tvst

Review

Inflammatory and Fibrogenic Factors in Proliferative Vitreoretinopathy Development

Rishika Chaudhary[1,2,3], Robert A. H. Scott[4], Graham Wallace[2], Martin Berry[2], Ann Logan[2,3], and Richard J. Blanch[2,3,5,6]

[1] Academic Unit of Ophthalmology, Birmingham and Midland Eye Centre, Birmingham, UK
[2] Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[3] NIHR Surgical Reconstruction and Microbiology Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[4] Edgbaston Eye Consultants, Birmingham, UK
[5] Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[6] Academic Unit of Military Surgery and Trauma, Royal Centre for Defence Medicine, Birmingham, UK

Correspondence: Richard J. Blanch. Neuroscience and Ophthalmology, Robert Aitken Building, University of Birmingham, Birmingham B15 2TT, UK. e-mail: r.j.blanch@bham.ac.uk

Received: August 22, 2019
Accepted: November 11, 2019
Published: February 21, 2020

Keywords: retina; cytokine; biomarkers; proliferative vitreoretinopathy; vitreous humor

Citation: Chaudhary R, Scott RAH, Wallace G, Berry M, Logan A, Blanch RJ. Inflammatory and fibrogenic factors in proliferative vitreoretinopathy development. Trans Vis Sci Tech. 2020;9(3):23, https://doi.org/10.1167/tvst.9.3.23

Purpose: Proliferative vitreoretinopathy (PVR) occurs in 5%–10% of rhegmatogenous retinal detachment cases and is the principle cause for failure of retinal reattachment surgery. Although there are a number of surgical adjunctive agents available for preventing the development of PVR, all have limited efficacy. Discovering predictive molecular biomarkers to determine the probability of PVR development after retinal reattachment surgery will allow better patient stratification for more targeted drug evaluations.

Methods: Narrative literature review.

Results: We provide a summary of the inflammatory and fibrogenic factors found in ocular fluid samples during the development of retinal detachment and PVR and discuss their possible use as molecular PVR predictive biomarkers.

Conclusions: Studies monitoring the levels of the above factors have found that few if any have predictive biomarker value, suggesting that widening the phenotype of potential factors and a combinatorial approach are required to determine predictive biomarkers for PVR.

Translational Relevance: The identification of relevant biomarkers relies on an understanding of disease signaling pathways derived from basic science research. We discuss the extent to which those molecules identified as biomarkers and predictors of PVR relate to disease pathogenesis and could function as useful disease predictors. (http://www.umin.ac.jp/ctr/ number, UMIN000005604)

Pathogenesis of Proliferative Vitreoretinopathy

Proliferative vitreoretinopathy (PVR) describes the accentuated retinal scarring that is the main cause of retinal reattachment surgical failure in 5%–10% of rhegmatogenous retinal detachment (RRD) cases.[1] Clinically, PVR is characterized by the growth and contraction of predominantly retinal pigment epithelium (RPE)-derived cellular fibrotic membranes with myofibroblastic transformation within the hyaloid and on both the inner and outer retinal surfaces. The traction exerted by these epiretinal membranes causes progressive retinal detachment, which either reopens treated retinal breaks, creates new retinal breaks, or distorts the macula. The clinical manifestations of PVR are associated with a sequence of underlying inflammatory and fibrotic changes. The post-RRD extracellular matrix (ECM), including proteoglycans, collagen and fibronectin, and fibrosis that culminates in the appearance of PVR epiretinal membranes may be distinct from that associated with proliferative diabetic retinopathy (PDR) and penetrating ocular trauma.[2] For example, fibronectin levels are higher in

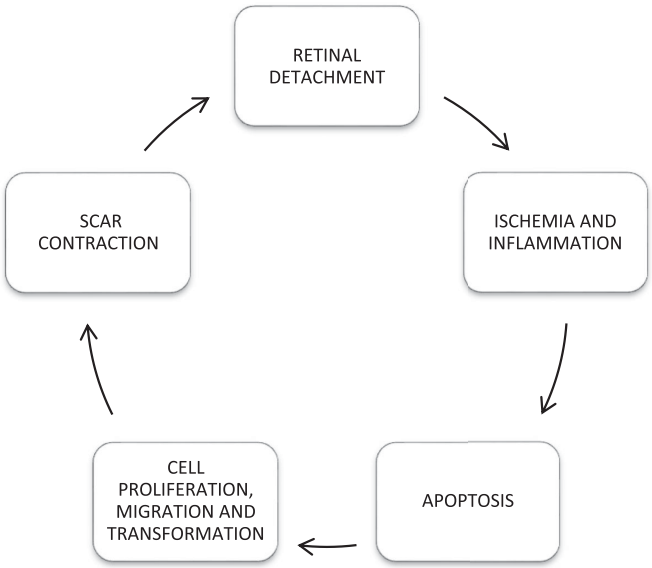

Figure. The key phases of PVR pathogenesis.

