Biochemical and Biophysical Research Communications 410 (2011) 68–74

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Role of Pin1 in UVA-induced cell proliferation and malignant transformation in epidermal cells

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ARTICLE INFO

Article history:
Received 16 May 2011
Available online 24 May 2011

Keywords:
UVA
Skin cancer
Pin1
Cyclin D1
Proliferation
Transformation

ABSTRACT

Ultraviolet A (UVA) radiation (λ = 320–400 nm) is considered a major cause of human skin cancer. Pin1, a peptidyl prolyl isomerase, is overexpressed in most types of cancer tissues and plays an important role in cell proliferation and transformation. Here, we demonstrated that Pin1 expression was enhanced by low energy UVA (300–900 mJ/cm^2) irradiation in both skin tissues of hairless mice and JB6 C141 epidermal cells. Exposure of epidermal cells to UVA radiation increased cell proliferation and cyclin D1 expression, and these changes were blocked by Pin1 inhibition. UVA irradiation also increased activator protein-1 (AP-1) minimal reporter activity and nuclear levels of c-Jun, but not c-Fos, in a Pin1-dependent manner. The increases in Pin1 expression and in AP-1 reporter activity in response to UVA were abolished by N-acetylcysteine (NAC) treatment. Finally, we found that pre-exposure of JB6 C141 cells to UVA potentiated EGF-inducible, anchorage-independent growth, and this effect was significantly suppressed by Pin1inhibition or by NAC.

1. Introduction

Environmental ultraviolet (UV) radiation has been considered as an important etiologic factor in the development of skin cancers as well as other pathological conditions of the skin. UVA radiation (λ = 320–400 nm) constitutes the largest portion of UV radiation that reaches the earth's surface. UVA is the most important risk to exposed human skin because most UVB (280–320 nm) and all UVC (200–280 nm) are absorbed by the ozone layer [1]. UVA radiation has been shown to be a complete carcinogen, one that can not only initiate and promote tumors, but also, cause their progression. Several mechanisms contribute to the tumorigenic effects of UVA [1]. UVA increases the formation of reactive oxygen species (ROS), which causes DNA damage. UVA also induces diverse cellular signaling pathways. Nevertheless, our understanding of the molecular mechanisms underlying the ability of UVA to induce skin cancer is still unclear.

One possible mechanism involves Pin1, a peptidyl prolyl isomerase, which specifically recognizes phosphorylated serine or threonine preceding a proline (pSer/Thr-Pro) and isomerizes the peptide bond [2]. Since most protein kinases and phosphatases recognize substrates in a conformation-dependent manner, Pin1-dependent isomerization of Ser/Thr-Pro motifs can be crucial for diverse enzyme activities [3,4]. Cell proliferation is a consequence of cell division during cell cycle progression in mammalian cells; its dysregulation can cause uncontrolled cell growth, which is one of the main malignant properties of cancer cells. Cell cycle progression is controlled by three checkpoints: G1/S, S-phase DNA damage and G2/M. Activation of oncogenes or inactivation of tumor suppressor genes can dysregulate G1/S control of cell cycling, and this may be involved in tumorigenesis. Pin1 recognizes various proteins, including mitotic proteins and transcription factors, as substrates. Cyclin D1, one of the key regulators of the G1/S transition [5], is Pin1's best understood target [6]. It has been shown that inactivation of cyclin D1 inhibits the growth of colon cancer cells and induces apoptosis in human squamous carcinomas [7,8]. Pin1 up-regulates cyclin D1 expression via c-Jun/activator protein-1 (AP-1) activation [9]. Moreover, cyclin D1 and Pin1 are overexpressed in most types of cancer tissues including skin cancer [10,11].

Although many studies have focused on the role of Pin1 in cancer development, we found no reports on the effect of UVA exposure on Pin1 expression and the possible role of Pin1 in UVA-mediated skin carcinogenesis. In the present study, we demonstrate for the first time that Pin1 expression is increased by low energy UVA exposure in epidermal cells and that induction of Pin1 plays an important role in UVA-induced AP-1 activation and in cyclin D1 expression, which ultimately increases cell proliferation and malignant transformation. In addition, scavenging of reactive oxygen species (ROS) inhibits UVA-mediated Pin1 induction and AP-1 activation in epidermal cells.

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doi:10.1016/j.bbrc.2011.05.106

2. Materials and methods

2.1. Materials

The antibodies against Pin1, c-Jun and c-Fos were supplied by Santa Cruz Biotechnology (Santa Cruz, CA). Anti-cyclin D1 antibody and horseradish peroxidase (HRP)-linked anti-rabbit and anti-mouse IgGs were obtained from Cell Signaling Technology (Beverly, MA). The siRNA targeting mouse Pin1 was acquired from Ambion (Austin, TX). 5-Bromo-4-chloro-3-indoylphosphate/nitroblue tetrazolium and phRL-SV40 plasmid were obtained from Promega (Madison, WI). The anti-actin antibody as well as other reagents for molecular studies was purchased from Sigma Chemical (St. Louis, MO). Hairless mice (HR-1, 20–25 g) were provided by Dr. H.K. Choi (Chosun University, Gwangju, South Korea).

