# Taurine accelerates the synthesis of ceramides and hyaluronic acid in cultured epidermis and dermal fibroblasts

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**Abstract.** Taurine is a sulfur-containing amino acid derivative that can be found in the majority of mammalian tissues. Taurine is also present in the skin and is involved in maintaining skin homeostasis by exerting osmoregulatory and antioxidant effects. Previous studies have indicated that taurine treatment is effective against age-, ultraviolet- or detergent-induced skin dysfunction. To determine the mechanism responsible for the beneficial actions of taurine in the skin, the present study aimed to evaluate the effects of taurine on epidermal components (ceramides and filaggrin) and on the dermal extracellular matrix, in three-dimensionally (3D) cultured epidermis and dermal fibroblasts, respectively. These cells were cultured in the presence of 3-50 mM taurine, and cells or culture medium were collected for analysis. The effects of taurine on transepidermal water loss (TEWL) in the skin and the expression of inflammatory cytokines, including IL-1α, IL-1β and IL-1 receptor antagonist, were investigated in acetone-treated 3D-cultured epidermis using a Tewameter and reverse transcription-quantitative PCR (RT-qPCR), respectively. The mRNA expression levels of MMP-1 and hyaluronic acid (HA) production were measured in skin dermal fibroblasts using RT-qPCR and ELISA, respectively. Taurine was found to suppress acetone-induced elevation in TEWL in 3D-cultured epidermis. Taurine also stimulated the mRNA expression of ceramide synthase 4 and filaggrin, a major structural protein in the stratum corneum, in 3D-cultured epidermis. In skin dermal fibroblasts, taurine inhibited the IL-1α-stimulated mRNA and protein expression of MMP-1. In addition, taurine treatment increased HA synthase-2 mRNA expression and in turn HA production. Results from the present study suggest that the protective effect of taurine on the skin is associated with the enhancement of epidermal barrier component expression and modulation of dermal extracellular matrix metabolism.

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*Key words:* taurine, skin, ceramide, filaggrin, hyaluronic acid, MMP-1

## Introduction

The skin is the largest multi-functional organ in the human body, with barrier properties that are essential for maintaining body homeostasis. The skin is typically structured into the following three layers: Epidermis, dermis and the subcutaneous fat tissue (1,2). The stratum corneum makes up the outermost layer of the epidermis of the skin that serves two major functions as a physical barrier (1,2). It serves a water-retention function by preventing the evaporation of water, which would otherwise result in dry skin. It also serves a barrier function, preventing the invasion of pathogens whilst fending off various chemical assaults (1,2). The stratum corneum consists of ceramides, cholesterol, and free fatty acids. These lipids are normally synthesized in keratinocytes before being extruded into the extracellular domains, forming lipid-rich extracellular layers (3). In particular, natural moisturizing factors (NMF) are a major contributor to the moisturizing function of the stratum corneum. NMF include free amino acids and their derivatives, organic acids, and mineral salts (4). Furthermore, the amino acids that account for the majority of NMF are derived from the hydrolysis of a protein called filaggrin (5). In addition to the stratum corneum, tight junction structures present in the stratum granulosum also serve an important role as a barrier in the skin (6,7). Claudin and occludin serve a central role in the intercellular barrier at tight junctions and are essential proteins for the maintenance of homeostasis in living organisms (6,7). Dysfunction of these tight junctions has been reported to be associated with the development of skin disorders, such as atopic dermatitis (8). By contrast, the dermis is a tissue that is rich in extracellular matrix (ECM), which consists of collagen and elastic fibers produced by fibroblasts. In addition, hyaluronic acid (HA), produced by fibroblasts, exists to fill the area around these fibers and holds the water in the dermis (9). During the aging process, the dermis undergoes significant changes. Skin aging is accompanied with reduced elasticity and wrinkle formation, which is the result of reductions in the quantity of ECM in the dermis (10).

Taurine is a sulfur-containing amino acid derivative that is present in the majority of mammalian tissues (11). Taurine is distributed throughout the body of living organisms, including humans, which serves roles in maintaining cell homeostasis through osmoregulatory, antioxidant, anti-inflammatory, protein-stabilizing and calcium-regulating actions (11). In the skin, taurine is mainly localized in the epidermis and is involved in modulating the skin moisture content (12,13). The distribution of taurine and taurine transporters in the skin was previously found to be in proximity with the location of tight junctions in the epidermis, suggesting that taurine may have a part in regulating tight junction function (14). A previous study has also reported that oral taurine supplementation can ameliorate ultraviolet (UV) beam-induced wrinkle formation in hairless mice (15). Since taurine is known to be an organic osmolyte in the body, modulation of osmotic pressure and maintenance of cell volume are possible mechanisms responsible for the anti-wrinkle action of taurine (15). Considering the diverse array of functions taurine can serve, other mechanisms may be involved in the suppression of wrinkle formation. Taurine has been reported to stimulate wound healing by increasing skin collagen synthesis in mice (16), in addition to stimulating collagen synthesis in osteoblast-like UMR-106 cells (17). These aforementioned observations suggest that taurine is able to exert functions on the ECM, including collagen, in the skin. Despite the various reported beneficial actions of taurine on skin function, the underlying mechanisms remained elusive.

