InnoVationinfo

Journal of
Health Science and Development

ISSN: 2581-7310
Volume 7: 1
J Health Sci Dev 2024

Differences in Extracellular Matrix Protein Accumulation between TGFβ Isoforms in Trabecular Meshwork

Chen-Yu Xu[1,2,3]

Jia-Hong Wei[1,4]

Si-Yu Zhao[1,4]

Dan Song[1]

Ming-Min Hou[1]

Tao Guo[*1,2,3]

[1]*Bengbu Medicine College, Bengbu 233030, Anhui, China*

[2]*Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

[3]*Shanghai Key Laboratory of Orbital Diseases and Ocular Oncology, Shanghai 200011, China*

[4]*Department of Ophthalmology, Tongji Hospital Affiliated with Tongji University School of Medicine, Shanghai, China.*

Abstract

Primary open-angle glaucoma (POAG) is a prevalent formation of glaucoma primarily caused by the accumulation of extracellular matrix (ECM) in the trabecular meshwork (TM). The abnormal deposition of ECM components leads to TM fibrosis and elevated intraocular pressure. Transforming growth factor β (TGFβ) is a crucial driver of ECM accumulation and is overexpressed in TM tissues of POAG patients. However, there is no information available about the unique functions of TGFβ1 and TGFβ2 isoforms in TM fibrosis. In this current study, we have discovered that both TGFβ1 and TGFβ2, at the same concentration, contribute to excessive ECM protein deposition in human TM cells. Relative to TGFβ1, TGFβ2 exhibits heightened efficacy in instigating the accumulation of ECM proteins and the expression of TGFβ receptor (TGFBR) 2. Notably, this proclivity for ECM protein induction by TGFβ2 was not observed in A549 and ARPE-19 cells. Conclusively, our results indicate that TGFβ2 contributes significantly to the ECM protein accumulation specifically in TM, potentially associated with alterations in TGFBR2.

Keywords: Extracellular matrix, Trabecular meshwork, Transforming growth factor β, Transforming growth factor β receptors, Primary open-angle glaucoma.

Introduction

Glaucoma is a type of advanced optic nerve disease and it is the world's leading cause of irreversible blindness. The disease is commonly characterized by slow progressive degeneration of retinal ganglion cells and development of axon recession, which causes optic disc damage and is associated with decreased vision. It's estimated that 112 million individuals globally would suffer from glaucoma by 2040 [1]. A prevalent kind of glaucoma known as primary open angle glaucoma (POAG) is defined by damage to the characteristic glaucomatous optic papilla and visual field, as well as an intraocular pressure (IOP) of 21 mmHg or above in at least one eye that appears normal [2,3]. The primary factor contributing to the rise of IOP in POAG is the trabecular meshwork's (TM) aqueous humor (AH) outflow resistance, which is intimately linked to the accumulation of extracellular matrix (ECM) proteins and a

Article Information

Article Type: Research Article

Article Number: JHSD-155

Received Date: 19 February, 2024

Accepted Date: 14 March, 2024

Published Date: 21 March, 2024

***Corresponding author:** Tao Guo, Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 639 Zhizaoju Road, Huangpu, Shanghai 200011, China.

Citation: Guo T, Xu CY, Wei JH, Zhao SY, Song D, Hou MM (2024) Differences in Extracellular Matrix Protein Accumulation between TGFβ Isoforms in Trabecular Meshwork. J Health Sci Dev Vol: 7, Issue: 1 (19-27).

decrease in phagocytosis [4-7].

Transforming growth factor β (TGFβ), a member of the transforming growth factor superfamily has three isoforms: TGFβ1, TGFβ2, and TGFβ3. All members can combine with TGFβ receptor (TGFBR) 2 and then recruit and activate TGFBR1, which activates the TGFβ signaling pathway [8,9]. Multifunctional mediator TGFβ influences the proliferation, migration, adhesion, differentiation and apoptosis of various cell types, including neutrophils, dendritic cells, activated T and B cells, macrophages and immature hematopoietic cells [10, 11]. It is commonly recognized that TGFβ is a critical factor regulating ECM-protein accumulation and it is widely expressed in fibrotic eye, kidney, liver, heart, lung and other tissues [8,12-18]. In intraocular tissues, induction of TM cells by TGFβ1 and TGFβ2 can lead to epithelial-mesenchymal transition and ECM-protein accumulation [19-21]. During fibrosis, the TGFβ isoforms have the same function and induce fibroblast activation and ECM-protein accumulation, and inhibit ECM-protein degradation by activating the classical Smad signaling pathway [8,12,15-17].

Another function of TGFβ1 is the promotion or inhibition of microRNA (miRNA) changes to stabilize mesenchymal gene translation and reduce antifibrotic pathways [22]. In addition to fibrosis, TGFβ1 protects cardiomyocyte apoptosis by participating in the p42/p44 mitogen-activated protein kinase signaling pathway [23]. TGFβ2 induces expression and secretion of thrombospondins (TSP)-1, which activate TGFβ2 that then binds to many ECM proteins such as type IV collagen (COL-IV), fibronectin (FN) and laminin (LN) in vivo. TSP-1 function can be inhibited by TSP-2 competitive binding to TGFβ2 [24, 25]. Accordingly, there may be a local positive feedback autocrine loop where increased production of TGFβ2 causes TSP-1 secretion, and subsequently activates ECM-sequestered TGFβ2, which is competitively inhibited by TSP-2 [26].

TGFBR has three isoforms, namely TGFBR1, TGFBR2, and TGFBR3. Although TGFBR3 lacks kinase activity, TGFBR1 and TGFBR2 are dual-specificity kinases, functioning as both tyrosine and serine/threonine kinases [9]. TGFBR1 plays a pivotal role as the essential mediator for transmitting extracellular signals to the TGFβ signaling pathway, and it is susceptible to phosphorylation at numerous sites [9]. Activated TGFBR1 can phosphorylate downstream Smad2 and Smad3, or noncanonical signaling, such as Rho-ROCK, PI3K-Akt, P38/JNK [27]. TGFBR2 is a constitutively active kinase that does not depend on ligand binding, phosphorylation, TGFBR1 or other receptors [9]. The canonical TGFβ signal is stimulated when TGFβ combines with TGFBR2, thereby recruiting TGFBR1 which is then phosphorylated by TGFBR2, and further phosphorylates Smad2/3 [28-31].

