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THE ROLE OF EPITHELIAL MESENCHYMAL TRANSITION AND EXTRACELLULAR MATRIX REMODELING IN PROLIFERATIVE VITREORETINOPATHY: A LITERATURE REVIEW

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ABSTRACT

Proliferative vitreoretinopathy (PVR) is a fibrotic complication of retinal detachment and the leading cause of failure after retinal reattachment surgery. Its pathogenesis involves retinal pigment epithelial (RPE) cells that undergo epithelial-mesenchymal transition (EMT), together with remodeling of the extracellular matrix (ECM), yet these two processes are often discussed separately. This literature review integrates current evidence on how EMT and ECM remodeling interact in PVR. After retinal injury and breakdown of the blood-retinal barrier, RPE cells lose polarity and intercellular junctions and acquire a mesenchymal, myofibroblast-like phenotype regulated by TGF-β/SMAD, Wnt/β-catenin, PI3K/Akt, PDGF receptor, and related pathways. These cells produce collagen I, fibronectin, and other matrix components that form contractile fibrocellular membranes. In turn, altered matrix composition and stiffness activate mechanotransduction pathways, including integrins, RhoA, and YAP/TAZ, which may reinforce the mesenchymal phenotype and sustain fibrosis, suggesting a bidirectional feedback loop that is supported mainly by experimental data. Current treatment relies on vitrectomy-based surgery, whose success remains limited in PVR, and no pharmacological agent has been approved, most clinical trials have failed to show benefit. Preclinical studies targeting EMT pathways, mechanotransduction, and drug-delivery systems are promising, but the evidence is mostly experimental, and combined targeting of EMT and ECM remodeling has not been tested directly. Further studies are needed to examine the EMT-ECM circuit as a whole, define the role of matrix stiffness in human PVR, and translate multi-target strategies into clinical trials.

Keywords: Proliferative Vitreoretinopathy; Epithelial-Mesenchymal Transition; Extracellular Matrix Remodeling; Retinal Pigment Epithelium; Mechanotransduction; Therapy

1 INTRODUCTION

Proliferative vitreoretinopathy (PVR) is a complication of retinal detachment (RD) characterized by retinal stiffening and the formation of contractile membranes on or beneath the retinal surface [1]. It is estimated to occur in 5-10% of all retinal detachments, and its incidence has remained largely unchanged for about 25 years despite advances in vitreoretinal surgery [2,3]. Reattachment surgery succeeds in most uncomplicated cases (about 98%) [4]. Nevertheless, satisfactory anatomical and visual outcomes are still not consistently achieved: about 10% of patients need additional surgery for recurrent RD, and the main cause of this failure is PVR [3,5]. Risk factors for PVR include preoperative factors, such as extensive RD; intraoperative factors, such as vitreous and subretinal hemorrhage; and postoperative factors, such as choroidal detachment [3]. PVR is graded clinically with standardized classifications. Several schemes exist, including the original Retina Society classification (1983), the Silicone Study classification (1989), and the updated Retina Society classification, which is the one most frequently used in treatment studies [6].

One mechanism that plays a crucial role in the development of PVR is epithelial-mesenchymal transition (EMT). EMT is a process in which epithelial cells lose their epithelial properties, such as polarity and cell-cell junctions, and migrate, proliferate, and produce excess extracellular matrix (ECM) [3,4]. Retinal pigment epithelial (RPE) cells that undergo EMT become the main source of ECM production, and the resulting ECM then provides a scaffold that supports contraction of the PVR membrane [1,3,7]. EMT and ECM remodeling are therefore closely interrelated, and for this reason the two mechanisms need to be discussed in an integrated manner.

This narrative review therefore aims to summarize the pathophysiology of PVR, describe the roles of EMT and ECM remodeling, examine how the two processes may reinforce each other, and outline current and emerging therapeutic approaches that target them.

2 METHODS

This study is a narrative literature review that synthesizes current evidence on how EMT and ECM remodeling interact in the pathogenesis of PVR. A narrative approach was chosen because the available evidence is heterogeneous and consists mainly of experimental (in vitro and animal) studies and narrative reviews, which precludes quantitative pooling. The review was organized around three questions: (1) how EMT contributes to PVR, (2) how ECM remodeling contributes to PVR, and (3) how the two processes interact and whether they can be targeted therapeutically. Literature searches were performed in PubMed, Scopus, and Google Scholar for articles published up to November 2026. Search terms combined keywords: ("proliferative vitreoretinopathy" OR "PVR") AND ("epithelial-mesenchymal transition" OR "EMT" OR "retinal pigment epithelium" OR "extracellular matrix" OR "matrix remodeling" OR "mechanotransduction" OR "YAP" OR "TGF-β" OR "treatment" OR "therapy"). The reference lists of key articles were also screened manually to identify additional relevant publications.

