Proliferative vitreoretinopathy (PVR) describes a retinal scarring process that occurs in 5% to 10% of rhegmatogenous retinal detachment (RRD) patients and up to 50% of open globe injury patients and is the main cause of surgical failure after retinal detachment surgery. Clinically, PVR is characterized by the growth and contraction of cellular fibrotic membranes within the vitreous, retina, and subretinal space, which exert traction, open treated breaks, create new breaks, and cause redetachment or distort the macula. Although the clinical manifestations of PVR are wide, they share a common sequence of underlying cellular responses that are associated with RRD and vitreous changes, and eyes with existing PVR are at higher risk of increased retinal cell proliferation after repeat vitreoretinal surgery.

The TGF-β superfamily modulates cell growth, inflammation, matrix synthesis, and apoptosis. TGF-β exists in two main forms (TGF-β1 and TGF-β2), with TGF-β2 being the predominant form in the posterior segment of human eyes. Both in vitro and in vivo, TGF-β isoforms regulate synthesis and degradation of extracellular matrix (ECM) proteins, causing increased collagen accumulation and fibrosis, which makes them key candidate prognostic biomarkers for PVR development and important therapeutic targets for prophylaxis and treatment of PVR. TGF-β is secreted as part of a latent form in the posterior segment of human eyes. Both in vitro and in vivo, TGF-β isoforms regulate synthesis and degradation of extracellular matrix (ECM) proteins, causing increased collagen accumulation and fibrosis, which makes them key candidate prognostic biomarkers for PVR development and important therapeutic targets for prophylaxis and treatment of PVR.
myofibroblast-like in the absence of normal cell-cell or cell-matrix interactions in vitro. There are separate TGF-β1 and TGF-β2 receptors, though many of these are cross-reactive. Several studies have found elevated TGF-β2 levels in vitreous samples from patients with PVR, suggesting a role in pathogenesis and potential as a predictive biomarker for PVR development.

Decorin is a small leucine-rich proteoglycan matrix-constitu-ent that opposes the actions of TGF-β by interacting with TGF-β and other cytokines. Decorin modulates matrix metalloproteinase (MMP) activity by increasing levels of plasmino-gen favoring higher ECM turnover leading to ECM degradation. Decorin elevates MMP2 and MMP9 levels, reduces fibronectin and laminin deposition, and attenuates fibrosis in animal models of many pathological conditions, including proliferative vitreoretinopathy, renal fibrosis, lung fibrosis, juvenile communicating hydrocephalus, and spinal cord injury.

We hypothesized that TGF-β would induce EMT in RPE cells in vitro and that decorin would oppose EMT. We also predicted that, in humans, high vitreous TGF-β and low vitreous decorin levels would predict the subsequent development of PVR in patients with RRD and that RRD patients would have higher vitreous TGF-β levels than patients with macular holes (MH).

We investigated the effects of TGF-β2 and decorin on ARPE-19 cell EMT in vitro, and for immunohistochemistry evidence of EMT in human PVR membranes, and we performed a prospective noninterventional cohort study of MH and RRD patients, following them up for 6 months to determine PVR development. Eyes with macula holes do not develop intraocular scarring despite having a retinal break and were used as a control for retinal detachment cases where there is a retinal break and a risk of intraocular scarring.

### Methods

#### Cell Culture

ARPE-19 cells (CRL-2302; ATCC, Manassas, VA, USA) were grown in Dulbecco’s modified Eagle’s medium/F12 supplemented with 100 U/mL penicillin/streptomycin and 10% heat-inactivated fetal bovine serum. Cells were incubated at 37°C in a humidified environment containing 5% CO2. For real-time PCR (qPCR), 300,000 cells/well were seeded in a six-well plate, grown in Dulbecco’s modified Eagle’s medium/F12 supplemented with 100 U/mL penicillin/streptomycin and 10% heat-inactivated fetal bovine serum. Cells were incubated at 37°C in a humidified environment containing 5% CO2. For real-time PCR (qPCR), 300,000 cells/well were seeded in a six-well plate, incubated overnight, and washed with PBS to remove FBS. Cells were then either treated with serum plus medium, 10 ng/mL transforming growth factor β2 (TGF-β2) in serum-free medium or given serum medium only. After 72 hours, cells were treated with decorin concentrations from 1 ng/mL up to 100 µg/mL with and without the previous treatment of TGF-β2 in serum medium and left for a further 72 hours, after which they were harvested. All cell cultures were performed in triplicate experiments, and each experiment was repeated on three independent occasions (n = 3 repeats in total).

