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Angiotensin-converting enzyme inhibitor (enalapril maleate) accelerates recovery of mouse skin from UVB-induced wrinkles

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ABSTRACT

Angiotensin-converting enzyme (ACE) activity and angiotensin II signaling regulate cell proliferation, differentiation, and tissue remodeling, as well as blood pressure, while in skin, angiotensin II signaling is involved in wound healing, inflammation, and pathological scar formation. Therefore, we hypothesized that angiotensin II is also involved in photoaging of skin. In this study, we examined the effect of enalapril maleate, an ACE inhibitor, on recovery of wrinkled skin of hairless mice exposed to long-term UVB irradiation. Immunohistochemical observation revealed that expression of ACE, angiotensin II, and angiotensin II type 1 (AT1) and type 2 (AT2) receptors in the skin was increased after UVB irradiation (3 times/week at increasing intensities for 8 weeks). Administration of enalapril maleate (5 times/week for 6 weeks, starting 1 week after 10-week irradiation) accelerated recovery from UVB-induced wrinkles, epidermal hyperplasia and epidermal barrier dysfunction, as compared with the vehicle control. Our results indicate that ACE and angiotensin II activity are involved in skin photoaging, and suggest that ACE inhibitor such as enalapril maleate may have potential for improvement of photoaged skin.

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1. Introduction

Angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II, an octapeptide that is a major effector of the rennin-angiotensin blood pressure regulation system. Angiotensin II signaling is also known to play important roles in regulation of cell proliferation, differentiation, apoptosis and tissue remodeling, and two types of angiotensin II receptors, AT1 and AT2, are expressed in mammalian cells.

In skin, angiotensin II signaling is involved in wound healing, fibrosis, hypertrophic scar formation and inflammatory responses [1–5]. Angiotensinogen, ACE, and angiotensin II receptors are expressed in skin [6], and keratinocytes and fibroblasts in wounded skin express high levels of angiotensin II receptors [1]. As regards the molecular mechanism through which angiotensin II contributes to wound healing, it has been reported that angiotensin II promotes re-epithelization through formation of reactive oxygen species (ROS) and induction of epidermal growth factor (EGF) receptor expression in epidermis [2,3,7], and also stimulates synthesis of extracellular matrix components via TGF-β signaling in dermis [8]. Moreover, ACE expression is higher in pathologic scars than in normal or wounded skin [4]. Over-expression of ACE and high levels of angiotensin II signaling also participate in inflammation and fibrosis associoated with pathologic scar formation [2,3,5,8]. It was reported that exogenous angiotensin II induced differentiation of fibroblasts to myofibroblasts and migration of inflammatory cells via increased expression of pro-inflammatory chemokines in mouse skin [5].

UVB is thought to be a major contributor to photoaging [9]. UVB damages skin cells and tissues both directly and indirectly through inflammation and production of reactive oxygen species [10,11]. In epidermis, increased expression of epidermal growth factor receptor (EGFR) induced by UVB via ROS synthesis causes epidermal hyperplasia and keratosis [12,13]. In dermis, on the other hand, UVB induces an imbalance of production and degradation of extracellular matrix (ECM) components and damages the ECM, causing loss of skin elasticity and wrinkle formation [14–17]. Exogenous matrix metalloproteinase (MMP) inhibitors or endogenous tissue inhibitor of MMPs (TIMPs) have a protective effect against UVB-induced wrinkle formation [18,19]. The skin of hairless mice repeatedly exposed to UVB has been used as a model of photoaged skin for investigating mechanisms of UVB-induced wrinkle formation and repair [18], and the mechanism of wrinkle repair, as well as the effects of retinoids on it, have been studied using this animal model [20,21].

Skin responses to UVB irradiation and photoaging processes exhibit similarities to the processes of wound healing and inflammation, which involve angiotensin II signaling. Therefore, we hypothesized that angiotensin II is also involved in photoaging of

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skin. In this study, we examined the participation of ACE activity and angiotensin II signaling in skin photoaging in a UVB-irradiated hairless mouse model, and investigated the effect of an ACE inhibitor, enalapril maleate.