According to the ECM-protein accumulation of TM, our research group successfully tested various types of clinically confirmed patients with glaucoma including: acute angle closure glaucoma, chronic angle closure glaucoma, primary angle closure glaucoma and POAG during ophthalmic surgery. The concentration of bioactive TGFβ2 was quantified utilizing the ELISA technique [32]. The research findings demonstrated that the expression of TGFβ2 is specifically elevated in the AH of individuals diagnosed with POAG, aligning with previous studies on this subject matter [33-35]. Furthermore, our study provided evidence that the administration of salidroside and osthole effectively mitigated the TGFβ2-induced accumulation of ECM proteins in human TM cells and resulted in a reduction in IOP [36,37]. The above-mentioned results indicate that TGFβ2 causes the accumulation of ECM proteins (COL-IV, FN and LN), which have the potential to increase AH outflow resistance and further cause IOP elevation in patients diagnosed with POAG [24,38,39].

The eyes of individuals diagnosed with POAG exhibit significantly elevated levels of TGFβ2 expression. Nevertheless, limited studies have reported an enhanced expression of TGFβ1 in the TM tissues or AH of patients diagnosed with POAG, and there is no study on the differences between the two isoforms in promoting ECM-protein accumulation in TM [33,35,40-44]. Therefore, it is imperative to investigate the effect of inhibiting TGFβ isoforms on accumulation of ECM proteins in TM for the potential treatment of POAG. We aimed to compare the differences in the expression of COL-IV, FN and LN proteins in human TM cells after induction by TGFβ1 and TGFβ2 isoforms, and to preliminarily explore the mechanisms causing the differences in the ECM protein levels.

Materials and Methods

Ethical approval

All experiments complied with the Declaration of Helsinki and trabecular meshwork samples from patients were acquired from Shanghai Jiao Tong University School of Medicine's Ninth People's Hospital after the institutional research ethics board granted its clearance (No. SH9H-2019-TK204-1)

Cell culture and treatment

Primary human TM (HTM) cells were derived from human trabecular meshwork tissue obtained from ophthalmic surgery and processed in passages 3 to 9. The cells were cultured and identified essentially as described in detail previously [36,37,45]. The human lung cancer cell line A549 and human retinal pigment epithelial cell line ARPE-19 were cultured at 37°C in 5% CO_2 using DMEM medium containing 10% FBS.

Induction of TGFβ1 and TGFβ2

All treatments were performed when cells made up approximately 80% of the dish. Cells were serum-starved for 24 h using Dulbecco's modified Eagle's medium without FBS. Subsequently, the cells were induced by TGFβ1 or TGFβ2 (5 ng/ml, MedChemExpress) for 48 h.

Real time quantitative PCR (RT-qPCR)

The RNA extraction from HTM cells was performed using Trizol (Takara, Tokyo, Japan) followed by cDNA synthesis using the PrimeScript™ RT Reagent Kit (Takara) according to the manufacturer's instructions. RT-qPCR was performed using SYBR Green Master Mix (Qiagen, Inc., Valencia, CA,

USA) to assess mRNA levels. The internal control human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used to standardize the results from HTM cells. Table 1 displays the primer sequences that were employed in the qPCR experiments.

Western blot analysis (WB)

The RIPA lysis buffer (Invitrogen) was used with protease and phosphatase inhibitor cocktails (5872; Cell Signaling Technology, CST) to isolate cellular content from HTM cells. The operation procedure has been described in previous study [36,37]. Subsequently, using the ECL Plus Western Blot Detection Kit (Tanon), the membranes were processed using the Omni-ECL™ Femto Light Chemiluminescence Kit (Epizyme Biotech, China), scanned, and then quantified by gray values using ImageJ software. Primary antibodies included COL-IV (Abcam), FN (Abcam), LN (Abcam) and rabbit GAPDH polyclonal antibody (CST). Total antibodies were diluted with Antibody Signal Enhancer (Merck) or Universal Antibody Diluent (New Cell & Molecular Biotech, NCM).

Immunocytochemistry (ICC)

In 24-well plates, HTM cells were inserted on coverslips, fixed with 4% PFA for 30 min at 4°C, permeabilized with 0.5% Triton X-100, and blocked for 1 h at 4°C with 10% goat serum. Subsequently, the primary antibodies (COL-IV, FN and LN polyclonal antibody) and fluorescent secondary antibody (Invitrogen) were added to cells as described in previously research [36,37]. Finally, the fluorescence images were captured under the fluorescence microscope (Nikon).

Target Genes	RT-PCR Primer Sequences	
	Forward Primer (5'-3')	Reverse Primer (5'-3')
FN (human)	TGACAAGCAGACCAGCTCAG	TTGGTGGGCTGACATTCTCC
LN (human)	CTAATCCTCGGGGTTGCACA	CGCCACCCATCCTCATCAAT
COL-IV (human)	GGCTGGTGAGCCAGGTTTTA	TTTGCGCCCAGGTATCCTTT
GAPDH (human)	CGAGATCCCTCCAAAATCAA	GTCTTCTGGGTGGCAGTGAT

Table 1: The Primer Sequences for RT-PCR.

