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Original

TGF-β promotes retinal pigment epithelial cell migration via MRTF-pathway

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Abstract

Some retinal pigment epithelial (RPE) cells migrate and cause proliferative vitreoretinopathy and age-related macular degeneration. Transforming growth factor-β (TGF-β) is a major factor in these diseases and promotes cellular migration in RPE cells. Myocardin-related transcription factor A (MRTF-A) is a key factor in cell migration that regulates actin-associated proteins, such as gelsolin. In this study, we examined whether MRTF-A and gelsolin are related to the promotion of cellular migration in RPE cells induced by TGF-β. Using a wound-healing assay, the migration of adult retinal pigment epithelial cell line-19 (ARPE-19) cells treated with both 12.5 ng/ml TGF-β2 and/or 3 μM CCG-203971, an inhibitor of MRTF-A, or 0.1% DMSO (vehicle) was measured 24 h after wounding. The expression levels of gelsolin were examined by quantitative real-time PCR and western blot. TGF-β2 led to increased migration of ARPE-19 cells. This promotion of cell migration was diminished by CCG-203971. TGF-β2 led to increased gelsolin mRNA and protein expression in ARPE-19 cells. These expression levels were also reduced by CCG-203971. These results suggest that the MRTF-A pathway is related to TGF-β-induced promotion of ARPE-19 cell migration.

Key words: retinal pigment epithelial cells, migration, myocardin-related transcription factor A, transforming growth factor-β, CCG-203971

I. Introduction

In some proliferative retinal diseases, such as proliferative vitreoretinopathy [1, 2] and age-related macular degeneration [3-5], retinal pigment epithelial (RPE) cells migrate and produce extracellular matrix, mainly composed of type I collagen [6]. These RPE cells express α-smooth muscle actin, a myofibroblast biomarker [7]. This transdifferentiation is recognized as epithelial-mesenchymal transition (EMT) and causes severe visual disturbances [2, 8].

Transforming growth factor-β (TGF-β) is a major factor in the EMT of RPE cells [2, 8-10]. TGF-β not only induces α-smooth muscle actin and type I collagen production [11-13] but also

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promotes cellular migration in RPE cells [12, 14-18].

Myocardin-related transcription factor A (MRTF-A), a transcriptional coactivator, is a master regulator of EMT and a potent inducer of the myofibroblast phenotype [19]. It interacts with serum response factor (SRF) to promote the expression of type I collagen and α-SMA in various types of cells related to EMT [19-24]. Moreover, MRTF-SRF activity also influences the actin cytoskeleton and cell motility by controlling the expression of proteins that regulate the state of F-actin reorganization and actin polymerization [25], such as gelsolin [26], one of the most important actin-binding proteins [27].

TGF-β activates MRTF-A by translocation from the cytoplasm into the nucleus in RPE cells, and promotes the expression of α-SMA and type I collagen via the MRTF-A pathway. However, it is unknown whether the MRTF-A pathway is related to the promotion of RPE cell migration induced by TGF-β. To explore this possibility, we examined the effects of CCG-203971, an MRTF-A inhibitor, on RPE cell migration and gelsolin expression induced by TGF-β.

II. Methods

1. ARPE-19 cell culture

Human retinal pigmented epithelial (ARPE-19) cells were purchased from American Type Culture Collection (ATCC; Rockville, MD, USA). They were cultured in Dulbecco's modified Eagle's medium (DMEM) (Nacalai Tesque, Inc., Kyoto, Japan) containing 10% (v/v) fetal bovine serum (FBS) (GE Healthcare Life Sciences, South Logan, Utah, USA) in a humidified atmosphere of 5% CO_2 at 37℃. To authenticate the cell line, a short tandem repeat (STR) analysis was performed by BEX Co., Ltd. (Tokyo, Japan) using the GenePrint 10 System (Promega, Madison, WI, USA).

Confluent ARPE-19 cells were cultured in DMEM without FBS. Then, the cells were treated with 12.5 ng/ml TGF-β2 (Sigma, St. Louis, MO, USA) for 24 h. CGG203971 was dissolved in ethanol and diluted with DMEM to 3 μM (0.1% ethanol). Confluent ARPE-19 cells were treated with either 3 μM CGG203971 or 0.1% ethanol (vehicle) 1 h after TGF-β2 treatment.

