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Original Article

Antioxidant *Houttuynia Cordata* Extract Upregulates Filaggrin Expression in an Aryl Hydrocarbon-Dependent Manner

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Abstract

The plant *Houttuynia cordata*, which is called "dokudami" in Japanese, is known as a potent antioxidant herb that has been traditionally consumed as a folk medicine for various ailments, such as diabetes, obesity, cough, fever and skin diseases, in Asia. However, its antioxidant mechanism remains largely unknown. In the present study, we investigated the effects of *Houttuynia cordata* extract (HCE) on human keratinocytes. HCE activated aryl hydrocarbon receptor (AHR) and nuclear factor E2-related factor 2, with subsequent induction of the antioxidative enzyme NAD(P)H : quinone oxidoreductase 1 gene. HCE inhibited the generation of reactive oxygen species (ROS) in keratinocytes stimulated with tumor necrosis factor α or benzo(α)pyrene. Moreover, HCE upregulated the gene expression of filaggrin, an essential skin barrier protein, in an AHR-dependent manner. HCE may be beneficial for treating ROS-related photoaging and barrier-disrupted skin conditions.

Key words : *Houttuynia cordata* extract・Aryl hydrocarbon receptor・Nuclear factor E2-related factor 2・Reactive oxygen species・filaggrin

Introduction

The plant *Houttuynia cordata*, which is called "dokudami" in Japanese, is an aromatic medicinal herb that has been traditionally eaten as a folk medicine for various ailments, such as diabetes, obesity, cough, fever and skin diseases, in Asia[1)]. *Houttuynia cordata* extract (HCE) showed potent inhibitory action on corn oil-induced hyperlipidemia in mice[2)]. It also exhibited anti-inflammatory activity on carrageenan-induced inflammation by inhibiting the production of tumor necrosis factor α (TNFα)[3)]. The systemic administration of HCE was additionally shown to produce significant decreases in fasting plasma glucose, total lipid profile, blood urea and creatinine in streptozotocin-induced diabetic rats[4)]. Another important aspect of HCE is its antioxidant activity. It was shown to prevent gentamicin-induced oxidative stress and subsequent nephrotoxicity in rats[5)]. It also potently inhibited the oxidative DNA damage of lymphocytes treated with hydrogen peroxide[6)]. However, its antioxidant mechanism remains largely unknown.

A recent study by Fischedick et al. demonstrated that certain phytochemicals activate nuclear factor E2-related factor 2 (NRF2)[7)], which is a key transcription factor that upregulates a series of antioxidant enzymes such as NAD(P)H : quinone oxidoreductase 1 (NQO1)[8)~10)]. Moreov-

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er, there is compelling evidence that the activation of NRF2 is exerted via the activation of aryl hydrocarbon receptor (AHR)[11)12)]. AHR is a small-molecule sensor originally identified as a receptor for halogenated and nonhalogenated polycyclic aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and benzo [*a*] pyrene (BaP)[13)14)]. Upon ligand binding, cytoplasmic AhR is activated and translocates into the nucleus. The ligand/AHR complex then binds to its specific DNA recognition site, namely, the xenobiotic-responsive element or dioxin-responsive element, upregulating the transcription of a series of responsive genes, including cytochrome P450 family enzymes such as CYP1A1 (subfamily A, polypeptide 1)[13)14)]. In addition to polycyclic aromatic hydrocarbons, various phytochemicals, *Malassezia* metabolites and tryptophan photoproducts can bind to AhR with a wide range of affinities[14)]. Some phytochemicals and medicinal drugs are known to exert their antioxidant effects by activating AHR-NRF2 signaling[12)14)~16)].

In the present study, we show that HCE did activate the AHR-NRF2 battery with increased gene expression of *CYP1A1* and *NQO1* and that it inhibited the generation of reactive oxygen species (ROS) in human keratinocytes stimulated with TNF*α* or BaP. Furthermore, the AHR activation by HCE was also confirmed by the enhanced expression of filaggrin (FLG), an epidermal barrier protein. The antioxidant and barrier-protecting activity of HCE, mediated by AHR-NRF2 signaling, may be applicable to the treatment of barrier-disrupted skin conditions.