Therefore, the present study was undertaken to determine the mechanisms by which taurine regulates skin function using three-dimensionally (3D) cultured human epidermis and human dermal fibroblasts.

## Materials and methods

*3D epidermis culture*. 3D epidermis culture specimens and assay medium (401124E6; LabCyte EPI-MODEL24 6D) were purchased from Japan Tissue Engineering Co., Ltd. The 3D epidermis cultures were maintained at 37˚C with 5% $CO_2$ in a defined assay medium (EPI-MODEL) or assay medium containing 3 or 30 mM taurine (Fujifilm Wako Pure Chemical Corporation) (18). The medium was changed daily for 7 days. After 6 days of incubation at 37˚C with 5% $CO_2$, 100 $\mu$l 100% acetone was added to the 3D epidermal culture from the stratum corneum side. After 5 min, the acetone was removed by suction with a pipette at room temperature. The acetone addition and removal procedure was repeated twice. After 7 days, the transepidermal water loss (TEWL) of the 3D epidermis culture was measured. Thereafter, only the epidermis was collected from the 3D culture cups using RNAlater™ Stabilization Solution (Invitrogen; Thermo Fisher Scientific, Inc.) and the samples were stored at 4˚C until further use.

*Measurement of TEWL*. On the 7th day of culture, the 3D epidermis culture specimens were transferred to a new 24-well plate and allowed to stand at room temperature for 20 min with the plate lid open under aseptic conditions. TEWL was measured by placing a Tewameter (TM300; Courage + Khazaka Electronic GmbH) directly on top of the cup of the 3D epidermis culture.

*Normal human dermal fibroblast (NHDFs) culture*. NHDFs were purchased from Kurabo Bio-Medical Department (KF-4009; Kurabo Industries, Ltd.) and maintained at 37˚C with 5% $CO_2$ in a defined FibroLife S2 Comp Kit medium (Kurabo Industries, Ltd.; Lifeline Cell Technology). These cells were used for experiments examining collagen and MMP-1. For the experiments examining HA, NHDFs purchased from RIKEN BioResource Center (NB1RGB, cell no. RCB0222) were used and maintained at 37˚C with 5% $CO_2$ in DMEM (Sigma-Aldrich; Merck KGaA) supplemented with 10% FCS (Sigma-Aldrich; Merck KGaA), 100 U/ml penicillin, and 100 $\mu$g/ml streptomycin (Sigma-Aldrich; Merck KGaA). NHDFs with two to four cell passages were used for the experiments. The NHDFs were then incubated with 3-50 mM taurine and IL-1α (PeproTech, Inc.) for 24 or 48 h at 37˚C. NHDFs cultured in medium without IL-1α and taurine were used as the control. Cells and their culture supernatant were then collected. The total RNA of the cells was extracted for reverse transcription-quantitative PCR (RT-qPCR), whereas the culture supernatant was collected for ELISA.

*RT-qPCR*. Total RNA was extracted from the 3D epidermis culture or NHDF cells using QI-Azol lysis reagent and an RNeasy Mini kit (both Qiagen GmbH). For the 3D epidermis culture, a tissue lysis solution was prepared using a high-speed cell disruption system (Precellys® 24; Bertin Technologies) to extract RNA from cells. Complementary DNA was synthesized from the RNA by reverse transcription (37˚C for 15 min and 85˚C for 5 sec) using the PrimeScript® RT Master Mix (Takara Bio, Inc.) and subsequent qPCR was performed using the Fast SYBR® Green Master Mix (Invitrogen; Thermo Fisher Scientific, Inc.) in a StepOnePlus® Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.). The following amplification profile was used: 20 sec at 95˚C, followed by 40 cycles of 3 sec at 95˚C and 30 sec at 60˚C. The primer sequences are indicated in Table I. Amplification was normalized to the housekeeping gene GAPDH. The gene expression level was quantified using the standard curve method (19).

*ELISA*. The levels of HA and MMP-1 were measured in the culture supernatant using ELISA kits for HA (Seikagaku Corporation) and MMP-1 (cat. no. ab100604; Abcam), respectively, according to the manufacturer's protocol. The protein concentration in the cell lysate was measured using a BCA protein assay kit (Thermo Fisher Scientific, Inc.). Protein levels of MMPs are presented as amounts per cell protein. Cellular protein concentrations were measured in cell lysates. MMP-1 was measured in the culture supernatant, which was applied to the ELISA plate.