2. Materials and methods

2.1. Reagent

Enalapril maleate was purchased by Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

2.2. Animals

Male hairless mice of the SKH-1 strain were purchased from Charles River Laboratories Japan, Inc. (Tokyo, Japan). These animals were approximately 6 weeks old at the start of the experiment. They were fed water and a commercial diet (CRF-1, Oriental Yeast Co., Ltd, Tokyo, Japan) ad. libitum. All experimental procedures using mice were approved by the Animal Experiment Committee of Tokyo University of Agriculture and Technology (approval number 24–82).

2.3. UVB irradiation and drug treatment of hairless mice

As a source of UVB, 10 Toshiba FL-20 SE fluorescent lamps (Toshiba Electric, Tokyo, Japan) were used in the same way as in other studies [13,22]. These lamps emit UV light mainly in the wavelength range from 280 to 340 nm, with a maximum at 305 nm. The intensity of irradiation was set at 0.3 mW/cm^2 by using UV-Radiometer (CVR-305/365D II, Topcon, Tokyo, Japan). The irradiation time was adjusted to control the UVB energy applied to the dorsal region of each mouse.

Wrinkles were formed by long-term repeated UVB irradiation according to the method described by Schwartz et al. [23], which was partially modified so that wrinkle formation could be induced within a shorter period of time while minimizing the occurrence of severe inflammatory changes, such as edema, and skin cancer. Briefly, the initial dose was set at 36 mJ/cm^2, which was subsequently increased to 54, 72, 108, 144, 162, 180, and 198 mJ/cm^2 at 1-week intervals and finally to 216 mJ/cm^2 at weeks 9 and 10. The frequency of irradiation was set at three times per week. The total exposure dose was about 2.8 J/cm^2 in 8 weeks and 4.6 J/cm^2 in 10 week. In this protocol, wrinkles began to be observed macroscopically in the dorsal region from about 5 weeks after initiation of the irradiation, and deep wrinkles were formed at 8–10 weeks. For immunohistological analysis of angiotensin II, ACE, AT1 and AT2 receptors, mouse dorsal skin was obtained at 8 weeks. To examine the effect of enalapril maleate, its treatment was started at 1 week after 10-week irradiation. One hundred microliters of 1% w/v enalapril maleate dissolved in 30 vol% ethanol solution or 30 vol% ethanol (control) was applied 5 times a week for 6 consecutive weeks to the whole dorsal skin of each of the mice. Each of the experimental groups and the control group comprised 5 or 6 mice.

2.4. Evaluation of wrinkle formation

At 3 and 6 weeks after the start of administration of ACE inhibitor, each hairless mouse was anesthetized, and the UVB-exposed dorsal area (site of wrinkle formation) was photographed. Three investigators individually evaluated the degree of wrinkle formation from the photograph of each animal according to the grading scale described in supplementary data, while being blinded as to the animal group; this procedure is a modification of the method described by Bisett et al. [24]. Statistical analysis of intergroup differences was conducted by using the Mann–Whitney *U* test.

2.5. Biophysical measurements of the skin

Skin thickness was measured three times at the same site with a dial thickness gauge (Ozaki Mfg. Co., Ozaki, Japan). Transepidermal water loss (TEWL) was measured three times with a Vapometer (Delfine Technologies Ltd., Finland). Analysis of the statistical significance of intergroup differences was conducted by using Student's *t*-test.