3 DISCUSSION

3.1 Pathophysiology of PVR

PVR is a multifactorial process triggered by RD [3]. A retinal tear causes migration of RPE cells and glial cells into the vitreous cavity, as well as breakdown of the blood-retinal barrier (BRB) [1,4]. BRB breakdown allows cytokines and growth factors to enter the retina, which promotes inflammation, cell migration, and the development of fibrosis [1].

At this stage, RPE cells undergo EMT, a change from epithelial characteristics toward a mesenchymal phenotype, marked by a decrease in epithelial markers (ZO-1, E-cadherin, cytokeratin) and an increase in mesenchymal markers (vimentin, N-cadherin, fibronectin) [3]. EMT does not always proceed completely and can produce various intermediate phenotypes [3]. RPE cells that undergo EMT resemble fibroblasts and promote ECM deposition and the formation of contractile PVR membranes [1]. This series of cellular processes, namely EMT, cell migration, chemotaxis, proliferation, formation of basement membrane and collagen, and cellular contraction, ultimately produces overt retinal pathology [8]. The process results in epiretinal and subretinal membranes [3].

The development of PVR involves various molecular mediators, including inflammatory cytokines, growth factors, chemokines, and wound-healing molecules [1]. Among them, PDGF, IL-6, IL-8, and TNF-α are considered particularly important [9]. After RD, macrophages, RPE cells, glial cells, and fibroblasts migrate into the vitreous, where they proliferate and form ECM proteins that assemble into a membrane [10]. The complexity of these interactions suggests that PVR probably involves dysregulation of diverse immunological and cellular pathways, without a single specific causative molecule having been identified [1]. Genetic predisposition is also thought to play a role, with polymorphisms in the LTA, TP53, MDM2, BCL2, and BAX genes associated with PVR, although their functional consequences are not yet fully understood [1].

3.2 Epithelial-Mesenchymal Transition in PVR

EMT is the process by which epithelial cells transform into cells with mesenchymal characteristics [7]. In PVR, this process is classified as type 2 EMT, which is associated with wound healing and fibrosis [7]. Retinal injury triggers the release of cytokines and growth factors that cause loss of cell-cell adhesion between RPE cells, so that the cells become activated, detach from Bruch's membrane, migrate, proliferate, and undergo EMT toward a mesenchymal or myofibroblast-like phenotype [7,11]. Damage to the cell-cell adhesion complexes causes RPE cells to lose apical-basal polarity and change shape into a spindle form [7]. These changes are marked by a decrease in epithelial markers such as E-cadherin and ZO-1 and an increase in mesenchymal markers such as N-cadherin, vimentin, α-smooth muscle actin (α-SMA), and fibronectin [4,7,11]. As a result, RPE cells show increased migration and proliferation, resistance to apoptosis, and greater ECM production and remodeling, which together contribute to PVR membrane formation [7,11]. During EMT in RPE cells, extracellular signals alter the expression of genes encoding epithelial and mesenchymal proteins and influence cellular behaviors such as migration, proliferation, and apoptosis, through a network of interacting signaling pathways [7]. This process is controlled by various extracellular signals, including cytokines, growth factors, and ECM components, which influence the activity of EMT transcription factors [7].

One of the key regulators of EMT in RPE cells is TGF-β. In the classical pathway, the TGF-β type I receptor phosphorylates SMAD2/3, and SMAD4 then forms a complex that enters the nucleus and regulates EMT-related genes [7]. The result is increased type I collagen and ECM and differentiation of fibroblasts into myofibroblasts [12]. EMT turns RPE cells into myofibroblast-like cells that migrate, proliferate, produce ECM, and express α-SMA, which increases contractility [7,11]. TGF-β promotes this differentiation [12], and the TGF-β/Smad3 and Stat3 pathways increase the expression of fibrotic genes [11].

