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Impact of anticancer drugs on human Tenon's fibroblast proliferation: implications for glaucoma surgery

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ABSTRACT

Objective Elevated intraocular pressure (IOP) is a major risk factor for glaucoma and the primary target of current therapies. When IOP-lowering drugs are insufficient, surgical intervention may be required; however, conjunctival and subconjunctival scarring often limits long-term success. Although intraoperative and postoperative antimetabolite treatments help preserve surgical outcomes, they are associated with ocular side effects. This study investigated the effects of selected anticancer drugs on the proliferation of human Tenon's fibroblasts (HTFs), key mediators of postoperative scarring.

Methods and analysis Primary HTFs were isolated from explants obtained during glaucoma surgery and characterised by immunofluorescence. The cytotoxic effects of candidate drugs were assessed using the MTT and LDH assays, while HTF migration and proliferation were evaluated by wound-healing assays. Additional cytotoxicity testing was performed on primary human trabecular meshwork cells (HTMCs) to assess ocular safety.

Results Under the experimental conditions used, HTF proliferation, rather than migration, was the main driver of wound closure. Among the drugs tested, pemigatinib and sorafenib significantly slowed wound closure. Pemigatinib showed no cytotoxicity in either HTFs or HTMCs, whereas sorafenib induced a moderate (28%) cytotoxic effect in HTMCs.

Conclusions Pemigatinib and sorafenib, two Food and Drug Administration-approved anticancer agents, effectively reduced HTF proliferation, with pemigatinib showing a more favourable safety profile. These findings identify selective fibroblast growth factor receptor (FGFR) inhibition as a promising strategy for modulating postoperative fibrosis and support further preclinical studies to evaluate the safety and efficacy of FGFR inhibitors as potential adjuncts in glaucoma surgery.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Postoperative fibrosis, particularly involving Tenon's capsule fibroblasts, is a major cause of failure in glaucoma filtration surgery. Current antiscarring treatments, such as antimetabolites, carry significant ocular side effects, highlighting the need for safer, targeted antifibrotic strategies.

WHAT THIS STUDY ADDS

⇒ This study identifies pemigatinib and sorafenib as effective inhibitors of Tenon's fibroblast proliferation with minimal cytotoxicity and highlights fibroblast proliferation—rather than migration—as the primary driver of wound closure in this context.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest the potential repurposing of Food and Drug Administration-approved cancer drugs as adjuncts in glaucoma surgery, providing a foundation for preclinical studies aimed at improving long-term surgical outcomes with reduced risk of adverse effects.

INTRODUCTION

Glaucoma is a leading cause of blindness worldwide, characterised by progressive retinal ganglion cell death and optic nerve damage. Key risk factors include advanced age, severe myopia, family history and, most importantly, elevated intraocular pressure (IOP), the only modifiable risk factor.[1 2] Because glaucoma is a chronic neurodegenerative disease, long-term IOP reduction is necessary to match the patient's life expectancy. Treatment options include medications, laser therapy and surgery, with surgical intervention typically reserved for cases where pharmacological or laser treatments fail to provide adequate IOP control or are poorly tolerated.

Among surgical options, trabeculectomy remains the most commonly performed incisional procedure.[3] This technique creates a guarded fistula that allows aqueous humour to drain into a subconjunctival bleb, thereby lowering IOP. Despite refinements over the past 50 years, long-term success is often limited by fibrotic scarring, which progressively closes the drainage site.[4] To prevent this, antimetabolite drugs such as mitomycin C and 5-fluorouracil are frequently applied intraoperatively. While these agents improve surgical outcomes, they carry significant risks,

including hypotony, bleb leakage, corneal toxicity and increased susceptibility to infections.[5 6]

To explore novel pharmacological strategies for preventing postoperative scarring and maintaining fistula patency, we investigated four antiproliferative drugs—sorafenib, pemigatenib, pacritinib and dovitinib—on human Tenon's fibroblasts (HTFs), the primary mediators of episcleral fibrosis.[4] Among the drugs tested, sorafenib, a multikinase inhibitor with off-target effects on fibroblast growth factor receptors (FGFRs) and pemigatinib, a selective FGFR inhibitor, significantly reduced HTF proliferation. Pemigatinib exhibited a safer cytotoxicity profile than sorafenib, suggesting that selective FGFR inhibition may offer advantages over non-specific inhibitors, which may be associated with ocular toxicity.