2.6. Histological and immunohistological analysis

The dorsal skin was fixed with cold acetone at 4 °C, and embedded by the AMeX method [25]. Briefly, the acetone-fixed skin was immersed in methyl benzoate and xylene, and then embedded in paraffin. Sections (3 μm) were stained with hematoxylin and eosin. Immunohistological staining was performed with Envision+ system HRP-labeled polymer and Liquid DAB+ substrate chromogen (DAKO) according to the manufacturer's instructions. Deparaffinized and rehydrated sections were incubated in 3% H_2O_2 to inactivate endogenous peroxidases, and then incubated with 10% normal goat serum (Histofine, Nichirei, Tokyo, Japan) to block nonspecific binding. As primary antibodies, rabbit polyclonal anti-angiotensin II (Abbiotec, San Diego, USA), anti-ACE (ab28311, Abcam), anti-AT1 and anti-AT2 (sc-1173, sc-9040, Santa Cruz Biotechnology, Inc.) antibodies were used. The sections were counterstained with hematoxylin, dehydrated, coverslipped and finally observed under a light microscope. Epidermal thickness was determined by microscopic observation of hematoxylin and eosin-stained skin sections. The thickness of the uncornified epidermal layer was measured and the average of each skin section was calculated based on the values at four randomly selected points. The statistical significance of intergroup differences was evaluated by using Student's *t*-test.

3. Results

3.1. UVB induces angiotensin II signaling in epidermis of mouse skin

In hairless mouse skin before UVB treatment, angiotensin II was not detectable (Fig. 1A), though strong staining for ACE was detected in epidermal cells and dermal cells (Fig. 1B). The AT1 receptor was distributed in some dermal cells and epidermal basal cells (Fig. 1C), while AT2 receptor was expressed only in some dermal cells (Fig. 1D). After 8-week UVB irradiation, the skin exhibited marked epidermal hyperplasia (Fig. 1E–H). Angiotensin II expression was induced in the epidermis (Fig. 1E), and ACE signals in epidermal cells were slightly increased (Fig. 1F). In addition, AT1 receptor was increased in UVB-irradiated mouse skin compared with that before UVB treatment (Fig. 1G). In the irradiated skin, AT1 receptor staining was positive in almost all epidermal basal cells and some suprabasal cells. AT1-positive cells were also present in the dermis, but there was no difference between irradiated and unirradiated mouse skin in this respect. On the other hand, AT2 receptor-positive cells were increased in upper dermis of irradiated skin as compared to unirradiated mouse skin. No apparent staining for AT2 receptor was observed in epidermis of either group. These results indicate that UVB irradiation enhanced ACE expression, angiotensin II production and signaling through AT1 receptors in epidermis and through AT2 receptors in dermis.

