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Role of Autophagy in Psoriasis

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Abstract

Autophagy is a complicated cellular mechanism that maintains cellular and tissue homeostasis and integrity via degradation of senescent, defective subcellular organelles, infectious agents, and misfolded proteins. Accumulating evidence has shown that autophagy is involved in numerous immune processes, such as removal of intracellular bacteria, cytokine production, auto antigen presentation, and survival of lymphocytes, indicating an apparent and important role in innate and adaptive immune responses. Current studies indicate that autophagy is important for the regulation of inflammation through disruption of multiple steps of inflammasome activation, therefore preventing inflammation.

Psoriasis is a chronic immune-mediated inflammatory skin disease that affects approximately 2% of the population worldwide. Importantly, studies have shown that constitutive granular layer autophagy is deregulated in psoriasis patients. Moreover, autophagy could down regulate pro-inflammatory cytokine production, exert a protective role in inflammatory diseases, and clear cellular materials such as damaged mitochondria to maintain cellular homeostasis; all these effects play a supporting role in the protection against inflammation associated skin diseases. In psoriasis, autophagy may reduce inflammation and proliferation of keratinocytes and may also promote bacterial clearance.hemistepsin A, lupiwighteone may be promising therapeutic targets in psoriasis treatment.

Introduction

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: macro autophagy, micro autophagy, and chaperone-mediated autophagy. Macro autophagy 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. Micro autophagy 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 two processes, involves direct translocation of the targeted proteins with a consensus peptide sequence across the lysosomal membrane by specific chaperone complexes [(3, 4)].

Autophagy consists of several sequential steps: sequestration, transport to lysosomes, degradation, and utilization of degradation products [(5).] 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. 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 [(7).] To understand the various roles of autophagy, it may be useful to sub classifymacro autophagy into “basal autophagy” and “induced autophagy” [(8)]. 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 [(5).] The presence of autophagosomes in dying cells raises the possibility that autophagy may also play an active role in cell death [(9).] 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 [(8).] Defective autophagy has been implicated in the pathogenesis of diverse disease states, such as myopathy [(10),] neuronal degeneration [(11),] microbial infection [(12),] inflammatory bowel disease[(13, 14),] aging [(15),] and cancer [(16).] Besides its basal function, autophagy also plays a role in nutrient deprivation [(17-20)]metabolic stress [(19, 21, and 22),] endoplasmic reticulum (ER) stress [23, 24] radiation [25], and anticancer drugs [26–29]. Therefore, it may be difficult to draw simplified connections between autophagy and skin diseases.

Psoriasis is a chronic immune-mediated inflammatory skin disease that affects approximately 2% of the population worldwide [30]. It is a multifactorial disorder, influenced by both genetic and environmental factors [31], and pathologically characterized by inflammation and epidermal proliferation. Several pathogens, such as bacteria, viruses and even fungi, have been linked to psoriasis [32]. 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 [33]. Autophagy eliminates the bacteria 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[34]and present an increased level in psoriasis [35]. 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 [36], while regulatory T (Treg) cells, which release anti-inflammatory cytokines like IL-10 and transforming growth factor-β1, which was associated with reductions in Th1 and Th17 was enhanced when Th17 decreased and Treg cells increased, tumorcells [38, 39]. Since CD147 contributes to the occurrence the ratio of Th17 to Treg cells was elevated in the pathogenesis of psoriasis. Several studies demonstrated that CD147 played an important role in the inhibitory regulation of autophagy and autophagic cell death in tumor cells. Since CD147 contributes to the occurrence of psoriasis, and CD147 can modulate autophagy through the PI3K/Akt/mTOR pathway[37]. Several studies demonstratedTh17 cells became converted into Treg cells via stem cells that overexpressed sRAGE displayed enhanced sRAGE (receptor for advanced glycation end-products, responsible for the genesis and development of regulation of autophagy and autophagic cell death in RAGE) overexpressing mesenchymal stem cells potently psoriasis. It is higher on neutrophils in psoriatic lesions protein, belongs to the immunoglobulin superfamily, significantly patients with psoriasis; thus, decreased autophagy could of psoriasis. Meanwhile, mesenchymal inhibited Th1, Th17 cell differentiation and increased the higher in the patients with psoriasis than those in enhanced autophagy [40].