MATERIALS AND METHODS

Isolation of HTFs

Samples of human Tenon's capsules tissue obtained from explants during trabeculectomy were cut into approximately 2–3 mm pieces under sterile conditions and seeded in separated 60 mm culture dishes. Samples were maintained in Dulbecco's modified Eagle's medium/nutrient mixture F-12 (DMEM/F12, Lonza, Basel, Switzerland) supplemented with 10% fetal calf serum (FCS, Euroclone, Milan, Italy), 100 U/mL penicillin and 100 µg/mL streptomycin (Euroclone) in a 5% CO_2 humidified atmosphere at 37°C (figure 1A). Approximately 2 weeks after seeding, primary cultures were passaged with trypsin-EDTA solution (Euroclone) into 25 cm^2 culture flasks. HTFs from passages 3–9 were used in the experiments.

Human trabecular meshwork cells

Primary cultures of human trabecular meshwork cells (HTMCs), derived from normal healthy adult human eyes, together with the corresponding trabecular meshwork growth medium, were purchased from Cell Applications (San Diego, California; catalogue no. 634–05 a) and used in this study at passages 5–6.

Vimentin staining

Second passage HTFs were seeded on culture slides and incubated for 24 hours in complete culture media. After fixation and permeabilisation with ice-cold methanol, non-specific binding sites were blocked with 3% BSA. Cells were then incubated for 1 hour with a polyclonal rabbit antivimentin antibody (Euroclone, 1:200 in PBS), followed by labelling with an anti-rabbit Alexa Fluor 488 secondary antibody (Invitrogen, Massachusetts, 1:500 in PBS). During the last 10 min of incubation, cell nuclei were stained by adding the fluorescent dye TO-PRO–3 (Thermo Fisher Scientific, Massachusetts). Stained cells were observed using the appropriate filters on a Leica TCS SP2 confocal microscope (Plan-Apochromat x60 oil-immersion objective, numerical aperture 1.4).