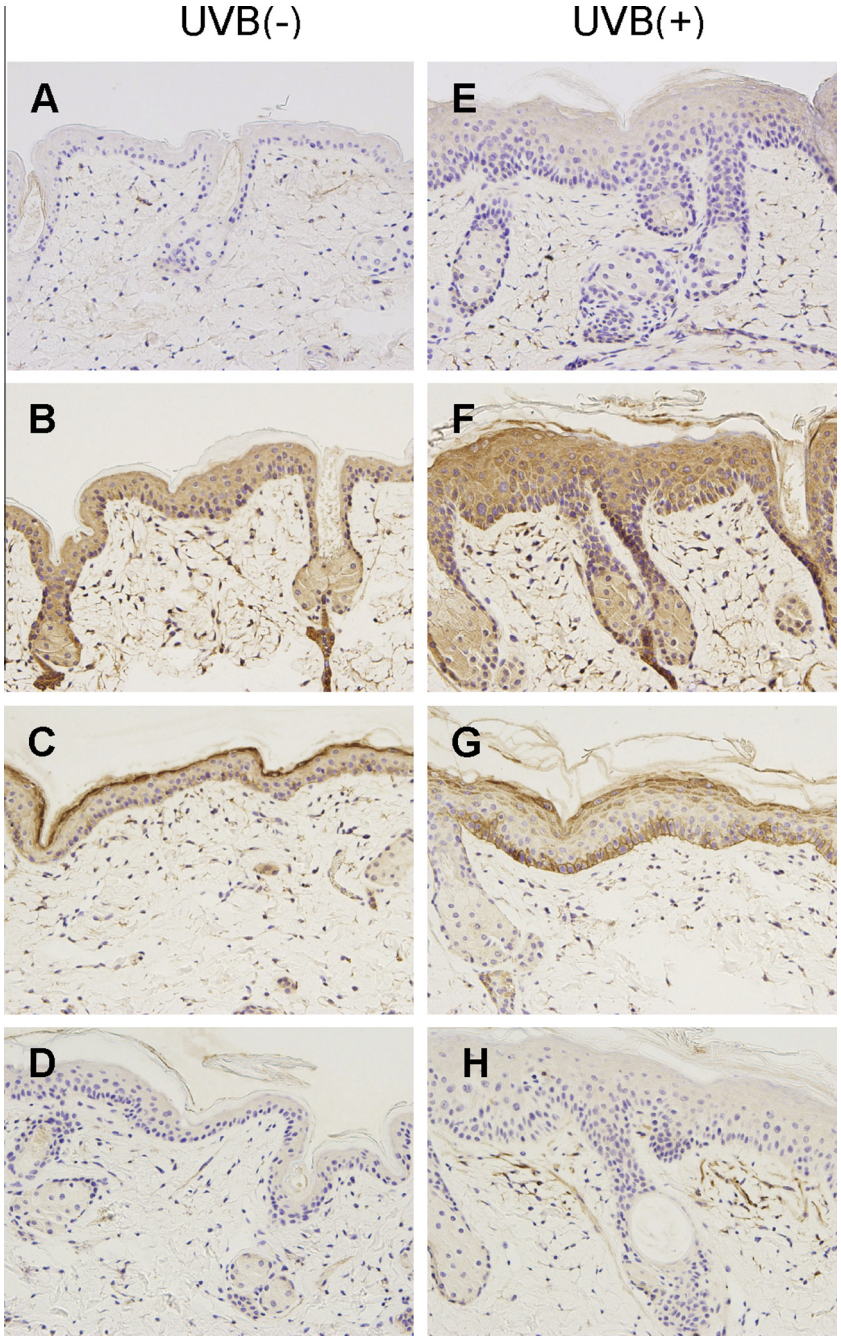

Fig. 1. Immunohistochemical staining of angiotensin II, ACE, AT1 and AT2 receptors in UVB-irradiated mouse skin. Sections of mouse skin without UVB treatment (A–D) and after 8-week UVB irradiation (E–H) were immunohistochemically stained with polyclonal antibodies for angiotensin II (A and E), ACE (B and F), AT1 receptor (C and G) and AT2 receptor (D and H).

3.2. Enalapril maleate ameliorates UVB-induced wrinkles in hairless mouse skin

Dorsal skin developed wrinkles after repeated UVB irradiation for 10 weeks. The mean values of wrinkle grades of each group ranged from 7.2 to 7.5. After the 10-week UVB-irradiation and a 1-week interval, we treated mouse dorsal skin with vehicle (30% ethanol) or 1% enalapril maleate in 30% ethanol solution for 6 weeks. Although the wrinkles of control mice tended to improve, the extent of the improvement was less than 1 grade on average at 6 weeks after the treatment. Dorsal skin of the control mice still showed epidermal hyperplasia (Fig. 3A), and staining for angiotensin II remained strong in the epidermis (Fig. 3B). On the other hand, wrinkles of mouse skin treated with enalapril maleate showed rapid improvement as compared to control mice: the grade of wrinkles decreased to 5.4 at 3 weeks after the start of inhibitor treatment, and to 4.8 at 6 weeks after completion of treatment (Fig. 2). The treated mice showed reduced staining for angiotensin II in the epidermis (Fig. 3D) and epidermal hyperplasia was improved (Fig. 3C). Epidermal thickness measured in hematoxylin and eosin sections showed a significant decrease in the treated mouse skin as compared to control skin (Fig. 3E).