Materials and Methods

Reagents and antibodies

Dimethyl sulfoxide (DMSO) and BaP were purchased from Sigma-Aldrich (St. Louis, MO). TNF*α* was purchased from Peprotech (Rocky Hill, NJ). Anti-AHR rabbit polyclonal IgG antibody (H-211), anti-NRF2 polyclonal rabbit IgG antibody (H-300) and normal rabbit IgG were purchased from Santa Cruz Biotechnology (Dallas, TX). HCE was kindly provided as a dry powder by P&G Innovation Godo Gaisha (Kobe, Japan). In accordance with the manufacturer's recommendation, we used 100 μg/ml HCE throughout the present study. No cytotoxic effects on keratinocytes were observed at this concentration.

Cell culture

Normal human epidermal keratinocytes (NHEKs) obtained from Clonetics-BioWhittaker (San Diego, CA) were grown in culture dishes at 37℃ in 5% CO_2. They were cultured in serum-free keratinocyte growth medium (Lonza, Walkersville, MD) supplemented with bovine pituitary extract, recombinant epidermal growth factor, insulin, hydrocortisone, transferrin and epinephrine. Culture medium was replaced every two days. Near confluence (70-90%), cells were disaggregated with 0.25 mg/ml trypsin/0.01% ethylenediamine tetraacetic acid and subcultured. Second-to-fourth-passage NHEKs were used in all experiments. NHEKs (1×10^5) were seeded in 24-well culture plates, allowed to attach for 24 hr and then treated with or without HCE, DMSO, TNF*α* or BaP.

Immunofluorescence and confocal laser scanning microscopic analysis

NHEKs (2×10^4) were cultured on slides (Lab-Tek, Rochester, NY) with or without HCE for 6 hr. Slides were then washed in phosphate-buffered saline (PBS), fixed with acetone for 10 min and blocked using 10% bovine serum albumin (Roche Diagnostics, Basel, Switzerland) in PBS for 30 min. Samples were incubated with primary rabbit anti-AHR (1 : 50) or anti-NRF2 (1 : 50) antibody in Western breeze blocker diluent (Invitrogen, Carlsbad, CA) overnight at 4℃. Slides were washed with PBS before incubation with anti-rabbit secondary antibody (Alexa Fluor 546 or 488 ; Molecular Probes, Eugene, OR) for 1 hr at room temperature. Slides were then mounted with

UltraCruz mounting medium (Santa Cruz Biotechnology). All samples were analyzed using a D-Eclipse confocal laser scanning microscope (Nikon, Tokyo, Japan).

Reverse-transcription PCR and qRT-PCR analyses

Total RNA was extracted using the RNeasy Mini kit (Qiagen, Courtaboeuf, France). Reverse transcription was performed using PrimeScript RT-reagent kit (Takara Bio, Otsu, Japan). qRT-PCR was performed on the Mx3000p real-time system (Stratagene, La Jolla, CA) using SYBR Premix Ex Taq (Takara Bio). Amplification was started at 95℃ for 30 s as the first step, followed by 40 cycles of qRT-PCR at 95℃ for 5 s and at 60℃ for 20 s. mRNA expression was measured in triplicate and was normalized to the β-actin expression level. The primer sequences from Takara Bio and SABiosciences (Frederick, MD) are shown in Table 1.

Detection of ROS production by microscopy

DCFH-DA (Molecular Probes) is a cell-permeable non-fluorescent probe that is de-esterified intracellularly and oxidized to highly fluorescent 2', 7'-dichlorofluorescein in the presence of ROS. After treatment with or without TNFα (10 ng/ml) for 30 min or BaP (1 μM) for 3 hr in the presence or absence of 3% OFIE, NHEKs were incubated with DCFH-DA (5 μM) for 30 min at 37 ℃, and the fluorescence signal of 2', 7'-dichlorofluorescein (Ex. 490 nm), the oxidation product of DCFH-DA, was analyzed using a D-Eclipse confocal laser scanning microscope (Nikon).

Transfection with siRNA against AHR

Small interfering RNA (siRNA) against AHR (AHR siRNA, s1200), as well as siRNA consisting of a scrambled sequence that would not lead to specific degradation of any cellular message (control siRNA), was purchased from Ambion (Austin, TX). NHEKs cultured in 24-well plates were incubated with mix from HiPerFect Transfection reagent (Qiagen) containing 10 nM siRNA and 3.0 μl of HiPerFect reagent in 0.5 ml of culture medium. After a 48-hr incubation period, siRNA-transfected NHEKs were treated with or without HCE for 6 hr. The transfection of siRNA had no effect on cell viability, as demonstrated by microscopic examination (data not shown). The transfection of AHR siRNA inhibited AHR mRNA expression by 91.9 ± 2.1% in NHEKs.