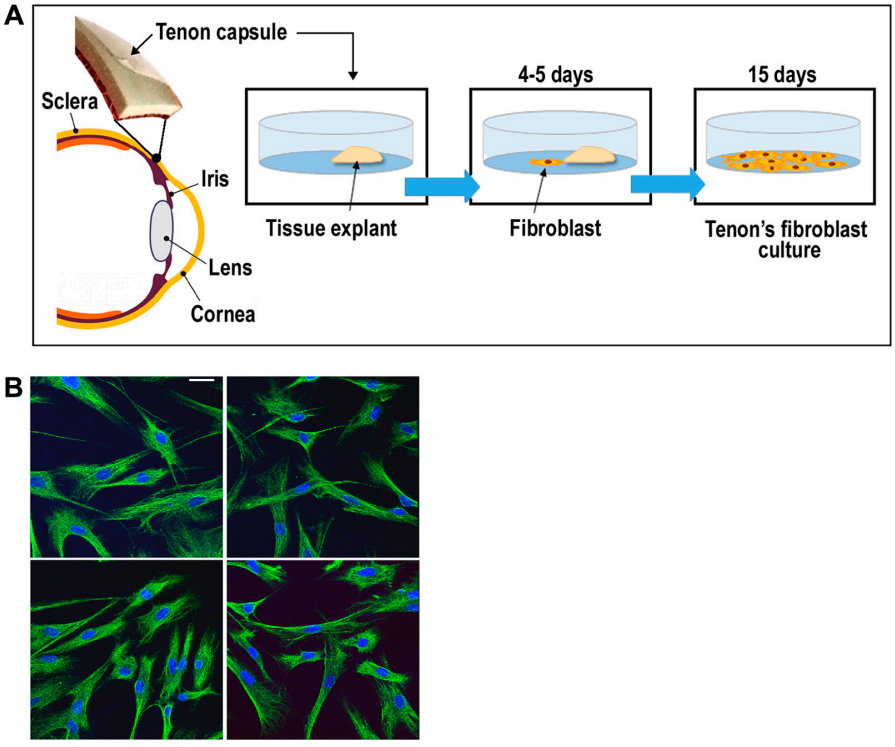

Figure 1 Isolation and characterisation of HTFs. (A) Graphic representation of HTF isolation from tissue explants (n=4). (B) Confocal images of HTF cultures from four different tissue explants (after passage two) showing the fibroblast marker vimentin (green fluorescence). Nuclei (blue fluorescence) were labelled with TO-PRO–3. Scale bar=200 µm. HTF, human Tenon's fibroblast.

Antiproliferative treatments

Sorafenib, pacritinib, pemigatinib and dovitinib were purchased from MedChemExpress (New Jersesy, USA), dissolved in dimethyl sulfoxide (DMSO) to reach the concentration of 10 mM and stored in aliquots at −20°C until use. Control cells received the same volume of DMSO as the treated samples (≤ 1:1000 v/v).

Cytotoxicity assays

Cell viability was assessed by metabolic activity using the MTT (3-(4.5-dimethylthiazol-2-yl)−2.5-diphenyl-tetrazoliumbromide) assay and by membrane integrity using the lactate dehydrogenase (LDH) release assay (Cytotoxicity Detection Kit^{Plus} LDH, Sigma-Aldrich, Munich, Germany). For the MTT assay, cells were seeded at 15 000 cells per well in 96-well plates, and for the LDH assay, at 300 000 cells per well in six-well plates. In both cases, cells reached approximately 70% confluency at the time of drug treatment, which was performed in medium containing 10% FCS (MTT assay) or serum-free medium (0% FCS; LDH assay). At the end of the assays, absorbance was measured using the iMark Microplate Absorbance Reader (Bio-Rad, Munich, Germany).

Wound-healing assay

HTFs were cultured to confluence in 24 multiwell plates. A thin vertical scratch was then introduced into the cell monolayer using a 200 µl pipette tip. After washing with PBS, cells were treated as indicated, and phase-contrast microscope images were captured at baseline and at regular intervals throughout the wound-healing process. Scratch area quantification was performed using ImageJ Fiji software. The wound area was measured by defining the region of interest and calculating the pixel-based area within the scratch. Threshold adjustments and edge detection tools were applied to ensure accurate quantification of cell migration over time.

Statistical analysis

Results are expressed as mean ± SE of the mean. Statistical analyses were performed using GraphPad Prism (GraphPad Software, California), with one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc test, or two-way ANOVA followed by Tukey's post-hoc test, as indicated in each figure legend. A p-value of <0.05 was considered statistically significant.

RESULTS

Culture and characterisation of HTFs

Primary cultures of HTFs were established from tissue specimens obtained during glaucoma filtering surgery. The cells grew as monolayers and exhibited a spindly, elongated morphology under a light microscope. To further characterise them, we performed immunostaining for vimentin, a widely used fibroblast marker

