ORIGINAL ARTICLE

Aryl Hydrocarbon Receptor and Autophagy-Related Protein Microtubule-Associated Protein Light Chain 3 Expression in Psoriasis

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Background: The aryl hydrocarbon receptor (AHR) and autophagy are both important to maintain skin homeostasis. However, they are also involved in skin disorders. So far, their roles in psoriasis pathogenesis are unknown. **Objective:** We studied the immunohistochemical and gene expression of AHR, CYP1A1, and microtubule-associated protein light chain 3 (LC3) in lesional skin of psoriasis patients to determine correlations among them. **Methods:** We included 24 psoriasis patients and ten healthy volunteers. Skin biopsies were collected. AHR, CYP1A1, and LC3 protein expression was examined by immunohistochemistry, immunofluorescence, and western blotting. *AHR, CYP1A1, LC3, ATG5, BECN1* and *Nrf2* mRNA levels were measured by quantitative polymerase chain reaction. **Results:** AHR and CYP1A1 protein expression were higher in psoriasis lesional skin than in normal skin. LC3 protein expression was lower in psoriasis lesions than in normal controls. AHR and CYP1A1 protein expression in psoriasis lesions showed significant positive correlations with mean epidermal thickness and inflammatory cell density. Significant negative correlations were noted between LC3 protein expression in psoriasis lesions and the mean epidermal thickness or inflammatory cell density. A significant negative correlation was found between AHR and LC3 expression in psoriatic skin. AHR, CYP1A1 and Nrf2 mRNA expression were upregulated while LC3, ATG5, and BECN1 mRNA were down-regulated, in psoriatic lesional skin compared with normal controls. **Conclusion:** AHR and autophagy could play a role in psoriasis pathogenesis by modifying epidermal hyperproliferation and inflammation. AHR and autophagy regulation are potential therapeutic targets in chronic inflammatory skin diseases. **(Ann Dermatol 33(2) 138~146, 2021)**

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disorder affected by both genetic and environmental factors. Epidemiologic reports confirm correlations between psoriasis and exposure to environmental pollutants, such as polycyclic aromatic hydrocarbons (PAHs) including benzo[a]pyrene as an aryl hydrocarbon receptor (AHR) ligand[1,2]. AHR is a ligand-activated transcription factor expressed in various human tissues including skin, lung, liver, thymus,

and kidney. AHR in the cytoplasm can be activated by environmental factors and migrate into the nuclei of skin cells[3]. In the nucleus, AHR dimerizes with the AHR nuclear translocator (ARNT) and participates in canonical signaling. The ligand−AHR−ARNT complex binds the xenobiotic-responsive element of its specific DNA recognition site causing target gene transcription, such as CYP1A1, which is a xenobiotic-metabolizing enzyme[4]. Environmental toxicants, dioxins including 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD), activate AHR by functioning as high-affinity AHR ligands, subsequently upregulating CYP1A1 expression. The AHR-CYP1A1 pathway also stimulates oxidative stress generation, which in turn induces inflammatory cytokine release[5]. AHR can also interact in a non-canonical manner with other signaling pathways, such as inflammatory and immune regulatory cascades, including the NF-κB[6], mitogen−activated protein kinases[7], and signal transducer and activator of transcription (STATs) pathways[8]. AHR was also recently suggested to be a critical skin integrity and immunity modulator, which are crucially involved in the pathogenesis of multiple skin diseases[9].

Autophagy is the endogenous housekeeping process responsible for degrading dysfunctional and redundant cellular organelles and proteins[10]. Autophagy not only serves a physiological function in maintaining skin homeostasis, but is also related to pathological processes in multiple skin disorders[11]. Cellular microtubule-associated protein light chain 3 (LC3) is an autophagy marker that indicates autophagosome quantity as the lipidated form of LC3-II accumulates in autophagosomal membranes[12]. Evidence shows that dysfunctional autophagy leads to inflammatory immune responses[13,14]. In cultured keratinocytes, autophagy defects result in increased inflammatory cytokine production and cell proliferation, suggesting a role in promoting psoriasis development[15].