2.2. Cell culture and UVA irradiation

JB6 Cl41 mouse epidermal cells were maintained in Minimum Essential medium containing 5% fetal calf serum, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. For UVA irradiation to JB6 Cl41 cells, the culture medium was removed, and cells were washed with sterile PBS. UVA exposure was performed with fluorescent lamps (UVP, Upland, CA) with the dish lids off. In selected experiments, cells were preincubated with inhibitors for 30 min prior to irradiation.

2.3. Immunoblot analysis and immunohistochemistry

After washing the cells with sterile PBS, they were lysed in buffer containing 20 mM Tris Cl (pH 7.5), 1% Triton X-100, 137 mM sodium chloride, 10% glycerol, 2 mM EDTA, 1 mM sodium orthovanadate, 25 mM β-glycerophosphate, 2 mM sodium pyrophosphate, 1 mM phenylmethylsulfonylfluoride, and 1 μg/ml leupeptin. Total cell lysates were centrifuged at 10,000*g* for 10 min to remove cell debris, and proteins were fractionated on a 10% SDS–PAGE gel. The fractionated proteins were then transferred electrophoretically to nitrocellulose paper and immunoblotted with specific antibodies. A universal immunoenzyme polymer method was used for Pin1 immunostaining in skin tissues [12].

2.4. Reporter gene assay

Promoter activity was determined using a dual-luciferase reporter assay system (Promega, Madison, WI). Briefly, cells were transiently transfected with 1 μg of AP-1-Luc reporter plasmid and 5 ng of phRL-SV plasmid (hRenilla luciferase expression was used for normalization) (Promega, Madison, WI) using Hilymax® reagent (Dojindo Molecular Tech., MD). The cells were then incubated in serum-free culture medium for 18 h. The firefly and hRenilla luciferase activities in the cell lysates were then measured using a luminometer (LB941, Berthold Tech., Bad Wildbad, Germany).

2.5. MTT assay

Cells were plated at 5×10^3 cells/well in 48 well plates and viable adherent cells were stained with MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] (2 mg/ml) for 4 h. Media were then removed and cells were dissolved by adding 200 μl dimethylsulfoxide/well. Absorbance was assayed at 550 nm.

2.6. Colony formation assay

JB6 Cl41 cells were exposed to UVA in the presence or absence of epidermal growth factor and incubated for 24 h in a 5% CO_2 incubator. Cells (8×10^3/ml) were maintained in 1 ml of 0.3% basal medium Eagle's agar containing 10% FBS with or without epidermal growth factor (EGF, 0.1 ng/ml) at 37 °C for 11 days. After the incubation, cell colonies were scored using a microscope.

2.7. Data analysis

Scanning densitometry was carried out using an Image Scan and Analysis System (LAS-3000mini, Fujifilm, Japan). One-way analysis of variance (ANOVA) was used to assess the significance of differences between the treatment groups. The Newman–Keuls test was used to compare multiple group means for each significant treatment effect.

3. Results

3.1. Increase in Pin1 expression by UVA in both JB6 Cl41 epidermal cells and skin tissues of hairless mice

To determine whether UVA affects the expression of Pin1, we measured Pin1 protein levels in JB6 C141 mouse epidermal cells after UVA irradiation (90–900 mJ/cm^2). The expression level of Pin1 was increased by UVA exposure in an energy-dependent manner (Fig. 1A). Next, we determined whether UVA exposure induces Pin1 *in vivo*. Hairless mice were exposed to UVA, skin tissue lysates were extracted and Pin1 protein expression was detected by western blot analysis. Pin1 protein levels were significantly increased in UVA-exposed skin tissues (300 and 3000 mJ/cm^2, Fig. 1B). Immunohistochemistry confirmed that the frequency of Pin1 immuno-positive cells was increased in the epidermis of hairless mice exposed to UVA (3000 mJ/cm^2) (Fig. 1C). These results clearly demonstrate that UVA increases Pin1 expression in both JB6 Cl41 epidermal cells and hairless mice skin tissues.