2. RNA preparation and RT-PCR analysis

Total RNA from ARPE-19 cells was prepared using ISOGEN reagent (NIPPON GENE, Toyama, Japan). According to the manufacturer's protocol, cDNAs were prepared from 1 μg of total RNA using PrimeScript reverse transcriptase (Takara Bio, Kyoto, Japan). PCR amplification was performed using ExTaq polymerase (Takara Bio) at 30 cycles, with each cycle consisting of denaturation at 94℃ for 0.5 min, annealing at 60 ℃ for 0.5 min, and extension at 72 °C for 1 min. Quantitative real-time-PCR (RT-PCR) was carried out using the EcoTM RT-PCR system (Illumina, San Diego, CA, USA) according to the manufacturer's instructions. The primers used were 5′- ATTGCCGACCGAATGCAGAAG -3′ (sense); 5′ - AGAGGCCAGGATGGAGCCAC -3′(antisense) for human smooth muscle actin (ACTA2); 5-TGGACCAGCAGACTGGCAAC -3′ (sense); 5′ - TCGTGCAGCCATCGACAGTGAC -3′ (antisense) for human collagen type 1A; 5′ - ACGGACCCAGCCAATCG -3′ (sense); 5′- CATCATCCCAGCCAAGGAA -3 (antisense) for human gelsolin; and 5′ - AGGTCATCCATGACAACTTTG -3′ (sense) and 5′ - TTCAGCTCAGGGATGACCTT -3′ (antisense) for mouse GAPDH.

3. Wound-healing assay

Confluent ARPE-19 cells were cultured in DMEM without FBS. The cells were scraped in a straight line to create a "wound" with a p200 pipet tip. One hour before scraping, the cells were treated with 12.5 ng/ml TGF-β 2 (Sigma, St. Louis, MO, USA) and/or 3 μM CCG-203971(Cayman Chemical, Ann Arbor, MI, USA) or 0.1% DMSO (vehicle). CCG-203971 was dissolved in DMSO and diluted with DMEM to 3 μM (0.1% DMSO). The cells treated with only 0.1% DMSO were used as controls. The migration of the cells to fill the wound was monitored by recording images over the course of 24 h. The wound area was measured using ImageJ 1.38x public domain software.

4. Cell proliferation assay

Cellular proliferation was measured following bromodeoxyuridine (BrdU) incorporation, as described previously [30]. Cultures were incubated with 10 μM BrdU for 2 h. Cells were then fixed and stained for BrdU using streptavidin–biotin (Invitrogen, Carlsbad, CA, USA), and labeled cells were counted using ImageJ.

5. Miscellaneous methods

Sample preparation for western blotting, gel preparation, and electrophoretic conditions was performed as described previously [31]. Western blot analyses were carried out using an anti-gelsolin antibody (G4896, Sigma, St. Louis, MO, USA) and an anti-GAPDH antibody (Chemicon International, Temecula, CA, USA). The band intensity in the immunoblot was semiquantified using ImageJ software.

6. Statistics

Data are presented as the mean ± standard error. The unpaired Student's t-test, one-way ANOVA followed by a post hoc comparison using Fisher's least significant difference (LSD) test and post-hoc Scheffe test were used for statistical analysis with KaleidaGraph version 4.1 software (Synergy Software, Reading, PA, USA). A level of $p < 0.05$ was considered statistically significant.

III. Results

To assess the effects of TGF-β2 and MRTF-A on ARPE-19 cell migration, we performed an *in vitro* wound-healing assay. Twenty-four hours after scratching, untreated ARPE-19 cells (control) covered 43.4 ± 3.1% of the original area. In the presence of 12.5 ng/ml TGF-β 2, the covered wound area (54.7 ± 3.6%) was significantly larger than that in the control dishes. This promotion by TGF-β2 was abolished by 3 μM CCG-203971 (38.6 ± 2.4%), an MRTF-A inhibitor (Fig. 1A, B). TGF-β 2 stimulated ARPE19 cell migration to about 1.2 folds over that elicited by untreated ARPE-19 cells (control). However, CCG-203971 abolished the TGF-β 2-induced ARPE19 cell migration. These observations indicate that CCG-203971 is effective in the prevention of TGF-β 2-induced ARPE19 cell migration.

The proliferation of ARPE-19 cells was determined by measuring the DNA synthesis rate. The percentages of BrdU incorporation were 0.95% in untreated ARPE-19 cells (control) to 0.79% in 3 μM CCG-203971 treated cells, 0.75% in 12.5 ng/ml TGF-β 2 treated cells and 0.63% in 12.5 ng/ml TGF-β 2 with 3 μM CCG-203971 treated cells, respectively. Compared with untreated ARPE-19 cells (control), treatment with 12.5 ng/ml TGF-β 2 or 3 μM CCG-203971 significantly diminished DNA synthesis (Fig. 2).