Previously, we reported that crosstalk between the AHR pathway and autophagy may be linked to psoriasis pathogenesis in human keratinocytes. Specifically, AhR activation reduced autophagy, promoting skin inflammation through the p65NF-κB/p38MAPK pathways[16]. To validate the potential roles of the AHR pathway and autophagy in human psoriasis, we examined the expression of AHR, its downstream molecule CYP1A1, and autophagy marker LC3 in skin biopsies from psoriasis and normal controls, and evaluated the correlation among these markers in psoriasis skin tissues.

MATERIALS AND METHODS

Patients

This study included 24 patients with psoriasis vulgaris, and 10 normal control subjects from the Outpatient Clinic of the Department of Dermatology, Hallym University Kangnam Sacred Heart Hospital. Psoriasis was diagnosed by 2 dermatologists based on clinical and pathological features.

No subjects received topical or systemic treatment at least 3 months before skin biopsy. Patients with any other dermatological or uncontrolled systemic diseases and pregnant or lactating woman were excluded. A complete history was obtained from each patient, and all patients underwent general and dermatological examinations of disease severity using PASI scoring for psoriasis[17].

Ethics statement

Written informed consent was provided by all subjects before their participation. The protocol was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (IRB no. 2018-05-024).

Skin biopsies

Four-millimeter punch skin biopsies were taken under local anesthesia from lesional skin of psoriasis and control subjects. Specimens embedded in paraffin blocks were divided into 4 sections (each 4-μm thick); one was stained with hematoxylin and eosin to evaluate pathological changes and the other three were placed onto poly-L-lysine-coated slides for immunostaining. Skin tissues were also preserved in liquid nitrogen to prepare total RNA and total protein lysate.

Immunohistochemistry

Immunohistochemistry was conducted in 10% formalin-fixed, paraffin-embedded tissues. Dissected tissues were cleansed twice with distilled water, and residual fixatives were removed by 1 hour treatment with 1% sodium. The tissues were pre-treated with 3% hydrogen peroxide for 10 minutes, cleansed with distilled water; and cultured for 5 minutes with 1 TBST (Tris-buffered 5 saline with 0.1% Tween 20). To prevent nonspecific reactions, tissues were treated with normal goat serum (Vector Laboratories, Burlingame, CA, USA) at room temperature for 1 hour, and then cultured overnight with rabbit anti-AHR (1:300; Abcam, Cambridge, MA, USA), rabbit anti-CYP1A1 (1:300; Abcam), and rabbit anti-LC3 (1:300; Novus Biologicals, Littleton, CO, USA). Tissues were cleansed with 1 TBST, and cultured with biotinylated secondary antibody solution from the Dako REAL EnVision Detection System (Dako, Glostrup, Denmark) for 30 minutes at room temperature. The tissues then then cleansed with distilled water; counterstained with hematoxylin (Sigma-Aldrich, St. Louis, MO, USA); dehydrated and clarified based on a conventional method; and then prepared for Leica microsystem DFi8 LASX software light

microscopy (Leica, Wetzlar, Germany).

Immunohistochemical analysis

The staining pattern was evaluated using 4 separate fields in the epidermal cell layers. According to previous studies, brown cytoplasmic and/or nuclear staining for AHR, brown cytoplasmic staining for CYP1A1, and brown cytoplasmic and/or nuclear staining for LC3 were considered positive[18,19].

AHR, CYP1A1, and LC3 intensity scoring was performed via quantitative evaluation of the immunostained slides. Positive keratinocyte counts were described as the percentage of total keratinocyte counts from 0 to +3 as follows: 0 (negative expression)=no staining, +1 (mild expression) <25%, +2 (moderate expression)=25%~50%, and +3 (strong expression) >50%[20]. A positive percentage was given in epidermis after counting 500 cells in each section[21].