3.2. Role of Pin1 in UVA-induced cyclin D1 expression, cell proliferation and malignant transformation

Cyclin D1, a proto-oncogene, functions as a key cell cycle regulator of the G1/S check point and plays a crucial role in cell proliferation and cancer development [13]. Cyclin D1 expression is positively controlled by Pin1 through transcriptional or posttranslational mechanisms and this regulation may be required for the Pin1-mediated tumorigenesis [14]. Hence, we determined the expression level of cyclin D1 after exposure of JB6 C141 cells to UVA. UVA irradiation (90–900 mJ/cm^2) significantly enhanced cyclin D1 expression in epidermal cells and the expression pattern was similar to that of Pin1 (Fig. 2A). Moreover, UVA-induced cyclin D1 expression was suppressed by juglone, a chemical Pin1 inhibitor (Fig. 2B). We then performed MTT assays to assess the effect of low energy UVA irradiation on cell proliferation and the possible involvement of Pin1. The cell proliferation rate of JB6 C141 cells exposed to 300 mJ/cm^2 UVA was higher than that of sham-operated cells; 3 μM juglone reversed the UVA-stimulated cell proliferation (Fig. 2C). These results suggest that Pin1 induction is required for UVA-stimulated cyclin D1 increases and the subsequent cell proliferation.

Since high expression of Pin1 and cyclin D1 is considered an important factor contributing to malignant transformation, soft agar colony formation assays were performed to check the pathological implications of UVA-inducible Pin1 and cyclin D1 overexpression during skin tumorigenesis. In addition, JB6 Cl41 cells are