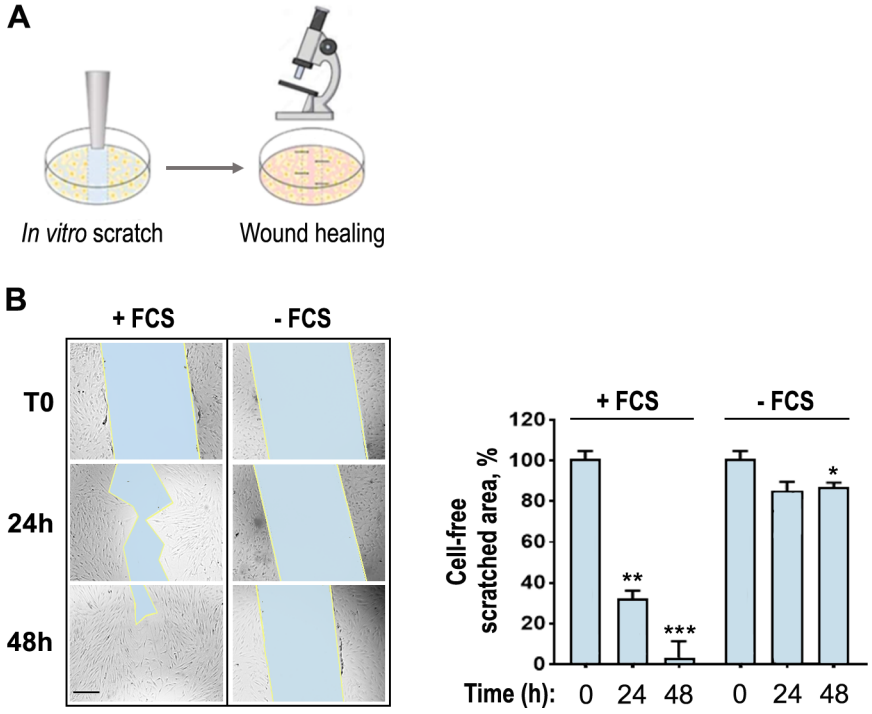

Figure 2 Serum deprivation inhibits in vitro wound healing by HTFs. (A) Graphic description of the wound-healing assay. (B) After seeding, HTFs were maintained for 24 hours in medium containing 10% FCS (+FCS) or in serum-free medium (0% FCS; −FCS;). Under these conditions, the confluent monolayers were wounded by manual scratching, and the scratched areas were observed under an optical microscope at the indicated time points and analysed using ImageJ Fiji software. Scale bar=300 µm. Bar graph shows mean±SEM from three independent experiments. *p<0.05, **p<0.01 and ***p<0.001 vs the corresponding T0 group (one-way analysis of variance (ANOVA), Dunnett's post-test). FCS, fetal calf serum; HTFs, human Tenon's fibroblasts; SEM, SE of the mean.