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 [41]. Now that autophagy plays an important role in immune regulation including thymic selection, lymphocyte development and survival, antigen presentation, and tissue homeostasis [42], research found that polymorphisms in Atg16L1 gene (rs10210302, rs12994971, rs2241880, rs2241879, and rs13005285) contributes to the risk of psoriasis vulgaris [43]. Atg16L1 gene encodes the Atg16L1 protein, a key component of a large protein complex essential for autophagy [44]. 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. The excessive epithelial keratinocyte (KC) proliferation and abnormal apoptosis are important features of psoriasis [(45),] and inhibition of the excessive proliferation of
KCs is an effective treatment method [(46)]. Studies have recently shown that autophagy deficiency leads to inflammatory cytokine production and cell proliferation in KCs [(47).] 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 orTLR4 in KCs and p62 expression is up regulated through induction of NADPH oxidases 2 and 4 and the generationof 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-κB 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[(48).] Autophagy is up regulated when superfluous reactive oxygen species accumulate resulting in mitochondria damage to prevent cells from further damage under hypoxia [(49).] Hypoxia-inducible factor 1a is the key factor to induce autophagy in hypoxia, and it is demonstrated that hypoxia-inducible factor 1a expression is markedly increased in psoriatic lesions compared to normal skin. Therefore, we speculate psoriasis up regulateshypoxia induciblefactor 1a, then promotes beclin-1 expression, and induces autophagy to clear the damaged mitochondria, hence suppressing mitochondrial-mediated apoptosis and promoting proliferation of KCs[(50)]. Notably, a link between autophagy and psoriasis has been observed because polymorphisms in the autophagy gene *ATG16L1* (autophagy related 16 like 1) are associated with psoriasis[(51)]. Bone marrow-derived cell (BMDC) autophagy induces the degradation of MYD88 (MYD88 innate immune signal transduction adaptor) and controls the activation of MYD88-dependent cytokines upon imiquimod (IMQ) stimulation in a mouse model of psoriasis[(51).] These findings imply that autophagy might play a pivotal function in psoriasis.

Importantly, studies have shown that constitutive granular layer autophagy is deregulated in psoriasis patients[(52).]

IL17A enhances autophagic flux in KCs to promote the degradation of cholesterol, and this effect is related to psoriasis [52].

The inhibition of autophagy via activation of PI3K/ AKT/mTOR has been suggested as a therapeutic method for the treatment of IL-17a-mediated psoriasis [53].Current studies indicate that autophagy is important for the regulation of inflammation throughdisruption of multiple steps of inflammasome activation, therefore preventing inflammation [53]. Moreover, autophagy could down regulate pro-inflammatory cytokine production, exert a protective role in inflammatory diseases, and clear cellular materials such as damaged mitochondria to maintain cellular homeostasis; all these effects play a supporting role in the protection against inflammation associated skin diseases [54].