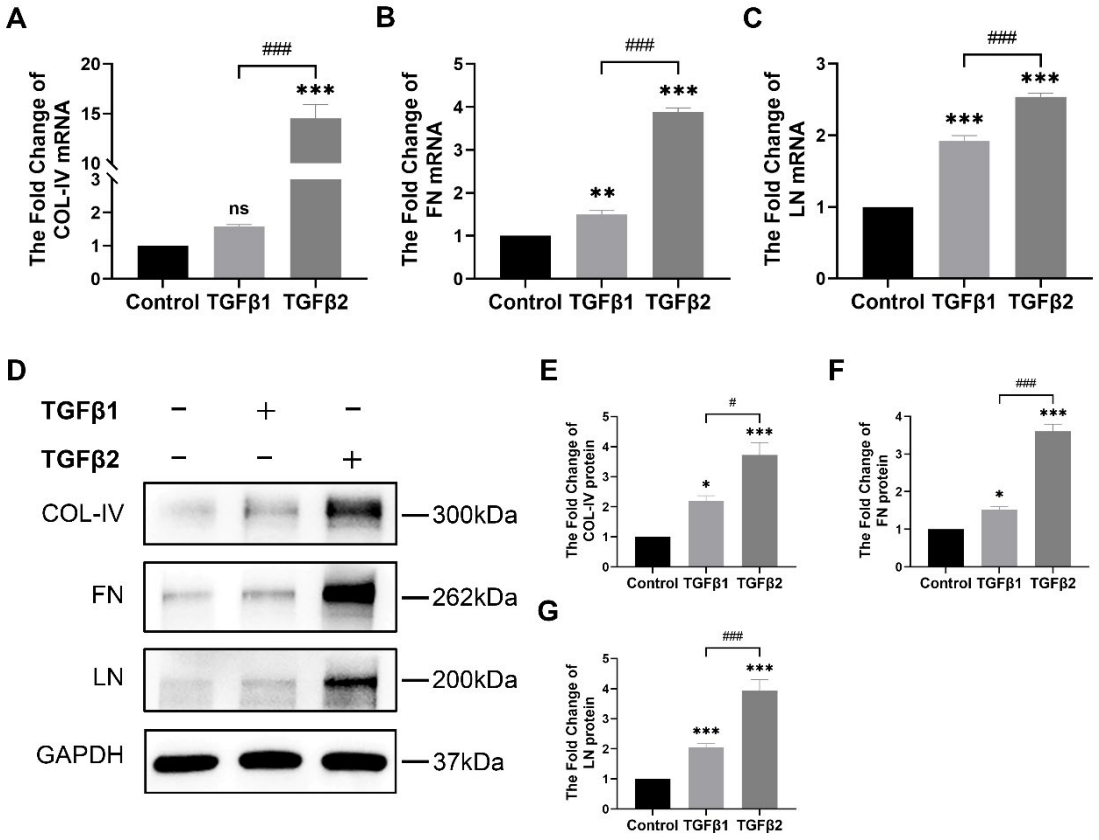

Figure 1: TGFβ1 and TGFβ2 effects on ECM expression in HTM cells. TGFβ2 has stronger effect on ECM than TGFβ1. The mRNA level of COL-IV(**A**), FN (**B**) and LN (**C**) in HTM cells with TGFβ1 and TGFβ2 treatment. (**D**) The ECM proteins in TGFβ1 and TGFβ2-treated HTM cells as determined by WB. The statistical result of WB regarding COL-IV (**E**), FN (**F**) and LN (**G**) proteins. All results used 2 HTM cell strains. Error bars: mean ± SEM (n = 3-5). *P < 0.05, **P < 0.01, ***P < 0.001 compared to control, $^{\#}$P < 0.05, $^{\#\#\#}$P < 0.001 compared to TGFβ1, ns = no statistical significance, one-way ANOVA test.