Quantitative morphometric analysis was conducted with LASX computerized digital image analysis software (Leica). Using a calibrated ruler, epidermis thickness was measured from the bottom of the rete ridge to the bottom of the stratum corneum; the mean was calculated from the measurements in 4 fields at ×100 magnification. Inflammatory cell density was calculated by identifying the area with the maximum density of inflammatory cells at low magnification (×100), after which inflammatory cells were counted in 4 fields at ×400. The mean density of inflammatory cells was calculated as the inflammatory cell count/dermal area. The results are described as the mean±standard deviation of the optical density of five different digital images[20]. All immunohistochemical analyses were determined independently by a single pathologist (LHJ) and single dermatologist (KJE) blinded to patient identity or clinical outcome. Disagreements were resolved through a consensus conference. The rate of initial concurrences was >90% in our study.

Immunofluorescence staining

Formalin-fixed, paraffin-embedded human tissue sections were deparaffinized and rehydrated in xylene and ethanol. More details are included in the Supplementary Materials.

Western blotting

Human skin tissues were harvested in pro-prep lysis buffer (Intron, Seoul, Korea) with a protease inhibitor cocktail (Roche Diagnostics, Mannheim, Germany). The copper (II) sulfate solution in bicinchoninic acid solution (Sigma-Aldrich) was used to measure protein concentrations. The same amount of protein (20 μg) was separated by 10% SDS-PAGE and transferred to enhanced chemiluminescence (ECL) nitrocellulose membranes (GE Healthcare, Buckinghamshire, UK), and blocked for 1 hour with 5% skim milk in TBST. The membranes were incubated overnight at 4°C with rabbit anti-LC3 (1:1,000; Abcam) antibodies. Primary antibodies were detected with horseradish peroxidase-conjugated secondary antibodies (goat anti-rabbit, 1:1,000; Abcam) and chemiluminescent luminol (LUMINOGRAPH II; Atto, Tokyo, Japan). Immunocomplexes were detected using an enhanced horseradish peroxidase/luminol chemiluminescence system (ECL Plus; Amersham International PLC, Little Chalfont, UK). Glyceraldehyde-3-phosphate dehydrogenase was used as a loading control.

Table 1. Clinical characteristics of psoriasis and control groups

Variable	Psoriasis group (n=24)	Control group (n=10)	p-value
Age (yr)			0.38
Mean±SD	42.1±15.47	36.78±13.65	
Median	41	42	
Range	10~67	13~55	
Sex, n (%)			0.704
Male	14 (58.3)	6 (60.0)	
Female	10 (41.7)	4 (40.0)	
Duration (mo)		-	-
Mean±SD	98.9±128.32		
Median	24		
Range	1~480		
PASI score		-	-
Mean±SD	10.74±7.14		
Median	10.2		
Range	1.4~30.6		

SD: standard deviation, PASI: psoriasis area and severity index, -: not available.

Table 2. Epidermal thickness and inflammatory cell density in psoriasis and control groups

Variable	Psoriasis group (n=24)	Control group (n=10)	p-value
Epidermal thickness (μm)			<0.001*
Mean±SD	729.19±331.37	215.28±109.21	
Median	690.23	214.45	
Range	210.34~1,663.75	71.31~434.76	
Inflammatory cell (density/mm^2)			<0.001*
Mean±SD	5,489.4±2,149.1	1,773.34±235.79	
Median	4,963.2	1,768.6	
Range	1,683.5~9,683.5	1,368.9~2,065.1	

SD: standard deviation. *$p<0.05$.

Quantitative reverse transcriptase-polymerase chain reaction

Based on manufacturer instructions, the RNeasy Plus Mini Kit (Qiagen, Hilden, Germany) was used to extract total RNA. The transcriptor First Strand cDNA synthesis kit (Roche Applied Science, Mannheim, Germany) was used to synthesize cDNA from 1 μg of total RNA. Quantitative reverse transcriptase-polymerase chain reaction (PCR) was performed three times using the TaqMan master mix (Applied Biosystems, Foster City, CA, USA) and the real-time PCR System (Applied Biosystems). The primers for mRNA detection are included in the Supplementary Materials. mRNA levels of *AHR*, *CYP1A1*, *LC3*, *ATG5*, *BECN1* and *NRF2* were normalized to that of *GAPDH*. Relative quantification was performed using a Light Cycler® 96 Instrument (Roche Diagnostics).

