Biochemistry and Biophysics Reports 4 (2015) 180–186

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

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

Recovery of extracellular matrix components by enalapril maleate during the repair process of ultraviolet B-induced wrinkles in mouse skin

Yuko Matsuura-Hachiya [a], Yuji Nakai [b], Keiko Abe [c,d], Toshio Nishiyama [a], Koji Y. Arai [a,*]

[a] Scleroprotein Research Institute, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan
[b] Institute for Food Sciences, Hirosaki University, 2-1-1 Yanagawa, Aomori, 038-0012, Japan
[c] Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan
[d] Project on Health and Anti-aging, Kanagawa Academy of Science and Technology, Life Science and Environment Research Center (LiSE) 4 FC-4, 3-25-13 Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, 210-0821, Japan

ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form
10 August 2015
Accepted 15 September 2015
Available online 21 September 2015

Keywords:
Skin
Ultraviolet irradiation
Extracellular matrix
Wrinkle

ABSTRACT

The renin–angiotensin system is known to be involved in skin remodeling and inflammation. Previously, we reported that ultraviolet B (UVB) irradiation enhanced angiotensin-converting enzyme (ACE) expression and angiotensin II levels in hairless mouse skin, and an ACE inhibitor, enalapril maleate (EM), accelerated repair of UVB-induced wrinkles. In this study, we analyzed gene expression profiles by DNA microarray and protein distribution patterns using an immunofluorescence method to clarify the process of EM-accelerated wrinkle repair in UVB-irradiated hairless mouse skin. In the microarray analysis, we detected EM-induced up-regulation of various extracellular matrix (ECM)-related genes in the UVB-irradiated skin. In the immunofluorescence, we confirmed that type I collagen α1 chain, fibrillin 1, elastin and dystroglycan 1 in the skin decreased after repeated UVB irradiation but staining for these proteins was improved by EM treatment. In addition, ADAMTS2 and MMP-14 also increased in the EM-treated skin. Although the relationship between these molecules and wrinkle formation is not clear yet, our present data suggest that the molecules are involved in the repair of UVB-induced wrinkles.

1. Introduction

Skin photoaging is a consequence of chronic exposure to sunlight. Ultraviolet B (UVB) is thought to contribute greatly to photoaging [1]. UVB damages skin cells and tissues both directly and indirectly through inflammation and production of reactive oxygen species [2,3]. In dermis, UVB induces an imbalance between production and degradation of extracellular matrix (ECM) components and damages ECM; it causes loss of skin elasticity and wrinkle formation [4–7]. Retinoids are well known to have wrinkle repairing effects [8,9].

As well as retinoids, enalapril maleate (EM), one of the angiotensin-converting enzyme (ACE) inhibitors, has potential to promote repair of UVB-induced wrinkles as we reported previously [10]. ACE converts inactive angiotensin I (Ang I) to active angiotensin II (Ang II), a major player in the renin-angiotensin system (RAS). Ang II is a key factor for the pathogenesis of hypertension and atherosclerosis, and ACE inhibitors are used as antihypertensive drugs [11,12]. Besides the cardiovascular system, RAS also plays as a local regulator of cell functions and involved in tissue pathologies in many tissues such as skin [13–18].

ACE expression and Ang II levels in hairless mouse skin were enhanced by repeated UVB irradiation, and EM and other ACE inhibitors accelerated recovery of skin from UVB-induced wrinkles [10]. Furthermore, EM treated hairless mouse skin was thinner and showed lower transepidermal water loss (TEWL) than control mice [10]. Because the effect of ACE inhibitors on wrinkle repair is a quite novel phenomenon, it is very valuable to reveal the mechanism responsible for the anti-wrinkle effect. To clarify the process responsible for the EM accelerated wrinkle repair, we used DNA microarray technology and analyzed gene expression patterns in UVB-irradiated, EM-treated hairless mouse skin. As a result, we found changes in expression of various ECM and ECM-related genes. Furthermore, changes in expression and distribution of proteins encoded by these genes in the skin were examined by immunofluorescence method.

* Corresponding author. Fax: +81 42 367 5791.
E-mail address: kojiarai@cc.tuat.ac.jp (K.Y. Arai).

http://dx.doi.org/10.1016/j.bbrep.2015.09.012

2. Materials and methods

2.1. Reagent

Enalapril maleate (1-[N-((S)-1-Carboxy-3-phenylpropyl)-L-alanyl]-L-proline 1′-ethyl ester, maleate) was purchased from 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 six weeks old at the start of experiment. They were fed a commercial diet (CRF-1, Oriental Yeast Co., Ltd, Tokyo, Japan) ad libitum and allowed free access to water. 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

The dorsal region of each mouse was repeatedly irradiated with UVB for 10 weeks as described previously [10]. EM treatment was started at one week after the 10-week irradiation. One hundred microliters of 1% w/v EM dissolved in 30% v/v ethanol solution or 30% v/v ethanol (control) was applied five times a week for two or six consecutive weeks to the whole dorsal skin of each of the mice without anesthesia. Each group comprised six mice. After the two- or six-week drug treatment, mice were killed by cervical dislocation under isoflurane anesthesia, and skin samples were collected for microarray analysis and immunofluorescence. For microarray analysis, 1 cm^2 skin samples of the two-week-treated mice were collected in 2 mL sampling tubes on ice and immediately immersed in liquid nitrogen and stored at −80 °C until isolation of total RNA. For immunofluorescence, skin samples of the two- or six-week-treated mice were fixed with cold acetone at 4 °C, and embedded by the AMeX method [19].