*Statistical analysis*. All data are expressed as the mean ± standard deviation (n=3-6). The statistical analyses were performed using the SAS preclinical package software (version 5.0; SAS Institute Japan Co., Ltd.). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Sequences of the primers used for reverse transcription-quantitative PCR.

| Primers | Sequence (5'-3') |
|---|---|
| IL-1α | Forward: CTCAATTGTATGTGACTGCCCAAGA |
| | Reverse: AACAAGTTTGGATGGGCAACTGA |
| IL-1β | Forward: GCTGATGGCCCTAAACAGATGAA |
| | Reverse: TCCATGGCCACAACAACTGAC |
| IL-1RN | Forward: CTGTCCTGTGTCAAGTCTGGTG |
| | Reverse: TCTCGCTCAGGTCAGTGATGTTA |
| FLG | Forward: CATGGCAGCTATGGTAGTGCAGA |
| | Reverse: ACCAAACGCACTTGCTTTACAGA |
| SPTLC1 | Forward: AGACCATCCTGCTCTCAACTACAA |
| | Reverse: CTAGGGTTATCCAACAATCCAAGAA |
| SMPD1 | Forward: TCTATGAAGCGATGGCCAAG |
| | Reverse: GATCCGTGGAGTTGATCAAGAG |
| CERS2 | Forward: CATCCGAGCTGGGACTCTAATCA |
| | Reverse: GGGTACACCAGGGTGCAATG |
| CERS4 | Forward: ATGGCTGTGGGCACCAGTAA |
| | Reverse: GAGGTAGAAACCCAGCTCCAAGA |
| COL1A1 | Forward: GCTTGGTCCACTTGCTTGAAGA |
| | Reverse: GAGCATTGCCTTTGATTGCTG |
| COL3A1 | Forward: ATGAAGGTGAATTCAAGGCTGAAG |
| | Reverse: CCACCAATGTCATAGGGTGCAATA |
| COL4A1 | Forward: CAGCCGCTGCCAAGTCTGTA |
| | Reverse: AGGTCAATGAAGCAGGGTGTGTTAG |
| COL7A1 | Forward: AGAAGGGAGAAGCTGCACTGA |
| | Reverse: GCAGTGTCTGCAGCATAACTAGG |
| MMP-1 | Forward: CCAAATGGGCTTGAAGCTG |
| | Reverse: GGTATCCGTGTAGCACATTCTGTC |
| HAS-2 | Forward: GACAGGCATCTCACGAACCG |
| | Reverse: CAACGGGTCTGCTGGTTTAGC |
| GAPDH | Forward: GCACCGTCAAGGCTGAGAAC |
| | Reverse: TGGTGAAGACGCCAGTGGA |

CERS, ceramide synthase; IL-1RN, interleukin-1 receptor antagonist; COL, collagen.

## Results

*Effects of taurine on TEWL and skin inflammation in 3D cultured epidermis*. The effects of taurine on TEWL in the skin and the expression of inflammatory cytokines were investigated using 3D cultured epidermis. The addition of acetone to the cultured epidermis significantly increased TEWL, whereas this effect was significantly reversed by treatment with 30 mM taurine (Fig. 1). Acetone also significantly increased the mRNA expression of inflammatory cytokines IL-1α, IL-1β and IL-1 receptor antagonist (IL-1RN) (Fig. 2). However, taurine did not affect the mRNA expression of these aforementioned cytokines. The potential effects of taurine on the mRNA expression of ceramide-related molecules were next examined in 3D-cultured cells. The mRNA expression of ceramide synthase 2 (CERS2) was found to be significantly increased by acetone treatment (Fig. 3A). However, the

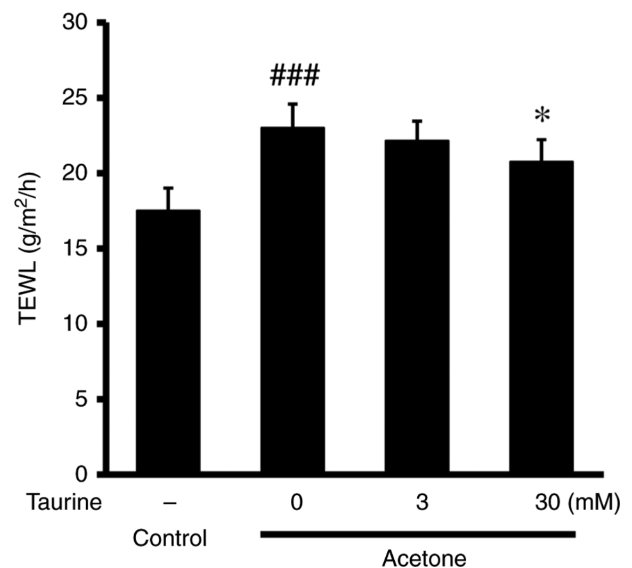


Figure 1. Effects of taurine on TEWL in acetone-treated 3D cultured epidermis. TEWL was measured using a Tewameter. Data are presented as the mean ± standard deviation (n=6). *P<0.05 vs. Acetone control (0 mM taurine). ###P<0.001 vs. Control. TEWL, transepidermal water loss.

acetone-induced changes in the mRNA expression of other ceramide-related enzymes CERS4 (Fig. 3B), sphingomyelin phosphodiesterase 1 (Fig. 3C) and serine palmitoyltransferase long chain base subunit 1 (Fig. 3D) were not observed to be significant. Treatment with 30 mM taurine did significantly increase the mRNA expression of CERS4 and filaggrin compared with that in the acetone-only group (Fig. 3B and E).