PVR compared with PDR membranes,[3] with greater retinal and immune cell proliferation.[4] Eyes with either pre-existing or established PVR are at a higher risk of increased retinal inflammation and fibrosis after repeated vitreoretinal surgery.[5,6]

PVR development is characterized by a sequence of distinct cellular and trophic responses that are described in the sections set out below (Fig). Retinal ischemia develops immediately after retinal detachment, followed by progressive photoreceptor apoptosis and contraction of fibrotic epiretinal membranes.[7] PVR retinal fibrosis is initiated by fibroblasts derived from RPE cells that undergo epithelial-mesenchymal transition (EMT) and begin collagen and ECM deposition,[8] orchestrated by a dysregulated panel of proinflammatory, chemotactic cytokines and mitogenic growth factors,[7] which induce an exaggerated inflammatory reaction at sites of retinal tears and detachment.[9] The early identification of inflammatory/fibrotic factors (IFF) that predict the subsequent development of PVR and direct treatments aimed at impeding/inhibiting PVR development after retinal reattachment surgery would constitute a significant clinical advance.

Pathological Phases of Post-Retinal Detachment PVR Development

Ischemic Phase

In the human retina, the inner two-thirds and outer one-third of the retina are supplied by retinal vessels and diffusion through the RPE from choroid plexus vessels, respectively.[10] After retinal detachment, the inner retina remains perfused, but the outer retina immediately becomes ischemic with consequent breakdown of the blood-retinal barrier in the inner retina, probably caused by diffusion of hypoxic products from the outer retina.[11–13] Approximately 20% of photoreceptors die by necrosis, caspase-dependent apoptosis and necroptosis after 3 days of retinal detachment and >50% die by 28 days,[14,15] and the structural changes associated with macula-off retinal detachment exacerbate the ensuing reduced vision.[16,17] Receptor interacting protein kinase (RIPK1 and RIPK3) mediate the principal photoreceptor cell death signaling pathways when caspases are inhibited by the pan-caspase inhibitor Z-VAD caspases after retinal detachment.[18] PVR pathogenesis involves ischemic processes driving the up-regulation of angiogenic and inflammatory growth factors and cytokines.[19] Inflammation triggers ischemia-induced angiogenesis, fibrogenesis and glial (astrocytes and microglia) proliferation.[20] The severity of retinal detachment correlates with the extent of blood-retinal barrier breakdown and the presence of IFF.[21–23]

Inflammatory Phase

Serum factors released into the vitreous, such as thrombin, stimulate the inflammatory phase of PVR development.[24] The development of PVR subretinal and epiretinal membranes is associated with vitreal accumulation of inflammatory cells,[25] including a significant elevation CD163/CD206-expressing M2 macrophages.[26–28] Microglia, which regulate macrophage infiltration, proliferate and infiltrate through the retina and into the subretinal space within days of detachment.[29,30] peritoneal macrophages injected into the vitreous of the rabbit trans-differentiate into fibroblast-like cells and initiate intraretinal fibrosis similar to that seen in PVR.[31] Macrophages clear retinal debris, alter vitreal structure through matrix protein-proteolysis and secrete fibroblast growth factor (FGF) and transforming growth factor–beta (TGFβ) which stimulate the accumulation and proliferation of fibroblast-like-cells within the incipient PVR epiretinal membranes.[32,33] T-helper cells have both profibrotic and antifibrotic potential, demonstrated by the release of antifibrogenic cytokines such as interleukin-10 and profibrogenic cytokines such as FGF2, platelet-derived growth factor (PDGF), TGFβ and vascular endothelial growth factor (VEGF),[34–36] as well as antifibrotic interferon-gamma, which inhibits collagen synthesis in vitro.[37] Vitreous cytokine changes in early PVR

suggest the importance of T helper responses in early PVR, with T helper (TH) cells identified in vitreous and PVR membranes, with both TH1- and TH2-associated cytokines implicated, although in immunocompromised mice lacking antigen-specific T- and B-cell responses, intravitreal dispase still induces PVR.[38,39]