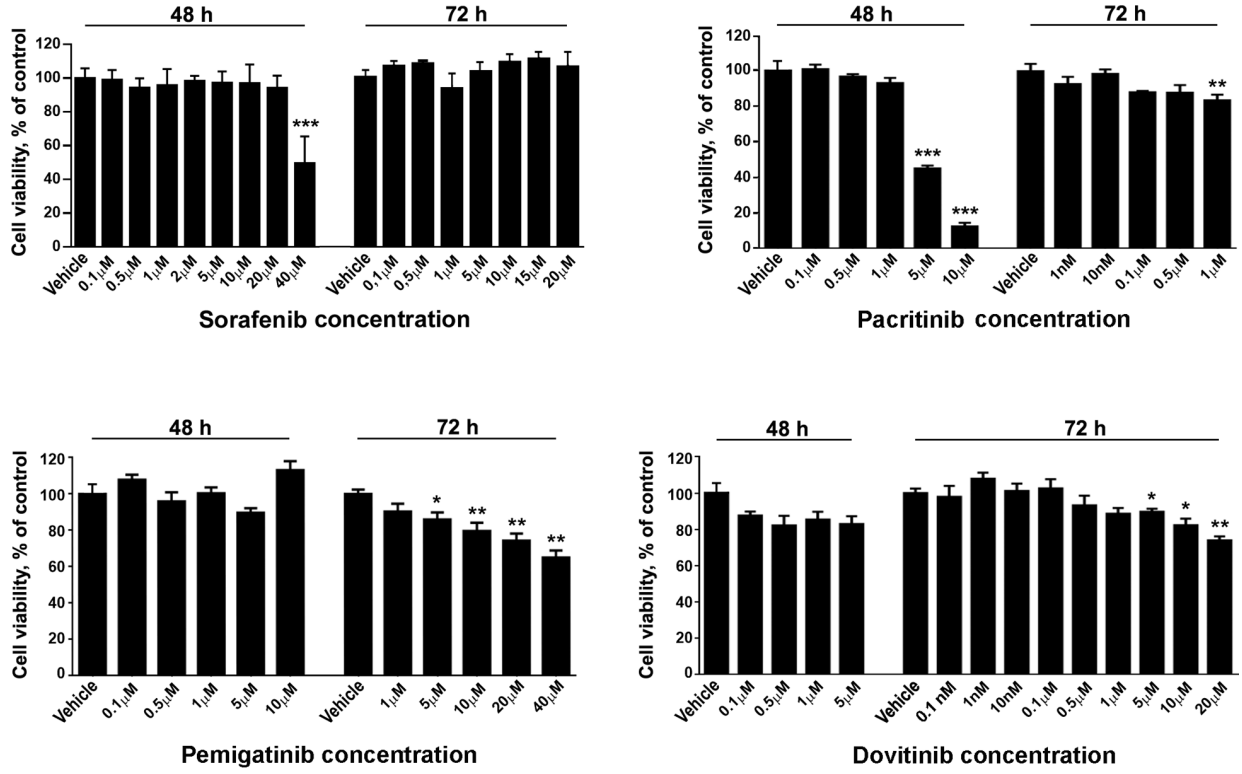

Figure 3 Cytotoxic potential of selected drugs. HTFs were incubated for 48 and 72 hours with different concentrations of each drug and then processed for MTT [3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyl-tetrazoliumbromide] assay. Control samples received the same amount of DMSO (vehicle) as treated samples (≤ 1:1000 v/v). Data are presented as mean±SEM from at least four independent experiments. *p<0.05, **p<0.01 and ***p<0.001 vs the corresponding vehicle-treated group (one-way analysis of variance (ANOVA), Dunnett's post-test). DMSO, dissolved in dimethyl sulfoxide; HTFs, human Tenon's fibroblasts; SEM, SE of the mean.

encoded by the *VIM* gene.[7] As shown in figure 1B, all cultured cells were positive for vimentin, confirming the high purity of the isolated HTFs and their suitability for this study.

In vitro wound healing is mainly due to HTF proliferation

Fibroblast proliferation and migration are key processes in wound healing.[8 9] To determine the relative contributions of these two factors to wound closure following trabeculectomy, we performed an in vitro wound-healing assay using HTFs under normal and serum-free conditions.

As shown in figure 2B, HTFs cultured in FCS-containing medium filled approximately 70% of the scratched area within 24 hours and nearly completed wound closure by 48 hours. In contrast, under serum-free conditions, HTFs exhibited markedly reduced closure, with 85% of the scratched area remaining cell-free after 48 hours. Since serum deprivation does not impair cell migration in this assay,[10 11] our results suggest that HTF proliferation plays a predominant role in the process of wound closure.

Sorafenib and pemigatinib slow down wound closure by HTFs

The above findings prompted us to investigate whether molecules with antiproliferative effects could interfere with wound closure by HTFs. To this end, we selected four small-molecule protein kinase inhibitors with reported antineoplastic activity (online supplemental figure 1). To determine suitable concentrations that affect proliferation without inducing cytotoxicity, HTFs were exposed to increasing doses of each drug, and their metabolic activity was assessed after 48 and 72 hours (figure 3). Based on the results obtained, we identified a concentration range that was considered safe for use in the wound-healing assay.