3.3. Enalapril maleate improves biophysical properties of UVB irradiated mouse skin

In control mice, the thickness of dorsal skin showed no change until 6 weeks after the last UVB irradiation, whereas the skin thick-

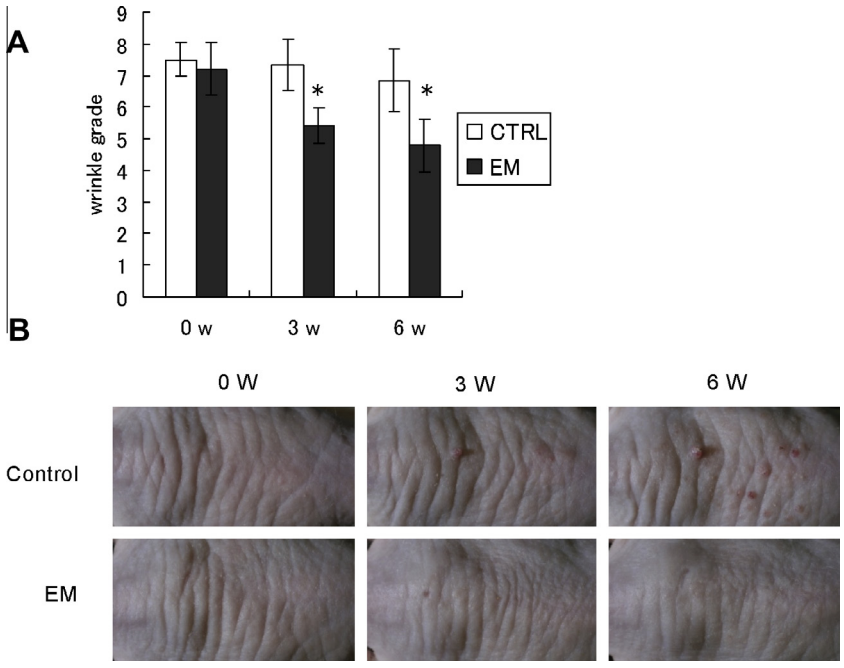

Fig. 2. Wrinkle grades and typical photographs for the control and enalapril maleate groups. After 10-week UVB irradiation followed by a 1-week interval, mouse dorsal skin was treated with 30% EtOH as control (CTRL) or 1% enalapril maleate (EM) dissolved in 30% ethanol solution for 6 weeks. The average values of wrinkle grade after treatment were calculated (A). $^{*}p<0.05$, $^{**}p<0.01$ vs. control. Photographs showing typical appearance of dorsal skin of control mouse and enalapril maleate-treated mouse (B).

