Pharmacologic Soluble Guanylate Cyclase Activation for Suppression of Epithelial-Mesenchymal Transition in Retinal Pigment Epithelial Cells: Implications for Wet Age-Related Macular Degeneration

Background

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in older adults. In wet (neovascular) AMD, vision loss is often driven not only by abnormal blood vessel growth—but also by subretinal fibrosis, a permanent scarring process that current therapies cannot prevent.

Subretinal Fibrosis Mechanism:

- Subretinal fibrosis is the formation of fibrous scar tissue beneath the retina, often caused by chronic inflammation or unresolved injury.
  - Driven by epithelial-to-mesenchymal transition (EMT) in retinal pigment epithelial (RPE) cells
- Transforming growth factor beta (TGFβ) is secreted as a central pro-fibrotic signal that promotes EMT and also suppresses nitric oxide (NO)–soluble guanylate cyclase (sGC) signaling, a pathway that normally limits fibrosis.

sGC-NO Signaling Pathway:

- When activated by NO, sGC catalyzes conversion of guanosine triphosphate (GTP) into the second messenger cyclic guanosine monophosphate (cGMP) which promotes anti-inflammatory and anti-fibrotic responses, helping limit permanent scarring.
  - Under oxidative stress, NO–sGC signaling becomes impaired, weakening anti-fibrotic control.

Therapeutic Strategy: sGC Activation with Runcaciguat

- Runcaciguat is an sGC activator with established anti-fibrotic effects in other organs (heart, kidney, lung).
- Unlike therapies that require NO, runcaciguat can directly stimulate oxidized or heme-free sGC and restore cGMP signaling under oxidative conditions
- This makes runcaciguat especially valuable for wet AMD, where oxidative stress is common and may contribute to fibrosis progression.

Objective: Investigate whether the sGC activator runcaciguat can suppress TGFβ1–induced epithelial-mesenchymal transition of RPE cells, as a strategy to inhibit subretinal fibrosis in wet AMD.

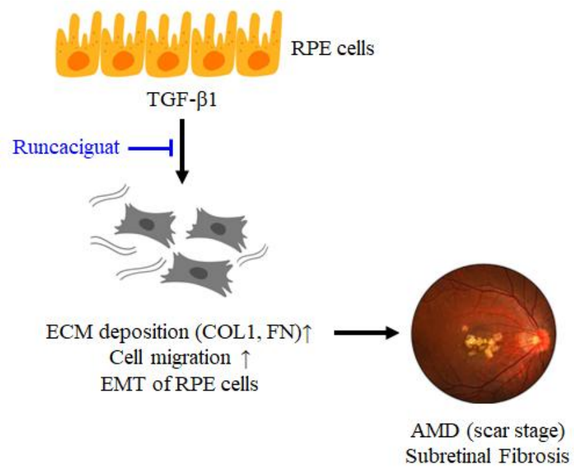

Figure 1. Schematic diagram of the hypothesis of runcaciguat on suppression of TGFβ1-induced EMT in ARPE-19 cells. Graphic created by author and adapted from doi:10.3389/fopht.2022.1060087 using Microsoft Powerpoint, 2025.