2.4. Microarray experiment

Total RNA was isolated with Isogen reagent (NIPPON GENE CO., LTD., Tokyo, Japan) and purified with RNAeasy mini kit (QIAGEN, California, USA) according to the manufacturer's instructions. Total RNA concentration and purity were checked with NanoDrop spectrophotometer (NanoDrop Technologies Inc., Delaware, USA). The quality of total RNA was assessed by electrophoretic separation on an RNA Nano lab chip, using a 2100 Bioanalyzer (Agilent Technologies Inc., California, USA). The total RNA samples were amplified and labeled with Cy3 by using the Quick Amp labeling Kit and hybridized with an Agilent 4 × 44 K Whole Mouse Genome Microarray (Agilent Technologies Inc.). Then, the array was scanned with Dual-Laser microarray Scanner G2565AA (Agilent Technologies Inc.). The scanned data were analyzed using Feature Extraction Software 9.1 (Agilent Technologies Inc.), which tagged the data as signals recognized as being outliers or equal to the background. The fold change of each gene was calculated as the ratio of signal intensity between the experimental average data and the control average data.

2.5. Microarray data analysis

The data were analyzed by weighted average difference (WAD) [20] method using a free software environment R [R Development Core Team (2008) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria]. WAD method was designed for accurate gene ranking which calculated on signal significance. Briefly, WAD statistic is calculated by average difference (AD); difference between the average of two group log signals (i.e. log fold-change), and weight (w); relative average log signal intensity. WAD statistic is obtained by multiplication of AD and w [20]. WAD rank and WAD statistic value were obtained and 500 most up-regulated genes and 500 most down-regulated genes in WAD statistics were listed respectively. Using these up- or down-regulated gene lists, the significance of the enrichment of the Gene Ontology (GO) categories in each gene list was obtained by the Database for Annotation, Visualization and Integrated Discovery (DAVID) [21]. The full complement of the expression data is available at Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo; accession number GSE61708).

2.6. Immunofluorescent analysis

Rabbit polyclonal antibodies for type I collagen, a disintegrin and metalloprotease with thrombospondin repeats 2 (ADAMTS2) (ab34710, ab125226 Abcam plc, Cambridge, UK), fibrillin 1, elastin, (AP06122PU-N, BP8022, Acris Antibodies Inc., California, USA), MMP-14 (AB6004, Millipore, Darmstadt, Germany) and dystroglycan 1 (11017-1-AP, Proteintech Group, Inc., Illinois, USA) were used as primary antibodies. Deparaffinized and rehydrated sections were incubated with the primary antibodies in phosphate-buffered saline (PBS) containing 12% bovine serum albumin overnight at 4 °C. Then, the sections were washed eith PBS and incubated with Alexa Fluor® 488 Donkey Anti-Rabbit IgG (H+L) Antibody (Life Technologies Japan Inc., Tokyo, Japan). Following to washing, the sections were coverslipped with Vectashield mounting medium with DAPI (H-1200, Vector Laboratories, Inc., California, USA) and observed with Olympus BX51 microscope (Olympus Corporation, Tokyo, Japan).

3. Results

3.1. Expression of ECM-related genes were up-regulated in enalapril maleate-treated mouse skin

There were 1150 up-regulated genes and 612 down-regulated genes in the EM-treated mouse skin with *p*-values less than 0.05 when the data were analyzed with the Benjamini–Hochberg procedure. The most up-regulated 500 genes and most down-regulated 500 genes in WAD statistics were obtained and GO terms specifically enriched with the up- or down-regulated genes were analyzed with DAVID. The mean WAD statistics of up-regulated 500 genes was 0.238 (from 1.900 to 0.157). The mean WAD statistics of down-regulated 500 genes were −0.735 (from −1.959 to −0.632). In the GO terms of up-regulated genes, ECM-related terms were involved as shown in Table 1. The up-regulated genes involved in the ECM-related terms are shown in Table 2. Genes involved in connective tissue constituents such as fibrillar collagen components *Col*1 *a*1, *Col*1*a*2, *Col*27*a*1), elastic system fiber components (*Eln*, *Fbn*1, *Fbn*2, *Col*6*a*1) and basement membrane components (*Lama*2, *Dag*1) were up-regulated (Table 2).

3.2. ECM components in UVB-irradiated skin were increased by enalapril maleate treatment

To examine distribution of ECM components encoded by the up-regulated genes and their contribution to wrinkle formation and repair in the UVB-irradiated mouse skin, immunofluorescent analysis for type I collagen, fibrillin 1, elastin and dystroglycan 1 was performed (Fig. 1). The sections of three mice of each group were tested in the immunofluorescent staining (Supplementary

Table 1
Gene ontology categories overlapping with the list of up-regulated genes in the EM-treated mouse skin. Two hundred and sixty three DAVID IDs were assigned from up-regulated 500 genes to DAVID. The enriched GO terms of biological process (BP), cellular component (CC) and molecular function (MF) associated with up-regulated genes were obtained and the terms whose value of Benjamini–Hochberg FDR-corrected EASE score were smaller than 0.05 were listed. Count: number of genes involved in the term; Category: category of GO term; %: percentage of involved genes per total assigned genes; *P*-value: EASE score (modified Fisher's exact *p*-value); Benjamini: Benjamini–Hochberg FDR-corrected EASE score.