Statistical analysis

Unpaired Student's *t*-test (when two groups were analyzed) and one-way ANOVA (for three or more groups) were used to analyze the results, and a p-value < 0.05 was considered to indicate a statistically significant difference.

Results

Activation of AHR and NRF2 by HCE

It is well known that ligand binding activates AHR, induces its cytoplasmic-to-nuclear translocation and upregulates *CYP1A1* expression[13)17)]. This was the case in HCE. AHR was mainly localized in the cytoplasm of untreated NHEKs (Fig. 1A), while HCE appeared to translocate AHR into the nucleus (Fig. 1B), with significant upregulation of *CYP1A1* (Fig. 1C). The upregulation of *CYP1A1* expression by HCE was

Table 1 Primers for qRT-PCR

Gene	Forward primer	Reverse primer	SABiosciences ID
NQO1	5'-GGATTGGACCGAGCTGGAA-3'	5'-AATTGCAGTGAAGATGAAGGCAAC-3'	
CYP1A1			PPH01271E
FLG	5'-CATGGCAGCTATGGTAGTGCAGA-3'	5'-ACCAAACGCACTTGCTTTACAGA-3'	
β-actin	5'-ATTGCCGACAGGATGCAGA-3'	5'-GAGTACTTGCGCTCAGGAGGA-3'	

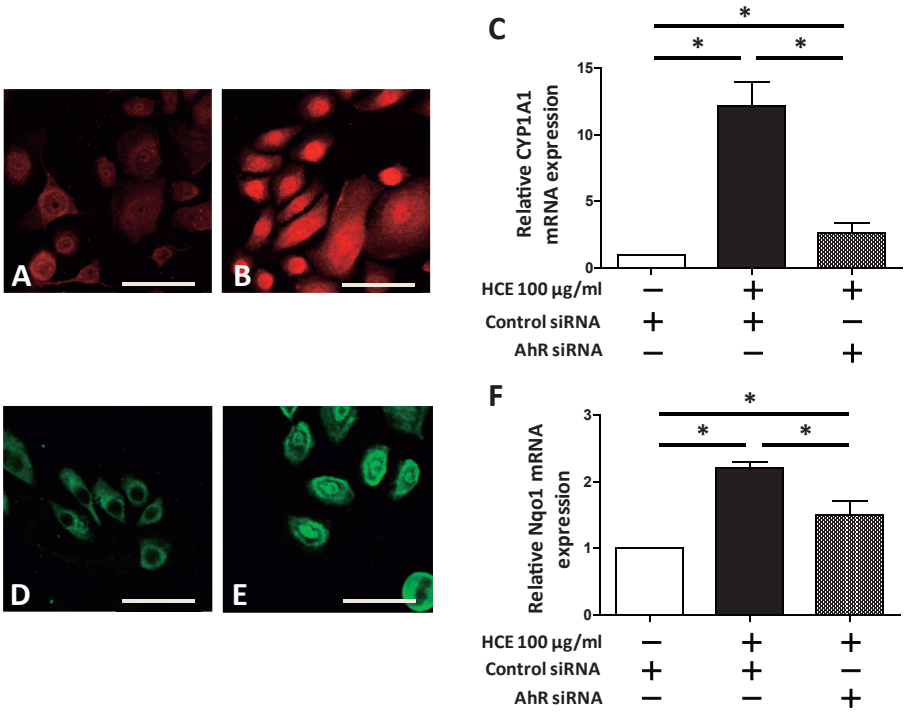

Fig. 1 **A** : AHR was mainly localized in the cytoplasm of control keratinocytes. **B** : HCE induced the cytoplasmic-to-nuclear translocation of AHR. **C** : HCE upregulated the *CYP1A1* expression of NHEKs, which was canceled in the NHEKs transfected with AHR siRNA. **D** : NRF2 was localized mainly in the cytoplasm of control keratinocytes. **E** : HCE induced the cytoplasmic-to-nuclear translocation of NRF2. **F** : HCE upregulated the *NQO1* expression of NHEKs, which was canceled in the NHEKs transfected with AHR siRNA. Scale bar = 50 μm. $^{*}p < 0.05$.