Results

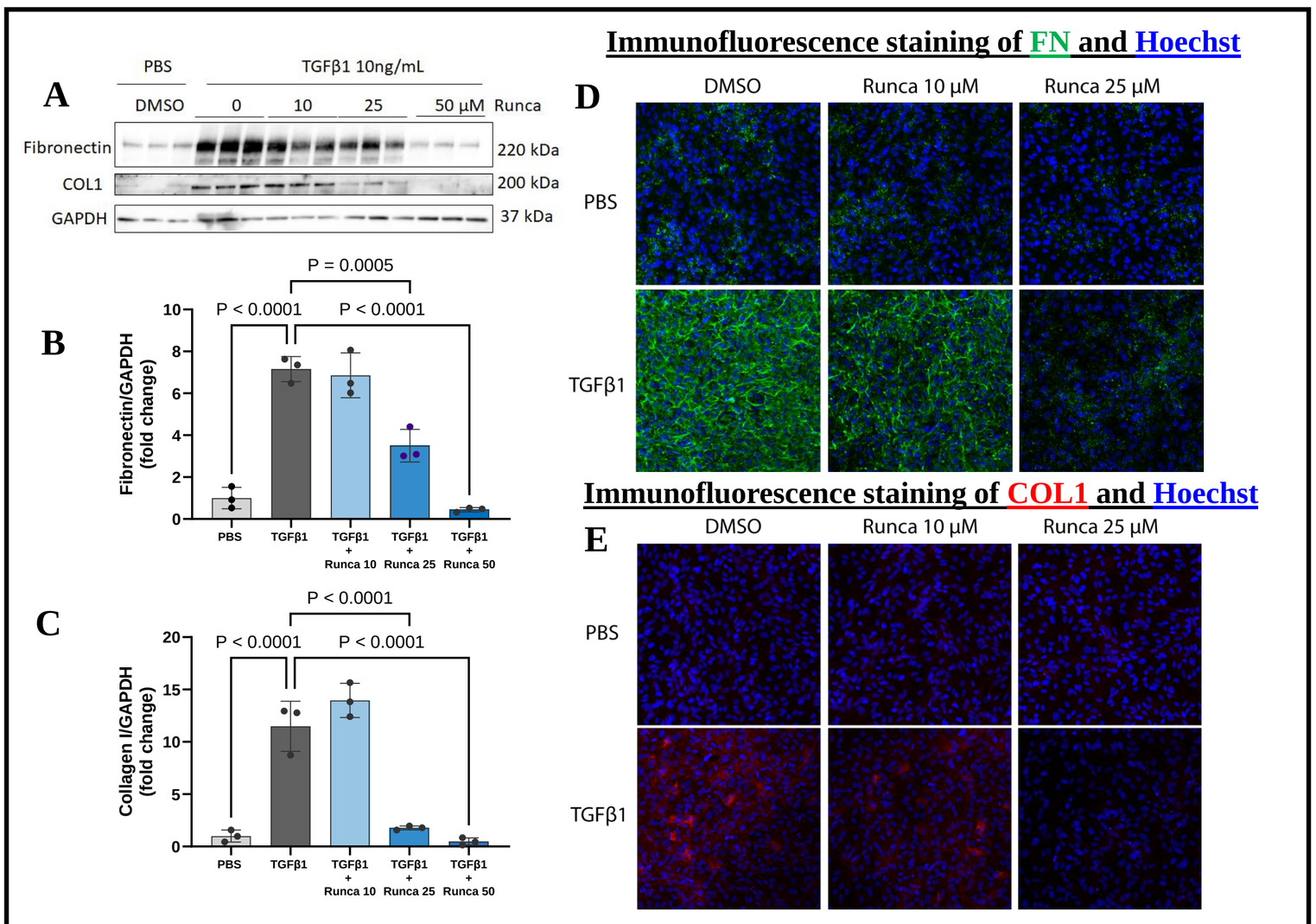

Figure 2. Runcaciguat reduces TGFβ1-induced Fibronectin and Collagen I expression in ARPE-19 cells.
(A) Western blot analysis of fibronectin and Collagen I in TGFβ1- and runcaciguat-treated cells. Graphic created by author using Microsoft Powerpoint, 2025. (B) and (C) Densitometry analysis of the Western blot results for fibronectin and Collagen I. Graphs created by the student researcher using GraphPad Prism (10.5.0), 2025. (D and E) Immunofluorescence staining of fibronectin (green) and Collagen I (red) in TGFβ1- and 10 runcaciguat-treated cells. Hoechst for nuclei staining (blue). The images were taken at 10× objective. Grapha created by author Microsoft Powerpoint, 2025.