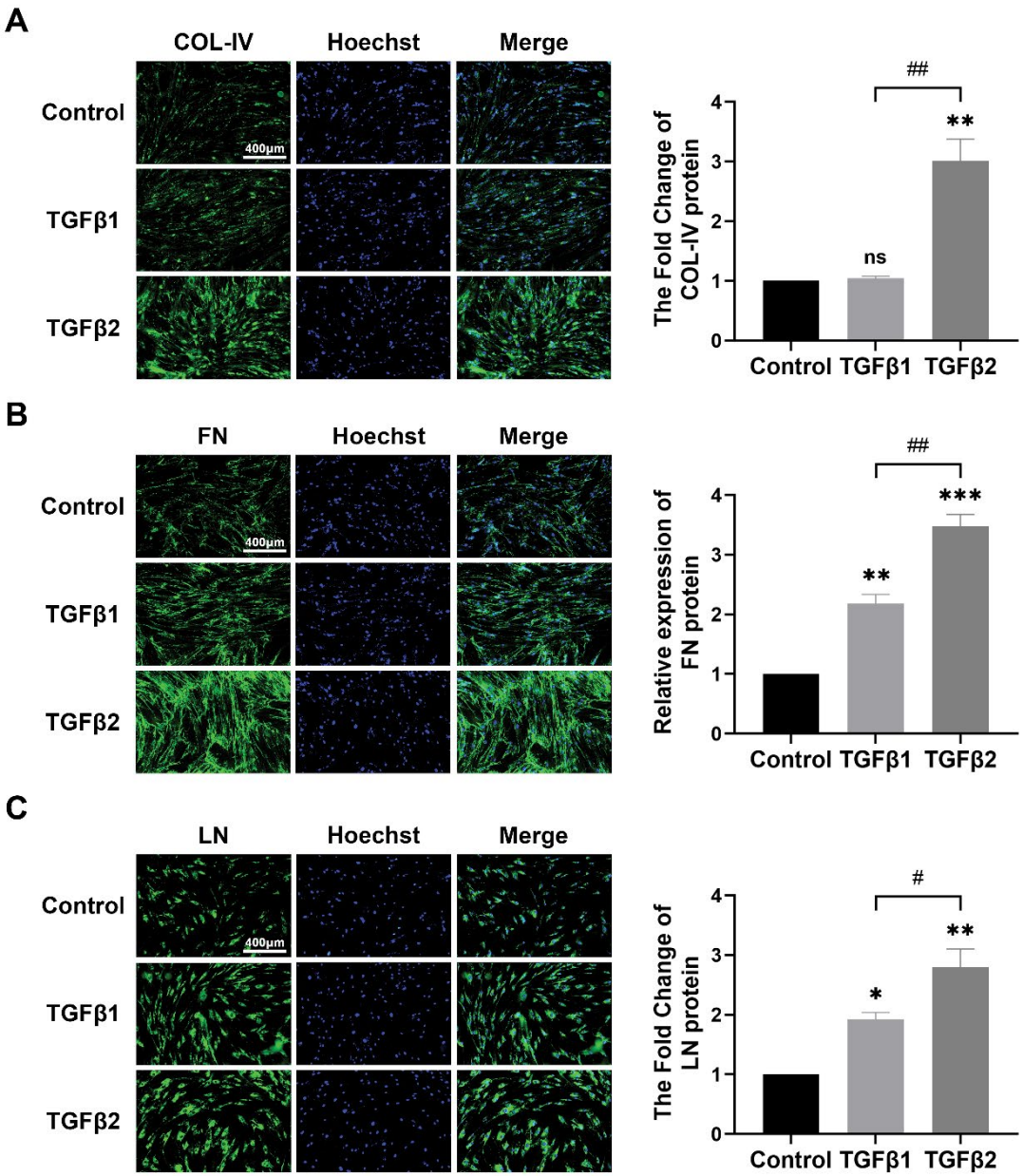

Figure 2: TGFβ1 and TGFβ2 effects on ECM immunofluorescence in HTM cells. TGFβ2 has a stronger effect on extracellular matrix proteins than TGFβ1. The COL-IV(**A**), FN (**B**) and LN (**C**) proteins were detected by ICC of HTM cells with TGFβ1 and TGFβ2 treatment. The data were analyzed by Image J. All results used 3 HTM cell strains. Error bars: mean ± SEM (n = 3). *P < 0.05, **P < 0.01, ***P < 0.001 compared to control, #P < 0.05, ##P < 0.01 compared to TGFβ1, ns = no statistical significance, one-way ANOVA test. Scale bars: 400μm.

Statistical analysis

Mean ± standard error of mean (SEM) was used to express the data. P < 0.05 denoted that the difference was statistically significant in one-way analysis of variance (ANOVA) and Turkey's test for comparisons among several groups of experimental data. For every study, n ≥ 3.

Results

TGFβ2 had a greater effect than TGFβ1 did on ECM proteins in HTM cells

In order to explore the distinct impacts of TGFβ1 and TGFβ2 induction on ECM protein expression, we analyzed the variations of three ECM proteins following TGFβ1 and TGFβ2 treatment. TGFβ1 and TGFβ2 were applied to HTM cells for 48 h at a dose of 5 ng/mL, whereas no TGFβ therapy was given to the control group. The RNA was extracted from the treated cells, reverse transcribed to obtain cDNA, and then used for RT-qPCR analysis to measure the mRNA levels of COL-IV, FN, and LN. WB and ICC were employed to assess the differences in ECM protein expression levels. As depicted in figure 1A-C, with exception of COL-IV, the mRNA levels of ECM were markedly elevated in HTM cells following TGFβ1 stimulation compared with control. Simultaneously,

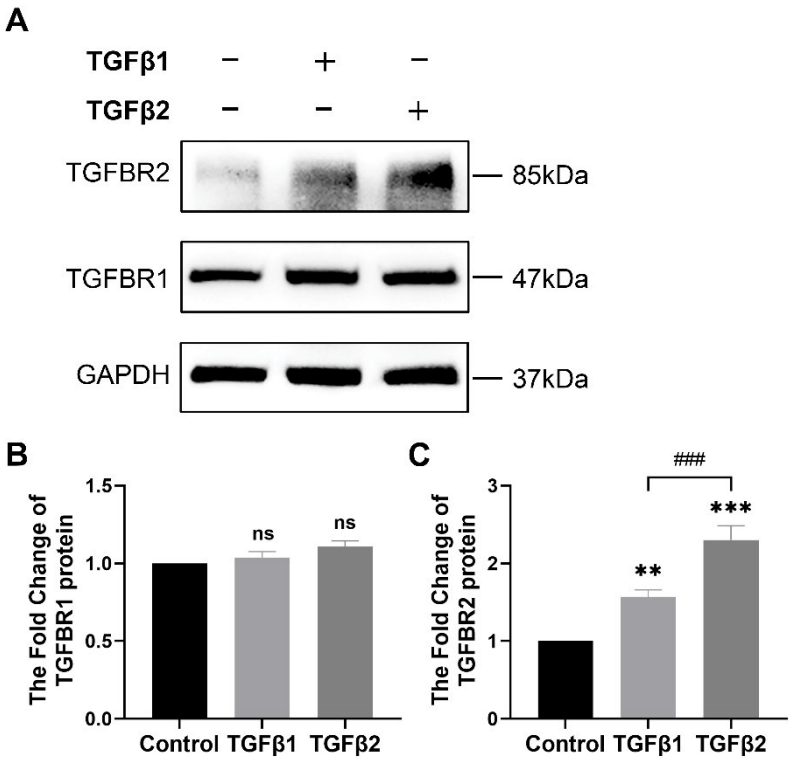

Figure 3: TGFβ1 and TGFβ2 effects on TGFBRs expression in HTM cells. TGFβ2 has a stronger effect on TGFβ receptor 2 than TGFβ1. (**A**) WB was utilized to measure the TGFBR1 and TGFBR2 protein levels. The protein level of TGFBR1 (**B**) and TGFBR2 (**C**). All results used 2 HTM cell strains. Error bars: mean ± SEM (n = 4-8). **P < 0.01, ***P < 0.001 compared to control, ##P < 0.01 compared to TGFβ1, ns = no statistical significance, one-way ANOVA test.