#### Real-Time Quantitative qPCR Analysis

RNA was extracted from ARPE-19 cells using a purification mini kit according to the manufacturer's instructions (Qiagen RNaseasy; Qiagen, Hilden, Germany). RNA was reverse transcribed using a cDNA synthesis kit (Sensifast; Bioline, London, UK). qPCR was carried out using a fluorescent dye (SYBR Green Master Mix; Applied Biosystems, Foster City, CA, USA) in 20-µL reactions using a multicolor qPCR detection system (CFX; Bio-Rad, Watford, UK). Primers were optimized using a seven-point standard curve (Supplementary Table S1). Genes of interest were normalized to human GAPDH using the ΔΔct method based on primer efficiencies (HK-SYhu-1200; Primer-design, Camberley, UK). Data are presented normalized to TGF-β2-treated groups or the –serum group.

#### Bromodeoxyuridine (BrdU) ELISA

The ELISA was performed as previously described. Please see Supplementary Methods.

#### Clinical Studies

This cohort study was approved by the Solihull National Research Ethics Service committee and the use of tissue for immunohistochemistry by Arden Tissue Bank. The study was conducted in accordance with the Declaration of Helsinki.

We included patients in the cohort study who were undergoing vitrectomy for new RRD, MH, and established PVR and who were capable of consenting to participation. We excluded patients who had any previous vitreoretinal surgery (except for the established PVR group) or were aged under 10.

Tissue for immunohistochemistry was collected with consent from patients who were undergoing vitrectomy with membrane peel for PVR or internal limiting membrane (ILM) peel for MH repair. Total number of samples collected for each group is represented in Supplementary Figure S1.

#### Sample Collection

Vitreous was collected into a 5-mL syringe through an unprimed cutter at the start of surgery in the largest safe volume possible, ranging between 0.5 and 2 mL, before the infusion was turned on. Samples were refrigerated for up to 4 hours before being centrifuged at 12,500 g for 10 minutes and the supernatant collected and frozen at −80°C until analysis.

#### 3, 3-Diaminobenzidine (DAB) Staining of Human PVR and ILM Tissues

The membranes were removed from fixative and embedded in warm agar. Set agar blocks were processed into paraffin wax using a tissue processor (study reference: 17-0477) (Path-Center, Shandon Scientific, Runcorn, UK).

Blocks were sectioned at 5 µm using a microtome (Bright 5040; Bright Instruments, Luton, UK) and placed onto slides (Superfrost; Thermo Fisher Scientific UK Ltd, Loughborough, UK) and dried overnight at 50°C. Slides were stained by DAB according to the manufacturer’s instructions (Leica, Wetzlar, Germany). Please see Supplementary Methods.

#### TGF-β2 and Decorin ELISA

Sandwich ELISAs (R&D Systems, Minneapolis, MN, USA) were used to measure TGF-β2 and decorin levels in human vitreous samples after vitrectomical surgery. Total number of samples used for each assay is shown in Supplementary Figure S1. Vitreous samples were normalized according to volume as the protein content was below the level of sensitivity. TGF-β2 and decorin ELISAs were performed in accordance with manufacturer’s instructions. Please see Supplementary Methods.

