardt T, Carbone FR, and Heath WR. Memory T cell subsets, migration patterns, and tissue residence. *Annual review of immunology* 2013; 31: 137-161.
51. Lucae S, Schmid-Grendelmeier P, Wüthrich B, Kraft D, Valenta R, and Linhart B. IgE responses to exogenous and endogenous allergens in atopic dermatitis patients under long term systemic cyclosporine A treatment. *Allergy*, 2016; 71(1): 115-118.
52. Wang X, Zhang A, Gao J, Chen W, Wang S, Wu X et al. Trichomide A, a natural cyclodepsipeptide, exerts immunosuppressive activity against activated T lymphocytes by upregulating SHP2 activation to overcome contact dermatitis. *Journal of Investigative Dermatology*, 2014; 134(11): 2737-2746.
53. Wang, X., Hu, C., Wu, X., Wang, S., Zhang, A., Chen, W et al. Roseotoxin B improves allergic contact dermatitis through a unique anti-inflammatory mechanism involving excessive activation of autophagy in activated T lymphocytes. *Journal of Investigative Dermatology*, 2016; 136(8): 1636-1646.
54. Kezic S, Novak N, Jakasa I, Jungersted JM, Simon M, Brandner JM, et al. Skin barrier in atopic dermatitis. *Front Biosci (Landmark Ed)*, 2014; 19:542-556.
55. Elias PM and Steinhoff M. "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. *Journal of Investigative Dermatology*, 2008; 128(5): 1067-1070.
56. Kezic S, Kemperman PM, Koster ES, de Jongh CM, Thio HB, Campbell LE, et al. Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *The Journal of investigative dermatology*, 2008; 128(8): 2117-2119.
57. Janssens M, van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, et al. Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. *Journal of lipid research*, 2012; 53(12):2755-2766.
58. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *Journal of the American Academy of Dermatology*, 2002; 47(2):198-208.
59. Qian M, Fang X, Wang X. Autophagy and inflammation. *Clinical and translational medicine* 2017; 6 (1):24.
60. Kwon SH, Lim CJ, Jung J, Kim HJ, Park K., Shin JW, et al. The effect of autophagy-enhancing peptide in moisturizer on atopic dermatitis: a randomized controlled trial. *Journal of Dermatological Treatment*, 2018; 30(6):558-564.
61. Ljubojevic S, Skerlev M. HPV-associated diseases. *Clinics in dermatology* 2014; 32(2): 227-234.
62. Zhou XB and Münger K. Expression of the human papillomavirus type 16 E7 oncoprotein induces an autophagy-related process and sensitizes normal human keratinocytes to cell death in response to growth factor deprivation. *Virology*, 2009; 385(1): 192-197.
63. Zhou X, Spangle JM, and Münger K. Expression of a viral oncoprotein in normal human epithelial cells triggers an autophagy-related process: is autophagy an "Achilles' heel" of human cancers?. *Autophagy*, 2009; 5(4): 578-579.
64. Lafaille FG, Pessach IM, Zhang SY, Ciancanelli MJ, Herman M, Abhyankar A, et al. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. *Nature*, 2012; 491(7426):769-773.
65. Leroux-Roels G, Clément F, Vandepapelière P, Fourneau M, Heineman T, and Dubin G. Immunogenicity and safety of different formulations of an adjuvanted glycoprotein D genital herpes vaccine in healthy adults: a double-blind randomized trial. *Human vaccines & immunotherapeutics*, 2013; 9(6): 1254-1262.
66. English L, Chemali M, Duron J, Rondeau C, Laplante A, Gingras D, et al. Autophagy enhances the presentation of endogenous viral antigens on MHC class I molecules during HSV-1 infection. *Nature immunology*, 2009; 10(5): 480.
67. Orvedahl A, Alexander D, Tallóczy Z, Sun Q, Wei Y, Zhang W, et al. HSV-1 ICP34.5 confers neurovirulence by targeting the Beclin 1 autophagy protein. *Cell host & microbe*, 2007; 1(1): 23-35.
68. Lee HK, Mattei LM, Steinberg BE, Alberts P, Lee YH, Chervonsky A, et al. In vivo requirement