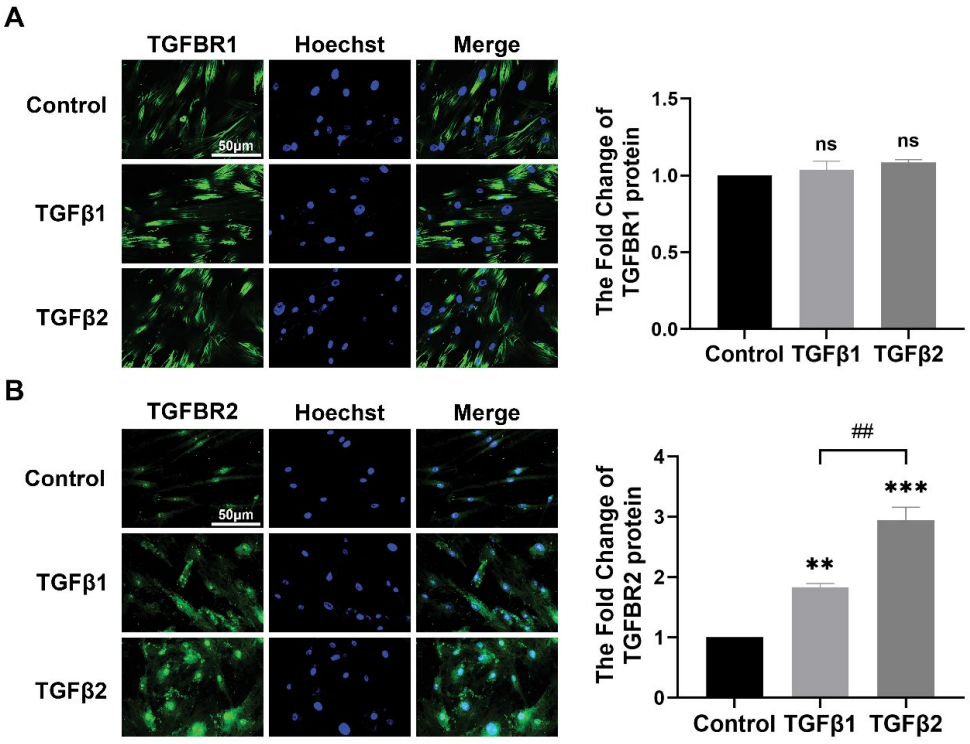

Figure 4: TGFβ1 and TGFβ2 effects on TGFBRs immunofluorescence in HTM cells. TGFβ2 has a stronger effect on TGFβ receptor 2 than TGFβ1. ICC shows the protein level of TGFBR1 (**A**) and TGFBR2 (**B**) in HTM cells with TGFβ1 and TGFβ2 treatment. The data were analyzed by Image J. All results used 3 HTM cell strains. Error bars: mean ± SEM (n = 6-8). **P < 0.01, ***P < 0.001 compared to control, ##P < 0.01 compared to TGFβ1, ns = no statistical significance, one-way ANOVA test. Scale bars: 50μm.

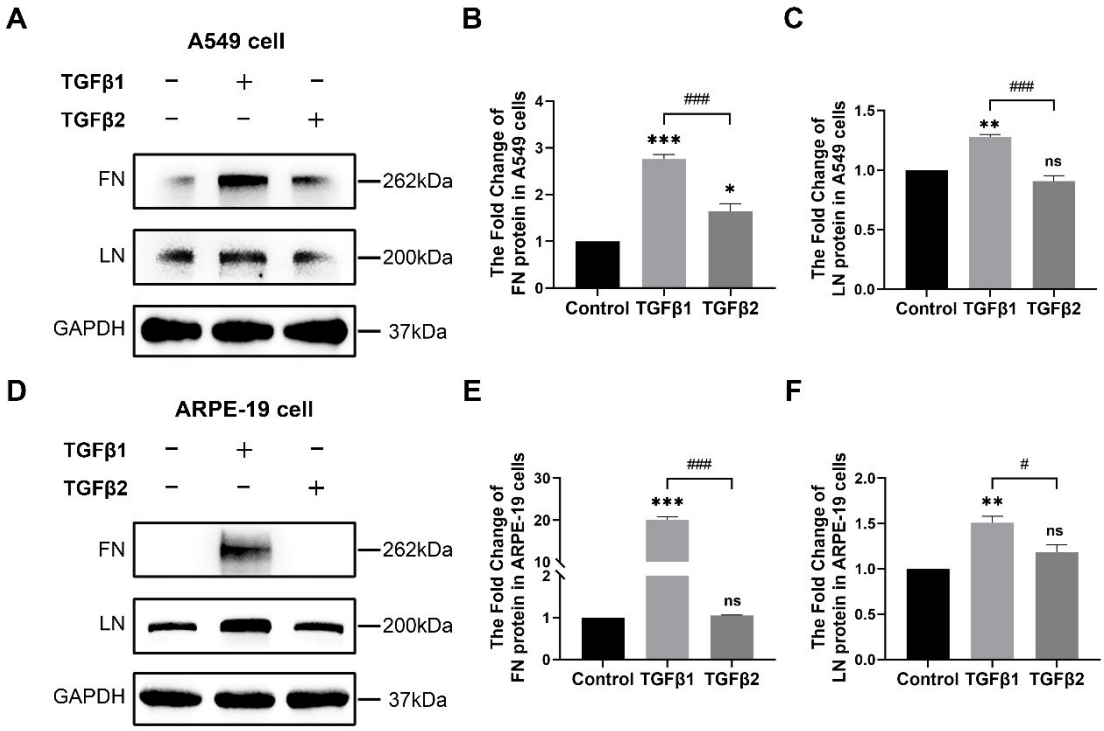

Figure 5: TGFβ1 and TGFβ2 effects on ECM expression in A549 and ARPE-19 cells. TGFβ1 has stronger effect on ECM than TGFβ2. (**A**) The ECM proteins in TGFβ1 and TGFβ2-treated A549 cells as determined by WB. The statistical result of WB regarding FN (**B**) and LN (**C**) proteins. (**D**) The ECM proteins in TGFβ1 and TGFβ2-treated ARPE-19 cells as determined by WB. The statistical result of WB regarding FN (**E**) and LN (**F**) proteins. All results used 3 A549 and ARPE-19 cell strains. Error bars: mean ± SEM (n = 3). *P < 0.05, **P < 0.01, ***P < 0.001 compared to control, #P < 0.05, ###P < 0.001 compared to TGFβ1, ns = no statistical significance, one-way ANOVA test.

all three ECM mRNA levels increased upon TGFβ2 treatment. Furthermore, compared to TGFβ1, the ECM mRNA levels in the TGFβ2 group were considerably higher (FN: 2.387 ± 0.005-fold, P < 0.0001; LN: 0.617 ± 0.024-fold, P = 0.0004; COL-IV: 12.955 ± 1.287-fold, P < 0.0001 compared to the TGFβ1 group). Figure 1D-G demonstrated that COL-IV, FN, and LN protein levels were significantly upregulated after induction by both TGFβ isoforms in HTM cells. Nonetheless, the TGFβ2 group had greater quantities of ECM proteins than the TGFβ1 group did (FN: 2.078 ± 0.118-fold, P < 0.0001; LN: 1.882 ± 0.231-fold, P = 0.0002; COL-IV: 1.531 ± 0.235-fold, P = 0.0032 compared to the TGFβ1 group). Similar results were observed in the ICC experiment (Figure 2) (FN: 1.291 ± 0.050-fold, P = 0.0018; LN: 0.875 ± 0.187-fold, P = 0.0361; COL-IV: 1.971 ± 0.325-fold, P = 0.0014 compared to the TGFβ1 group). These findings indicate that TGFβ2 exerts a greater effect than TGFβ1 on ECM protein expression levels