As shown in figure 4A, treatment with 5 µM sorafenib left 63% of the scratched area open after 24 hours and 18% after 48 hours, representing a 2-fold and 9.4-fold decrease in wound closure compared with controls, respectively. However, no significant differences were observed after 72 hours, as both control and treated cells had completely closed the wound. A stronger effect was observed with 0.5 µM pemigatinib, which maintained 22% of the scratched area open even after 72 hours. In contrast, pacritinib and dovitinib did not produce significant effects.

To further confirm the absence of cytotoxic effects for pemigatinib and sorafenib, LDH release assays were performed on HTFs and on an additional type of primary human cells derived from the trabecular meshwork (HTMCs). Consistent with the MTT results, pemigatinib showed no cytotoxicity in either cell type, whereas sorafenib induced a 28% cytotoxic effect specifically in HTMCs (figure 4B).

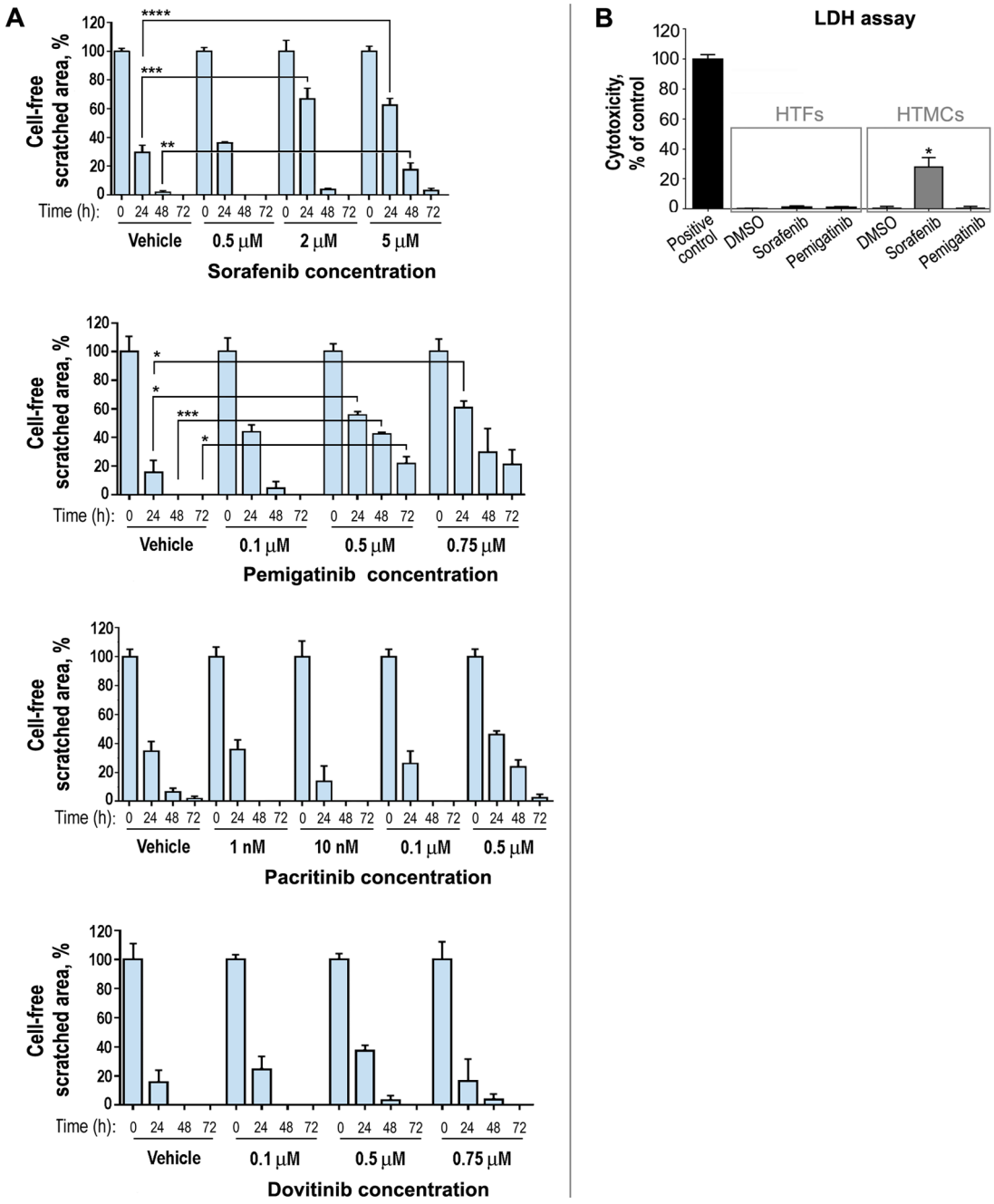

Figure 4 (A) Effect of selected drugs on wound healing. Confluent HTF cultures maintained in medium containing 10% FCS were manually scratched and immediately treated with the indicated drug concentrations. Scratched areas were observed under an optical microscope at the indicated times and analysed using ImageJ Fiji software. Data are presented as mean±SEM from three independent experiments. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001 (two-way analysis of variance (ANOVA), Tukey's post-test). (B) Effect of sorafenib and pemigatinib on LDH release. HTFs and HTMCs were treated with 5 µM sorafenib, 1 µM pemigatinib or an equivalent volume of vehicle (DMSO) for 24 hours in serum-free medium. At the end of the incubation period, conditioned media were collected and subjected to LDH analysis. The cytotoxic treatment provided with the LDH detection kit was used as a positive control. Data are presented as mean±SEM from four independent experiments. *p<0.001 vs corresponding DMSO-treated group (one-way ANOVA, Dunnett's post-test). FCS, fetal calf serum; HTFs, human Tenon's fibroblasts; HTMCs, human trabecular meshwork cells; LDH, lactate dehydrogenase; SEM, SE of the mean.