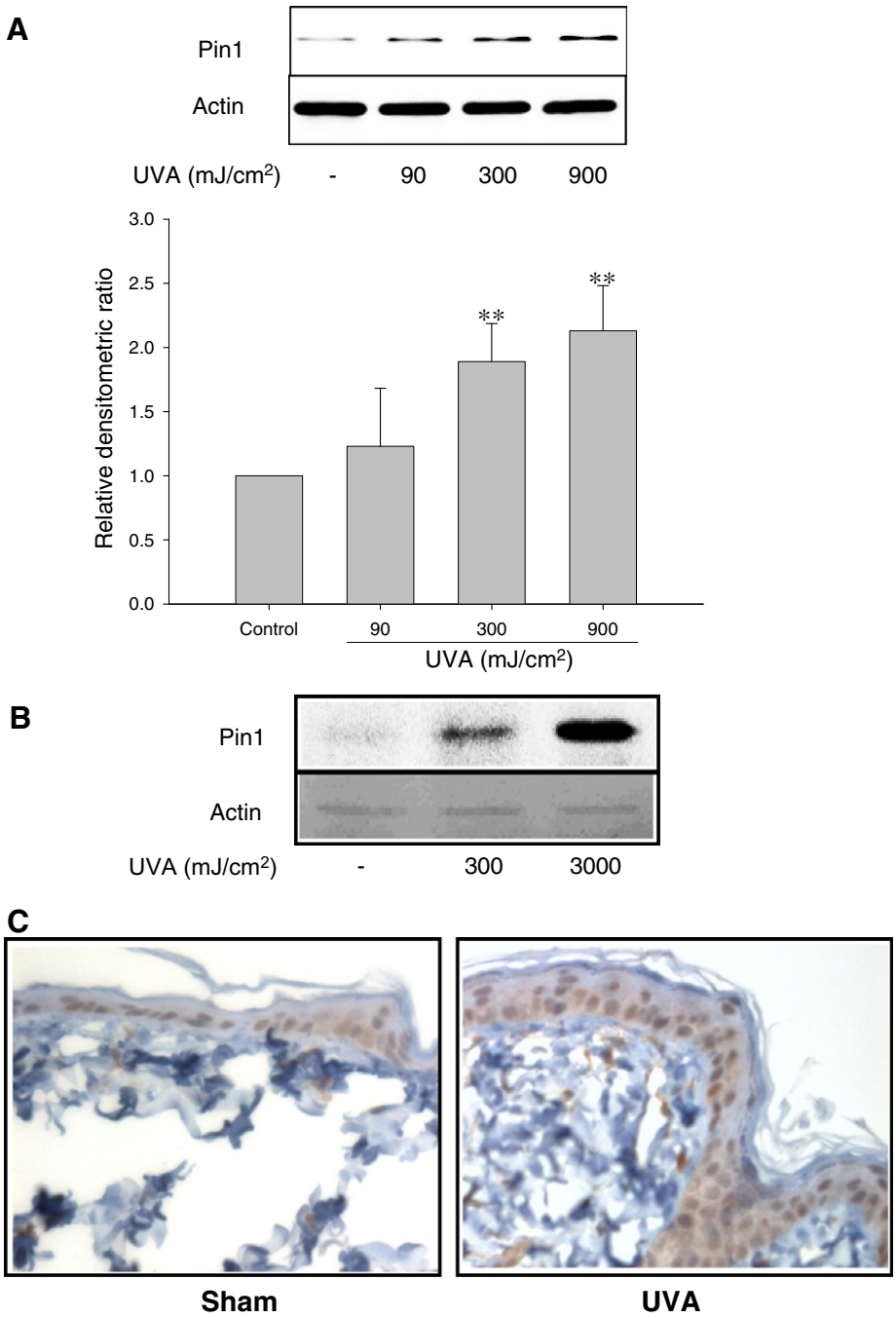

Fig. 1. Pin1 induction by UVA exposure. (A) Immunoblot analysis of Pin1 in JB6 C141 epidermal cells. JB6 C141 cells were exposed to UVA (90–900 mJ/cm^2) and the total cell lysates were obtained 24 h after UVA irradiation. Scanning densitometry was used to assess the relative change in Pin1. The data represents the mean ± SD of three separate experiments (significant compared to the control, $^{**}p < 0.01$; control level = 1). (B) Immunoblot analysis of Pin1 in the skin tissue lysates of hairless mice. A representative immunoblot shows the Pin1 protein in the tissue lysates of hairless mice exposed to UVA (300 and 3000 mJ/cm^2) (24 h). (C) Immunohistochemistry analysis of Pin1 in the skin tissues (×400). Hairless mice skin tissues were removed 24 h after exposure to UVA (3000 mJ/cm^2). The brown color staining represents cellular Pin1 expression. For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

appropriate for studying malignant transformation using anchorage-independent growth determination [15]. After JB6 C141 cells were exposed to UVA irradiation, with or without juglone, the cells were incubated in soft agar plates for 11 days and colony numbers were determined. Colony numbers were greater in cells treated with epidermal growth factor (EGF, 0.1 ng/ml) than in untreated cells (Fig. 2D). Moreover, UVA enhanced the frequency and the size of colonies promoted by EGF stimulation (Fig. 2D), whereas pretreatment with juglone (3 μM) abrogated the stimulatory effect of UVA on colony formation (Fig. 2D).

3.3. Involvement of Pin1 in UVA-stimulated AP-1 activation

The activator protein-1 (AP-1) transcription factor acts as a homo- or hetero-dimer form. Jun, Fos and Fra proteins are representative components of AP-1 [16]. It has been reported that activation of AP-1 regulates cell proliferation and is ultimately crucial for the multistage development of tumors [17]. In particular, c-Jun or c-Fos is *cis/trans* isomerized by Pin1 to activate AP-1-dependent gene transcription after phosphorylation by mitogen-activated protein kinase [9,18]. Here, we found that UVA exposure increased