*Effects of taurine on collagen HA in human dermal fibroblasts*. The addition of 12.5-50 mM taurine to the dermal fibroblasts did not significantly affect the mRNA expression of collagens collagen (COL)IA1 (Fig. 4A), COLIIIA1 (Fig. 4B), COLIVA1 (Fig. 4C) and COLVIIA1 (Fig. 4D). The possible effects of taurine on the degradation of collagen were then evaluated in IL-1α-stimulated human dermal fibroblasts by measuring the mRNA and protein expression of MMP-1. Although IL-1α significantly increased the mRNA expression and protein expression levels of MMP-1, further taurine treatment significantly counteracted this effect of IL-1α, in a dose-dependent manner (Fig. 5A and B). In addition, higher doses of taurine (25 and 50 mM) significantly increased the HA content in the culture medium and the mRNA expression of hyaluronan synthase 2 (HAS-2), an HA synthetic enzyme, in the skin dermal fibroblasts (Fig. 6A and B).

## Discussion

The present study revealed that taurine can modulate components of the epidermal barrier and dermal ECM *in vitro*. These effects can potentially contribute to the modulation of the homeostatic action in the skin exerted by taurine. Taurine is distributed in the skin and has a pivotal role in maintaining skin homeostasis (12,13). The effects of taurine administration on skin function have been evaluated in animals, humans and cultured cells (12,15,20). It was indicated that the topical application of taurine attenuated TEWL in surfactant-treated