Term	Category	Count	%	*P*-value	Benjamini
Extracellular matrix	CC	20	7.6046	1.63E-08	1.91E-06
Extracellular matrix part	CC	12	4.5627	2.51E-08	1.95E-06
Proteinaceous extracellular matrix	CC	20	7.6046	8.58E-09	2.01E-06
Extracellular region part	CC	28	10.6464	1.89E-06	1.11E-04
Extracellular region	CC	44	16.7300	5.11E-06	2.39E-04
Epidermis development	BP	11	4.1825	7.86E-06	0.006147
Morphogenesis of an epithelium	BP	12	4.5627	2.46E-05	0.006407
Epithelium development	BP	16	6.0837	4.48E-06	0.006998
Ectoderm development	BP	11	4.1825	1.36E-05	0.007094
Tissue morphogenesis	BP	14	5.3232	2.28E-05	0.007111
Gland morphogenesis	BP	9	3.4221	1.83E-05	0.007148
Basement membrane	CC	7	2.6616	3.47E-04	0.013435
Extracellular matrix structural constituent	MF	6	2.2814	5.46E-05	0.017861
Vesicular fraction	CC	10	3.8023	5.76E-04	0.019087
Biological adhesion	BP	20	7.6046	2.40E-04	0.046040

Table 2
Up-regulated ECM and related genes in the enalapril maleate-treated mouse skin. The genes were listed according to WAD statistic.

Gene symbol	Gene name	WAD statistic	Fold change
*Dag*1	dystroglycan 1	0.403717	2.62
*Col1a*1	collagen, type I, alpha 1	0.402896	1.86
*Fbn*1	fibrillin 1	0.329296	2.14
*Chl*1	cell adhesion molecule with homology to L1CAM	0.255440	5.43
*Adamts*2	a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 2	0.254100	2.44
*Mmp*14	matrix metallopeptidase 14	0.247086	1.81
*Fn*1	fibronectin 1	0.223204	1.85
*Spon*2	spondin 2, extracellular matrix protein	0.216120	1.72
*Fbn*2	fibrillin 2	0.216081	2.03
*Col27a*1	collagen, type XXVII, alpha 1	0.204232	3.39
Eln	Elastin	0.200950	1.73
*Wnt*1	wingless-related MMTV integration site 1	0.190974	1.13
Bgn	Biglycan	0.187014	1.65
*Smoc*2	SPARC related modular calcium binding 2	0.181531	1.63
*Col15a*1	collagen, type XV, alpha 1	0.176043	2.06
*Col6a*1	collagen, type VI, alpha 1	0.175368	1.56
Tnc	tenascin C	0.174481	1.63
*Ntn*1	netrin 1	0.170001	1.82
*Lama*2	laminin, alpha 2	0.169368	1.68
*Col1a*2	collagen, type I, alpha 2	0.161055	2.00

Fig. 1). Type I collagen was densely stained in dermis in intact skin (Fig. 1a) and the staining slightly decreased after the 10-week UVB irradiation (Fig. 1b). Staining for fibrillin 1 and elastin was observed in upper dermis before the UVB irradiation (Fig. 1e and i), and the staining decreased after the 10-week UVB irradiation (Fig. 1f and j). Dystroglycan 1 was stained at the dermal–epidermal junction of hair follicles and interfollicular area in intact skin (Fig. 1m). However, after the 10-week UVB irradiation, it was rarely detected at the region (Fig. 1n). After the six-week treatment period following to the UVB irradiation, the distribution patterns of these ECM components tended to recover in the control mice (Fig. 1c, g, k and o), and they were more strongly stained in the EM-treated mice (Fig. 1d, h, l and p) than the control mice. These results indicated that the EM treatment increased expression of various ECM components and promoted reconstruction of UVB-damaged collagen fibers, elastic system fibers and basement membrane.

3.3. ADAMTS2 and MMP-14 were decreased by UVB irradiation, and enalapril maleate opposed the effects of UVB

In addition to ECM components, EM-induced up-regulation of *Adamts*2 and *Mmp*14, which encode a procollagen I N-proteinase and the membrane type 1 matrix metalloprotease (MT1-MMP) respectively, was detected in the microarray analysis (Table 2). In immunofluorescence, ADAMTS2 was stained in the cell membrane of epidermal basal cells and some cells in upper dermis (Fig. 2a), and disappeared after the 10-week UVB irradiation (Fig. 2b). After the two-week treatment period following to the UVB irradiation, After UVB irradiation, distribution of ADAMTS2 was recovered more rapidly in EM-treated mouse skin than control mice (Fig. 2c–f). MMP-14 was stained in whole epidermal cell layers before the UVB irradiation (Fig. 2g) and there were no obvious change in the epidermis just after the 10-weeks UVB irradiation (Fig. 2h). However, the staining markedly decreased after the two-week treatment period following to the 10-week UVB irradiation (Fig. 2i and j). After the six-week treatment with EM, strong staining for MMP-14 was observed in the epidermis (Fig. 2l), while only moderate staining was observed in the time-matched control mice (Fig. 2k). The sections of three mice of each group were tested in the immunofluorescent staining (Supplementary Fig. 2).

4. Discussion

We previously demonstrated that UVB-irradiation induced expression of ACE and angiotensin II, and treatment with the ACE inhibitor enalapril maleate improved UVB-induced wrinkles and skin damage in hairless mouse skin [10]. Then, in present study, we demonstrated that the expression of ECM components was increased by treatment with EM during the repairing process of the UVB-induced wrinkles by microarray analysis with WAD method. WAD method is superior to avoid falsely detecting low expression genes as high-ranked genes because highly expressed genes are highly ranked in this method [20]. We detected many genes involved in ECM components as top-ranked genes.