DISCUSSION

Long-term modulation of the scarring response remains a major challenge in glaucoma surgery. Although anti-metabolites are widely used to prevent postoperative scarring, their application is associated with sight-threatening complications, primarily due to the toxic effects on the conjunctiva and Tenon's capsule.[12] HTFs play a key role in postoperative wound healing and surgical failure, yet the underlying molecular mechanisms remain poorly understood.[13 14] Recent studies have employed HTFs to model fibrotic responses, including tissue contraction and extracellular matrix remodelling, providing valuable

insights into the pathways involved.[15–17] Here, we used primary HTF cultures derived from glaucoma surgery explants as an in vitro model to evaluate potential therapeutic agents aimed at improving filtration surgery outcomes.

Under our experimental conditions, HTF proliferation—rather than migration—was the dominant driver of wound closure. Accordingly, we focused on reducing cell proliferation and tested four antiproliferative agents: sorafenib, pemigatinib, pacritinib and dovitinib. Among these, only sorafenib and, to a greater extent, pemigatinib significantly reduced HTF proliferation and wound closure.

Sorafenib is an oral multikinase inhibitor that targets Raf serine/threonine kinases and receptor tyrosine kinases implicated in tumourigenesis and tumour progression. It has demonstrated antitumour activity in multiple cancers and is Food and Drug Administration-approved for the treatment of unresectable hepatic and advanced renal malignancies.[18] Its broad efficacy is attributed to its multiple molecular targets. Notably, although sorafenib does not directly target FGFRs, its off-target effects on FGFRs have been found to be clinically relevant.[19]