TGFβ2 had a stronger effect than TGFβ1 did on TGFβR2 in HTM cells

To ascertain the reason for the increased impact of TGFβ2 on ECM-protein accumulation in comparison to TGFβ1, the expression of TGFBR1 and TGFBR2 in HTM cells were analyzed. As shown in figure 3 and 4, the TGFBR2 protein was upregulated by both TGFβ isoforms, and the increased expression of TGFBR2 treated with TGFβ2 was more significant than that treated with TGFβ1 (WB: 0.731 ± 0.093-fold, P = 0.0005; ICC: 1.120 ± 0.141-fold, P < 0.0001 compared to TGFβ1), whereas the TGFBR1 protein had no change among the three groups. These findings demonstrate that TGFβ isoforms cause different ECM-protein accumulation, and the difference is dependent on the differences in TGFBR2 expression stimulated by the TGFβ isoforms.

TGFβ1 had a greater effect than TGFβ2 did on ECM proteins in A549 and ARPE-19 cells

To investigate whether the enhanced effect of TGFβ2 is specific to HTM cells, we employed the same methodology to evaluate A549 and ARPE-19 cells. As depicted in figure 5A-C, TGFβ1 administration to A549 cells resulted in an increase in FN and LN proteins, whereas TGFβ2 only upregulated FN protein, and the effect was less pronounced than that of TGFβ1 (1.116 ± 0.061-fold, P = 0.0008 compared with TGFβ2 group). A similar trend was observed in ARPE-19 cells, where TGFβ1 exhibited a comparable effect (FN: 19.037 ± 0.729 -fold, P < 0.0001; LN: 0.323 ± 0.008-fold, P = 0.0243; figure 5D-F). These results imply that after inducing TGFβ, the ECM protein increase in A549 and ARPE-19 cells is different from that in HTM cells.

Discussion

The main characteristic of TM in POAG is the increased deposition of ECM proteins such as FN, COL-I, -III, -V, -VI, -XI, -XII, and –XIV [46,47]. TGFβ is the main pathological mechanism for the elevation of outflow resistance in TM [48]. POAG develops after excessive synthesis and deposition of ECM proteins in TM and a further increase in IOP [49-51]. In the current investigation, we discovered that HTM cells

treated with TGFβ had considerably higher expression levels of FN, LN, and COL-IV, and the ECM-protein accumulation induced by TGFβ2 was higher than TGFβ1 induced (Figure 1 and 2), which indicated that TGFβ2 had a greater effect on ECM-protein accumulation than TGFβ1 did in HTM cells.

Herein, we explored whether the efficiency of ECM-protein accumulation induced by two TGFβ isoforms is due to the differential expression of TGFBR1 and/or TGFBR2. We found that TGFβ1 and TGFβ2 had no effect on TGFBR1, whereas the expression of TGFBR2 was markedly upregulated and the efficiency of TGFβ2 was better than that of TGFβ1 (Figure 3 and 4). Accordingly, we hypothesized that the ECM proteins expression after TGFβ1 induction was lower than that after TGFβ2 treatment in HTM cells due to the high expression of TGFBR2 induced by TGFβ2, which further phosphorylates TGFBR1 and then stimulates the Smads signal pathway.

In order to ascertain the specificity of TGFβ2's predominant efficacy for HTM cells in ECM accumulation, a comparative analysis involving two TGFβ isoforms was undertaken on alternative cellular models. Specifically, A549, representing a human lung cancer cell line, and ARPE-19, a human retinal pigment epithelial cell line, were subjected to further investigation. Results demonstrated that in A549 cells, TGFβ1 stimulation significantly upregulated the FN and LN proteins expression levels, whereas TGFβ2 only increased FN protein expression. These results align with earlier research conducted by [52,53]. Similarly, TGFβ1 exhibited the ability to enhance FN and LN protein expression in ARPE-19 cells, as reported by, while TGFβ2 did not have the same effect (Figure 5). These results are distinct from those observed in HTM cells, and no researches have previously compared the effects of TGFβ1 and TGFβ2 on ECM protein accumulation [54].

This is the first study to report a comparison of TGFβ1 and TGFβ2 in relation to ECM-protein accumulation. TGFβ2 promoted more accumulation of ECM proteins in HTM cells than TGFβ1 did. However, the specific mechanisms behind the differences between the two TGFβ isoforms was not fully elucidated. The study focused on the expression of TGFBR and not the degree of TGFBR turnover on the cell membrane surface. Nevertheless, literature has indicated that TGFβ1 has the capacity to increase the levels of two TGFβ isoforms in HaCaT keratinocytes and human lung cancer A549 cells [55]. The precise molecular and cellular mechanisms for TGFβ isoforms will be explored in future research.

Conclusion

In conclusion, this study indicates that TGFβ2 significantly contributes to the accumulation of TM ECM proteins by upregulating TGFBR2 expression. It establishes a more advantageous foundation for the clinical treatment targeting TGFβ2 in POAG. Future studies can target the degree of TGFBR1 phosphorylation on the cell membrane surface, and explore whether there is an interaction between the two TGFβ isoforms, its influence on phagocytosis of HTM cells, and the specific mechanisms of the two TGFβ isoforms.

Acknowledgements

The research study was conceived and designed by Tao Guo. Chenyu Xu, Jiahong Wei, and Siyu Zhao conducted the experiments. Chenyu Xu conducted the data analysis with help from Siyu Zhao and Jiahong Wei. Human TM tissues were collected by Dan Song and Mingmin Hou.

Declaration of Competing Interest

No conflicts of interest have been disclosed by the authors.

Data Availability

Data will be made available on request.