Several studies have reported that changes in ECM components are involved in wrinkle formation and repair [5,8,22,23]. UVB irradiation in skin activates proteases including MMPs and elastase, and decreases ECM components [6,7,22]. On the other hand, retinoid treatment increases expression of ECM components such as collagen and elastin during wrinkle repair in human and mouse skin [8,23,24]. The effect of EM on UVB-irradiated mouse skin is similar to that of retinoids in this respect [23,25,26].

The present study demonstrated that type I collagen, a major fibrous collagen in skin, decreased after the UVB irradiation. UVB irradiation is well known to induce degradation of ECM components by activating MMPs [4,5,27–29]. In this study, expression of *Col1a*1 was up-regulated by treatment with EM. Furthermore *Col27a*1, *Col15a*1 and *Col6a*1 gene expression was upregulated by EM Type VI collagen forms a branching filament structure and is connected to collagen fiber and basement membrane in skin [30]. The expression of Type XXVII collagen and type XV collagen in dermis were reported previously [31,32]. Although the functions of these minor collagens are not clear, they may also be involved in

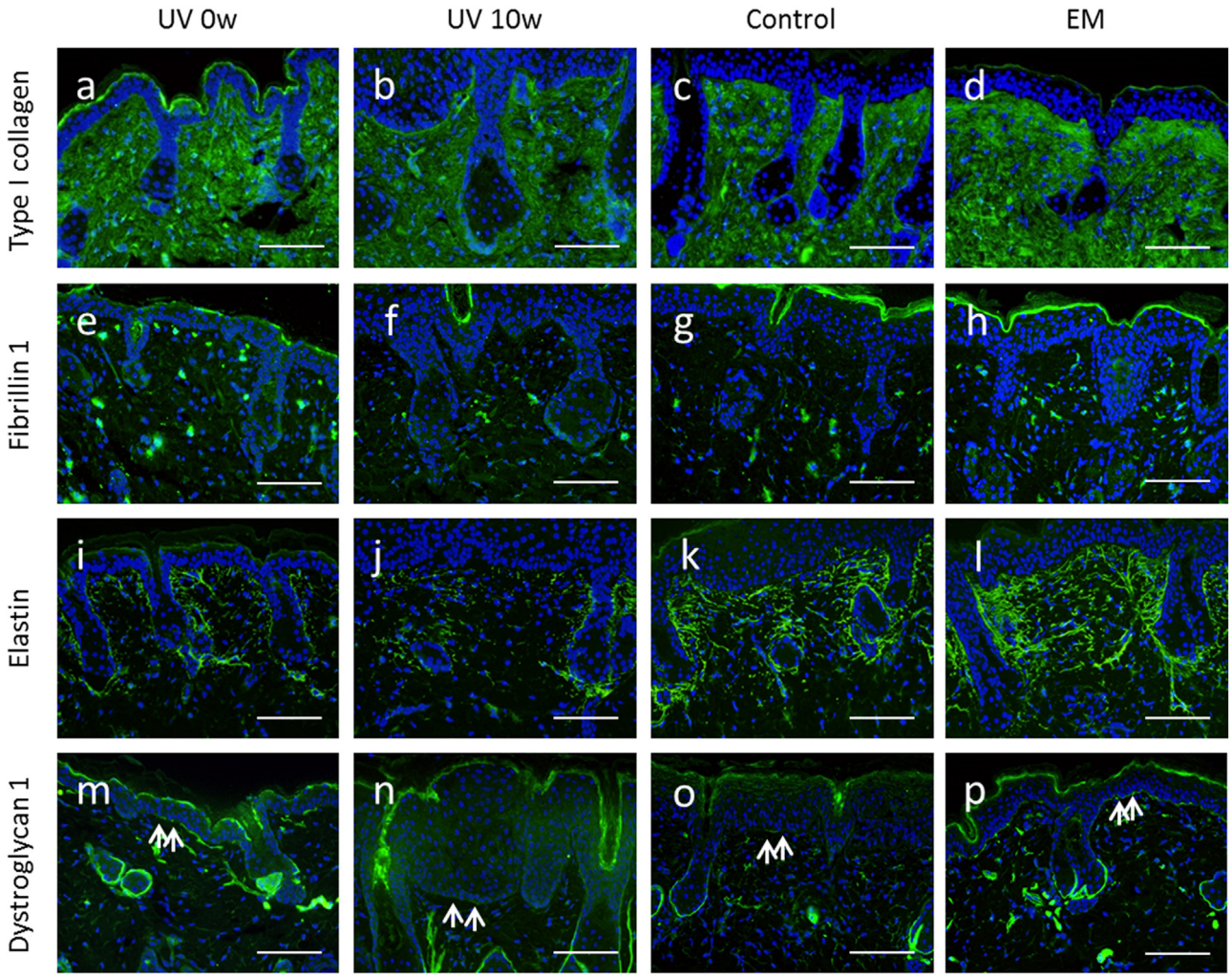

Fig. 1. Distribution of ECM components in hairless mouse skin. Mouse skin samples were obtained before (a, e, i and m) and after (b, f, i and n) 10-week UVB irradiation, and after 6-week treatment with 30% ethanol (control; c, g, k, and o) or enalapril maleate (EM; d, h, l and p) following to 10-week UVB irradiation and a one-week interval period. Skin sections were stained with antibodies for type I collagen (a–d), fibrillin 1 (e–h), elastin (i–l), and dystroglycan 1 (m–p) and fluorescent signals specific to the antibodies were visualized as green. Nuclei were counterstained with DAPI (blue). Arrows indicate the dermal–epidermal junction. Scale bars indicate 100 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the process of wrinkle repair together with type I collagen.