To determine whether TGF-β 2 affects the expression of gelsolin and whether MRTF-A is related to these expression levels, we cultured

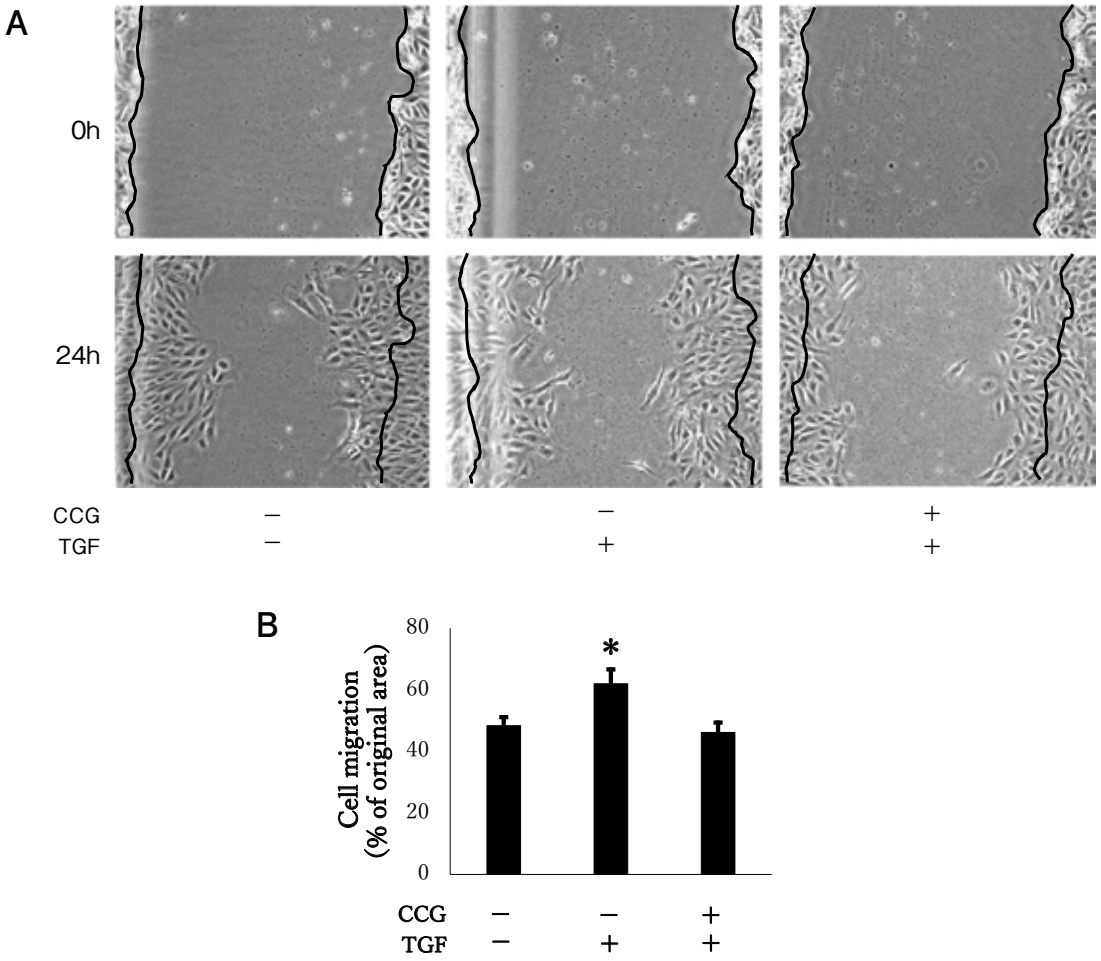

Fig. 1. Representative images of the scratch wound at 0 and 24 h after wounding (A). Wound closure areas at 24 h after wounding ($p = 0.0022$; one-way analysis of variance). TGF-β2 promoted wound closure, but CCG-203971, an MRTF-A inhibitor, diminished this promotion. Data are represented as the means ± SEMs of five independent experiments. CCG: 3 μM CCG-203971, TGF: 12.5 ng/ml TGF-β2.
* Significant differences were detected between cells treated with 12.5 ng/ml TGF-β2 and other two groups (post-hoc Scheffe test) (B). bar 100 μm.