Funding

This work was supported by the Shanghai Industrial Collaborative Technology Innovation Project (Grant number XTCX-KJ-2022-35); the Science and Technology Commission of Shanghai (Grant number 19411961500); the Clinical Research Program of 9th People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine (Grant number JYLJ201804); and the National Natural Science Foundation of China (Grant number 82201137).

Conflicts of Interest

None.

References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, et al. (2014) Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 121: 2081-2090.
2. Weinreb RN, Aung T, Medeiros FA (2014) The pathophysiology and treatment of glaucoma: a review. JAMA 311: 1901-1911.
3. Weinreb RN, Khaw PT (2004) Primary open-angle glaucoma. Lancet 363: 1711-1720.
4. Tamm ER, Fuchshofer R (2007) What increases outflow resistance in primary open-angle glaucoma? Surv Ophthalmol 52: S101-104.
5. Fuchshofer R, Tamm ER (2009) Modulation of extracellular matrix turnover in the trabecular meshwork. Exp Eye Res 88: 683-688.
6. Last JA, Pan T, Ding Y, Reilly CM, Keller K, t al. (2011) Elastic modulus determination of normal and glaucomatous human trabecular meshwork. Invest Ophthalmol Vis Sci 52: 2147-2152.
7. Lai WF, Wong WT (2020) Roles of the actin cytoskeleton in aging and age-associated diseases. Ageing Res Rev 58: 101021.
8. Ma TT, Meng XM (2019) TGF-beta/Smad and Renal Fibrosis. Adv Exp Med Biol 1165: 347-364.
9. Vander Ark A, Cao J, Li X (2018) TGF-beta receptors: In and beyond TGF-beta signaling. Cell Signal 52: 112-120.
10. Leeuwis JW, Nguyen TQ, Dendooven A, Kok RJ, Goldschmeding R (2010) Targeting podocyte-associated diseases. Adv Drug Deliv Rev 62: 1325-1336.
11. Xu P, Liu J, Derynck R (2012) Post-translational regulation of TGF-β receptor and Smad signaling. FEBS Lett 586: 1871-1884.
12. Meng XM, Nikolic-Paterson DJ, Lan HY (2016) TGF-beta: the master regulator of fibrosis. Nat Rev Nephrol 12: 325-338.

13. Yu L, Border WA, Huang Y, Noble NA (2003) TGF-beta isoforms in renal fibrogenesis. Kidney Int 64: 844-856.

14. Camoretti-Mercado B, Solway J (2005) Transforming growth factor-beta1 and disorders of the lung. Cell Biochem Biophys 43: 131-148.

15. Xu F, Liu C, Zhou D, Zhang L (2016) TGF-beta/SMAD Pathway and Its Regulation in Hepatic Fibrosis. J Histochem Cytochem 64: 157-167.

16. Park SA, Kim MJ, Park SY, Kim JS, Lee SJ, et al. (2015) EW-7197 inhibits hepatic, renal, and pulmonary fibrosis by blocking TGF-beta/Smad and ROS signaling. Cell Mol Life Sci 72: 2023-2039.

17. Aomatsu K, Arao T, Sugioka K, Matsumoto K, Tamura D, et al. (2011) TGF-beta induces sustained upregulation of SNAI1 and SNAI2 through Smad and non-Smad pathways in a human corneal epithelial cell line. Invest Ophthalmol Vis Sci 52: 2437-2443.

18. Yang J, Savvatis K, Kang JS, Fan P, Zhong H, et al. (2016) Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment. Nat Commun 7: 13710.

19. Chakraborty M, Sahay P, Rao A (2021) Primary Human Trabecular Meshwork Model for Pseudoexfoliation. Cells 10: 3448.

20. Choi JA, Ju HH, Kim JE, Lee J, Jee D, et al. (2021) Cytokine profile and cytoskeletal changes after herpes simplex virus type 1 infection in human trabecular meshwork cells. J Cell Mol Med 25: 9295-9305.

21. Nakamura N, Honjo M, Yamagishi R, Igarashi N, Sakata R, et al. (2021) Effects of selective EP2 receptor agonist, omidenepag, on trabecular meshwork cells, Schlemm's canal endothelial cells and ciliary muscle contraction. Sci Rep 11: 16257.

22. Bowen T, Jenkins RH, Fraser DJ (2013) MicroRNAs, transforming growth factor beta-1, and tissue fibrosis. J Pathol 229: 274-285.

23. Baxter GF, Mocanu MM, Brar BK, Latchman DS, Yellon DM (2001) Cardioprotective effects of transforming growth factor-beta1 during early reoxygenation or reperfusion are mediated by p42/p44 MAPK. J Cardiovasc Pharmacol 38: 930-939.

24. Kennedy SM, Sheridan C, Kearns VR, Bilir EK, Fan X, et al. (2019) Thrombospondin-2 is up-regulated by TGFβ2 and increases fibronectin expression in human trabecular meshwork cells. Exp Eye Res 189: 107820.

25. Fuchshofer R, Yu AH, Welge-Lüssen U, Tamm ER (2007) Bone morphogenetic protein-7 is an antagonist of transforming growth factor-beta2 in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 48: 715-726.

26. Wordinger RJ, Sharma T, Clark AF (2014) The role of TGF-β2 and bone morphogenetic proteins in the trabecular meshwork and glaucoma. J Ocul Pharmacol Ther 30: 154-162.

27. Mu Y, Gudey SK, Landström M (2012) Non-Smad signaling pathways. Cell Tissue Res 347: 11-20.

28. Hata A, Chen YG (2016) TGF-β Signaling from Receptors to Smads. Cold Spring Harb Perspect Biol 8: a022061.

29. Miyazono K, ten Dijke P, Heldin CH (2000) TGF-beta signaling by Smad proteins. Adv Immunol 75: 115-157.

30. Miyazono K (2000) TGF-beta signaling by Smad proteins. Cytokine Growth Factor Rev 11: 15-22.

31. Heldin CH, Moustakas A (2012) Role of Smads in TGFβ signaling. Cell Tissue Res 347: 21-36.

32. Guo T, Guo L, Fan Y, Fang L, Wei J, et al. (2019) Aqueous humor levels of TGFβ2 and SFRP1 in different types of glaucoma. BMC Ophthalmol 19: 170.