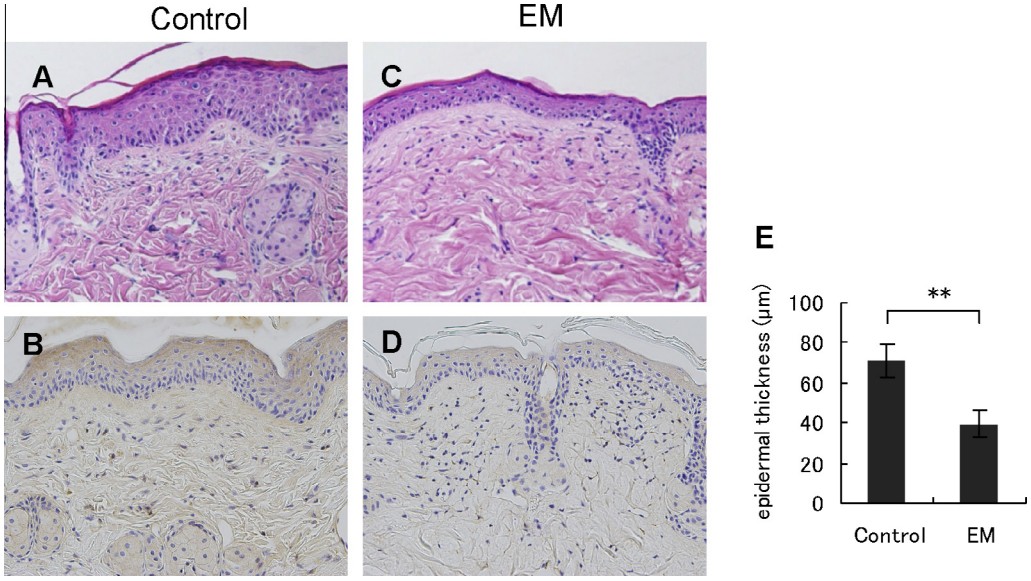

Fig. 3. Hematoxylin and eosin staining and immunohistochemical staining of angiotensin II in mouse dorsal skin after treatment with enalapril maleate. Mouse skin samples obtained after 6-week treatment with 30% EtOH (control, A and B) or enalapril meleate (C and D), started at 1 week after 10-week UVB irradiation, were fixed and embedded in paraffin. The sections were stained with hematoxylin and eosin (A and C) and immunohistologically stained with polyclonal antibody against angiotensin II (B and D). Epidermal thickness was measured by microscopic observation of hematoxylin and eosin-stained sections. $n = 6$, $^{**}p < 0.01$. Bar: standard deviation (E).

ness of enalapril maleate-treated mice was clearly decreased (Fig. 4A). TEWL values were significantly decreased in enalapril maleate-treated mice, while the values of control mice were unchanged (Fig. 4B). These results suggest that enalapril maleate improved epidermal barrier function.

4. Discussion

Expression and activity of ACE are enhanced in wounded skin, and are necessary for wound healing [2]. However, overexpression of ACE and increased angiotensin II signaling induce inflammatory responses that lead to pathological scar formation and fibrosis [1,4,5]. It is well known that UVB induces inflammation and various disorders in the skin [18,26,27], including epidermal hyperplasia, dysfunction of basement membrane, and degradation of ECM in the dermis [18]. These changes are thought to be related to wrinkle formation. In the present study, we found that expression of ACE was increased by repeated UVB irradiation. Moreover, staining for angiotensin II was still observed at 7 weeks after cessation of irradiation. Thus, ACE and angioensin II appear to be involved in

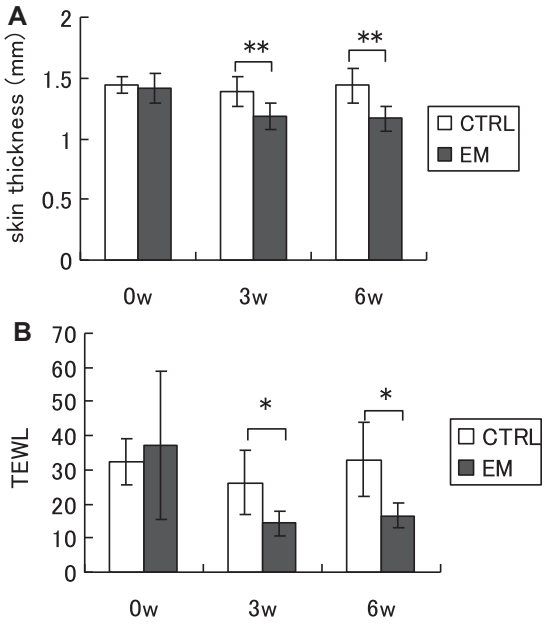

Fig. 4. Biophysical properties of UVB-irradiated and enalapril maleate-treated mouse skin. Skin thickness (A) and TEWL (B) of mouse skin were measured after 10-week UVB irradiation followed by a 1-week interval (0w), and then at 3 and 6 weeks (3w, 6w) after the start of subsequent treatment with 30% EtOH (control: CTRL) or enalapril maleate (EM). $^{*}p < 0.05$, $^{**}p < 0.01$, vs. control. Bar: standard deviation.

UVB-induced inflammatory responses and skin disorders, as well as in wound healing or pathological scar formation [4,6,28,29]. It seems likely that angiotensin II signaling plays a role in UVB-induced inflammation and injury to mouse skin.