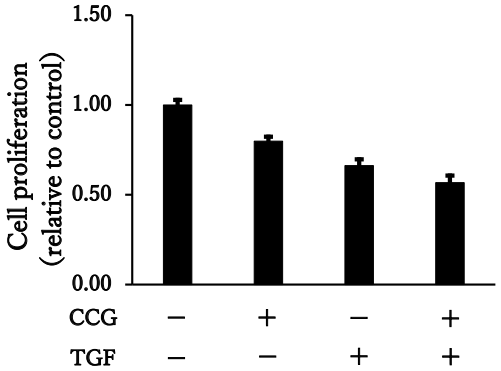

Fig. 2. The effect of TGF-β2 and CCG-203971 on ARPE-19 cell proliferation ($p < 0.0001$; one-way analysis of variance). Both decreased control proliferation. CCG: 3 μM CCG-203971, TGF: 12.5 ng/ml TGF-β2. Data are presented as the means ± SEMs of three independent experiments. Significant differences were detected between all groups, except between cells treated with only 12.5 ng/ml TGF-β and 3 μM CCG-203971 (Fisher's LED test).

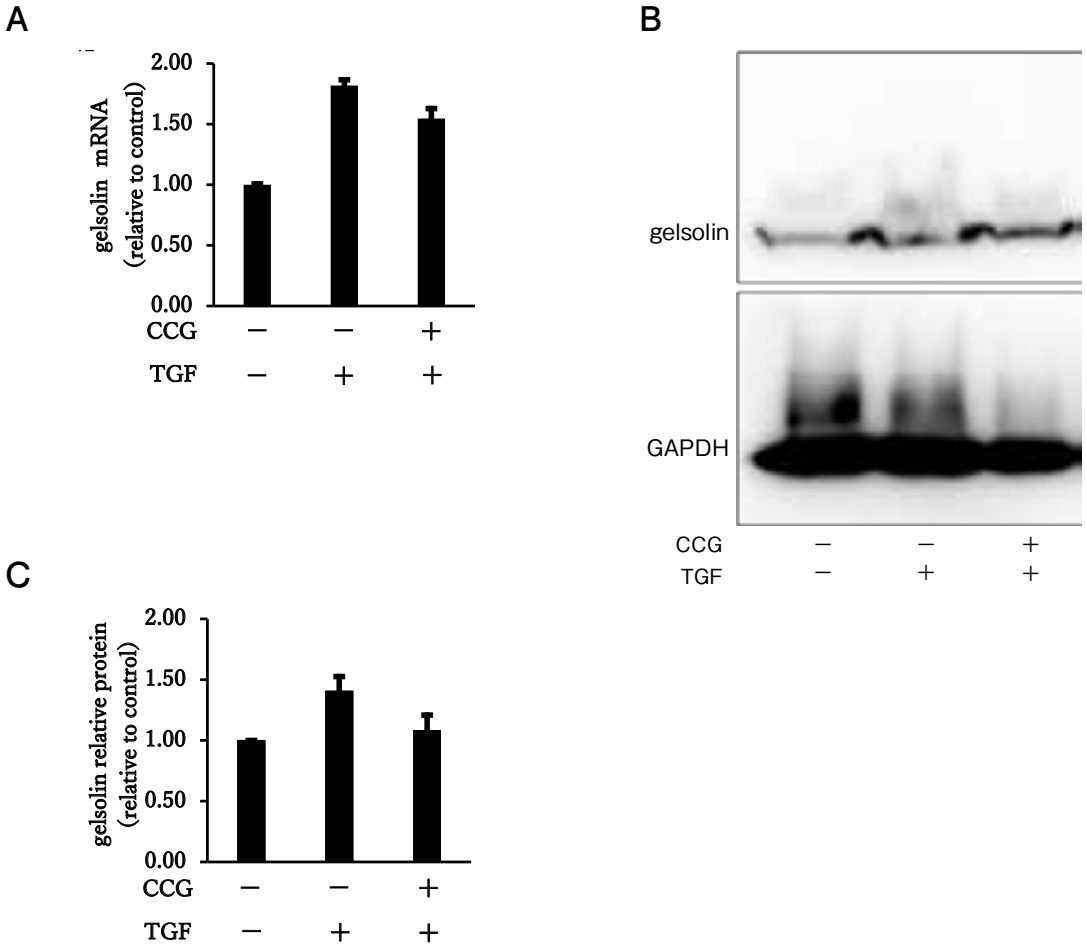

Fig. 3. The effect of CCG-203971 on gelsolin mRNA (A) and protein expression (B, C) in ARPE-19 cells stimulated with TGF-β2 ($p < 0.0001$ and $p = 0.0023$, respectively; one-way analysis of variance). Treatment with 12.5 ng/ml TGF-β2 increased gelsolin mRNA and protein expression levels in the cells, as determined by qRT-PCR or western blot, respectively. Densitometric analysis of the resulting bands, normalized to GAPDH is shown in (C). CCG-203971 decreased this promotion. CCG: 3 μM CCG-203971, TGF: 12.5 ng/ml TGF-β2. Data are presented as the means ± SEMs of three independent experiments. Significant differences were detected between all groups (A, C), except protein level (C) between control cells and cells treated with both 12.5 ng/ml TGF-β and 3 μM CCG-203971 (Fisher's LED test).