#### Statistics

Averages are displayed as means plus or minus standard error in text and figures.
Sample size calculation was performed with statistical power analysis software (G*Power, v. 3.1.4; Kiel University, Kiel, Germany) for a two-sample t-test with an expected allocation of one PVR case per 10 retinal detachment cases. Pilot data from 46 patients with retinal detachment and 16 patients with MH indicated that vitreous levels of decorin were \((1463 \pm 219\) vs. \(261 \pm 57\ \text{pg/mL}\)). Power calculation performed in G*Power for a two-sample t-test indicated that we would require group sizes of 7 and 71 patients to have 80% power to detect the observed difference.

Our prespecified analysis was a t-test to compare vitreous decorin levels between patients with retinal detachment who did and who did not develop postoperative PVR, as variances were not homogeneous between groups, the PVR group was therefore used to examine the effect of TGF-\(\beta\)-2 and decorin on ARPE-19 cells.

**RESULTS**

**ARPE-19 Cell Cultures**

To characterize the effects of decorin on RPE cells we developed an in vitro model of RPE EMT. Serum-free ARPE-19 cell cultures expressed low levels of mRNA for connective tissue molecules laminin, fibronectin, and collagen type I and higher levels of the RPE markers RPE65 and CK8. Consistent with not having undergone EMT and not being in a pro-fibrotic state, they also expressed low levels of vimentin and \(\alpha\)-SMA (Fig. 1). In comparison to serum, cultures supplemented with serum (+serum) had increased expression of laminin \((P < 0.001)\), fibronectin \((P < 0.05)\), and collagen I \((P < 0.004)\) and reduced expression of the RPE markers CK8 \((P < 0.013)\) and RPE65 \((P < 0.035)\). Vimentin and \(\alpha\)-SMA levels were not significantly altered with serum. Serum-free cultures were therefore used to examine the effect of TGF-\(\beta\)-2 and decorin on ARPE-19 cells.

**TGF-\(\beta\)-2 In Vitro**

Compared to serum, 10 ng/mL of TGF-\(\beta\)-2 increased mRNA levels of fibronectin \((P < 0.05, \text{Fig. 1A})\), laminin \((P < 0.001, \text{Fig. 1B})\), collagen I \((P < 0.05, \text{Fig. 1C})\), \(\alpha\)-SMA \((P < 0.03)\) and decreased CK8 \((P < 0.017)\), which is consistent with an EMT phenotype. However, RPE65 and vimentin expression were not significantly altered with TGF-\(\beta\)-2 treatment when compared to serum control. TGF-\(\beta\)-2 at 10 ng/mL did not affect its own expression or that of decorin (Supplementary Fig. S2).

**Cell Culture Effects of Decorin**

ARPE-19 cells serum--serum levels were treated with decorin in the range of 1 ng/mL to 100 \(\mu\)g/mL. There was a strong overall effect of decorin supplementation on laminin, fibronectin, \(\alpha\)-SMA, and vimentin (Fig. 2). Bonferroni post-hoc testing found no evidence that mRNA expression levels of laminin, fibronectin, \(\alpha\)-SMA, and vimentin (Fig. 2) were affected by decorin treatment in the range of 1 to 100 ng/mL. However, decorin concentrations higher than 100 ng/mL reduced fibronectin expression \((1 \mu\text{g/mL} [P < 0.002], 10 \mu\text{g/mL} [P < 0.02], 100 \mu\text{g/mL} [P < 0.001])\), laminin \((10 \mu\text{g/mL} [P < 0.048], 100 \mu\text{g/mL} [P < 0.029])\), and vimentin \((100 \mu\text{g/mL} [P < 0.009])\). \(\alpha\)-SMA levels were not significantly downregulated when compared to the serum control, but high-concentration decorin supplementation did reduce \(\alpha\)-SMA expression compared to the low concentration \((P < 0.001)\). There was weak evidence that collagen I expression was reduced by an increasing concentration of decorin. CK8 levels were upregulated by 1 \(\mu\)g/mL of decorin \((P < 0.046)\) and then reduced at 100 \(\mu\)g/mL \((P < 0.045)\) decorin when compared to 1 \(\mu\)g/mL RPE65 levels showed a weak evidence of a trend similar to that...
seen with CK8. Decorin did not regulate its own expression, but did reduce TGF-β2 expression (Supplementary Fig. S2).