Deposition of elastin and fibrillin-1 protein was remarkably affected by UVB irradiation. In a previous study of human photoaged skin, fibrillin 1 gene expression and protein deposition proximal to the dermal–epidermal junction were increased in an early stage of all-trans retinoic acid treatment [23]. The present and the previous studies indicate that fibrillin 1 and elastin fiber proximal to the dermal–epidermal junction are susceptible to UVB irradiation and the following repair.

Dystroglycan 1 is a cell surface component, which is expressed as a single polypeptide and converted into membrane-associated α-dystroglycan and transmembrane β-dystroglycan by post-translational modification [33,34]. It was reported that dystroglycan 1 was involved in cell-ECM interaction and essential for laminin assembly and basement membrane formation, and shed by IL-1β-stimulated proteinase in keratinocytes [4,33–35]. It is possible that UVB-irradiated epidermis promotes shedding of α-dystroglycan via IL-1β signaling [36]. Regeneration of dystroglycan 1 may have occurred during repair of the dermal–epidermal interaction prior to reconstruction of basement membrane structure in the EM-treated mice.

Besides structural constituents of ECM, gene expression of *Mmp*14 and *Adamts*2, which encode enzymes participating in ECM structure formation and degradation, was up-regulated in the EM-treated mouse skin. ADAMTS2, a secreted procollagen N-proteinase, is involved in processing of types I, II and III procollagens [37,38]. Procollagen α chains are hydroxylated and glycosylated, and form triple-helical procollagen molecules in intercellular space. Then, procollagen molecules are transported to extracellular space by HSP47, a specific molecular chaperone of procollagen [39]. Subsequently, N-terminus and C-terminus propeptides were cleaved by ADAMTS2 and BMP-1 respectively [37,38,40]. The processed triple-helical collagen molecules are cross-linked and mature to collagen fibers [41,42]. This processing is necessary for maturation of collagen fibers with tensile strength [43]. During the recovery process from the UVB irradiation, the EM-induced up-regulation of ADAMTS2 may have helped collagen fiber formation in combination with the up-regulation of type I collagen gene. MMP-14 degrades ECM components and regulates cellular functions via release and degradation of cell surface proteins such as growth factors. It was reported that MMP-14 was highly expressed in epidermis of wound healing skin and regulated angiogenesis [44]. It has been suggested that epidermal MMP-14 activity is involved in dermal–epidermal crosstalk regulating angiogenesis. Furthermore, Quan et al. reported that MMP14 mRNA was highly expressed in sun-protected human skin but decreased by UVB