Statistical analyses

Qualitative data were expressed as numerical values and percentages; quantitative data were expressed as the range, mean, standard deviation, and median. Comparisons between different groups of categorical variables were performed using Fisher's exact test. For continuous variables, Student's t-test wasused. By using Spearman's correlation coefficient, correlations between variables were determined. All statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). *p*-values ＜0.05 were considered statistically significant.

RESULTS

Clinicopathologic data

Demographic and clinical patient data are presented in Table 1. Histopathologic data are shown in Table 2. No significant differences were observed in age and sex between groups. Epidermal thickness in the psoriasis group (729.19±331.37 μm) was higher than that in the control group (215.28±109.21 μm, *p*＜0.001; Fig. 1). Inflammatory cell density/mm^2 in the psoriasis group (5,489.4±2,149.1) was higher than that in the control group (1,773.34±235.79, *p*＜0.001; Fig. 1).

AHR and CYP1A1 immunohistochemical expression

Positive AHR staining in epidermal keratinocytes was found in 100% of psoriasis patients and 30% of healthy controls. CYP1A1 was expressed in epidermal keratinocytes in 100% of psoriasis patients and 40% of controls. AHR and CYP1A1 expression intensities in psoriasis patients were stronger than those in controls (*p*＜0.001, *p*＜0.001, respectively;
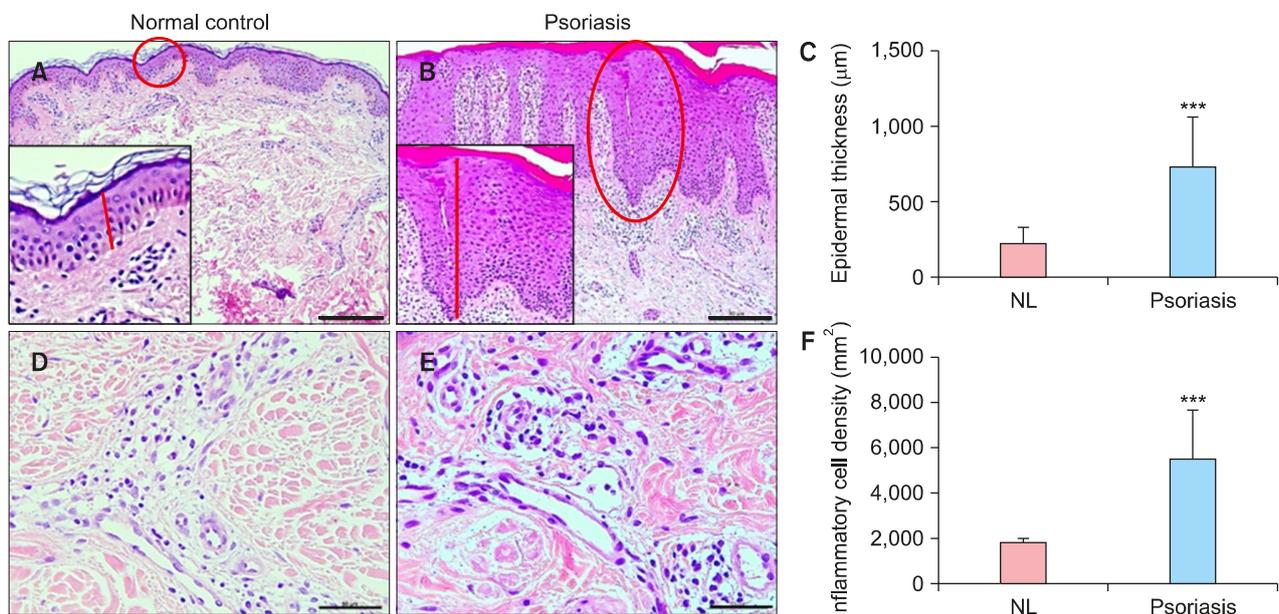