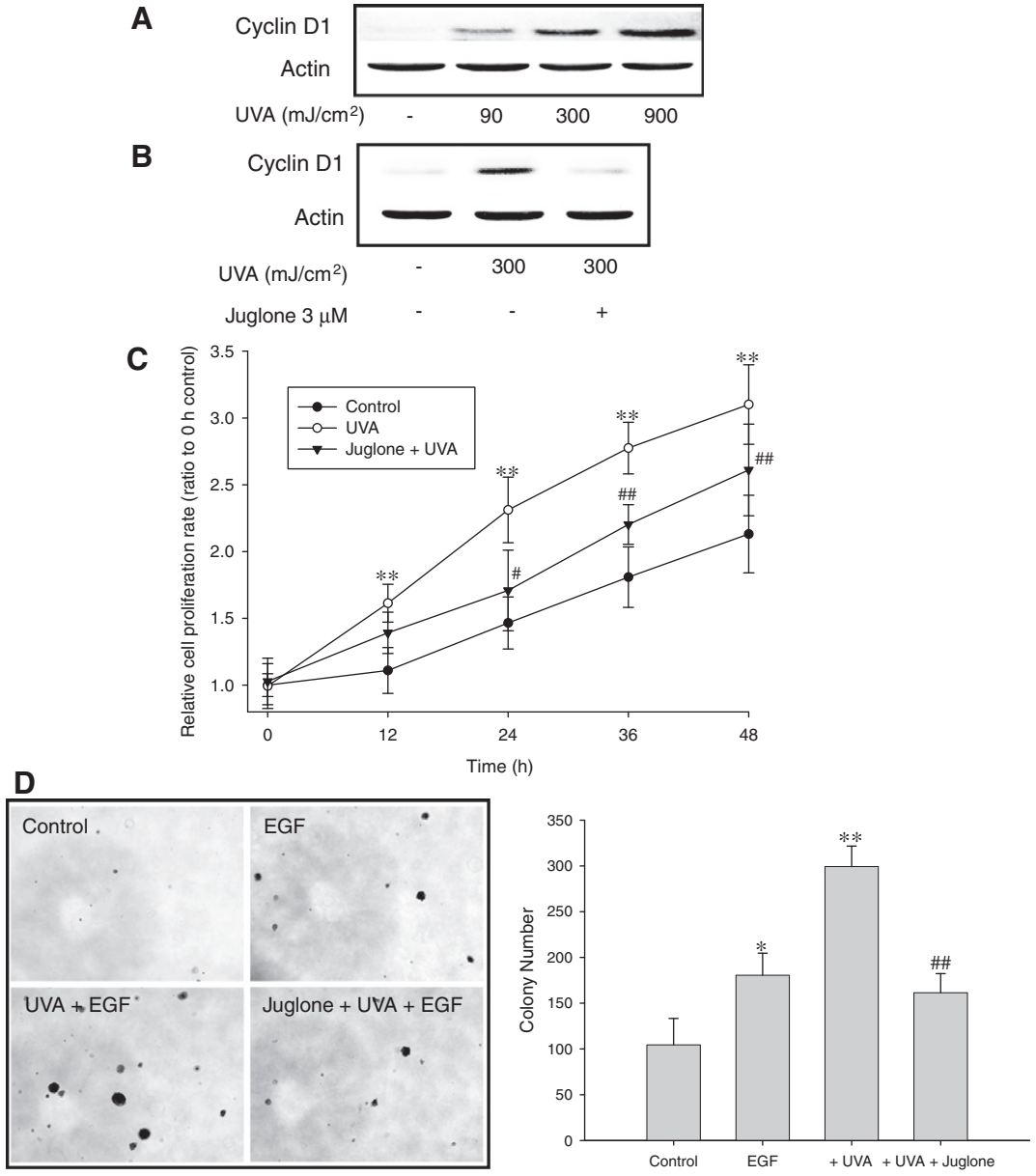

Fig. 2. Role of Pin1 in the UVA-induced proliferation and transformation of epidermal cells. (A) Western blot analysis of cyclin D1 in UVA-exposed JB6 C141 cells. Total cell lysates were obtained from JB6 C141 cells exposed to UVA (90–900 mJ/cm^2) for 24 h. (B) Effect of Pin1 inhibitor on cyclin D1 expression. JB6 C141 cells were preincubated with juglone (3 μM) for 30 min and then exposed to 300 mJ/cm^2 UVA irradiation. Twenty four hours after total cell lysates were subjected to immunoblotting. (C) Effect of Pin1 inhibitor on UVA-stimulated cell proliferation. JB6 C141 cells were plated at 5×10^3 cells/well in 48 well plates and then exposed to 300 mJ/cm^2 UVA. The UVA-pre-exposed or sham-operated cells were further incubated in 5% FBS-containing culture medium with or without juglone (3 μM) for 48 h. MTT assays were performed to determine relative cell numbers. The data represents the mean ± SD of four separate samples (significant compared to the control, $^{**}p < 0.01$; significant compared to UVA-alone exposed group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$). (D) Left, representative figures of colony formation assay. JB6 C141 cells exposed to UVA (300 mJ/cm^2) were incubated for 11 days with or without juglone (3 μM) and 0.1 ng/ml EGF in soft agar plates. Right, the quantitative colony numbers in each group ($n = 6$) (significant compared to the untreated control, $^{*}p < 0.05$; $^{**}p < 0.01$; significant compared to UVA-exposed group, $^{\#\#}p < 0.01$).

AP-1 minimal reporter activity in an energy-dependent manner (Fig. 3A). Moreover, nuclear c-Jun expression was elevated by 300 mJ/cm^2 UVA irradiation, but the nuclear level of c-Fos was rather decreased 9 or 24 h after UVA irradiation (Fig. 3B).

To assess whether Pin1 is involved in UVA-induced c-Jun/AP-1 activation, we used Pin1 siRNA and juglone. UVA-stimulated AP-1 reporter activity was diminished by 3 μM juglone treatment (Fig. 3C). Fig. 3D further shows that the UVA-stimulated increase in nuclear c-Jun was decreased by either Pin1 siRNA transfection or juglone treatment. Hence, UVA-mediated c-Jun/AP-1 activation via Pin1 induction is a possible mechanism for malignant transformation in response to UVA.

3.4. Role of ROS in UVA-induced Pin1 expression

ROS are generated by the reaction of UVA with endogenous photosensitizers in dermis and keratinocytes [19]. Because UVA-stimulated ROS production results in oxidative DNA damage and skin cancer development [20], ROS may participate in the overexpression of the Pin1 gene. Thus, we tested the effect of N-acetylcysteine (NAC, an ROS scavenger) on UVA-induced Pin1 and cyclin D1 expression in JB6 C141 cells. As shown in Fig. 4A, 10 mM NAC reduced Pin1 and cyclin D1 protein levels in UVA-exposed JB6 C141 cells, implying that ROS are involved in UVA-stimulated Pin1 expression. We then determined whether ROS removal affects