33. NikhalaShree S, Karthikkeyan G, George R, Shantha B, Vijaya L, e al. (2019) Lowered Decorin with Aberrant Extracellular Matrix Remodeling in Aqueous Humor and Tenon's Tissue from Primary Glaucoma Patients. Invest Ophthalmol Vis Sci 60: 4661-4669.

34. Igarashi N, Honjo M, Asaoka R, Kurano M, Yatomi Y, et al. (2021) Aqueous autotaxin and TGF-βs are promising diagnostic biomarkers for distinguishing open-angle glaucoma subtypes. Sci Rep 11: 1408.

35. Igarashi N, Honjo M, Yamagishi R, Kurano M, Yatomi Y, et al. (2021) Crosstalk between transforming growth factor β-2 and Autotaxin in trabecular meshwork and different subtypes of glaucoma. J Biomed Sci 28: 47.

36. Fan Y, Guo L, Wei J, Chen J, Sun H, et al. (2019) Effects of Salidroside on Trabecular Meshwork Cell Extracellular Matrix Expression and Mouse Intraocular Pressure. Invest Ophthalmol Vis Sci 60: 2072-2082.

37. Fan Y, Wei J, Guo L, Zhao S, Xu C, et al. (2020) Osthole Reduces Mouse IOP Associated with Ameliorating Extracellular Matrix Expression of Trabecular Meshwork Cell. Invest Ophthalmol Vis Sci 61: 38.

38. Tellios N, Belrose JC, Tokarewicz AC, Hutnik C, Liu H, et al. (2017) TGF-β induces phosphorylation of phosphatase and tensin homolog: implications for fibrosis of the trabecular meshwork tissue in glaucoma. Sci Rep 7: 812.

39. Fujimoto T, Inoue-Mochita M, Iraha S, Tanihara H, Inoue T (2021) Suberoylanilide hydroxamic acid (SAHA) inhibits transforming growth factor-beta 2-induced increases in aqueous humor outflow resistance. J Biol Chem 297: 101070.

40. Takai Y, Tanito M, Ohira A (2012) Multiplex cytokine analysis of aqueous humor in eyes with primary open-angle glaucoma, exfoliation glaucoma, and cataract. Invest Ophthalmol Vis Sci 53: 241-247.

41. Khalef N, Labib H, Helmy H, El Hamid MA, Moemen L, et al. (2017) Levels of cytokines in the aqueous humor of eyes with primary open angle glaucoma, pseudoexfoliation glaucoma and cataract. Electron Physician 9: 3833-3837.

42. Yang Q, Li Y, Luo L (2018) Effect of Myricetin on Primary Open-angle Glaucoma. Transl Neurosci 9: 132-141.

43. Micera A, Quaranta L, Esposito G, Floriani I, Pocobelli A, et al. (2016) Differential Protein Expression Profiles in Glaucomatous Trabecular Meshwork: An Evaluation Study on a Small Primary Open Angle Glaucoma Population. Adv Ther 33: 252-267.

44. Taurone S, Ripandelli G, Pacella E, Bianchi E, Plateroti AM, De et al. (2015) Potential regulatory molecules in the human trabecular meshwork of patients with glaucoma: immunohistochemical profile of a number of inflammatory cytokines. Mol Med Rep 11: 1384-1390.

45. Keller KE, Bhattacharya SK, Borrás T (2018) Consensus recommendations for trabecular meshwork cell isolation, characterization and culture. Exp Eye Res 171: 164-173.

46. Wordinger RJ, Fleenor DL, Hellberg PE, Pang IH, Tovar TO, et al. (2007) Effects of TGF-beta2, BMP-4, and gremlin in the trabecular meshwork: implications for glaucoma. Invest Ophthalmol Vis Sci 48: 1191.

47. Liton PB, Luna C, Challa P, Epstein DL, Gonzalez P (2006) Genome-wide expression profile of human trabecular meshwork cultured cells, nonglaucomatous and primary open angle glaucoma tissue. Mol Vis 12 774-790.

48. Stamer WD, Acott TS (2012) Current understanding of conventional outflow dysfunction in glaucoma. Curr Opin Ophthalmol 23: 135-143.

49. Zhao X, Ramsey KE, Stephan DA, Russell P (2004) Gene and protein expression changes in human trabecular meshwork cells treated with transforming growth factor-beta. Invest Ophthalmol Vis Sci 45: 4023-4034.

50. Pattabiraman PP, Rao PV (2010) Mechanistic basis of Rho GTPase-induced extracellular matrix synthesis in trabecular meshwork cells. Am J Physiol Cell Physiol 298: C749-C763.

51. Junglas B, Yu AH, Welge-Lüssen U, Tamm ER, Fuchshofer R (2009) Connective tissue growth factor induces extracellular matrix deposition in human trabecular meshwork cells. Exp Eye Res 88: 1065-1075.

52. Kim MS, Baek AR, Lee JH, Jang AS, Kim DJ, et al. (2019) IL-37 Attenuates Lung Fibrosis by Inducing Autophagy and Regulating TGF-β1 Production in Mice. J Immunol 203: 2265-2275.

53. Kato M, Takahashi F, Sato T, Mitsuishi Y, Tajima K, et al. (2020) Tranilast Inhibits Pulmonary Fibrosis by Suppressing TGFβ/SMAD2 Pathway. Drug Des Devel Ther 14: 4593-4603.

54. Zhou L, Shi DP, Chu WJ, Yang LL, Xu HF (2021) LRG1 promotes epithelial-mesenchymal transition of retinal pigment epithelium cells by activating NOX4. Int J Ophthalmol 14: 349-355.

55. Duan D, Derynck R (2019) Transforming growth factor-β (TGF-β)-induced up-regulation of TGF-β receptors at the cell surface amplifies the TGF-β response. J Biol Chem 294: 8490-8504.

Citation: Guo T, Xu CY, Wei JH, Zhao SY, Song D, Hou MM (2024) Differences in Extracellular Matrix Protein Accumulation between TGFβ Isoforms in Trabecular Meshwork. J Health Sci Dev Vol: 7, Issue: 1 (19-27).