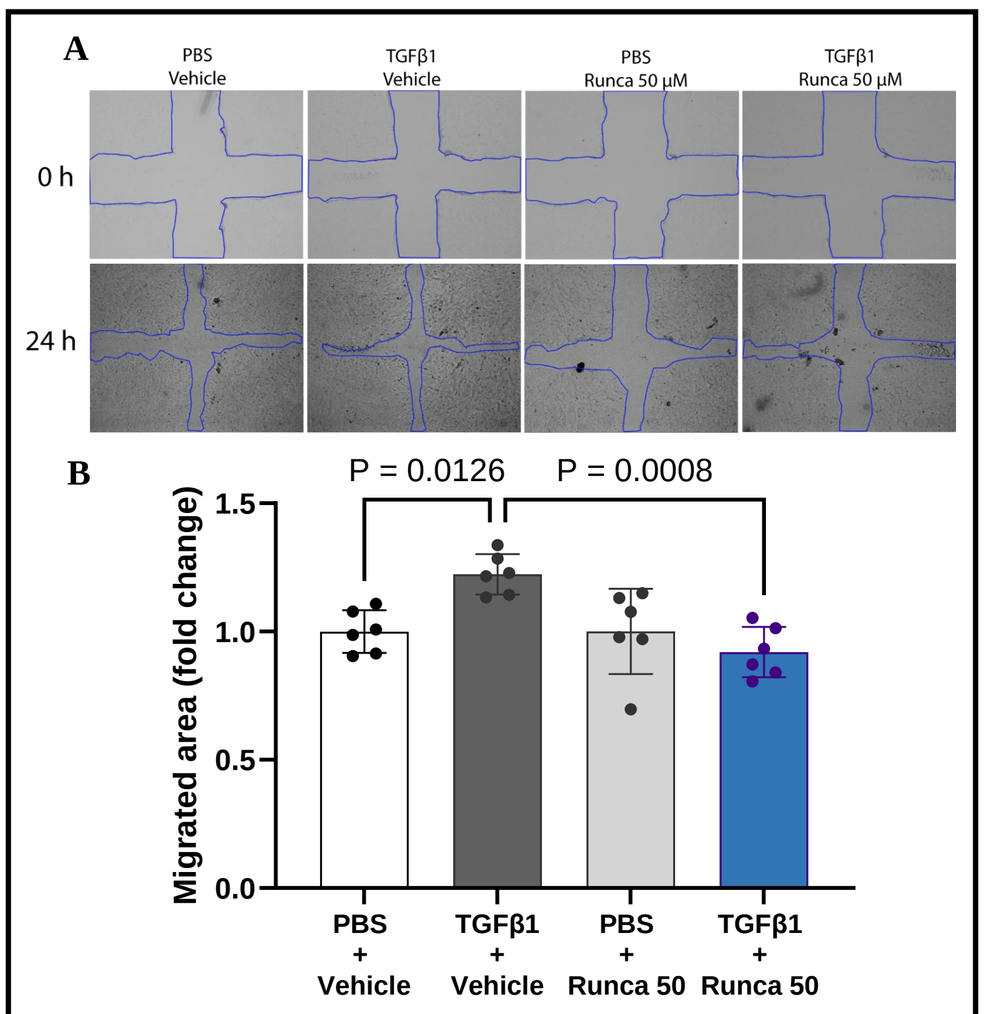

Figure 3. Runcaciguat suppresses TGFβ1-induced cell migration in ARPE-19 cells.
(A) Representative images of the scratched area in ARPE-19 cells at 0 and 24 h after the treatment with 50 μM runcaciguat and TGFβ1. Blue lines indicated the edges of the scratch. Scale bar: 650 μm. Graphic created by the student researcher using Microsoft Powerpoint, 2025. (B) Quantitative analysis of the migrated area, expressed as the fold change relative to the control (PBS + Vehicle) group. TGF-β1 significantly increases cell migration compared to the PBS-treated group. Runcaciguat completely inhibited TGF-β1-induced cell migration. Graph created by author using GraphPad Prism (10.5.0), 2025.

Conclusion

- TGFβ1 reliably induced a fibrotic/EMT-like response in ARPE-19 cells, increasing ECM deposition (fibronectin, collagen I) and promoting cell migration.
- Runcaciguat dose-dependently reduced TGFβ1–induced ECM protein expression and migration, indicating its anti-fibrotic potential.
- These findings establish sGC as a key regulator of EMT and the pro-fibrotic phenotype in RPE cells.
- sGC activation could be a novel therapeutic strategy to protect against subretinal fibrosis and prevent vision loss in nAMD.

References:

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