In RPE cells, the combination of EGF and FGF2 activates Wnt signaling, increases nuclear β-catenin, and promotes proliferation, and together with TGF-β1 it induces EMT through SMAD/Zeb1/2 [7]. TGF-β also activates canonical Wnt signaling through p38, and Wnt has a strong profibrotic effect [4]. Non-SMAD pathways include PI3K/Akt, MAPK, and Jagged/Notch [7]. TGF-β activates PI3K and Akt, which inhibit glycogen synthase kinase 3β (GSK-3β) and thereby promote EMT [7]. GSK-3β knockdown increases migration and collagen contraction, and this effect is reversed by GSK-3β overexpression or PI3K/Akt inhibitors [7]. Thrombin activates PI3K and increases cyclin D1 and proliferation [7]. TGF-β also activates TAK1, which relays signals to p38, JNK, and NF-κB; TAK1 inhibitors reduce migration, contractility, and α-SMA [7].

PDGF receptor signaling is another central pathway. PDGFRα is required in experimental PVR, but PDGFs themselves are not essential: growth factors outside the PDGF family, including VEGF acting through a non-canonical mechanism, activate PDGFRα indirectly and sustain its signaling [13]. PDGFR activation has also been linked to the transformation of RPE cells, Müller cells, and fibroblasts into myofibroblasts, and PDGF-BB promotes RPE proliferation and migration through MAPK and induces α-SMA [4].

Myofibroblasts in PVR membranes do not arise from RPE cells alone. Other proposed sources include Müller cells, resident fibroblasts, and Myo/Nog cells found in human PVR membranes [4]; circulating fibrocytes [14]; and macrophages undergoing macrophage-myofibroblast transition, predominantly of the M2 phenotype [4,15]. This heterogeneity suggests that EMT of RPE cells is an important, but probably not the only, route to ECM-producing cells in PVR.

3.3 Extracellular Matrix Remodeling in PVR

The ECM is a non-cellular structure that provides mechanical support and regulates tissue homeostasis and signal transduction [16]. Its components include collagen, fibronectin, laminin, elastin, proteoglycans, and glycosaminoglycans (GAGs) [4]. In the retina, the ECM is found mainly in basement membranes (Bruch's membrane, the internal limiting membrane [ILM], and blood vessels) and between the RPE and the ILM, with Müller cells, glia, and astrocytes as the main sources [16]. At the vitreoretinal interface there are collagens IV, VI, and XVIII, laminin, fibronectin, proteoglycans, and hyaluronan [17]. The vitreous itself contains collagens II, IX, and V/XI, with hyaluronan as the main GAG, and its age-related liquefaction can lead to posterior vitreous detachment, which contributes to rhegmatogenous RD [16].

In PVR, the ECM undergoes abnormal remodeling and deposition [4]. The preretinal PVR membrane contains collagens I and III, laminin, fibronectin, and tenascin [3], with collagen I predominant and associated with RPE and Müller cells [4]. Collagen deposition is driven by TGF-β [4] and by the TGF-β/Smad3 and Stat3 pathways [16], and the myofibroblasts that produce it promote fibrosis [4]. RPE cells from PVR cases have a different integrin profile, so they bind fibronectin more readily and promote ECM accumulation [3]. TGF-β2, which is elevated in the PVR vitreous, induces fibronectin containing extra domain A (FN-EDA), enhanced by connective tissue growth factor (CTGF), and fibronectin, whether from plasma or local cells, helps form the initial membrane structure and contractile units [3]. Matricellular proteins (tenascin, thrombospondin 1 [TSP1], and secreted protein acidic and rich in cysteine [SPARC])

facilitate detachment of cells from the substrate so that proliferation and migration can occur, and all three have been found in PVR membranes [3].

ECM production and degradation are tightly controlled, with matrix metalloproteinases (MMPs) and TGF-β1 as the main factors [3]. MMP-1 and MMP-2 predominate in epiretinal and subretinal PVR membranes [18]. The MMP/TIMP balance is regarded as critical for ECM homeostasis, with MMP-3 and TIMP-1 reported in PVR retina and IL-6 enhancing MMP activity [4]. Whether a disturbed MMP/TIMP balance directly drives membrane contraction in human PVR remains to be established.