Fig. 1. Epidermal thickness and inflammatory cell density of psoriasis and control groups. (A∼C) Epidermal thickness measurement from the bottom of the rete ridge to the bottom of the stratum corneum (red line). (A) Normal control specimen (H&E , ×200; bar＝75 μm). (B) Lesional skin of a psoriasis patient (H&E, ×200; bar＝75 μm). (C) Epidermal thickness qualification. The epidermal thickness in lesional skin of psoriasis was thicker significantly compared to that in controls. (D∼F) Morphometric counting of inflammatory cell density. (D) Normal control specimen (H&E, ×400; bar＝50 μm). (E) Lesional skin of a psoriasis patient (H&E, ×400; bar＝50 μm). (F) Inflammatory cell density qualification. Inflammatory cell density in lesional skin of psoriasis was higher significantly compared to that in controls. NL: normal control. Statistical significance was determined by Student's t-test (***p＜0.001).

Table 3, Fig. 2). In immunofluorescence staining, AHR expression was significantly higher in lesional psoriatic skin than in normal controls (Supplementary Fig. 1).

LC3 protein expression

Epidermal keratinocytes showed positive LC3 staining in 33.3% of psoriasis patients and 90% of controls. LC3 expression intensity was significantly lower in psoriasis patients than in controls ($p < 0.001$; Table 4, Fig. 2). Immunofluorescence analyses showed significantly lower LC3 protein expression in lesional psoriatic skin than in normal controls (Supplementary Fig. 3). There was a decrease in LC3-II protein in lesional skin tissue of psoriasis by western blot analysis (Supplementary Fig. 2).

Relationships among the lesional AHR, CYP1A1, and LC3 immunohistochemical expression, clinical data, and histopathological parameters in psoriasis patients

AHR expression in psoriasis lesions was significantly positively correlated with mean epidermal thickness (R = 0.57, $p = 0.002$) and mean inflammatory cell density (R = 0.56, $p = 0.002$). CYP1A1 expression also showed significant positive correlations with mean epidermal thickness (R = 0.59, $p = 0.001$) and mean inflammatory cell density (R = 0.57, $p = 0.006$). LC3 expression in psoriasis lesions was significantly negatively correlated with mean epidermal thick-

Table 3. Comparison between psoriasis and control groups according to AHR and CYP1A1 expression

Variable	Psoriasis group (n = 24)	Control group (n = 10)	p-value
AHR expression			
Intensity			<0.001*
None	0 (0)	7 (70.0)	
Mild	3 (12.5)	3 (30.0)	
Moderate	9 (37.5)	0 (0)	
Strong	12 (50.0)	0 (0)	
Distribution			<0.001*
Negative	0 (0)	7 (70.0)	
Basal	1 (4.2)	0 (0)	
Both basal and suprabasal	21 (87.5)	3 (30.0)	
Full thickness	2 (8.3)	0 (0)	
CYP1A1 expression			
Intensity			<0.001*
None	0 (0)	6 (60.0)	
Mild	0 (0)	4 (40.0)	
Moderate	7 (29.2)	0 (0)	
Strong	17 (70.8)	0 (0)	
Distribution			<0.001*
Negative	0 (0)	6 (60.0)	
Basal	0 (0)	0 (0)	
Both basal and suprabasal	17 (70.8)	4 (40.0)	
Full thickness	7 (29.2)	0 (0)	