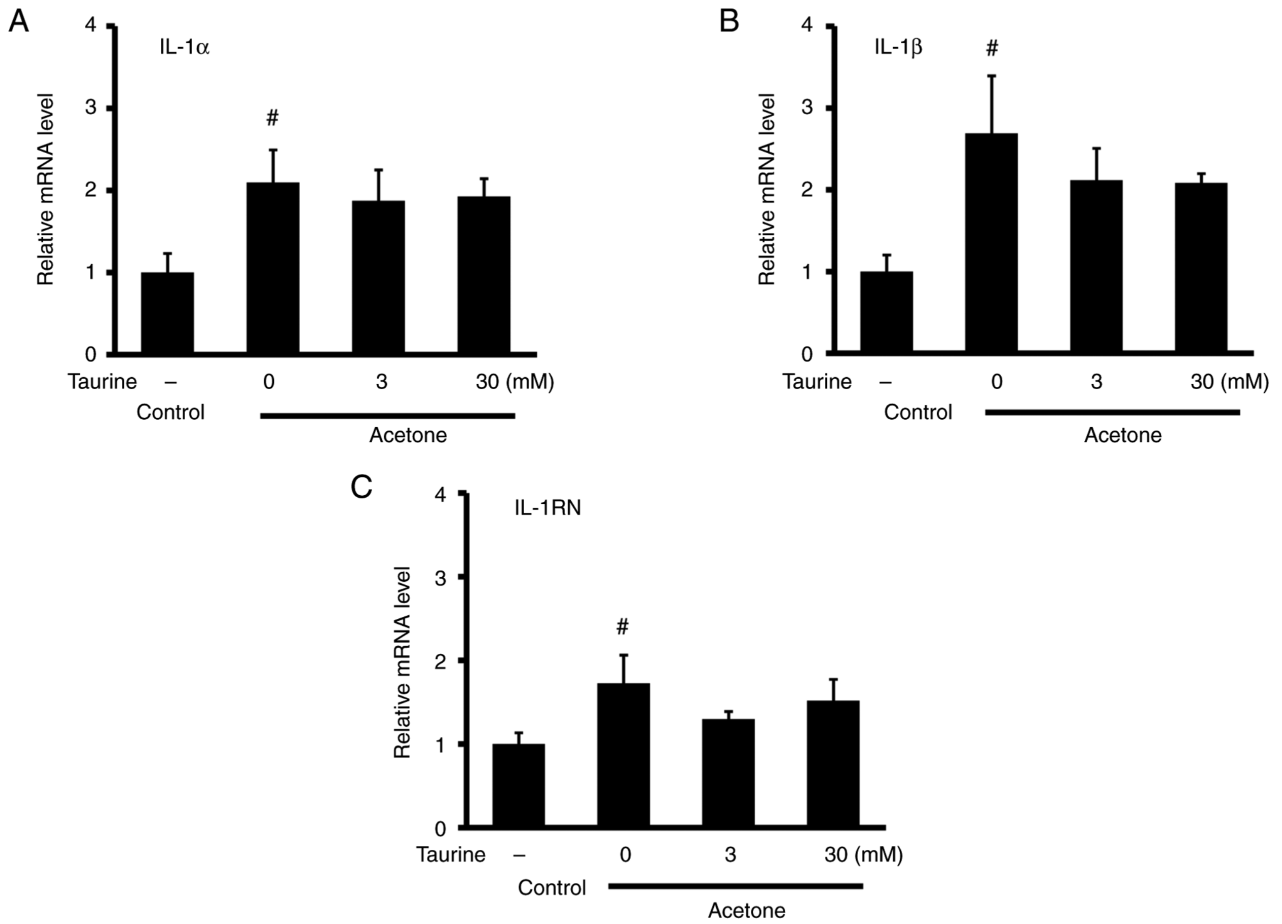


Figure 2. Effects of taurine on the mRNA expression of inflammatory factors in acetone-treated 3D cultured epidermis. The mRNA expression levels of (A) IL-1α, (B) IL-1β and (C) IL-1RN were analyzed using reverse transcription-quantitative PCR. Data are presented as the mean ± standard deviation (n=3). #P<0.05 vs. Control. IL-1RN, IL-1 receptor antagonist.

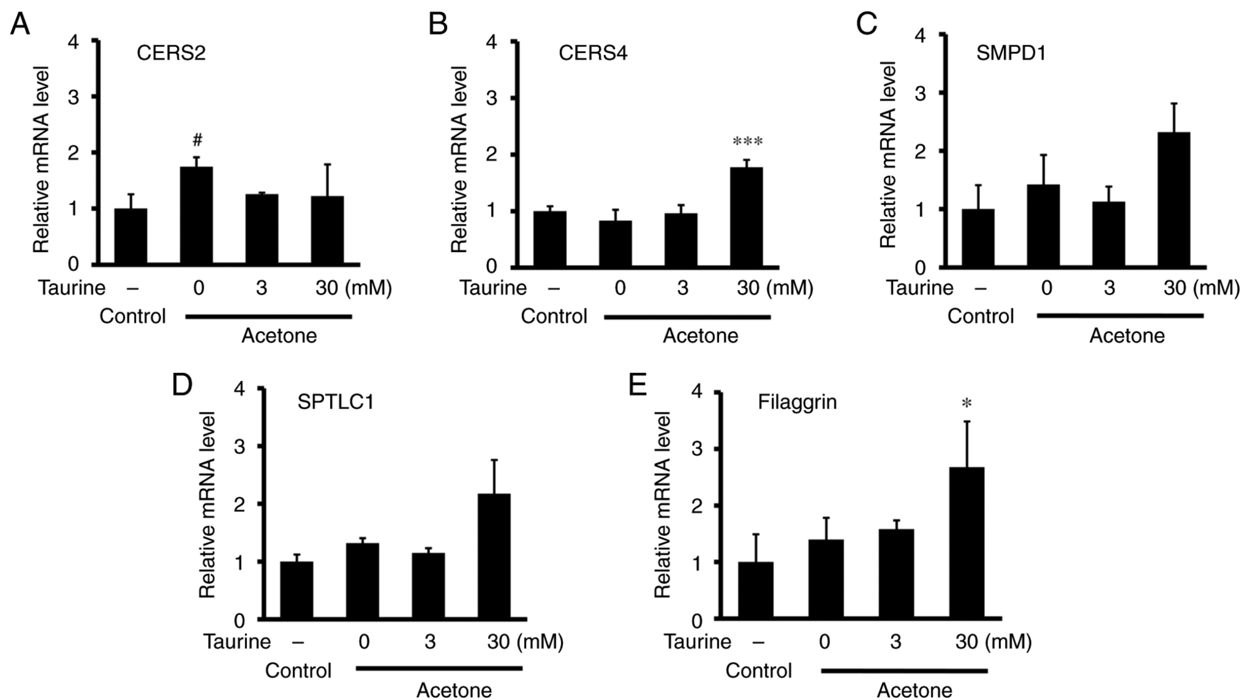


Figure 3. Effects of taurine on the mRNA expression of molecules related to the skin barrier in acetone-treated three-dimensional cultured epidermis. The mRNA expression levels of (A) CERS2, (B) CERS4, (C) SMPD1, (D) SPTLC1 and (E) Filaggrin were analyzed using reverse transcription-quantitative PCR. Data are presented as the mean ± standard deviation (n=3). *P<0.05 and ***P<0.001 vs. Acetone control (0 mM taurine). #P<0.05 vs. Control. CERS2, ceramide synthase 2; CERS4, ceramide synthase 4; SMPD1, sphingomyelin phosphodiesterase 1; SPTLC1, serine palmitoyl transferase long chain base subunit 1.