- for Atg5 in antigen presentation by dendritic cells. *Immunity*, 2010; 32(2): 227-239.
69. **Carpenter JE, Jackson W, Benetti L, Grose C.** Autophagosome formation during varicella-zoster virus infection following endoplasmic reticulum stress and the unfolded protein response. *Journal of virology*, 2011, 85(18), 9414-9424.
 70. **Henningham A, Barnett TC, Maamary PG, and Walker MJ.** Pathogenesis of group A streptococcal infections. *Discovery medicine*, 2012; 13(72): 329-342.
 71. **Nakagawa I, Amano A, Mizushima N, Yamamoto A, Yamaguchi H, Kamimoto T, et al.** Autophagy defends cells against invading group A Streptococcus. *Science*, 2004; 306(5698):1037-1040.
 72. **Amano A, Nakagawa I, and Yoshimori T.** Autophagy in innate immunity against intracellular bacteria. *Journal of biochemistry* 2006; 140(2): 161-166.
 73. **Grosset J.** Mycobacterium tuberculosis in the extracellular compartment: an underestimated adversary. *Antimicrobial agents and chemotherapy*, 2003; 47(3):833-836.
 74. **Vergne I, Chua J, Singh SB, and Deretic V.** Cell biology of Mycobacterium tuberculosis phagosome. *Annu. Rev. Cell Dev. Biol*, 2004; 20: 367-394.
 75. **Vergne I, Singh S, Roberts E, Kyei G, Master S, Harris J et al.** Autophagy in immune defense against Mycobacterium tuberculosis. *Autophagy*, 2006; 2(3): 175-178.
 76. **Lenz HD, Haller E, Melzer E, Kober K, Wurster K, Stahl M, et al.,** Autophagy differentially controls plant basal immunity to biotrophic and necrotrophic pathogens. *The Plant Journal*, 2011; 66(5): 818-830.
 77. **Masperi P, Dall'Olio G, Calefano A, and Vannini GL.** Autophagic vacuole development in Trichophyton mentagrophytes exposed in vitro to miconazole. *Sabouraudia*, 1984; 22(1): 27-35.
 78. **Leidal AM, Levine B, and Debnath J.** Autophagy and the cell biology of age-related disease. *Nature cell biology*, 2018; 20(12):1338-1348.
 79. **Ryazanov AG, Nefsky BS.** Protein turnover plays a key role in aging. *Mechanisms of ageing and development*, 2002; 123(2-3): 207-213.
 80. **Cuervo AM, Bergamini E, Brunk UT, Droge WF, french M, and Terman A.** Autophagy and aging: The importance of maintaining “clean” cells. *Autophagy*, 2015; 1:131–140.
 81. **Terman A.** The effect of age on formation and elimination of autophagic vacuoles in mouse hepatocytes. *Gerontology*, 1995; 41(2): 319-326.
 82. **Tashiro K, Shishido M, Fujimoto K, Hirota YY, Gomi T, and Tanaka Y.** Age-related disruption of autophagy in dermal fibroblasts modulates extracellular matrix components, *Biochemical and biophysical research communications* 2014; 443(1): 167-172.
 83. **Wang M, Charareh P, Lei X, and Zhong JL.** Autophagy: Multiple Mechanisms to Protect Skin from Ultraviolet Radiation-Driven Photoaging. *Oxidative Medicine and Cellular Longevity*, 2019.
 84. **Tuchayi SM, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC.** Acne vulgaris. *Nat Rev Dis Primers*, 2015;1(1):15029.
 85. **Dréno B, Layton A, Zouboulis CC, López-Estebarez JL, Zalewska-Janowska A, Bagatin E, et al.** Adult female acne: a new paradigm. *Journal of the European Academy of Dermatology and Venereology*, 2013; 27(9): 1063-1070.
 86. **Li X, He C, Chen Z, Zhou C, Gan Y, Jia Y.** A review of the role of sebum in the mechanism of acne pathogenesis. *Journal of Cosmetic Dermatology*, 2017; 16(2): 168-173.
 87. **Lee Y, Shin K, Shin KO, Yoon S, Jung J, Hwang E, Hwang E, ... and Jeong S. et al.** Topical application of autophagy-activating peptide improved skin barrier function and reduced acne symptoms in acne-prone skin. *Journal of Cosmetic Dermatology*, 20(3), 1009-1016
 88. **Schneider MR, Schmidt-Ullrich R, and Paus R.** The hair follicle as a dynamic miniorgan. *Current Biology*, 2009; 19(3): 132-142.
 89. **Chai M, Jiang M, Vergnes L, Fu X, de Barros SC, Doan NB, et al.** Stimulation of hair growth by small molecules that activate autophagy. *Cell Reports*, 2019; 27(12): 3413-3421.
 90. **Eckhart L, Tschachler E, Gruber F.** Autophagic control of skin aging. *Frontiers in Cell and Developmental Biology*, 2019; 7: 143.
 91. **Petukhova L, Patel AV, Rigo RK, Bian L, Verbitsky M, Sanna-Cherchi S, et al.** Integrative analysis of rare copy number variants and gene expression data in alopecia areata implicates an aetiological role for autophagy. *Experimental Dermatology*, 2020; 29(3): 243-253.
 92. **McDonagh AJ and Tazi-Ahmini R.** Epidemiology and genetics of alopecia areata, *Clinical and Experimental Dermatology: Clinical dermatology* 2002; 27(5): 405-409.
 93. **Richmond JM and Harris JE.** Immunology and skin in health and disease, *Cold Spring Harbor perspectives in medicine*, 2014; 4(12): 015339.
 94. **Tan JQ, Zhang HH, Lei ZJ, Ren P, Deng C, Li XY, et al.** The roles of autophagy and apoptosis in burn wound progression in rats, *Burns*, 2013; 39(8): 1551-1556.
 95. **An Y, Liu WJ, Xue P, Ma Y, Zhang LQ, Zhu B, et al.** Autophagy promotes MSC-mediated vascularization in cutaneous wound healing via regulation of VEGF secretion. *Cell death & diseases*, 2018; 9(2): 1-14.
 96. **Fischer J.** Autosomal recessive congenital ichthyosis. *Journal of investigative dermatology*, 2009; 129(6):1319-1321.