By contrast, pemigatinib, which exhibited a stronger antiproliferative effect in our study, is a selective FGFR inhibitor with no known activity against other protein kinases.[20] This suggests that FGFR signalling plays a central role in HTF proliferation. Supporting this interpretation, previous studies have shown that nintedanib—a multikinase inhibitor that also inhibits FGFR—reduces proliferation and migration of TGF-β-activated HTFs.[15] Selective FGFR inhibition may therefore represent an advance over non-specific kinase inhibitors. Notably, nintedanib has been associated with optic nerve, macula and retina complications.[21]

Cytotoxicity assays in HTMCs further characterised the safety profiles of these drugs. Pemigatinib was non-cytotoxic in both HTFs and HTMCs, whereas sorafenib induced a 28% cytotoxic effect in HTMCs. This likely reflects the lower selectivity of sorafenib compared with the highly selective FGFR inhibition of pemigatinib. However, the limited penetration of topically applied drugs into the trabecular meshwork suggests that such effects may be clinically negligible. Indeed, mitomycin C, which has been shown to be toxic to trabecular cells,[22] is conventionally used as an adjuvant in many filtering glaucoma procedures. In surgical glaucoma, trabecular cells are typically already dysfunctional, and the goal of surgery is to create an alternative pathway for aqueous humour outflow that bypasses the conventional trabecular route. For these reasons, we believe that cytotoxicity of a novel antifibrotic drug towards trabecular cells should not be considered a contraindication to further investigation as an adjuvant in glaucoma surgery.

The role of FGFR in HTF proliferation appears to be complex, as suggested by our results with dovitinib. Despite also being an FGFR inhibitor, dovitinib did not reduce proliferation to the same extent as pemigatinib. This discrepancy may be explained by its lower selectivity, as it inhibits multiple kinases that could counteract its antiproliferative effects (online supplemental figure 1). Furthermore, dovitinib does not inhibit FGFR2, which may represent the key FGFR isoform involved in HTF proliferation.

Importantly, the potential use of pemigatinib and sorafenib as adjuncts in glaucoma surgery should be evaluated in the context of current clinical practice. The standard agents used to limit postoperative scarring—mitomycin-C and 5-fluorouracil—are antimetabolites that inhibit DNA synthesis and cell proliferation by interfering with nucleotide metabolism. While effective, their non-selective cytotoxicity often leads to serious complications such as conjunctival thinning, bleb leakage and endophthalmitis. In contrast, the agents tested in our study act by modulating intracellular signalling pathways, such as FGFR and Raf kinases, rather than directly blocking DNA synthesis. This approach may allow for more controlled inhibition of fibroblast proliferation with potentially fewer adverse effects on surrounding ocular tissues.

In conclusion, our findings underscore the central role of HTF proliferation in postoperative wound healing and identify selective FGFR inhibition as a promising strategy to improve glaucoma surgery outcomes. Pemigatinib demonstrated potent antiproliferative effects and lack of cytotoxicity in HTMCs, highlighting its potential to modulate fibrosis while minimising off-target effects. Sorafenib showed weaker antiproliferative activity and limited cytotoxicity, which, given the low topical penetration into the trabecular meshwork, is unlikely to be clinically significant. Future research should validate these findings in vivo and assess the safety and efficacy of FGFR inhibitors as alternatives to conventional antimetabolite therapy in glaucoma filtration surgery.

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Competing interests CAC, MI and RR have filed a patent application (application number: 102025000002604) concerning 'Compounds for preventing and/or treating fibrosis resulting from glaucoma filtering surgery'.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Samples of human Tenon's capsules were obtained anonymously from tissue explants taken during trabeculectomy at the Eye Clinic of the University of Genoa, with the approval of the Institutional Ethics Committee (CET Liguria: 582/2023—DB id 13582). Informed consent from patients was not required for this study because the tissue samples used consisted exclusively of surgical waste obtained during routine ophthalmic procedures. The material was anonymised, and no additional interventions were performed for research purposes. In accordance with institutional and ethical guidelines, the use of discarded surgical tissue does not require specific patient consent when no identifiable information is collected.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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