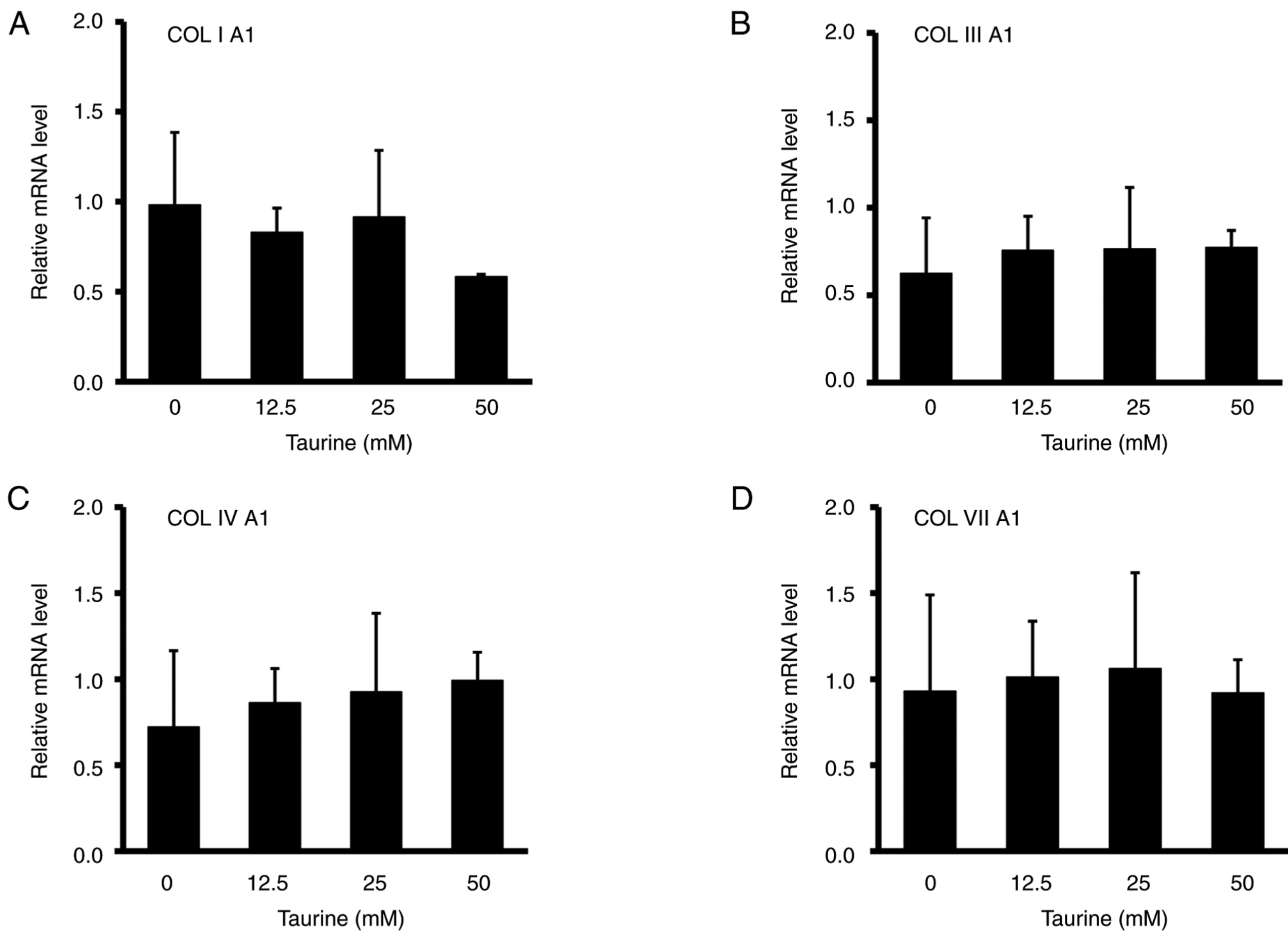


Figure 4. Effects of taurine on the mRNA expression of collagens in dermal fibroblasts. The mRNA expression levels of (A) COLIA1, (B) COLIIIA1, (C) COLIVA1 and (D) COLVIIA1 were analyzed using reverse transcription-quantitative PCR. Data are presented as the mean ± standard deviation (n=3). COLIA1, collagen type IA1; COLIIIA1, collagen type IIIA1; COLIVA1, collagen type IVA1; COLVIIA1, collagen type VIIA1.