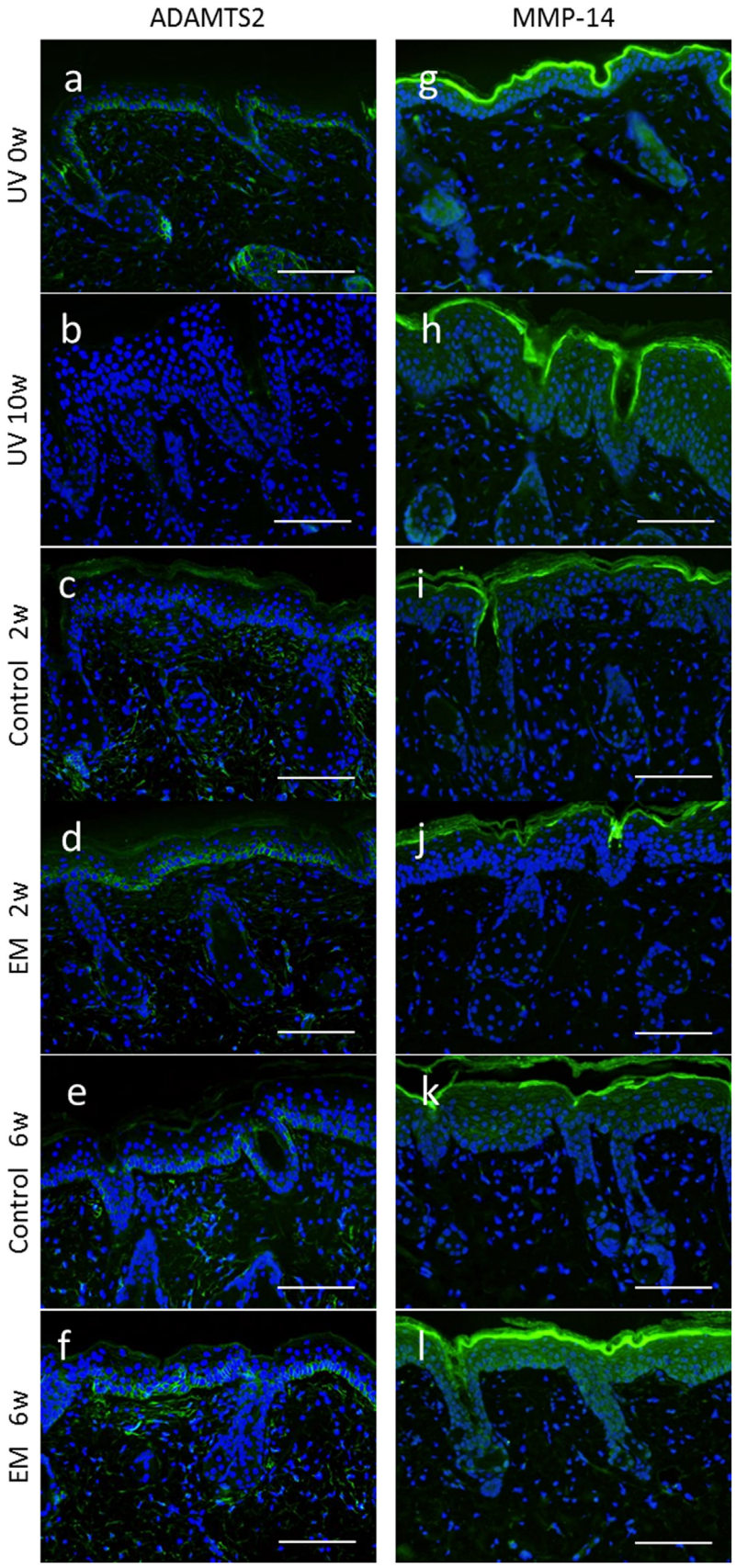

Fig. 2. Expression of ADAMTS2 and MMP-14 in hairless mouse skin. Mouse skin samples were obtained before (a and g) and after (b and h) 10-week irradiation, and after 2-week (c, d, i and j) or 6-week (e, f, k and l) treatment with 30% ethanol (control; c, e, i and k) or enalapril maleate (EM; d, f, j and l) following to 10-week UVB irradiation and a one-week interval period. Mouse skin sections were stained with anti-ADAMTS2 antibody (a–f) or anti-MMP14 antibody (g–l) and fluorescent signals specific to the antibodies were visualized as green. Nuclei were counterstained with DAPI (blue). Scale bars indicate 100 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stimulation [4]. A decrease in epidermal MMP-14 may cause failure of dermal–epidermal crosstalk followed by suppression of wrinkle repair. Further investigation for revealing functions of MMP-14 in skin remains to be done.

The mechanism by which EM up-regulates ECM components is not clear yet. However, involvement of ACE and angiotensin II in inflammation and anti-inflammatory effects of angiotensin receptor blocker in skin and other tissues have been reported [17,45–50]. In addition, previous studies indicate that angiotensin II augments IL-1β signaling [49,51]. Furthermore, other studies demonstrated that proinflammatory cytokines suppressed expression of ECM [52,53]. Thus, it is possible that EM promoted repairing of UVB-induced wrinkle through its anti-inflammatory effects. In contrast, during the process of wrinkle repairing by retinoids, not only up-regulation of ECM components but also inflammatory-like responses, such as hyperplasia of epidermis, or expression of pro-inflammatory cytokines are observed [54,55]. Therefore, the molecular mechanism of wrinkle repairing by EM is likely different from that by retinoids. However, both EM and retinoids induce up-regulation of ECM, suggesting that the increase in ECM expression is required for promoting wrinkle repair.

In conclusion, we detected up-regulation of ECM and related genes and improvement of distribution patterns of ECM components and related molecules by EM treatment following to UVB irradiation. Although the molecular mechanism by which EM increases these ECM components in mouse skin remains to be determined, it is suggested by comparing the effects of retinoids and EM that up-regulation of ECM components is crucial for improving UVB-induced wrinkles.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2015.09.012.