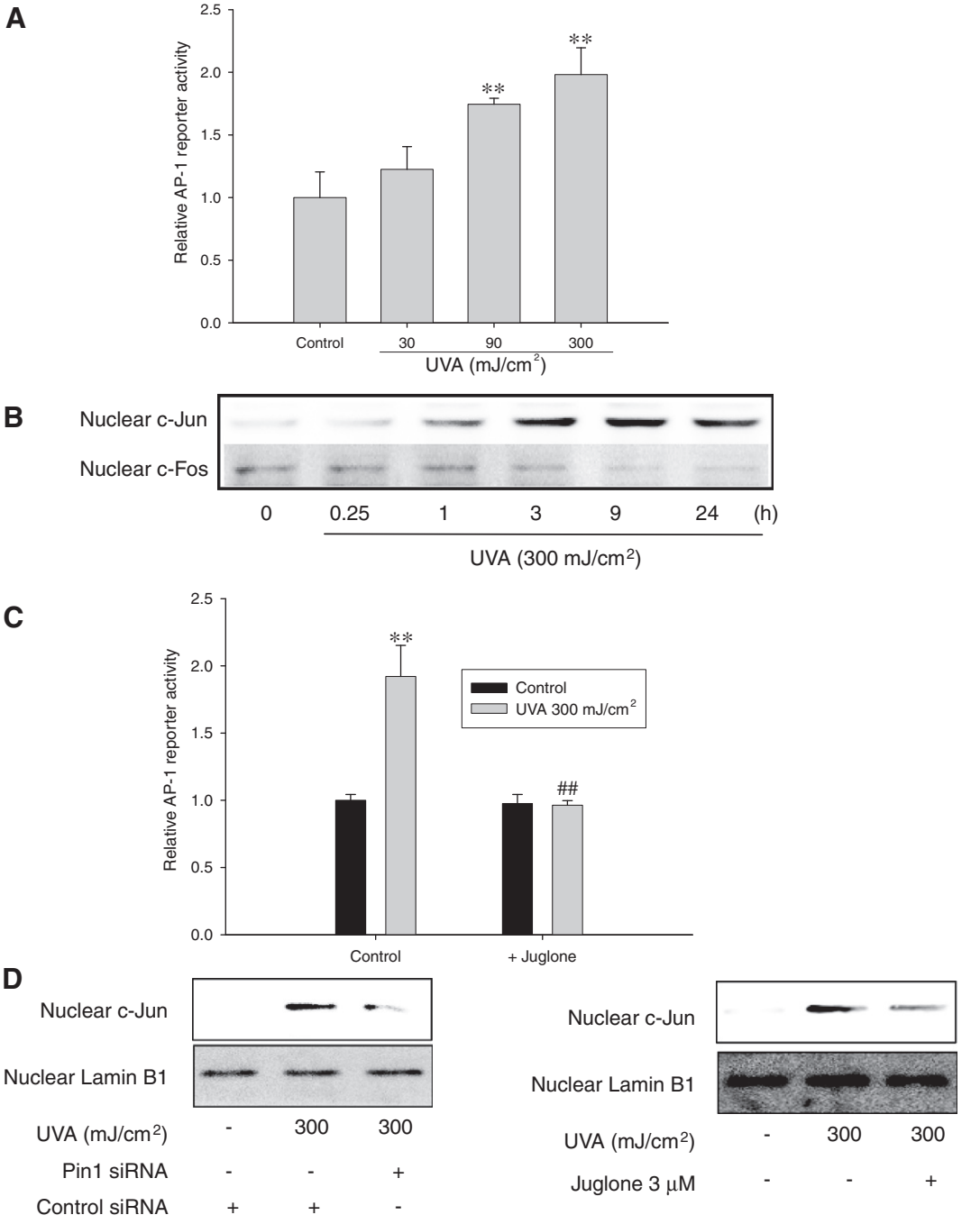

Fig. 3. Pin1-mediated AP-1 activation in UVA-exposed epidermal cells. (A) Induction of luciferase activity by UVA in JB6 C141 cells transiently transfected with AP-1 minimal reporter gene. A dual luciferase reporter assay was performed on the lysed cells co-transfected with the AP-1-Luc (firefly luciferase) and phRL-SV (hRenilla luciferase) (a ratio of 200:1) 18 h after exposure to UVA (30–300 mJ/cm^2). The data represents the mean ± SD of six separate samples (significant compared to the control, $^{**}p < 0.01$). (B) Western blot analyses of c-Jun and c-Fos in the nuclear fractions. The nuclear fractions were obtained from JB6 C141 cells exposed to UVA (300 mJ/cm^2) (15 min-24 h), and c-Jun and c-Fos in nuclear fraction were immunoblotted with the respective antibody. (C) Effect of juglone on UVA-stimulated AP-1 activation. Six hours after transient transfection of JB6 C141 cells with AP-1-Luc reporter gene, the cells were incubated in serum-free medium in the presence or absence of juglone (3 μM) for 18 h. The data represents the mean ± SD of four separate samples (significant compared to the control, $^{**}p < 0.01$; significant compared to UVA-alone exposed group, $^{\#\#}p < 0.01$). (D) Role of Pin1 in c-Jun activation. Left, effect of Pin1 siRNA (60 *p*mol) on nuclear c-Jun level. Right, effect of juglone (3 μM) on nuclear c-Jun level. JB6 C141 cells were transfected with Pin1 siRNA (60 *p*mol) or control siRNA (60 *p*mol) and then incubated in serum-free medium for 12 h. Nuclear extracts were obtained 9 h after UVA exposure.