3.4 Interplay between EMT and ECM Remodeling in PVR

EMT drives ECM production. EMT in RPE cells is considered a hallmark of PVR pathogenesis [19]. It is regulated by growth factors (TGF-β, PDGF, EGF), intracellular pathways (Smads, Wnt, Akt2, TAK1), transcription factors (Snail, ZEB), and microRNAs (miR-29b, miR-204/211), and antagonizing them modulates PVR in experimental models [19]. RPE cells that undergo EMT become the main source of ECM, and the ECM they deposit provides a scaffold that supports contraction of the PVR membrane [1,3,7].

ECM influences EMT in return. ECM components are among the extracellular signals that influence the activity of EMT transcription factors [7], and experimental studies suggest that matrix mechanics contribute to this feedback. Matrix stiffness activates RhoA and the actin cytoskeleton, followed by YAP/TAZ-TEAD signaling, which regulates RPE migration, proliferation, and contraction [16]. Targeting matrix stiffness-induced activation of RPE cells through the RhoA/YAP pathway ameliorates experimental PVR [20], and YAP is essential for PVR development through EMT of RPE cells [21]. Integrins may provide a further link: PVR-derived RPE cells have an altered integrin profile that favors fibronectin matrix assembly [3], and a disintegrin mutant that blocks integrins αvβ3 and α5β1 reduces the severity of experimental PVR [22]. In other fibrotic and epithelial settings, αv integrins are major activators of matrix-bound latent TGF-β, and contraction of the matrix can stretch latent TGF-β and facilitate its activation [23]; active TGF-β in turn increases αv integrin expression, creating a feed-forward loop that reinforces EMT [24]. Whether this mechanism operates in PVR has not been directly demonstrated.

A proposed feedback loop. Taken together, these observations support a model in which EMT-derived myofibroblast-like cells deposit and contract a collagen- and fibronectin-rich matrix, and the resulting change in matrix composition and stiffness feeds back through integrin-RhoA-YAP/TAZ signaling, and possibly through latent TGF-β activation, to sustain the mesenchymal phenotype. This loop is inferred mainly from separate experimental observations rather than from studies that test both arms together; combined inhibition of EMT and ECM remodeling has not been tested directly [4,20], and the role of matrix stiffness in human PVR remains to be defined.

3.5 Therapeutic Approaches

Surgery remains the main treatment for PVR, consisting of pars plana vitrectomy (PPV) with membrane peeling, retinectomy, and silicone oil or gas tamponade [25,26]. However, the success rate is only 69-75%, compared with 98% in uncomplicated RD [4], and the Silicone Oil Study reported 35-42% [5]. Surgery also does not halt the underlying biological process, so the risk of recurrence remains high [4]. To date, no drug has been approved for PVR [4].

Most clinical trials have failed to show benefit [4,27]. A dexamethasone implant reduced cystoid macular edema at 6 months but did not improve anatomical or functional success, triamcinolone in open-globe trauma showed no benefit, and 5-fluorouracil with low-molecular-weight heparin did not improve anatomical or visual outcomes [4,27]. A meta-analysis of 27 randomized trials (3,375 patients) of corticosteroids, antimetabolites, anti-VEGF agents, heparin, infliximab, methotrexate, and retinoic acid found no significant benefit for reattachment or visual acuity compared with surgery alone [4]. The neutral results have been attributed to heterogeneous patient selection, late timing of intervention, choice of endpoints, lack of drug specificity, and short intraocular half-lives [4]. Methotrexate is the main exception under investigation. In the phase 3 GUARD trial, a multicenter, randomized, controlled, adaptive trial in which intravitreal methotrexate 0.8% (ADX-2191) was injected repeatedly over 16 weeks after vitrectomy [28], re-detachment requiring reoperation within 6 months occurred in 24% of treated patients versus 39% in a historical control group [9], and later conference data reported fewer postoperative complications such as hypotony and cystoid macular edema [30]. These results should be interpreted cautiously because the control group was historical [29], and another study of repeated intravitreal methotrexate found no difference in re-detachment or visual acuity [4].

Several therapeutic targets are being explored at the preclinical level (Table 1). Among EMT-related pathways, these include TGF-β/Smad, YAP, Wnt/β-catenin, RUNX1, NFATc1, AKT, and Notch [4,21,31]. Targeting the PDGFRα axis, for example by neutralizing VEGF with aflibercept, protected rabbits from experimental PVR [13], and doxycycline, which inhibits MMPs and p38/MAPK in RPE cells, has been proposed as an anti-fibrotic candidate [4]. Among mechanotransduction pathways, targets include integrins αvβ3 and α5β1, Rho-kinase (ripasudil), and RhoA/YAP [20–

22,32]. A multi-target strategy is considered necessary. Combined inhibition of EMT and ECM remodeling has not been tested directly, but RhoA/YAP is a candidate because it influences both processes [4,20].