Reference

[1] Y. Matsumura, H.N. Ananthaswamy, Toxic effects of ultraviolet radiation on the skin, Toxicol. Appl. Pharmacol. 195 (2004) 298–308.
[2] T. Schwarz, A. Schwarz, DNA repair and cytokine responses, J. Investig. Dermatol. Symp. Proc. 14 (2009) 63–66.
[3] F. Ali, S. Sultana, Repeated short-term stress synergizes the ROS signalling through up regulation of NFkB and iNOS expression induced due to combined exposure of trichloroethylene and UVB rays, Mol. Cell Biochem. 360 (2012) 133–145.
[4] T. Quan, Z. Qin, W. Xia, et al., Matrix-degrading metalloproteinases in photoaging, J. Investig. Dermatol. Symp. Proc. 14 (2009) 20–24.
[5] E.C. Naylor, R.E. Watson, M.J. Sherratt, Molecular aspects of skin ageing, Maturitas 69 (2011) 249–256.
[6] G. Imokawa, Recent advances in characterizing biological mechanisms underlying UV-induced wrinkles: a pivotal role of fibrobrast-derived elastase, Arch. Dermatol. Res. 300 (Suppl. 1) (2008) S7–S20.
[7] G. Imokawa, Mechanism of UVB-induced wrinkling of the skin: paracrine cytokine linkage between keratinocytes and fibroblasts leading to the stimulation of elastase, J. Investig. Dermatol. Symp. Proc. 14 (2009) 36–43.
[8] S. Chen, I. Kiss, K.M. Tramposch, Effects of all-trans retinoic acid on UVB-irradiated and non-irradiated hairless mouse skin, J. Investig. Dermatol. 98 (1992) 248–254.
[9] E. Calikoglu, O. Sorg, C. Tran, et al., UVA and UVB decrease the expression of CD44 and hyaluronate in mouse epidermis, which is counteracted by topical retinoids, Photochem. Photobiol. 82 (2006) 1342–1347.
[10] Y. Matsuura-Hachiya, K.Y. Arai, R. Ozeki, et al., Angiotensin-converting enzyme inhibitor (enalapril maleate) accelerates recovery of mouse skin from UVB-induced wrinkles, Biochem. Biophys. Res. Commun. 442 (2013) 38–43.
[11] R.S. Meyers, A. Siu, Pharmacotherapy review of chronic pediatric hypertension, Clin. Ther. 33 (2011) 1331–1356.
[12] L. Edgar, A. Hogg, M. Scott, et al., ACE inhibitors for the treatment of hypertension drug selection by means of the SOJA method, Rev. Recent Clin. Trials 6 (2011) 69–93.
[13] A. Benigni, P. Cassis, G. Remuzzi, Angiotensin II revisited: new roles in inflammation, immunology and aging, EMBO Mol. Med. 2 (2010) 247–257.
[14] I. Zafar, Y. Tao, S. Falk, et al., Effect of statin and angiotensin-converting enzyme inhibition on structural and hemodynamic alterations in autosomal dominant polycystic kidney disease model, Am. J. Physiol. Renal. Physiol. 293 (2007) F854–F859.
[15] A. Molteni, L.F. Wolfe, W.F. Ward, et al., Effect of an angiotensin II receptor blocker and two angiotensin converting enzyme inhibitors on transforming growth factor-beta (TGF-beta) and alpha-actomyosin (alpha SMA), important mediators of radiation-induced pneumopathy and lung fibrosis, Curr. Pharm. Des. 13 (2007) 1307–1316.
[16] K. Morihara, S. Takai, H. Takenaka, et al., Cutaneous tissue angiotensin-converting enzyme may participate in pathologic scar formation in human skin, J. Am. Acad. Dermatol. 54 (2006) 251–257.
[17] L. Stawski, R. Han, A.M. Bujor, et al., Angiotensin II induces skin fibrosis: a novel mouse model of dermal fibrosis, Arthritis Res. Ther. 14 (2012) R194.
[18] U.M. Steckelings, B.M. Henz, S. Wiehstutz, et al., Differential expression of angiotensin receptors in human cutaneous wound healing, Br. J. Dermatol. 153 (2005) 887–893.
[19] Y. Sato, K. Mukai, S. Watanabe, et al., The AMeX method. A simplified technique of tissue processing and paraffin embedding with improved preservation of antigens for immunostaining, Am. J. Pathol. 125 (1986) 431–435.
[20] K. Kadota, Y. Nakai, K. Shimizu, A weighted average difference method for detecting differentially expressed genes from microarray data, Algorithms Mol. Biol. 3 (2008) 8.
[21] W. Huang, B.T. da, R.A. Sherman, Lempicki, Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources, Nat. Protoc. 4 (2009) 44–57.
[22] S. Inomata, Y. Matsunaga, S. Amano, et al., Possible involvement of gelatinases in basement membrane damage and wrinkle formation in chronically ultraviolet B-exposed hairless mouse, J. Investig. Dermatol. 120 (2003) 128–134.
[23] R.E. Watson, N.M. Craven, S. Kang, et al., A short-term screening protocol, using fibrillin-1 as a reporter molecule, for photoaging repair agents, J. Investig. Dermatol. 116 (2001) 672–678.
[24] L.H. Kircik, Histologic improvement in photodamage after 12 months of treatment with tretinoin emollient cream (0.02%), J. Drugs Dermatol. 11 (2012) 1036–1040.
[25] E. Schwartz, L.H. Kligman, Topical tretinoin increases the tropoelastin and fibronectin content of photoaged hairless mouse skin, J. Investig. Dermatol. 104 (1995) 518–522.
[26] T. Quan, Z. Qin, Y. Shao, et al., Retinoids suppress cysteine-rich protein 61 (CCN1), a negative regulator of collagen homeostasis, in skin equivalent cultures and aged human skin in vivo, Exp. Dermatol. 20 (2011) 572–576.
[27] A. Hachiya, P. Sriwiriyanont, T. Fujimura, et al., Mechanistic effects of long-term ultraviolet B irradiation induce epidermal and dermal changes in human skin xenografts, Am. J. Pathol. 174 (2009) 401–413.
[28] F. Trautinger, K. Mazzucco, R.M. Knobler, et al., UVA- and UVB-induced changes in hairless mouse skin collagen, Arch. Dermatol. Res. 286 (1994) 490–494.
[29] U. Yokose, A. Hachiya, P. Sriwiriyanont, et al., The endogenous protease inhibitor TIMP-1 mediates protection and recovery from cutaneous photodamage, J. Investig. Dermatol. 132 (2012) 2800–2809.
[30] D.R. Keene, E. Engvall, R.W. Glanville, Ultrastructure of type VI collagen in human skin and cartilage suggests an anchoring function for this filamentous network, J. Cell Biol. 107 (1988) 1995–2006.
[31] R.P. Boot-Handford, D.S. Tuckwell, D.A. Plumb, et al., A novel and highly conserved collagen (pro(alpha)1(XXVII)) with a unique expression pattern and unusual molecular characteristics establishes a new clade within the vertebrate fibrillar collagen family, J. Biol. Chem. 278 (2003) 31067–31077.
[32] T. Fukushige, T. Kanekura, E. Ohuchi, et al., Immunohistochemical studies comparing the localization of type XV collagen in normal human skin and skin tumors with that of type IV collagen, J. Dermatol 32 (2005) 74–83.
[33] P.D. Yurchenco, B.L. Patton, Developmental and pathogenic mechanisms of basement membrane assembly, Curr. Pharm. Des. 15 (2009) 1277–1294.
[34] C. Herzog, C. Has, C.W. Franzke, et al., Dystroglycan in skin and cutaneous cells: beta-subunit is shed from the cell surface, J. Investig. Dermatol. 122 (2004) 1372–1380.
[35] M. Masuda-Hirata, A. Suzuki, Y. Amano, et al., Intracellular polarity protein PAR-1 regulates extracellular laminin assembly by regulating the dystroglycan complex, Genes Cells 14 (2009) 835–850.
[36] T.H. Nasti, L. Timares, Inflammasome activation of IL-1 family mediators in response to cutaneous photodamage, Photochem. Photobiol. 88 (2012) 1111–1125.
[37] L. Tuderman, D.J. Prockop, Procollagen N-proteinase. Properties of the enzyme purified from chick embryo tendons, Eur. J. Biochem. 125 (1982) 545–549.
[38] W.M. Wang, S. Lee, B.M. Steiglitz, et al., Transforming growth factor-beta induces secretion of activated ADAMTS-2 A procollagen III N-proteinase, J. Biol. Chem. 278 (2003) 19549–19557.
[39] J.J. Sauk, N. Nikitakis, H. Siavash, Hsp47 a novel collagen binding serpin chaperone, autoantigen and therapeutic target, Front. Biosci. 10 (2005) 107–118.
[40] D.R. Hopkins, S. Keles, D.S. Greenspan, The bone morphogenetic protein 1/Tolloid-like metalloproteinases, Matrix Biol. 26 (2007) 508–523.
[41] S. Ricard-Blum, The collagen family, Cold Spring Harb Perspect Biol, 3, 2011, a004978.
[42] C.Z. Chen, M. Raghunath, Focus on collagen: in vitro systems to study fibrogenesis and antifibrosis state of the art, Fibrogenesis Tissue Repair 2 (2009) 7.
[43] F. Kesteloot, A. Desmouliere, I. Leclercq, et al., ADAM metallopeptidase with thrombospondin type 1 motif 2 inactivation reduces the extent and stability of