UVA-stimulated AP-1 activation and malignant transformation of JB6 C141 cells. UVA-induced increases in both AP-1 reporter activity and colony formation were partially, but significantly inhibited by 10 mM NAC treatment (Fig. 4B and C). These results raise the possibility that UVA-mediated ROS production is one of the dominant factors in the transformation of epidermal cells.

4. Discussion

Skin cancer is one of the most frequently diagnosed cancers in Western people and 95% of skin cancer cases are non-melanoma tumors [21]. Exposure of skin to UVA or UVB is believed to be a key pathological event in the development of human skin cancers

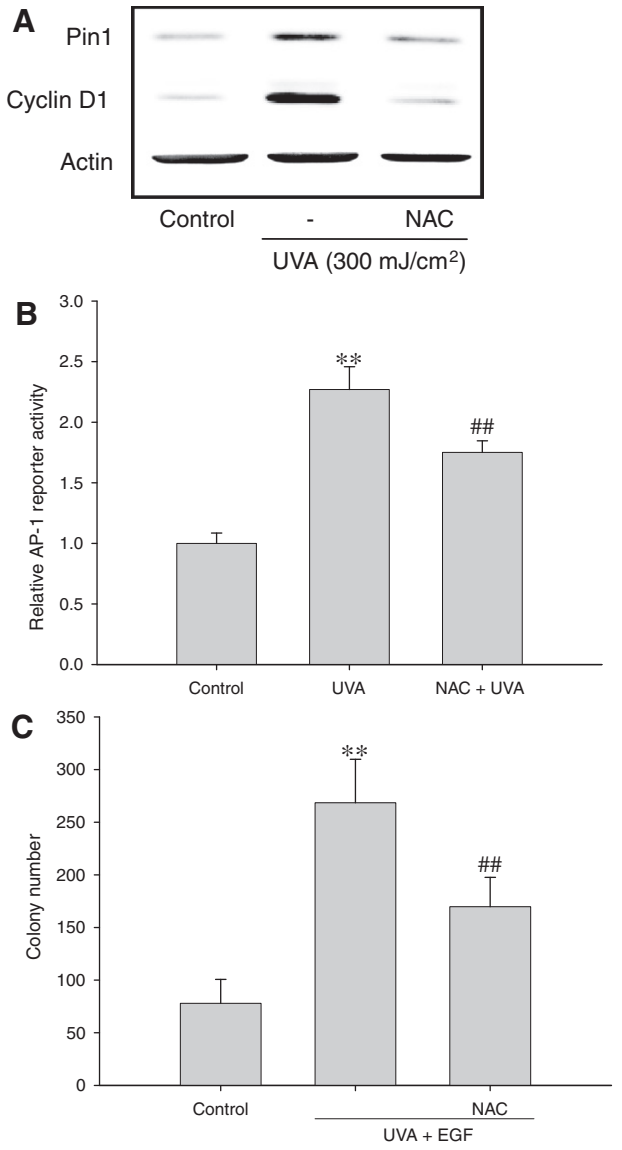

Fig. 4. Role of ROS production in UVA-induced Pin1 expression. (A) Effect of N-acetylcysteine on UVA-induced Pin1 expression. JB6 C141 cells were preincubated with N-acetylcysteine (NAC, 10 mM) for 30 min and then exposed to 300 mJ/cm^2 UVA irradiation. Twenty four hours after total cell lysates were subjected to Pin1 and actin immunoblottings. (B) Effect of NAC on UVA-stimulated AP-1 activation. Six hours after transient transfection of JB6 C141 cells with AP-1-Luc reporter gene, the cells were incubated in serum-free medium in the presence or absence of NAC (10 mM) for 18 h. The data represents the mean ± SD of four separate samples (significant compared to the control, $^{**}p < 0.01$; significant compared to UVA-exposed group, $^{\#\#}p < 0.01$). (C) Effect of NAC on colony formation of JB6 C141 cells. The epidermal cells exposed to UVA (300 mJ/cm^2) were incubated in EGF (0.1 ng/ml) containing soft agar plates for 11 days. For NAC treated group, 10 mM NAC was used. The data represents the mean ± SD of five separate samples (significant compared to the control, $^{**}p < 0.01$; significant compared to UVA-exposed group, $^{\#\#}p < 0.01$).