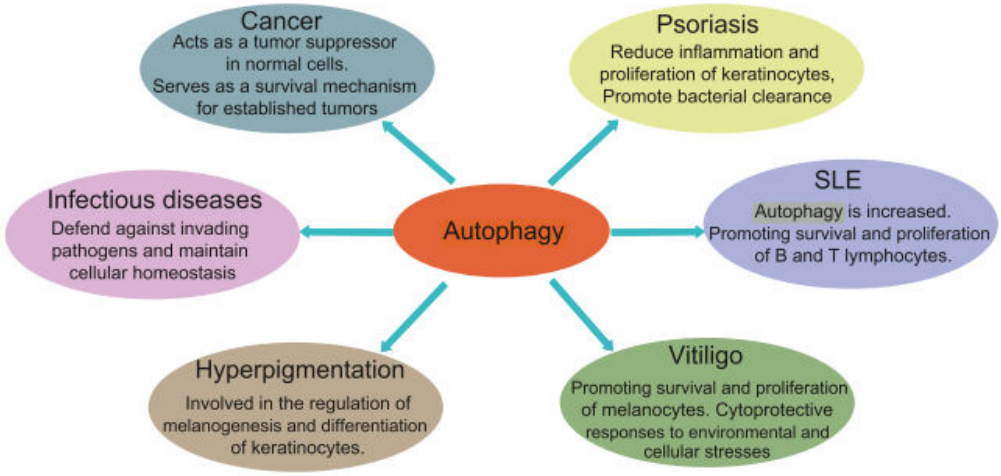

Figure: 1[55]. Effects of autophagy in skin diseases. Autophagy has been implicated in pathogenesis of skin diseases. In psoriasis, autophagy may reduce inflammation and proliferation of keratinocytes and may also promote bacterial clearance. In SLE, autophagy may promote survival and proliferation of B and T lymphocytes. In vitiligo, autophagy may promote survival and proliferation of melanocytes and may also involve in cytoprotective responses to environmental and

Vitiligo Promoting survival and proliferation of melanocytes. Cytoprotective responses to environmental and cellular stresses cellular stresses. In hyperpigmentation, autophagy may be involved in the regulation of melanogenesis and differentiation of keratinocytes. In infectious diseases, autophagy may defend against invading pathogens andmaintain cellular homeostasis. In skin cancer, autophagymay act as a tumor suppressor in normal cells and serve as a survival mechanism for established tumors.

Interplay Between Cytokine Secretion and Autophagy

It is no surprise that autophagy-regulated cytokine secretion by the secretory pathway shares some common functions with phagocytosis, such as vesicle trafficking and

membrane fusion, which facilitates the important role of autophagy in immune regulation.

ATG5 deficiency, for example, results in elevated IL-1 alpha secretion by macrophages [56], while inhibition of autophagy leads to promotion of IL-1 beta via reducing degradation [57] by antigen presenting cells(APCs) and increases IL-23 secretion as a consequence [57], which can further promote Th17-mediated inflammatory responses. On the other hand, cytokines can also regulate autophagy. IL-10, which is an anti-inflammatory cytokine, has been found to inhibit autophagy in murine macrophages via activation of mTOR complex 1 [57]. Another example is IL-6, which is a universal inflammatory cytokine involved in many autoimmune and inflammatory diseases. IL-6 has been illustrated to inhibit starvation-induced [58] and IFN-gamma-induced autophagy [59] by regulating Bcl-2 and Beclin1. However, IL-6 has also been found to be required for autophagy by promoting autophagosomal maturation [60, 61].In psoriasis, TNF-α was shown to negatively regulate the overexpression of progranulin (PGRN), which inhibited the inflammation of keratinocytes via Wnt/β-catenin signaling pathway. Specific silencing of PGRN stimulated the production of theinflammatory cytokines IL-1β, IL-6, COX-2, iNOs, and MCP-1. This silencing also promoted the expression of p62 and suppressed LC3II and Atg7 expression in HaCaT cells. Finally, knockdown of PGRN increasedthe expression levels of β-catenin, cyclin D1, and c-myc proteins.