In the epidermis, AT1 receptor staining in basal cells was increased by UVB irradiation. It has been reported that angiotensin II and AT1 receptor signaling accelerate keratinocyte migration and re-epithelization of wounded skin through EGFR signaling [2,3,7]. Angiontensin II is involved in EGFR signaling through induction of EGFR via AT1 receptor [29], and in heparin binding epidermal growth factor (HB-EGF) shedding via ADAM7 [30]. In HaCaT cells, angiotensin II promotes proliferation through ROS production and EGFR induction [7]. ROS induction and epidermal proliferation mediated by EGF or other growth factors have also been found in UV-stimulated skin or epidermal cells [12,31–33]. We observed epidermal hyperplasia and an increase in AT1 receptor in basal cells in UVB-irradiated mouse skin. Therefore, angiotensin II signaling via AT1 receptor may also be involved in UVB-induced ROS production and promotion of keratinocyte proliferation. In addition, angiotensin II was still detectable in the epidermis of hairless mice at 7 weeks after cessation of irradiation, and may play a role in maintaining hyperproliferation and epidermal disorder. Treatment with the ACE inhibitor enalapril maleate after irradiation improved epidermal hyperplasia and biophysical properties, supporting the idea that angiotensin II signaling via AT1 receptor may be involved in the UVB-induced hyperplasia.

Angiotensin II also acts in dermis during wound healing. Dermal fibroblasts in wound edges express more AT2 receptor than AT1 receptor during wound healing [1], suggesting that AT2 receptor signaling is involved in the process of dermal repair. On the other hand, high levels of angiontensin II signaling were observed in hypertrophic scar and in skin of patients with systemic sclerosis [5,6,29], and were associated with activation of the immune system, and abnormal ECM synthesis and accumulation. It was reported that exogenous angiotensin II injection promoted inflammation of mouse skin and induced differentiation of fibroblasts to myofibroblasts in dermis, as observed in fibrosis [5]. It was also reported that myofibroblasts express ACE, AT1 and AT2 receptors in pathologic scar tissues [4]. While the roles of AT1 and AT2 receptors in dermis remain controversial [4,34], angiotensin II signaling through AT1 and AT2 receptors is likely to enhance dermal inflammatory reaction. In the current study, both AT1 and AT2 receptor-positive cells were observed in UVB-irradiated skin. In particular, AT2 receptor-positive cells were observed in the upper layer of dermis in UVB-irradiated mouse skin, while there was no significant change in AT1 receptor expression in dermis. These AT2-positive cells may be partly responsible for the UVB-induced inflammatory responses and dermal disorder.

ACE inhibitors have long been used for treatment of hypertension [35–37], and are believed to have tissue-protective effects, such as prevention of cardiac fibrosis, lung fibrosis and kidney disease [28,38–41]. We investigated the effect of the ACE inhibitor enalapril maleate on recovery of hairless mouse skin from UVB-induced damage and wrinkles. The method has previously been used to investigate skin photoaging, and it was shown that UVB-induced wrinkles are improved by retinoid treatment [18,20,21,42]. In the current study, enalapril maleate promoted wrinkle repair in UVB-irradiated hairless mouse skin, ameliorated epidermal hyperplasia and improved epidermal barrier function. Other two ACE inhibitors, quinapril hydrochloride and lisinopril, also promoted wrinkle repair in UVB-irradiated mouse skin (data not shown). Thus, ACE inhibitors might suppress skin disfunction and inflammatory response mediated through the angiotensin II pathway. ACE inhibitors appear to be promising candidates for promoting repair of human wrinkles and photoaging damage.

In conclusion, the present study demonstrated that repeated UVB irradiation induces expression of ACE and angiotensin II in hairless mouse skin, similar to that occuring in wounded skin or pathologic scars. Treatment with the ACE inhibitor enalapril maleate improved UVB-induced wrinkles and skin damage. We suggest that ACE inhibitors are promising candidates for treatments to improve the condition or appearance of photoaged skin.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.10.162.

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