Values are presented as number (%). AHR: aryl hydrocarbon receptor. *$p < 0.05$.
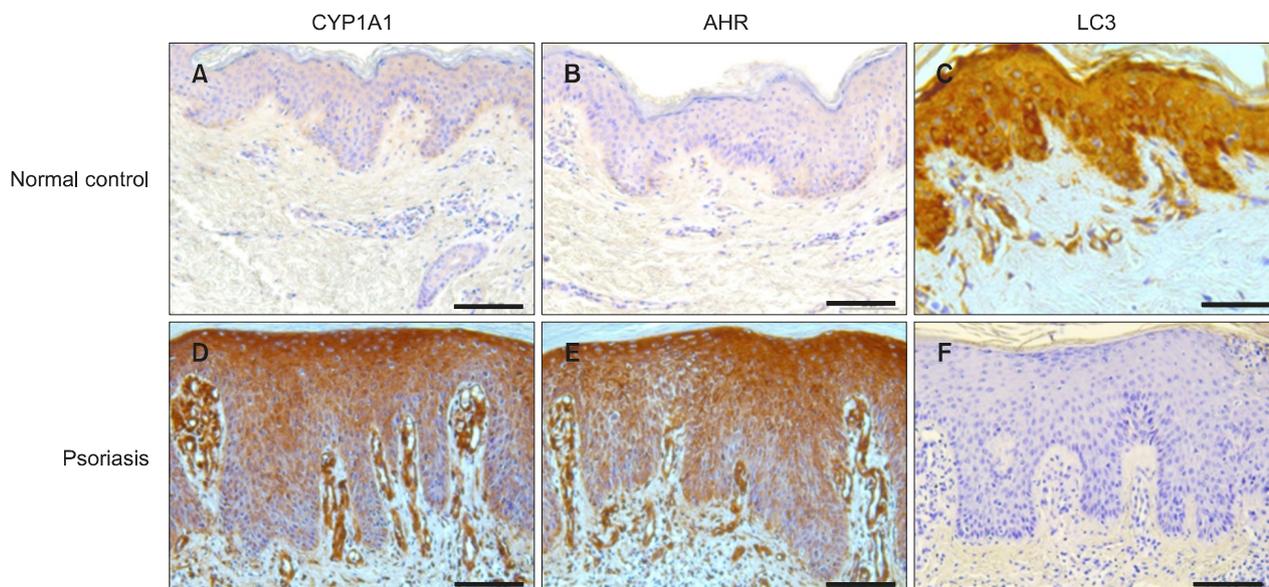

Fig. 2. AHR, CYP1A1, and LC3 immunohistochemical expression in psoriasis lesional skin and normal skin. (A) Normal control skin sample with mild (+1) basal pattern CYP1A1 expression (×200). (B) Normal control skin sample with negative. (0) AHR expression (×200). (C) Normal control skin sample with negative. (0) LC3 expression (×200). (D) Psoriasis specimen (lesional skin) showing a moderate (+2) basal and suprabasal pattern of CYP1A1 expression (×200). (E) Psoriasis specimen (lesional skin) showing a strong (+3) basal and suprabasal pattern of AHR expression (×200). (F) Psoriasis specimen (lesional skin) showing a mild (+1) basal and suprabasal pattern of LC3 expression (×200). Bar = 75 μm. AHR: aryl hydrocarbon receptor, LC3: microtubule-associated protein light chain 3.

Table 4. Comparison of LC3 expression between psoriasis and control groups

LC3 expression	Psoriasis group (n = 24)	Control group (n = 10)	p-value
Intensity			< 0.001*
None	16 (66.7)	1 (10.0)	
Mild	8 (33.3)	0 (0)	
Moderate	0 (0)	5 (50.0)	
Strong	0 (0)	4 (40.0)	
Distribution			0.001*
Negative	16 (66.7)	1 (10.0)	
Basal	0 (0)	0 (0)	
Both basal and suprabasal	8 (33.3)	4 (40.0)	
Full thickness	0 (0)	5 (50.0)	

Values are presented as number (%). LC3: microtubule-associated protein light chain 3. *$p < 0.05$.

ness (R = −0.59, $p = 0.001$) and mean inflammatory cell density (R = −0.47, $p = 0.01$). No significant correlation was observed between psoriasis severity and AHR, CYP1A1, and LC3 intensities (Supplementary Table 1).

Correlation among AHR, CYP1A1, and LC3 protein expression in psoriasis patients

There was a significant negative correlation between AHR and LC3 expression in psoriatic skin (R = −0.63, $p = 0.006$). In addition, a positive, significant correlation between AHR and CYP1A1 expression was found in skin lesions of psoriasis patients (R = 0.67, $p = 0.004$; Supplementary Table 1).