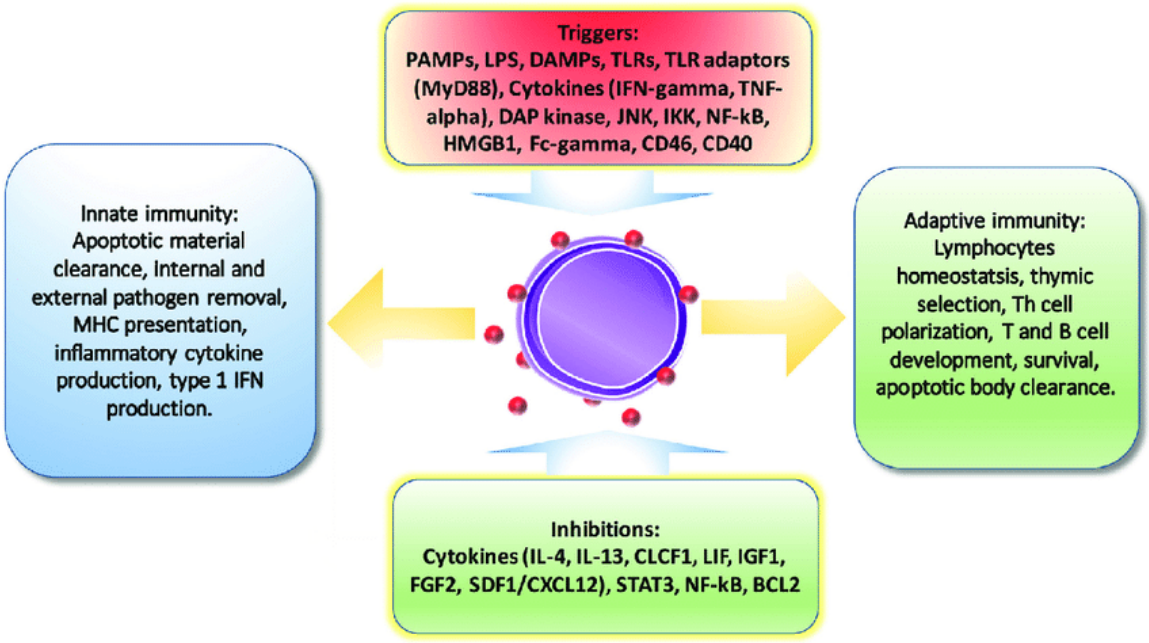

Figure: 2[62].The regulations of autophagy on immune system. Autophagy is triggered and inhibited by cytokines and molecules from immune system. And also, autophagy is involved in pathogen removal, cytokine secretion, lymphocyte survival and differentiation, MHC presentation, apoptotic cell clearance, and proinflammatory signaling.

Autophagy and psoriasis

Psoriasis is a chronic, autoimmune skin disease, characterized by heavily scaled red plaques. The increased epithelial keratinocyte proliferation is an important feature of psoriasis, and inhibition of the excessive proliferation of keratinocytes is an effective treatment method [(63).] The disease is strongly associated with streptococcal throat infection and has a strong genetic component. The pathogenic mechanism of psoriasis is poorly understood, but is postulated to be a combination of genetic predisposition and environmental factors. A recent study has linked several single nucleotide polymorphisms(SNPs) in ATG16L1 gene (rs10210302, rs12994971, rs2241880, rs2241879, and rs13005285) to susceptibility to psoriasis [(64).] It is not known how ATG16L1 mechanistically contributes to skin biology or psoriasis pathogenesis; however, given the fact that psoriasis is pathologically characterized by inflammation and epidermal proliferation, it is therefore not surprising that Lee et al. have recently shown that defects in autophagy lead to inflammatory cytokine production and cell proliferation in keratinocytes[(65).] They have reported that keratinocyte autophagy negatively regulates p62 expression, and genetic knockdown of p62 reduces the production of inflammatory cytokines and cell proliferation [(65).] Another speculation is that, since infection can trigger or exacerbate psoriasis and since autophagy plays a crucial role in bacterial clearance, it is possible that decreased autophagy in psoriasis leads to altered clearance of and/or altered immune responses to bacteria. Thus in this case, pharmacologic up regulation of autophagy may represent a novel strategy for the treatment of psoriasis. In support of this concept, many first line agents in the treatment of psoriasis, such as vitamin D analogs [(66),]retinoid[(67,68),] sirolimus [(69),] and UVB therapy [(70),] can induce activation of autophagy, though these drugs might provide clinical benefits independent of autophagy activation. This trend suggests that pharmaceutical agents approved for use in alternative conditions, which also induce autophagy, could be novel treatments for psoriasis. In addition, it would be critical to explore further genetic evidence, since autophagy is a pathway and other populations have not been thoroughly investigated.