**Cell Culture Effects of TGF-β2 and Decorin**

Serum-free cultures of ARPE-19 cells were treated with 10 ng/mL of TGF-β2 for 3 days followed by 3 days with or without decorin in the range of 1 to 100 μg/mL. BrdU analysis did not show evidence of toxicity in terms of reduced proliferation with TGF-β2 and decorin supplementation in the dose-ranges studied (Supplementary Fig. S5). The addition of decorin at concentrations of 10 to 100 μg/mL abrogated TGF-β2-induced upregulation of fibronectin (Fig. 3A; *P* < 0.001), laminin (Fig. 3B; *P* < 0.001), collagen I (Fig. 3C; *P* < 0.001), α-SMA (Fig. 3D; *P* < 0.001), and vimentin (Fig. 3E; *P* < 0.001). No changes were seen in CK8 expression; however, RPE65 expression increased at 1 ng/mL (*P* < 0.001) and decreased at higher concentrations of decorin.

**PVR and ILM Staining**

Immunohistochemical analysis of human ILM and PVR membrane staining showed strong staining for fibronectin and collagen I (Fig. 4A[i], [iv] PVR tissue; Fig. 4B[i], [iv] ILM tissue). Laminin had greater levels of staining in the PVR tissue (Fig. 4A[ii]) with little staining observed in the ILM tissue (Fig. 4B[ii]). Vimentin is present in both tissues but is stronger in the PVR membranes (Fig. 4A[v], Fig. 4B[v]). Very low levels of α-SMA, RPE65, and CK8 immunostaining were seen in the PVR and ILM (Fig. 4A[iii], [vi], [vii]; Fig. B[iii], [vi], [vii]).

**FIGURE 2.** mRNA expression analysis of EMT markers in ARPE-19 cells in the presence of low- and high-dose decorin only. ARPE-19 cells were serum starved and treated with decorin in the range of 1 ng/mL to 100 μg/mL for 3 days. The addition of increasing concentrations of decorin led to significant decreases in the mRNA expression of fibronectin (A), laminin (B), collagen I (C), α-SMA (D), vimentin (E). Decorin doses led to increases in the epithelial marker CK8 (F), which then decreased at the highest doses of 100 μg/mL. Decorin did not significantly alter the expression of RPE65 (G). Data are presented as a fold change over GAPDH. Each group is representative of *n* = 3 with three experimental repeats. Data were analyzed by 1-way ANOVA. *P* < 0.05, **P** < 0.01, ***P*** < 0.001.

**FIGURE 3.** Decorin inhibition of EMT induced in ARPE-19 cells with 10 ng/mL TGF-β2. ARPE-19 cells were serum starved and treated with 10 ng/mL of TGF-β2 for 3 days, after which they were treated with decorin in the range of 1 ng/mL to 100 μg/mL for 3 days. qPCR analysis for mRNA expression revealed an increase of EMT markers with TGF-β2 treatment, which was significantly downregulated with a dose-dependent increase of decorin treatment for fibronectin (A), laminin (B), collagen I (C), α-SMA (D), vimentin (E), CK8 (F), and RPE65 (G) were then analyzed. Data are presented as a fold change over GAPDH. Each group is representative of *n* = 3 with three experimental repeats. Data were analyzed by 1-way ANOVA. *P* < 0.05, **P** < 0.01, ***P*** < 0.001.
Vitreous Decorin

We included 85 patients with retinal detachment (of whom 14 developed PVR), 33 patients with MH, and seven with PVR at presentation (Supplementary Fig. S1). Primary analysis showed there was some evidence that vitreous decorin levels were higher in patients with retinal detachment who did develop postoperative PVR (2391 ± 708 pg/mL, SD 1873 pg/mL) than in those who did not (1232 ± 201 pg/mL, SD 1694 pg/mL) develop postoperative PVR (t-test P = 0.038; Mann-Whitney U test = 0.075). There was weak evidence that total vitreous decorin levels increased between MH (962 ± 252 pg/mL), RRD, and those patients who went on to develop postoperative PVR (P = 0.09, 1-way ANOVA; P = 0.075, Kruskal-Wallace; Fig. 5). Patients with established PVR (1352 ± 692) had vitreous decorin levels similar to that of RRD patients (1231 ± 201 pg/mL) and MH (962 ± 252 pg/mL) patients. The weak association between higher levels of decorin in detachment and those patients who developed postoperative PVR suggests that vitreous decorin levels do not reliably predict the development of PVR but does support the hypothesis that vitreous decorin biology is altered in RRD and PVR, even if the increase in expression is variable.