Retinal Apoptotic Phase

Apoptosis balances cell proliferation with cell loss and is mediated through either intrinsic or extrinsic signaling pathways initiated by intracellular death receptor-binding.[40] Apoptosis shares a number of PVR pathogenetic signaling pathways. For example, TGFβ upregulates the survival of RPE cells, induces proliferation and down-regulates the death-inducing signaling molecule FasL, blocking T cell–mediated apoptosis.[41,42] Proapoptotic Fas and tumor necrosis factor (TNF)–related apoptosis-inducing ligands are both upregulated in the vitreous after retinal detachment and in established PVR and single nucleotide polymorphisms in TNFα strongly associate with PVR risk.[43–45] TNF-related apoptosis-inducing ligand mRNA levels were significantly correlated with anti-apoptotic TGF-β2 titers, no correlation was found between TGF-β2 and Fas mRNA levels, although TUNEL measures of apoptosis did correlate with TGFβ levels.[43] Fas ligand receptor binding activates the extrinsic pathway of apoptosis in proliferating, but not in non-proliferating RPE cells.[43,46] The FasL/Fas system therefore has a probable role in removing excess RPE cells after retinal detachment and, may predispose to PVR when defective.[43] Fas ligation also increases intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression in nonocular endothelial cells in vitro.[47] Soluble ICAM-1, soluble VCAM-1, and FasL and Fas are raised in the subretinal fluid (SRF) of RRD eyes with established PVR and in those that develop PVR later.[48,49] Levels of soluble forms of ICAM-1 and VCAM-1 are upregulated at 7 days but not 28 days after experimental retinal detachment in rats, consistent with their early role in recruiting immune cells.[50] Thus vitreous levels of ICAM-1 and VCAM-1 are both associated with inflammation and may be upregulated by apoptotic signaling in photoreceptors and RPE cells,[51] but their inconsistent appearance in PVR makes both factors unlikely predictive PVR molecular biomarkers.

Cell Migratory and the Proliferative Phases

After retinal detachment, PVR is initiated by TGFβ-activated RPE cells, which undergo EMT and form multilayered dedifferentiated cell groups that migrate into the vitreous through breaks in the detached retina, with some evidence that Müller glia also undergo glial-mesenchymal transition under the influence of TGFβ.[52,53] Fibroblasts in PVR membranes may therefore be derived from EMT-transformed RPE cells, glial-mesenchymal transition–transformed Müller glia and circulating fibrocytes.[54] Epiretinal membranes have an acellular collagenous core and layers of transformed and untransformed RPE cells, proliferating Müller glia, and IL-2 receptor$^+$ T lymphocytes and macrophages, as well as astrocytes and microglia.[55,56] IFF stimulate ECM formation, while plasma fibronectin induces the deposition of a fibroblast-derived collagen matrix and the production of locally synthesized fibronectin, thrombospondin and other proteoglycans,[57] and the ensuing mature ECM regulates RPE and inflammatory cell migration.[58] RPE cells respond to retinal detachment by proliferating and switching to an ECM and profibrotic secretory phenotype.[52,59] Müller glia also proliferate and secrete ECM and profibrotic and inflammatory mediators.[60,61] Annexin AII is a Ca2+-dependent phospholipid-binding protein that regulates RPE-phagocytosis of photoreceptor outer segments and is expressed in photoreceptor apoptosis,[62] but it also interacts with tissue plasminogen activator to promote ECM degradation and is necessary for vitreal RPE cell migration in PVR.[63,64] Paracrine insulin-like growth factor–1 and epidermal growth factor stimulate tissue plasminogen activator expression, which regulates ECM turnover by converting plasminogen to plasmin,[65] activating procollagenase and initiating ECM degradation.[66] ECM degradation may release FGF-2 and TGFβ sequestered in the ECM, opposing further degradation and stimulating proliferation and ECM secretion.[67]

Scar Contraction Phase

After retinal detachment, transformed cells in PVR membranes differentiate into myofibroblasts.[52,53] Alpha-smooth muscle actin intermediate filament synthesis is stimulated by IL-1 and contraction in myofibroblasts is mediated by Annexin A2, exacerbating retinal detachment and releasing streams of RPE cells into the vitreous.[68] Such contractile activity measured by tissue culture assay reduces with both age and at longer times after initial diagnosis of retinal detachment, suggesting that activity is transient after retinal detachment but nonetheless correlates with subsequent PVR development.[69]