Hye Ran Kim demonstrate that AhR modulated autophagy leads to skin inflammation in human keratinocytes via the p65NF-κB/p38MAPK signaling pathways, suggesting that AhR signaling and autophagy might be involved in the pathogenesis of chronic inflammatory disorders such as psoriasis[(71).]

Zhen Wang demonstrated a significant positive correlation between functionally active autophagy and psoriasis severity[(52).]

Hemistepsin A (HsA)

Is a sesquiterpene lactone isolated from *Hemistepta lyrata* (Bunge) Bunge.A study shown HsApretreatment inhibited nitric oxide production, and reduced the expression of iNOS and COX-2 in Toll-like receptor ligand-stimulated RAW 264.7 cells. Additionally, has

decreased the secretion of proinflammatory cytokines in lipopolysaccharide (LPS)-stimulated Kupffer cells as well as in RAW 264.7 cells. HsA inhibited phosphorylation of IKK-□/□□and degradation of I□B□, resulting in decreased nuclear translocation of nuclear factor-□B (NF-□B) and its transcriptional activity. Moreover, HsA phosphorylated nuclear factor erythroid 2-related factor 2 (Nrf2), increased expression levels of antioxidant genes, and attenuated LPS-stimulated H2O2 production. Phosphorylation of p38 and c-Jun N-terminal kinase was required for HsA-mediated Nrf2 phosphorylation. In a D-galactosamine/LPS-induced liver injury model, HsA ameliorated Dgalactosamine/ LPS-induced hepatocyte degeneration and inflammatory cells infiltration. Moreover, immunohistochemical analyses using nitrotyrosine, 4-hydroxynonenal, and cleaved poly (ADP-ribose) polymerase antibodies revealed that HsA protected the liver from oxidative stress. Furthermore, has reduced the numbers of proinflammatory cytokine-positive cells in hepatic tissues. Thus, these studies suggest HsA may be a promising natural product to manage inflammation-mediated tissue injuries through inhibition of NF-kB and activation of Nrf2 [(72).]

Thus,not only antioxidant gene induction, but also Nrf2-dependent NF-□B inhibition, collectivelycontributes to attenuation of the inflammatory response by HsA.

In 2017 Kim, showed that chemical inhibitors of both p38 and JNK failed to phosphorylate Nrf2 and toinduce HO-1 expression by HsA. Although the differential role of HsA-mediated MAPKphosphorylation in inflammation and Nrf2 signaling, as well as the roles of other upstream kinases onHsA-mediated Nrf2 phosphorylation, need to be further established, the present studies suggest thatp38 and JNK phosphorylation by HsA contribute to the inhibition of the inflammatory responsethrough Nrf2 activation. Kim illustrated that HsA isolated from *H. lyrata* inhibitedproinflammatory responses *in vitro* and *in vivo*, mediated by inhibition of NF-□B and activation ofNrf2. Thus, HsA may be a promising candidate to manage inflammation-mediated tissue injury,particularly in the liver[(72)].Hemistepsin A (HsA), has the ability to ameliorate hepatitis in mice. However, the effects of H. lyrata and HsA on other types of liver disease have not been explored. HsA reduced the phosphorylation of IKKε and the transactivation of nuclear factor-κB (NF-κB). Moreover, HsA decreased the phosphorylation of Akt and its downstream signaling molecules. Transfection experiments suggested that inhibition of NF-κB or Akt is essential for HsA-induced apoptosis of Hematopoietic stem cells (HSCs). In a CCl4-induced liver fibrosis model, HsA administration significantly decreased ALT and AST activities. Furthermore, HsA attenuated CCl4- mediated collagen deposits and profibrogenic genes expression in hepatic tissue. Thus, HsA may serve as a natural product for managing liver fibrosis through inhibition of NF-κB/Akt-dependent signaling. HsA decreased the expression of Bcl-xL, and increased caspase-3 and PARP cleavage in LX-2 cells. HsA decreased the phosphorylation ofIKKε, but not TBK1, in primary activated HSCs in a concentration-dependent manner. Several upstream kinases, such as IKKα, IKKβ, IKKε,TBK1, and ribosomal S6 kinase, are known to directly