Vitreous TGF-β

Vitreous TGF-β levels were measured in the same patients as was decorin. Vitreous levels of TGF-β1 were undetectable by ELISA. Total vitreous TGF-β2 in patients operated for RRD (651 ± 69 pg/mL) and MH (598 ± 81 pg/mL) was not different between any of the groups (Fig. 5), including between RRD patients with an uncomplicated postoperative course, those who went on to develop PVR (685 ± 99 pg/mL), and those with established PVR (809 ± 224 pg/mL). Active TGF-β2 levels were low and similar for all groups (RRD 33 ± 12 pg/mL, MH 38 ± 14 pg/mL, developed PVR 45 ± 14 pg/mL, established PVR 62 ± 24 pg/mL).

DISCUSSION

In vitro TGF-β2 causes EMT and fibrosis, while decorin is an antifibrotic agent that drives ARPE-19 cells away from a fibrotic phenotype, with downregulation of the same markers of EMT expressed by human PVR membranes. In vivo, we assessed vitreous decorin and TGF-β2 levels in patients with retinal detachment who went on to develop PVR and those who did not and compared these to patients undergoing MH surgery. There was weak evidence of a relationship between the subsequent development of PVR and vitreous decorin levels, with higher levels in RRD compared to MH patients and levels higher still in patients who subsequently developed PVR. The weak relationship and high variability suggest that vitreous decorin at the time of retinal detachment repair would be an unreliable biomarker for PVR development, although the finding may be more mechanistically important, and it may be that a larger study would have had greater power to robustly demonstrate this effect. The absence of a reliable causative relationship from a single cytokine is perhaps not surprising given that PVR is a complex and multifactorial condition and probably represents the end point of a number of different disease processes. As an antifibrotic cytokine, the altered decorin levels may represent a reaction to the exaggerated pro-fibrotic response to retinal detachment seen in PVR.

Before PVR occurs, a retinal break usually exposes RPE cells to vitreous. The subsequent RPE fibrosis with epiretinal, subretinal, and vitreous membrane formation suggests the presence of EMT activators within the vitreous.25 The source of these activators is not known, the TGF-β superfamily of growth factors plays an important role as an EMT inducer in PVR.25–28 All three isoforms are present in the eye;25,27 however, TGF-β1 levels are low or undetectable in the vitreous in comparison to TGF-β2 levels, which are much higher.4,5,26 This is supported by our results.

Altered TGF-β2 levels have been demonstrated in established PVR and in patients with RRD who subsequently
developed PVR, but this does not reliably and independently predict subsequent PVR development.\(^5\,13\,28\) In our patients, neither latent nor active vitreous TGF-\(\beta\)-2 levels separated RRD from MH patients or patients with established PVR and did not predict subsequent PVR development at the time of initial RRD. The narrow confidence intervals for TGF-\(\beta\)-2 levels suggest that this negative finding is robust, and our study is not underpowered with respect to this outcome. Additionally, active TGF-\(\beta\)-2 levels were significantly lower than latent TGF-\(\beta\)-2 levels in all groups. Therefore, given that TGF-\(\beta\)-2 is associated with fibrosis, our data are consistent with RPE EMT caused by increased RPE exposure to vitreous TGF-\(\beta\)-2 after migration into the vitreous cavity, rather than elevated vitreous levels per se. It is also possible that TGF-\(\beta\)-2 levels vary during the course of PVR development, and our relatively low measurements preceded a rise in TGF-\(\beta\)-2 levels in our RRD patients, observed after its effect in the established PVR cases.