97. **Rodríguez-Pazos L, Ginarte M, Vega A, and Toribio J.** Autosomal recessive congenital ichthyosis. *Actas Dermo-Sifiliográficas* 2013; 104(4): 270-284.
98. **Zehmer JK, Huang Y, Peng G, Pu J, Anderson RG, Liu P.** A role for lipid droplets in intermembrane lipid traffic. *Proteomics*, 2009; 9(4): 914-921.
99. **Onal G, Kutlu O, Ozer E, Gozuacik D, Karaduman A, Emre SD.** Impairment of lipophagy by PNPLA1 mutations causes lipid droplet accumulation in primary fibroblasts of Autosomal Recessive Congenital Ichthyosis patients. *Journal of Dermatological Science*, 2019; 93(1): 50-57.
100. **van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, et al** Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science*, 1997; 277(5327): 805-808.
101. **Cao J, Tyburczy ME, Moss J, Darling TN, Widlund HR, and Kwiatkowski DJ.** Tuberous sclerosis complex inactivation disrupts melanogenesis via mTORC1 activation. *The Journal of clinical investigation*, 2017; 127(1): 349-364.
102. **Yang F, Yang L, Wataya-Kaneda M, Hasegawa J, Yoshimori T, Tanemura A, et al.** Dysregulation of autophagy in melanocytes contributes to hypopigmented macules in tuberous sclerosis complex. *Journal of dermatological science*, 2018; 89(2): 155-164.
103. **Hirai Y, Miyake T, Hamada T, Yamasaki O, Morizane S, Mori T, et al.** Autophagy in malnutrition associated dermatoses. *The Journal of Dermatology*, 2019; 46(1): 43-47.

المخلص العربي

الإلتهام الذاتي في أمراض الجلد الغير ورمية

عزة سامي عامر¹، رحاب منير سمكة²، نيرة حسن مفتاح³

¹ قسم الأمراض الجلدية، مستشفى دسوق العام، كفر الشيخ، جمهورية مصر العربية

² قسم الباثولوجيا، كلية الطب، جامعة المنوفية، المنوفية، جمهورية مصر العربية

³ قسم الأمراض الجلدية والتناسلية، كلية طب البنات، القاهرة، جامعة الأزهر، جمهورية مصر العربية

ملخص البحث

يعد الإلتهام الذاتي آلية خلوية معقدة تحافظ على التوازن الخلوي والنسجي عن طريق تفكك العضيات تحت الخلوية الشائخة والعوامل المعدية والبروتينات غير المطوية. من ناحية أخرى، أثناء الإجهاد الخلوي، مثل الحرمان من التغذية ونقص الأكسجين والإجهاد التأكسدي، والعدوى والإشعاع أو العلاج بالعقاقير المضادة للسرطان، يتم زيادة مستوى الإلتهام الذاتي، مما يؤدي إلى التكيف وبقاء الخلية.

ومع الاهتمام المتزايد بدراسة الإلتهام الذاتي اتضح أن هذه العملية تؤثر على كل أجهزة الجسم ولها دور فعال في قائمة موسعة من الأمراض وقد يكون للإلتهام الذاتي دور مُمرض أو علاجي في أمراض المناعة الذاتية.

والجلد الذي يعد أكبر عضو في الجسم يخدم كخط الدفاع الأول ضد العديد من المثبرات البيئية المختلفة؛ ومع ذلك، فهناك دراسات قليلة عن تأثير الإلتهام الذاتي على أمراض الجلد.

قد يعكس مستوى الإلتهام الذاتي درجة بعض الأمراض؛ لذلك قد يكون الكشف عن مستوى الإلتهام الذاتي طريقة غير مباشرة لتقييم بعض الأمراض. تقدم هذه المقالة لمحة عامة عن الدراسات الحديثة ذات الصلة بدور الإلتهام الذاتي في الأمراض الجلدية غير الورمية.

الهدف: يقدم هذا البحث مراجعة عامة عن النتائج الحديثة ذات الصلة بدور الإلتهام الذاتي في الأمراض الجلدية غير الورمية

الأستنتاجات: يلعب الإلتهام الذاتي دورًا مهمًا في تخفيف أو تفاقم الأمراض الجلدية المختلفة. إن فهم آليات الإلتهام الذاتي وتنظيمها في الأنسجة والخلايا المختلفة في ظل ظروف صحية ومرهقة سيساعد على فهم مسببات الأمراض الجلدية بشكل أفضل وتطوير أساليب علاجية أكثر فعالية.

الكلمات المفتاحية: حب الشباب ، التهاب الجلد التأتبي ، الإلتهام الذاتي ، الصدفية ، الأمراض الجلدية.

الباحث الرئيسي:

الاسم: عزة سامي عامر، قسم الأمراض الجلدية، مستشفى دسوق العام، كفر الشيخ، جمهورية مصر العربية.

الهاتف: 01011376182

البريد الإلكتروني: Azaasamyamer@gmail.com