[1]. Although UVB can directly cause DNA damage and subsequent mutations, a large proportion of UVB radiation is absorbed by the ozone layer [22]. In comparison to UVB, UVA constitutes more than 90% of the UV radiation to which human skin is exposed and it can easily penetrate the epidermal layer of skin [1]. The pathogenesis of UVA-induced diseases has been thought to be related to either ROS production or dysregulation of growth signaling [1]. Exposure of skin cells to higher energy UVA (>1.5 J/cm^2) reduces EGF-inducible extracellular signal-regulated kinase (ERK) activation [23]. In contrast, it has been reported that UVA persistently activates EGF receptor and ERK [1]. In our previous study, we demonstrated that low energy UVA (300–900 mJ/cm^2) caused a potent induction of ErbB2 in keratinocytes, and this might be required for neoplastic transformation [12].

Here, we show that expression of Pin1, a key regulator of cancer development, is induced by low energy UVA in epidermal cells and mouse skin. Pin1 activity is tightly controlled under normal growth conditions, but up-regulation of Pin1 expression is closely associated with cancer formation [24]. Pin1 overexpression accelerates the acquisition by cancer cells of a proliferative phenotype mainly through the control of the key G1/S transition regulator cyclin D1 [9,13]. Moreover, it has been reported that UVA induces cyclin D1 accumulation, and that cyclin D1 suppression by siRNA or anti-sense techniques blocks the cell cycle progression of keratinocytes and skin squamous cancer growth in xenografts [25,26]. In the present study, we found that cyclin D1 expression was increased by UVA exposure in JB6 C141 cells and that the expression was completely blocked by Pin1 inhibition. Considering the crucial role of cyclin D1 in cell proliferation and carcinogenesis, UVA-stimulated Pin1 and cyclin D1 induction may cause the overgrowth and transformation of epidermal cells. In fact, we found that UVA-induced increases in both the cell proliferation rate and colony formation by JB6 C141 cells were significantly diminished by Pin1 inhibition. Hence, Pin1 expression in response to UVA irradiation may act as an initial signal that subsequently activates cyclin D1 and exaggerates proliferation and malignant transformation of epidermal cells.

AP-1, a complex transcription factor, can be activated by UVA in skin tissues [27] and activation of AP-1 dependent target genes is crucially involved in the development of skin cancer [1]. AP-1 mediates a broad range of external stimuli that lead to gene transcription. Various stimuli stimulating AP-1, including phorbol ester, EGF and UV irradiation, are known to be positively related with tumorigenesis [28]. In particular, transgenic mice in which c-Jun transactivation mutant, showed a dramatic inhibition of papilloma induction in two-stage skin carcinogenesis experiments [29]. We showed that UVA selectively activated c-Jun/AP-1, and Pin1 inhibition blocked the activation by UVA of the AP-1 minimal reporter. Since AP-1 activity is important and required for the transformation of JB6 Cl41 cells [30], Pin1-dependent c-Jun/AP-1 activation may be critically involved in skin cancer development.

Considering our finding that Pin induction plays a key part in UVA-induced skin carcinogenesis, it will be important to elucidate the mechanism for Pin1 expression and AP-1 activation by UVA. Exposure of skin tissues to UVA in sunlight produces a variety of radicals [19]. ROS production during photocarcinogenesis also triggers the activation of AP-1 and causes genetic instability [31]. Although, it has been reported that Pin1 expression is dependent on growth factors and serum [32], the possible role of ROS has not been studied. Here, we demonstrate that a representative ROS scavenger, NAC, inhibits UVA-mediated Pin1 induction and AP-1 activation in epidermal cells. Moreover, clonal growth of JB6 C141 cells on soft agar was significantly suppressed by NAC, supporting the idea that UVA-stimulated ROS production is associated with malignant transformation via Pin1 and AP-1 activation. It has been reported that NADPH oxidase is the primary contributor to UVA-stimulated ROS production [33]. We also found that UVA-induced Pin1 expression was diminished in JB6 C141 cells treated with diphenyleneiodonium (an NADPH oxidase inhibitor) (data not shown). Thus, it seems plausible that NADPH oxidase participates in the Pin1 overexpression caused by UVA irradiation.

In conclusion, UVA increases the expression of Pin1 in JB6 Cl41 epidermal cells and in skin tissues of hairless mice. The increased Pin1 expression is associated with UVA-induced AP-1 activation. Cyclin D1 expression is also required for UVA-stimulated cell proliferation and malignant transformation. Moreover, UVA-induced

Pin1 expression and subsequent events are partly mediated by ROS formation. Although complexities regarding possible roles of Pin1 in UVA-mediated skin carcinogenesis remain, our findings suggest novel therapeutic target to prevent and treat skin cancers. Additionally, since we used relatively low energy UVA compared with previous studies, the data shown in this study might more closely reflect physiological conditions.

Acknowledgment

This work was supported by Chosun University Grant (2010).

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