Decorin antagonizes TGF-\(\beta\) and has independent anti-fibrotic properties. It presents itself as a strong therapeutic candidate to inhibit TGF-\(\beta\)-2-induced RPE fibrosis.\(^29\) It prevents fibrosis by directly binding and sequestering TGF-\(\beta\)-\(\beta\) and by inhibiting cell migration, proliferation, and extracellular matrix production.\(^30\,31\) Intravitreal injections of decorin reduced macroscopic fibrosis in a rabbit PVR model.\(^17\) It is therefore surprising that increased (not reduced) vitreous decorin levels were associated with PVR. We characterized the role of decorin in RPE EMT by developing an in vitro model of TGF-\(\beta\)-2-induced ARPE-19 cell EMT. TGF-\(\beta\)-2 induced expression of a wide selection of ECM and EMT markers combined with reduced epithelial marker expression in ARPE-19 cells. The mRNA changes in vitro reflected the human protein changes seen by immunohistochemistry, supporting the validity of this model.

The rate of PVR in our cohort was 11% (14/125; 95% confidence interval: 6.5%–18.4%), which is toward the upper end of published rates (5.1%–11.7%).\(^32\) The Birmingham and Midland Eye Centre is a regional tertiary referral center for vitreoretinal surgery and it may be that the case mix in our institution has a high risk of PVR. As the study was not designed to evaluate PVR rates, we cannot comment on the extent of preoperative risk factors that may affect these rates in our cohort.

We treated cells with decorin at a range of concentrations to compare physiologic vitreous levels and those that would occur after therapeutic supplementation. At low, physiologic concentrations, decorin did not inhibit the production of ECM markers induced by TGF-\(\beta\)-2 but did induce the expression of RPE65, a specific RPE marker. Decorin supplementation at higher concentrations (>1–10 \(\mu\)g/mL) significantly abrogated TGF-\(\beta\)-2-induced upregulation of ECM and EMT markers, confirming the feasibility of decorin as an antifibrotic agent. The effects of decorin on CK8 expression after TGF-\(\beta\)-2-induced upregulation of ECM were less pronounced. The variable effects of decorin at different concentrations suggest a biphasic dose-response, which may be related to steric hindrance for some effects at concentrations above 1 \(\mu\)g/mL\(^33\) or to a decorin-independent TGF-\(\beta\) pathway.\(^34\)

In burn patients, we have found that serum decorin correlates with injury severity,\(^35\) suggesting that its expression may be an injury response, with more severely damaged retinae expressing more decorin, though not at levels sufficient to prevent intraocular fibrosis. Unfortunately, we do not have sufficient clinical data to test this hypothesis. The most effective antifibrotic concentrations were in the microgram per milliliter range, suggesting that any therapeutic intervention to prevent or treat PVR should use decorin aiming for vitreous concentrations >1 \(\mu\)g/mL.

An important feature of PVR is the proliferation of RPE cells to produce epiretinal membranes. Our results suggest that this proliferation is not initiated by elevated vitreous TGF-\(\beta\)-2, consistent with current literature suggesting that TGF-\(\beta\)-s are not involved in the initiation of proliferation.\(^9,\,28\) Additionally, decorin, which antagonizes TGF-\(\beta\), did not affect RPE proliferation. Decorin has a variable antiproliferative effect, which differs between cell types.\(^29,\,36\) As the study was restricted in sample collection by clinical treatment, it was not possible to carry out more relevant serial assays that may have highlighted variations in decorin levels over time.

The data presented show that vitreous levels of TGF-\(\beta\)-2 and decorin in isolation are unlikely to be useful predictors of disease at the stages that we assayed, although elevated vitreous decorin may represent a response to injury. Our in vitro analysis shows that TGF-\(\beta\)-2 induces EMT in human RPE cells and that decorin reverts the cells to a more RPE-like
phenotype, meaning that decorin may have potential as part of a
treatment strategy for PVR.

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