AHR, autophagy-related molecules and *Nrf2* gene expression in psoriatic skin tissue

To further validate the significance of AHR and autophagy-related factors in psoriasis, we measured mRNA expression of *AHR*, *CYP1A1*, *LC3*, *BECN1*, and *ATG5* in psoriasis lesional skin tissue. These samples expressed relatively higher *AHR* and *CYP1A1* mRNA compared to that in normal controls. However, the autophagy-related factors *LC3*, *BECN1*, and *ATG5* were decreased in lesional skin of psoriasis compared with normal controls (Supplementary Fig. 3).

AHR signaling and autophagy both act upon the oxidative-stress response[22,23]. Thus, we examined the expression of *NRF2* gene as a redox-sensitive transcription factor in psoriatic skin tissue and found that psoriasis lesional skin had higher *NRF2* mRNA expression than normal controls (Supplementary Fig. 3).

DISCUSSION

Previously, we performed *in vitro* and *ex vivo* studies to confirm the effects of AHR activation on autophagy in human keratinocytes, as well as the relevance of AHR and autophagy in psoriasis pathogenesis. Results from *in vitro* polycytokine-stimulated human keratinocytes and *ex vivo* psoriasis skin tissues revealed that AHR activation decreased autophagy, inducing inflammation through p65NF-κB/p38MAPK pathways[16]. Here, we examined the relevance of both AHR (a ligand-dependent transcription factor with various ligands including environmental pollutants such as PAHs) and LC3 (autophagy marker) in skin lesions of psoriasis patients. Immunohistochemical staining showed that AHR and CYP1A1 (the downstream target of AHR) were upregulated in psoriasis lesions compared to expression in control samples. However, expression of the representative autophagy marker, LC3, was downregulated in psoriasis lesions compared to controls. Furthermore, AHR and CYP1A1 expression in psoriasis lesions showed significant positive correlations with mean epidermal thickness and mean inflammatory cell density. Alternatively, significant negative correlations were observed between LC3 expression in psoriasis lesions and mean epidermal thickness and mean inflammatory cell density. There was also a significant negative correlation between AHR and LC3 expression in psoriatic skin. Furthermore, *AHR* and *CYP1A1* mRNA expression were increased in psoriasis lesional skin compared to normal controls. The mRNA expression of autophagy-related molecules was decreased in psoriasis lesional skin compared with normal controls. Together, these findings suggest the important roles of AHR and autophagy in psoriasis development.

AHR is a member of the bHLH/PAS family that is widely expressed in many human tissues including skin. Evidence shows that AHR is involved in various pathways important to cell proliferation and differentiation and immune reactions[24,25]. Epidemiological studies report a relationship between psoriasis and exposure to AHR ligands in hazardous environmental pollutants (such as PAHs)[1,26]. Moreover, AHR activation was reported to affect inflammatory profiles in both an imiquimod-induced mouse model of psoriasiform inflammation and skin tissues of psoriasis patients[27]. Corroborating findings of the current study, researchers found that AHR and CYP1A1 proteins and mRNA were overexpressed in psoriasis skin lesions, and that a significant positive correlation existed between AHR and CYP1A1 protein expression and mean epidermal thickness and mean inflammatory cell density. Laboratory studies reported that AHR activation via PAHs such as TCDD or endogenous ligands affect the proliferation and

differentiation of Th17 cells, which have critical roles in psoriasis pathogenesis[28,29]. Together, AHR overexpression and activation might contribute to psoriasis pathogenesis.

It remains unclear whether AHR activation in skin disease is beneficial or harmful. Regarding this, it was speculated that AHR functions in ligand-specific, tissue-specific, and cell-specific manners[30-33]. In the context of psoriasis, Di Meglio et al.[27] found that transient AhR activation by endogenous, rapid-metabolizing AHR ligand, FICZ results in a decreased inflammatory reaction in a psoriasis mouse model and human psoriatic skin. In support of these findings, topical application of an AHR agonist, tapinarof, was reported to be efficacious in psoriasis clinical trials[34]. Tapinarof (5-[(E)-2-phenylethenyl]-2-[propan-2-yl] benzene-1, 3-diol) is a hydroxylated stilbene generated by bacterial symbionts of entomopathogenic nematodes. Tapinarof is a high-affinity AHR ligand that exhibits antioxidative activity via NRF2 activation. Tapinarof also repairs the skin barrier dysfunction by promoting FLG and IVL expression, while suppressing interleukin (IL)-17A production and enhancing IL-22 production by affecting T-helper 17 (Th17) and Treg cell differentiation[35]. However, we previously reported that slow-metabolizing dioxin, TCDD-mediated AHR activation induces inflammation in human keratinocytes and ex vivo skin biopsies of psoriasis[16].