carbon tetrachloride-induced hepatic fibrosis in mice, Hepatology 46 (2007) 1620–1631.
[44] P. Zigrino, O. Ayachi, A. Schild, et al., Loss of epidermal MMP-14 expression interferes with angiogenesis but not with re-epithelialization, Eur. J. Cell Biol. 91 (2012) 748–756.
[45] Q. Dai, M. Xu, M. Yao, et al., Angiotensin AT1 receptor antagonists exert anti-inflammatory effects in spontaneously hypertensive rats, Br. J. Pharmacol 152 (2007) 1042–1048.
[46] U.N. Das, Is angiotensin-II an endogenous pro-inflammatory molecule? Med. Sci. Monit. 11 (2005) Ra155–Ra162.
[47] T. Nakamura, K. Hasegawa-Nakamura, K. Sakoda, et al., Involvement of angiotensin II type 1 receptors in interleukin-1beta-induced interleukin-6 production in human gingival fibroblasts, Eur. J. Oral Sci. 119 (2011) 345–351.
[48] H. Bak, W.J. Lee, Y.W. Lee, et al., Expression of neuropeptides and their degrading enzymes in ACD, Clin. Exp. Dermatol. 35 (2010) 318–323.
[49] N.S. Sauter, C. Thienel, Y. Plutino, et al., Angiotensin II Induces IL-1beta-mediated islet inflammation and beta-cell dysfunction independently of vasoconstrictory effects, Diabetes 64 (2015) 1273–1283, http://dx.doi.org/10.2337/db14-1282.
[50] M. Platten, S. Youssef, E.M. Hur, et al., Blocking angiotensin-converting enzyme induces potent regulatory T cells and modulates TH1- and TH17-mediated autoimmunity, Proc. Natl. Acad. Sci. USA 106 (2009) 14948–14953.
[51] M. Alique, E. Sanchez-Lopez, S. Rayego-Mateos, et al., Angiotensin II, via angiotensin receptor type 1/nuclear factor-kappaB activation, causes a synergistic effect on interleukin-1-beta-induced inflammatory responses in cultured mesangial cells, J. Renin Angiotensin Aldosterone Syst. 16 (2015) 23–32, http://dx.doi.org/10.1177/1470320314551564.
[52] J.A. Solis-Herruzo, D.A. Brenner, M. Chojkier, Tumor necrosis factor alpha inhibits collagen gene transcription and collagen synthesis in cultured human fibroblasts, J. Biol. Chem. 263 (1988) 5841–5845.
[53] P.P. Kuang, J.L. Berk, D.C. Rishikof, et al., NF-kappaB induced by IL-1beta inhibits elastin transcription and myofibroblast phenotype, Am. J. Physiol. Cell Physiol. 283 (2002) C58–C65.
[54] L. Garcia-Serrano, M.A. Gomez-Ferreria, C. Contreras-Jurado, et al., The thyroid hormone receptors modulate the skin response to retinoids, PLoS One 6 (2011) e23825.
[55] J.E. Lee, J.Y. Chang, S.E. Lee, et al., Epidermal hyperplasia and elevated HB-EGF are more prominent in retinoid dermatitis compared with irritant contact dermatitis induced by benzalkonium chloride, Ann. Dermatol. 22 (2010) 290–299.