Table 1: Selected therapeutic strategies for PVR and the stage of supporting evidence.

Target or process	Intervention studied	Evidence stage and main finding	Ref.
PDGFRα axis (VEGF and non-PDGF growth factors)	VEGF neutralization (aflibercept)	Preclinical; protected rabbits from experimental PVR	[13]
YAP (EMT of RPE cells)	Targeting YAP	Preclinical; YAP is essential for PVR development via EMT	[21]
RhoA/YAP (matrix stiffness)	Targeting stiffness-induced RhoA/YAP activation	Preclinical; ameliorated experimental PVR	[20]
Integrins αvβ3 and α5β1	Disintegrin rhodostomin mutant	Preclinical; reduced severity of experimental PVR	[22]
Rho-kinase	Ripasudil (liposome-encapsulated)	Preclinical; liposomal encapsulation enhanced efficacy	[32]
AIM2 (suppressor of EMT)	Absent in melanoma 2	Preclinical; suppresses RPE EMT and experimental PVR	[31]
MMPs and p38/MAPK	Doxycycline	Preclinical; inhibits MMPs and p38/MAPK in RPE cells	[4]
Drug delivery	Exosome-based dual drug-loaded nanocarrier	Preclinical; targeted, multiple-drug PVR therapy	[33]
Inflammation (adjunct)	Dexamethasone implant	Clinical; fewer cases of cystoid macular edema, no difference in anatomical or functional success	[4]
Antimetabolite plus anticoagulant	5-Fluorouracil with heparin	Clinical trials; no improvement in anatomical or visual outcomes	[4,27]
Folate antagonist	Intravitreal methotrexate (ADX-2191)	Phase 3 (GUARD); 24% vs 39% re-detachment versus historical control	[28–30]

Targeted drug delivery (micelles, hydrogels, exosomes, and others) may overcome rapid drug clearance and toxicity [4,33].

Limitations and Future Directions

This review has several limitations. It is a narrative review without a registered protocol or formal risk-of-bias assessment, so selection bias cannot be excluded. A substantial proportion of the cited sources are themselves reviews, and many mechanistic statements rest on in vitro or animal studies whose findings may not transfer to human PVR. The GUARD data summarized here come from trade-press reports of conference presentations and a trial registry record [28–30].

Several questions remain open. First, the EMT-ECM circuit should be examined as a whole, for example by testing combined inhibition of EMT-related signaling and mechanotransduction in the same model. Second, the role of matrix stiffness in human PVR remains to be defined, so the stiffness-dependent arm of the loop cannot yet be confirmed in patients. Third, because earlier trials have been limited by patient selection, timing, endpoints, and short drug half-lives [4], multi-target strategies with sustained-release delivery systems should be evaluated in trials designed to address these problems.

4 CONCLUSION

This review shows that PVR can be understood as the result of an interaction between EMT and ECM remodeling. After retinal injury, RPE cells lose polarity and cell-cell junctions and then undergo EMT toward a mesenchymal phenotype, marked by a decrease in epithelial markers and an increase in mesenchymal markers. This EMT contributes to myofibroblast differentiation; myofibroblasts can also arise from Müller cells, fibrocytes, M2 macrophages, and

Myo/Nog cells. On the other side, ECM remodeling, consisting of accumulation of collagens I and III, fibronectin, and tenascin and involvement of matrix metalloproteinases and their tissue inhibitors, drives the formation and contraction of fibrotic membranes. The two processes appear to reinforce each other: EMT increases ECM production, whereas ECM composition and stiffness may regulate EMT through integrins, RhoA, and YAP/TAZ, a potential feedback loop that could sustain fibrosis. The TGF-β, PDGFRα, YAP, RhoA, and integrin pathways are potential therapeutic targets, but the evidence is still largely preclinical and most clinical trials to date have been neutral. Further research is needed to test the EMT-ECM circuit as a whole, to establish the role of ECM stiffness in human PVR, and to translate multi-target strategies into clinical trials.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflict of interest.

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