TGF-β2-treated (12.5 ng/ml) ARPE-19 cells in the presence or absence of CCG-203971 (3 μM). Indeed, TGF-β2 significantly induced the mRNA expression of gelsolin by 1.82 folds. Conversely, CCG-203971 treatment downregulated gelsolin mRNA expression by 15% (Fig. 3A). Moreover, TGF-β2 significantly induced the protein expression of gelsolin by 1.41 folds. Conversely, CCG-203971 treatment downregulated gelsolin protein expression by 23% (Fig. 3B, C). These observations indicate that CCG-203971 is effective in the prevention of TGF-β2-induced expression of gelsolin.

IV. Discussion

In this study, TGF-β2 led to increased ARPE-19 cell migration but decreased cell proliferation. CCG-203971, an MRTF-A inhibitor, diminished this promotion of cell migration. TGF-β2 led to increased gelsolin mRNA and protein expression in ARPE-19 cells. These expression levels were diminished by CCG-203971. These results suggest that the MRTF-A pathway is related to TGF-β-induced promotion of ARPE-19 cell migration.

In this study, TGF-β2 led to increased migration of ARPE-19 cells. This increase was abolished by CCG-203971, an MRTF-A inhibitor, suggesting that the promotion of migration by TGF-β is dependent on the SRF-MRTF-A pathway. However, TGF-β was reported to promote RPE cell migration by other factors. TGF-β induced activation of Rho, which indicated cytoskeletal changes, and filopodia formation affected cell motility [32] in RPE cells [33]. TGF-β affected integrin-mediated cell adhesion [34] and stimulated RPE cell migration due to increased release of MMPs [35]. Some related pathways may crosstalk with each other [7, 36-38]. The motility of RPE cells might also be regulated by these factors.

Gelsolin severs and caps actin microfilaments depending on calcium and plays a pivotal role in actin cytoskeleton remodeling, and affects cell motility [39]. A reduction in gelsolin expression by siRNA knockdown in pancreatic cancer cells resulted in a decrease in cell motility [40]. Conversely, gelsolin overexpression resulted in increased motility in various cells, such as NIH 3T3 fibroblasts, pancreatic cancer cells, and MDA-MB-231 breast cancer cells [40, 41]. Moreover, TGF-βincreased the expression of gelsolin and the migration of breast cancer cells [41], which is consistent with our results. These findings suggested that gelsolin may play an important role in RPE cell migration.

We examined the role of MRTF-A in RPE cell migration based on gelsolin expression. However, MRTF affects cell motility by regulating actin homeostasis because actin is the main transcriptional target of MRTF-SRF transcription [25]. MRTF is also related to the expression of cofilin [42], another actin-severing protein, and myosin light chain 9 [43], affecting actomyosin contractility [25]. These factors may be related to RPE migration promoted by TGF-β.

In conclusion, CCG-203971, an MRTF-A inhibitor, diminished the promoting effects of TGF-β2 on cell migration and gelsolin mRNA and protein expression in ARPE-19 cells. These results suggested that MRTF-A may play a pivotal role in the motility of RPE cells and imply the possibility of MRTF-A inhibitor administration as a novel PVR and AMD treatment.

Conflict of Interest: The authors have no conflict of interest to declare.

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TGF-βはMRTFの経路を介して網膜色素上皮細胞の遊走を促進する

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要旨

一部の網膜色素上皮細胞（RPE）の遊走が網膜疾患に関連している．これらの疾患では，トランスフォーミング増殖因子（TGF）-βがRPEの遊走を促進する主要な因子である．ミオカルディン関連転写因子（MRTF）-Aは gelsolin などのタンパク質を発現し遊走にも影響する．今回，MRTF-Aや gelsolin がTGF-βによるRPEの遊走促進へ関連しているか検討した．ヒト網膜色素上皮細胞株（ARPE-19）をTGF-β2と，MRTF-A阻害剤CCG-203971で処理し，ARPE-19細胞の遊走を wound-healing test を用いて，Gelsolinの発現はリアルタイムPCRと western blot を用いて検討した．TGF-β2はARPE-19の遊走と gelsolin の発現を促進し，CCG-203971によりこの促進が抑えられた．よってTGF-β2のARPE-19細胞の遊走促進にMRTF-Aの経路が関連している可能性が示唆された．