Few studies have evaluated the expression of autophagy-related proteins, including LC3, in psoriasis. Here, LC3 expression in psoriasis lesions was downregulated. A previous study showed that while LC3 expression was absent in all layers of psoriasis lesional skin epidermis, LC3 was expressed throughout the full thickness of the epidermis in normal sample[36]. Varshney and Saini[13] also found evidence of decreased LC3 expression in lesional psoriatic skin tissue compared to that in non-lesional tissue. These reports are consistent with our study. In addition, a previous report indicating that a lack of LC3 expression in psoriatic skin lesions is correlated with parakeratosis consistent with our results[36]. We also found significant negative correlations between LC3 expression in psoriasis lesions the mean epidermal thickness and mean inflammatory cell density. Notably, we found a significant negative correlation between AHR and LC3 expression in psoriatic skin. Based on these results, we speculate that the inverse functional correlation between AHR activation and autophagy could affect psoriasis development by modulating epidermal hyperproliferation and inflammation.

Moreover, NRF2 is a key factor involved in regulating antioxidant signaling. The relationship between NRF2 and AHR signaling and autophagy is plausible as AHR and autophagy also act on the oxidative/antioxidant axis[22,23]. We, therefore, measured the expression of NRF2 mRNA in psoriatic and healthy control skin tissues and found that it was increased in psoriatic skin lesions compared to that in normal controls. Similarly, a previous study reported that NRF2 mRNA and protein expression was increased in epidermis of psoriasis lesion compared to that in normal control skin. Furthermore, using human keratinocytes and an imiquimod-induced psoriasis mouse model, Yang et al.[37] demonstrated that IL-17 and IL-22 stimulated NRF2 translocation to the epidermis of psoriasis lesions, promoting upregulation of keratin 6, keratin 16, and keratin 17 and inducing keratinocyte proliferation, which is associated with psoriasis pathogenesis.

In this study, we found a significant difference in AHR, CYP1A1, and LC3 expression levels in lesional psoriatic skin in comparison to normal skin. However, no significant differences were observed in AHR, CYP1A1, and LC3 intensity according to the PASI score. These results might be explained by the fact that the local inflammation severity of psoriasis lesional skin tissue, which evaluated the expression levels of AHR, CYP1A1, and LC3, could be different to the PASI score in assessing the severity of the psoriasis in the whole body. In other words, even if the PASI score is high, it is possible that the local skin lesion severity of inflammation examined by biopsy is not severe, or vice versa. Furthermore, it is possible that AHR or autophagy could be related to psoriasis development (disease initiation stage), but not to disease severity. Further large-scale studies are needed to confirm this result.

Several limitations were noted. First, group sample sizes were small. Therefore, a large-scale study will be needed to confirm our results. Second, the temporal relationship between AHR and LC3 remains unclear as this study only demonstrated the overall expression of AHR and LC3 in skin tissues. Currently, only a limited number of studies have sought to unravel the complicated roles of AHR and autophagy in psoriasis pathogenesis; to our knowledge, this study is the first to demonstrate the negative correlation between AHR and the expression of the autophagy marker LC3 in lesional skin of psoriasis patients. We anticipate that this finding will aid in the discovery of more detailed mechanisms regarding psoriasis pathogenesis.

In conclusion, AHR and autophagy affected psoriasis pathogenesis through the regulation of epidermal hyperproliferation and skin inflammation. Therefore, AHR and autophagy modification may prove useful as novel therapeutic targets in psoriasis.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-33-138-s001.pdf.

CONFLICTS OF INTEREST

FUNDING SOURCE

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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