phosphorylateSer536 of p65 [73]. Moreover, IKKα/ β inhibition by sulfasalazine ameliorates CCl4-induced liver fibrosis by inducing apoptosis in activated HSCs [74]. Previously, studies showed HsA inhibits the phosphorylation of IKKα/β in lipopolysaccharide-stimulated macrophages [75].

Lupiwighteone

Lupiwighteone is an isoflavone present in the root of Glycyrrhiza glabra, which is a well-known medicinal herb that is also known as licorice and has long been used in beverages, herbalism and traditional medicine [76, 77].

Lupiwighteone treatment resulted in apoptotic cell death in breast cancer cells, which was characterized by DNA fragmentation, accumulation of apoptotic cells, and nuclear condensation. Yeong-Seon Won,also showed that treatment with lupiwighteone induced caspase-dependent apoptosis (up-regulation of caspase-3, -7, -8, -9, PARP, and Bax or down-regulation of

Bid, Bcl-2), induction of caspase-independent apoptosis (up-regulation of AIF and Endo G on cytosol), and inhibition of the PI3K/Akt/mTOR signaling pathway (down-regulation of PI3K, p-Akt, and p-mTOR) in both MCF-

7 and MDA-MB-231 cells [78].

The natural isoflavone phytoestrogen is widely distributed in plants such as licorice, soybean, and pomegranate, and is well known as a potent agent in the prophylaxis and treatment of cancer [79].

Lupiwighteone (Lup) is distributed widely in wild-growing plants such as Glycyrrhiza glabra, Lupinus, and Lotus pedunculatus. On the basis of existing research, Lup shows antioxidant and antimicrobial effects, but itsantitumor activity has not been reported as yet. Isoflavones have various pharmacologic properties, such as antioxidant properties, inhibition of tyrosine kinases, DNA topoisomerase I and II, ribosomal S6 kinase, and nuclear factor-kB activation [80]. The isoflavone 5,7, 40-trihydroxy-8- prenyliso-flavone (lupiwighteone) (was isolated from the pods and seeds of white lupin, roots of yellow lupin (Lupinos Luteus) and the leaves of Glycyrrhiza glabra [81].

Conclusion

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. Recently, studies have illustrated that autophagy is intricately related to skin diseases. Understanding of autophagymechanisms and their regulation in different tissuesand cells under healthy and stressed conditions willhelp us better understand the pathogenesis of skin diseases and develop more effective therapeutic approaches.

Autophagy has been regarded as an endogenous defense mechanism against environmental disturbances. Current studies indicate that autophagy is important for the

regulation of inflammation through disruption of multiple steps of inflammasome activation, therefore preventing inflammation. Moreover, autophagy could down regulate pro-inflammatory cytokine production, exert a protective role in inflammatory diseases, and clear cellular materials such as damaged mitochondria to maintain cellular homeostasis; all these effects play a supporting role in the protection against inflammation associated skin diseases such as psoriasis and may serve as a novel therapy in the treatment of psoriasis.

However, studies on the role of autophagy in psoriasis pathogenesis remain limited.

Hemistepsin A ameliorates acute inflammation in macrophages via inhibition of nuclear factor-κB and activation of nuclear factor erythroid 2-related factor 2(Nrf2)so HsA may be a promising natural product to manage psoriasis like inflammation.

Lupiwighteone can be also used for future treatment of psoriasis through inhibition of NfkB, TNF alfaactivation.

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