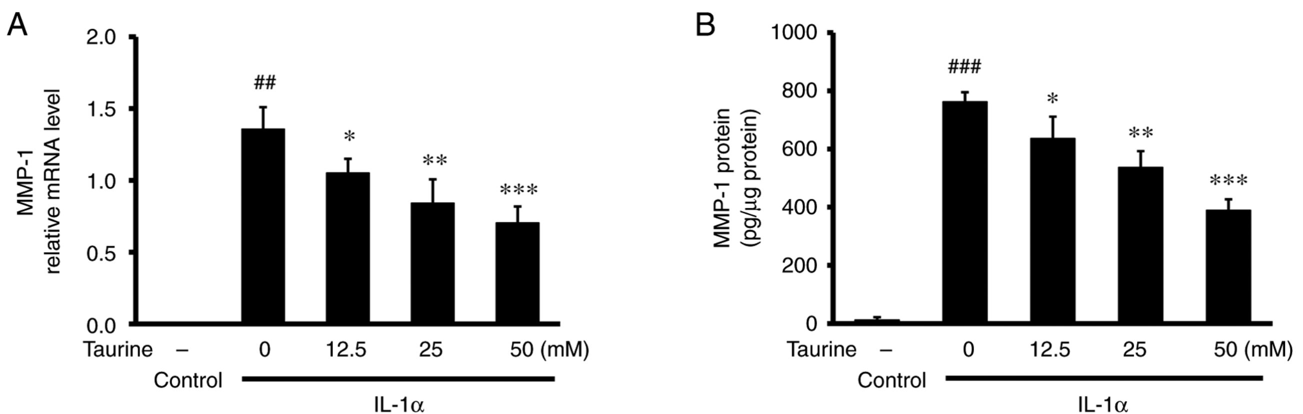


Figure 5. Effects of taurine on the mRNA and protein expression of MMP-1 in dermal fibroblasts. The levels of MMP-1 (A) mRNA and (B) protein expression were analyzed using reverse transcription-quantitative PCR and ELISA, respectively. Data are presented as the mean ± standard deviation (n=3). $^{*}$P<0.05, $^{**}$P<0.01 and $^{***}$P<0.001 vs. IL-1α control (0 mM taurine). $^{##}$P<0.01 and $^{###}$P<0.001 vs. Control.

human skin (20). A previous study also showed that the oral ingestion of taurine decreased UV beam-induced TEWL and suppressed the development of wrinkles in the skin of hairless mice (15). Furthermore, other previous animal experiments have demonstrated that oral taurine administration can restore the age-induced or UV-induced decline in the skin taurine content (15,21). Therefore, taurine supplementation may be beneficial for maintaining taurine levels and normal skin function. However, the mechanisms underlying the protective effects of taurine on the skin remain to be fully elucidated.

In the present study, TEWL, the mRNA expression levels of inflammatory cytokines and ceramide synthases were evaluated using an acetone-induced 3D cultured epidermis model. Acetone is known to disrupt skin barrier function by altering

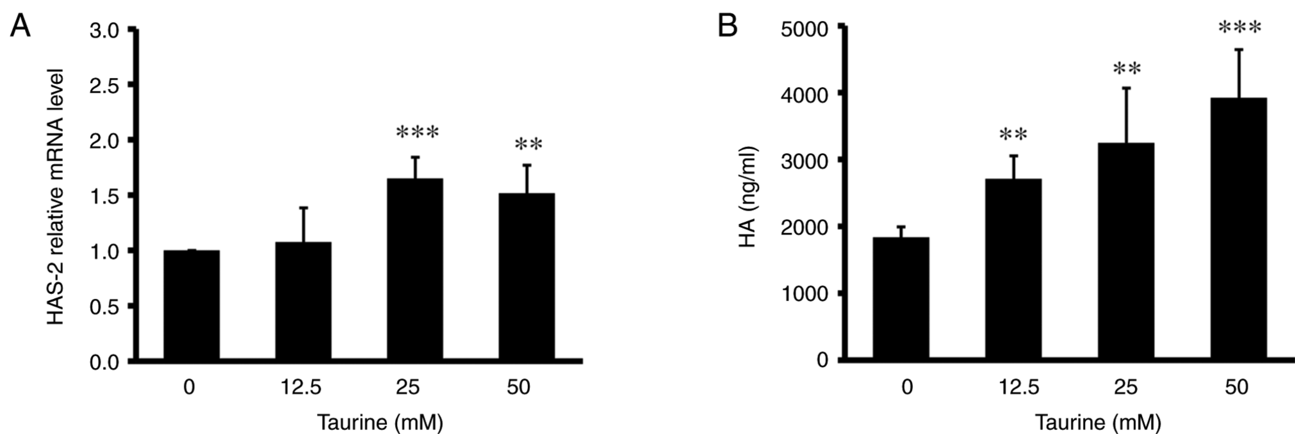


Figure 6. Effects of taurine on mRNA of HAS-2 and HA secretion in dermal fibroblasts. (A) mRNA expression levels of HAS-2 in the cells and (B) HA content in the medium were analyzed using reverse transcription-quantitative PCR and an ELISA, respectively. Data are presented as the mean ± standard deviation (n=3). **P<0.01 and ***P<0.001 vs. Control (0 mM taurine). HA, hyaluronic acid; HAS-2, HA synthase 2.