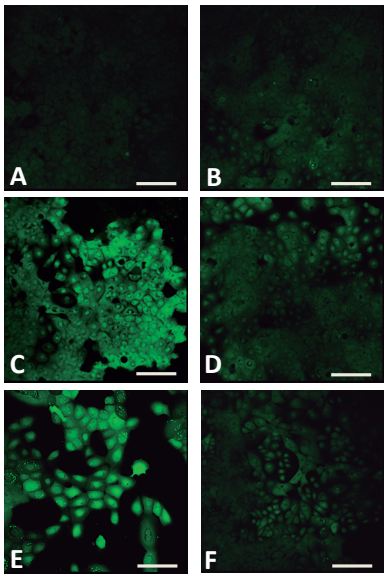

Fig. 2 ROS production of NHEKs was visualized by fluorescence analysis. Control (**A**) and HCE-treated (**B**) keratinocytes did not generate appreciable amounts of ROS. TNFα (10 ng/ml) (**C**) and BaP (1 μM) (**E**) induced robust ROS production. Simultaneous addition of HCE inhibited the TNFα -derived (**D**) or BaP-derived (**F**) ROS generation. Scale bar = 50 μm.

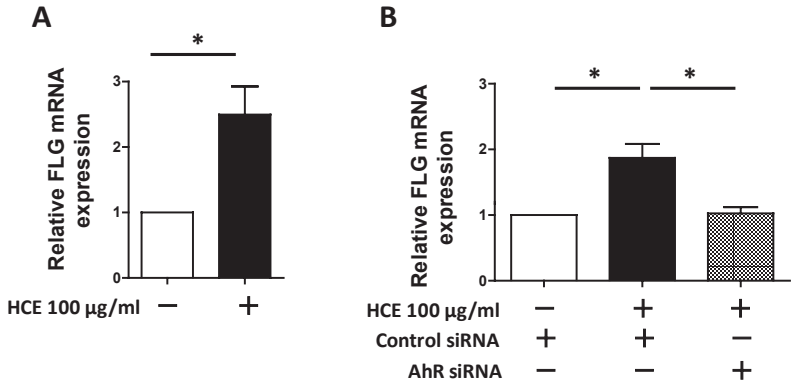

Fig. 3 A : HCE upregulated *FLG* expression in NHEKs.
B : The enhancing effect of HCE on *FLG* expression was canceled in the AHR-knockdown NHEKs. $^{*}p < 0.05$.

AHR-dependent because it was canceled in NHEKs transfected with AHR siRNA (Fig. 1C).

As has been reported previously[11], NRF2 was also located in the cytoplasm of untreated NHEKs (Fig. 1D). In the presence of HCE, some of the NRF2 was activated and clearly translocated into the nucleus (Fig. 1E). The activation of NRF2 by HCE upregulated downstream *NQO1* gene expression (Fig. 1F). The HCE-induced *NQO1* gene transcription was again significantly inhibited in the AhR-knockdown keratinocytes (Fig. 1F), showing its dependence on AHR.

Antioxidant activity of HCE

As the in vivo administration of HCE has been demonstrated to have an antioxidant effect[5)6)] (Kang, Lin), we next examined whether treatment with HCE inhibits ROS generation in keratinocytes stimulated with TNFα or BaP. Control and HCE-treated keratinocytes did not show ROS production (Fig. 2A and 2B). As has been reported previously[11)17)], both TNFα (Fig. 2C) and BaP (Fig. 2E) induced robust ROS generation in the treated keratinocytes, while this was inhibited in the presence of HCE (Fig. 2D and 2F).

HCE upregulated FLG expression in an AHR-dependent manner

In addition to the induction of *CYP1A1* gene expression, another hallmark of AHR activation is upregulation of the expression of epidermal barrier proteins such as FLG[18)19)]. In accordance with these previous findings, HCE significantly upregulated the expression of *FLG* in this study (Fig. 3A). In order to determine the dependence on AHR of *FLG* gene upregulation, we next examined the *FLG* expression in NHEKs transfected with AHR siRNA. The enhancing effects of HCE on *FLG* gene expression were canceled in the AHR-knockdown keratinocytes, as shown in Fig. 3B.

Discussion

The epidermis is a sophisticated biological barrier that protects the internal tissue from various external stimuli, such as ultraviolet rays, environmental pollutants and chemicals. Keratinocytes are the major constituents of the epidermal barrier, expressing sensor molecules such as AHR[13)14)]. AHR can bind to a wide range of pollutants, drugs and phytochemicals, such as TCDD, BaP, ketoconazole and quercetin. Recent studies have shown that AHR is a kind of double-faced receptor because it mediates both oxidation and antioxidation signals. The ligation of AHR by TCDD and BaP induces robust ROS production in keratinocytes[17)20)], while ketoconazole and quercetin activate AHR to switch on NRF2 activation, with the subsequent induction of

antioxidant enzymes such as NQO1[11)12)16)21)].

Although HCE was shown to exhibit potent antioxidant activity in vivo[4)5)], the mechanism by which this occurs remains largely unknown. In this study, we investigated the in vitro antioxidant mechanism of HCE using human keratinocytes. Like other AHR ligands, HCE induced cytoplasmic-to-nuclear translocation of AHR. The HCE-induced AHR activation was biologically active because it subsequently upregulated the expression of *CYP1A1*, a specific marker of AHR activation[13)14)]. Concordantly, HCE also activated NRF2 with its nuclear translocation and subsequent upregulation of downstream gene expression of *NQO1*. In keeping with the notion that the NRF2-NQO1 system plays a critical role in exerting antioxidant activity[11)16)21)22)], HCE potently inhibited the ROS production of keratinocytes treated with TNFα or BaP. HCE per se did not induce ROS generation in NHEKs. These findings indicate that the ligation of AHR by HCE did not induce an oxidation signal, but rather skewed the downstream response towards the NRF2-NQO1-mediated antioxidation pathway. Certain phytochemicals, such as glucosinolate derivatives and quercetin, are known to exert their antioxidant effects by activating AHR-NRF2-NQO1 signaling[15)16)]. The inhibitory action of HCE on TNFα signaling may be beneficial in therapeutic interventions for various skin diseases, such as psoriasis and photoaging, in which TNFα plays a critical role[23)24)].

In addition to its pivotal role in differentiating oxidation/antioxidation signaling pathways, AHR acts as a master switch for upregulating epidermal barrier proteins[14)20)], which is also supported by the findings in the present study. The expression of *FLG* was significantly upregulated in the presence of HCE. Moreover, the HCE-induced upregulation of FLG was canceled in the keratinocytes transfected with AHR siRNA. FLG is one of the most essential components of barrier proteins for maintaining skin barrier homeostasis[25)]. Some phytochemicals are reported to enhance the expression of FLG. Apigenin, a component of the chrysanthemum herb *Bracteantha bracteata*, significantly enhances epidermal barrier function in vivo with correlated upregulation of FLG expression[26)]. A citrus-derived flavonoid, hesperidin, also upregulates the expression of FLG in parallel with augmented recovery of barrier disruption induced by tape stripping[27)].

In conclusion, HCE was shown to act as a potent antioxidant via AHR-NRF2 activation and augmented the expression of FLG. HCE may be beneficial in treating photoaging and barrier-disrupted skin disorders.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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（和文抄録）

抗酸化性ドクダミエキスはアリルハイドロカーボン受容体依存性にフィラグリンの発現を上昇させる

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ドクダミ（*Houttuynia cordata*）は，抗酸化作用を有する薬草で，糖尿病，肥満，咳や発熱などに対する大衆療法として利用されている．しかし，その抗酸化作用の細胞学的な機序は明らかではない．本研究ではドクダミエキス（*Houttuynia cordata* extract ; HCE）の人表皮細胞への影響を検討した．我々は，HCE が表皮細胞内で aryl hydrocarbon receptor (AHR) および nuclear factor E2–related factor 2 を活性化し，その下流の抗酸化酵素である NAD(P)H : quinone oxidoreductase 1 の発現を亢進させることを明らかにした．実際に，HCE は tumor necrosis factor α や benzo(α) pyrene による reactive oxygen species (ROS) 産生を抑制した．さらに，HCE は表皮のバリア機能維持に関与するフィラグリンの発現も AHR 依存性に亢進させた．HCE は ROS 産生が関与する光老化や表皮バリア破壊を伴う皮膚疾患の治療に有用であるかもしれない．