the composition of intracellular lipids, thereby increasing TEWL (22). Consistent with the results from previous animal and human studies (19,20), taurine was found to suppress the acetone-induced elevation of TEWL in the 3D cultured epidermis in the present study. When skin is irradiated with UV, the inflammatory cytokine IL-1α is produced (23). IL-1α acts on dermal fibroblasts to increase the production of MMP-1 (24). Although taurine treatment did not affect the acetone-induced inflammatory response as evidenced by the lack of changes in the mRNA expression of IL-1α, IL-1β and IL-1RN, it did increase the mRNA expression of the ceramide synthetic enzyme CERS4. Ceramides are fatty acids in the skin that facilitate the maintenance of the skin barrier and to retain moisture (25). Taurine was also found to increase the mRNA expression of filaggrin in the acetone-induced 3D cultured epidermis. Filaggrin is a major structural protein in the stratum corneum, which provides NMF to hydrate the skin and preserve barrier functions (4,26). The effects of taurine on ceramides have been previously reported. In the reconstructed epidermis, taurine was found to stimulate the synthesis of barrier lipids, including ceramides, cholesterol and fatty acids (20). Recently, taurine was reported to enhance the barrier function of the skin by stimulating the expression of tight junction proteins, including claudin 1, claudin 4 and occludin, in cultured human keratinocytes (27). These findings suggest that the moisture retention effects of taurine may be partially associated with the potentiation of barrier structure and function by stimulating tight junction protein expression and barrier lipid synthesis. Another recent study revealed that the regulation of osmotic pressure was important for the protective effects of taurine on the skin (21), since taurine was indicated to be a major organic osmolyte in living organisms (28). The present study raised the possibility that enhancement of barrier function by increasing ceramide and filaggrin synthesis may also be important for keratinocyte hydration induced by taurine.

HA is a major component of the ECM. In the skin, large quantities of HA reside in the dermal connective tissue, where they can regulate water balance (9). Reduction in the HA content is a major factor responsible for wrinkle formation and loss of skin elasticity (29). HA is synthesized by HASs, whereby three different HAS isoforms have been identified to date (30). Since HAS-2 is a critical isoform responsible for HA synthesis in dermal fibroblasts (31), the present study investigated the effects of taurine on the mRNA expression of HAS-2 in skin dermal fibroblasts. Taurine was observed to stimulate HAS-2 mRNA expression and increase the secretion of HA into the medium. These findings suggest that taurine can promote HA synthesis by upregulating HAS-2 mRNA expression. Considering the important role of HA in maintaining skin integrity, architecture and water balance, an increase in HA synthesis may be associated with the previously reported anti-wrinkle effect of taurine (15).

The dermis predominantly consists of ECM components, such as collagen, which is produced by fibroblasts (32). Collagen is the principal component of the dermis (32). Specifically, type I and III collagen are found in abundance (32). Fibroblasts form the primary cell type found within the dermis, where they serve important roles maintaining the normal structure and function (33,34). When the structure of the ECM becomes impaired with age or UV irradiation, collagen production also becomes impaired (35). MMPs are a family of zinc-containing proteinases that are involved in the degradation of ECM proteins. MMP gene expression was reported to be upregulated by UV radiation, aging and inflammatory cytokines (36,37). In human skin, MMP-1 is the major protease involved in the fragmentation of native collagens (38). In the present study, addition of IL-1α to skin dermal fibroblasts increased the mRNA expression of MMP-1, whilst taurine treatment suppressed the increase in a dose-dependent manner. Although the possibility that taurine can affect collagen secretion could not be ruled out, the present results suggest that taurine can at least exert an effect on collagen degradation.

Collagen degradation products and collagen fragments were reported to inhibit the expression of HAS-2 mRNA and HA synthesis in human skin fibroblasts (39). Collagen fragments are also known to inhibit collagen synthesis (40). In the present study, taurine suppressed the degradation of collagen by inhibiting MMP-1, whilst taurine also increased the expression of HAS-2 mRNA. These findings suggest that the stimulation of HAS-2 mRNA expression by taurine is associated with the inhibition of the MMP-1 expression and the subsequent suppression of collagen degradation.

In summary, the present study using cultured cells revealed that taurine stimulated the expression of the skin barrier components, including CERS4 and filaggrin. Furthermore, taurine upregulated HA synthesis. These findings suggest that enhancement of the epidermal barrier function, dermal water retention and elasticity may contribute to the beneficial effects of taurine on the skin. Since the present study was conducted using cultured skin cells, it is necessary to confirm whether these mechanisms of action are also in place *in vivo*. In addition, taurine has an important role in the skin as an organic osmolyte. Therefore, its relevance to the results of the present study requires verification.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

TY, TS, TN and SM conceived and designed the experiments. TY, CM, JIN and TS performed the experiments and analyzed the data. TY and SM wrote the manuscript. TY and SM confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

**Ethics approved and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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