Table 1. Predictive Cytokines and Growth Factors in Subretinal Fluid

	Interleukin							Chemokine Ligand							CXC Ligand										
Author/year	1α	2	3	6	11	15	18	2	3	11	17	18	19	22	8	9	10	CTSS	ADIPOQ	Leptin	ICAM-1	VCAM-1	VEGF	Fas	FasL	TIMP-1
Ricker et al. 2012[112]	+	+	+*	+	+			+*	+	+	+	+	+	+*			+	+	+		+					-
Ricker et al. 2012[152]																		+	+*	+						-
Ricker et al.2011[10]	+	+	+*	+*		+	+														+*		+			
Ricker et al. 2011[44]																					+	+		+	+	
Ricker et al. 2010[113]				+				+		+	+	+	+	+	+	+										

Table 2. Predictive Cytokines and Growth Factors in Vitreous Samples

	IL-6	TGF-β2	FGF-2	Tot Prot	MMP-2	MMP-9	Cont Stim Fac	Decorin	miR-21
Kon et al. 2000[13]				+					
Kon et al. 1999[105]	+	+	+	+					
Kon et al. 1998[171]					+	+			
Hardwick et al. 1995[64]							+		
Begum et al. 2018[103]		+						+	
Usui-Ouchi et al. 2016[186]									+

Candidate Biomarkers for Predicting PVR After Retinal Detachment

Candidate predictive biomarkers are summarized in Tables 1 and 2.

PVR Inflammatory Phase Cytokines

Interleukin-6

Interleukin-6 (IL-6) is a multifunctional, pleiotropic cytokine that immune regulates, acute-phase inflammatory responses, hematopoiesis and inflammation.[70] IL-6 is produced by RPE, endothelial cells, fibroblasts, neutrophils, monocytes and macrophages in response to IL-1, IL-17 and TNF-α during systemic inflammation.[70,71] IL-6 is both proinflammatory and anti-inflammatory in the eye and elsewhere,[72–74] stimulating a paracrine and autocrine immune response by activating leukocytes and inducing the production of acute-phase proteins by hepatocytes.[70] IL-6 promotes T-cell proliferation, B-cell differentiation and survival, plasma-cell production of immunoglobulin G, A, and M and modulates metabolic, regenerative and intracellular signaling pathways.[70,75] IL-6 binds to an IL-6R, which also has a soluble form (sIL-6R). IL-6 bound to soluble IL-6R stimulates RPE cells proliferation in vitro and IL-6 is necessary for subretinal scarring in a laser-induced choroidal neovascularization mouse model.[76,77] IL-6 correlates with PVR severity and the production of matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression, particularly MMP2 and TIMP1, indicating a role in fibrosis.[78–83] IL-6 can also stimulate corneal epithelial cells and stromal fibroblasts (and macrophages) to produce profibrotic VEGF.[78]

Like most inflammatory cytokines, IL-6 is present in subretinal fluid in high titers during retinal detachment and RRD repair,[84,85] and their presence is correlated with the subsequent, development of postoperative PVR,[9] as well as being elevated in the vitreous of patients with early PVR,[38,86] and correlating with PVR severity when found in sub silicone-oil fluid,[87] but, because subretinal and vitreous IL-6 levels significantly overlap between patients with uncomplicated retinal detachment and severe or future PVR, they have limited biomarker potential.

Interleukin-1

Interleukin-1α (IL-1α) and IL-1β are the two major isoforms of IL-1, the former is biologically active, whereas the latter is activated by the inflammasome.[88] Once activated, both isoforms exert similar effects as potent proinflammatory cytokines that act as

endogenous pyrogens.[88] They have diverse potentiating effects on cell proliferation and differentiation and regulate the function of immunocompetent cells, initiating and potentiating immune and inflammatory responses.[88] In animal models, IL-1 induces a proliferative response, generating PVR membranes in mouse eyes with pre-existing retinal holes.[89] An early response to retinal detachment is the infiltration into the subretinal space of IL-1β–secreting macrophages which may contribute to photoreceptor death through the (nucleotide-binding oligomerization domain) NOD-like receptor family and pyrin-domain-containing-3 protein inflammasome,[90] as well as stimulating RPE cells to upregulate inflammatory cytokines, including IL-6.[91]

IL-1α and IL-1β are present in subretinal and vitreal fluid in cases of RRD and established PVR and are variably reported to be raised in PVR,[38,80,86] whereas other studies suggest that elevated IL-1α, but not IL-1β levels are associated with subsequent PVR risk.[9,92] Generic inflammatory cytokines are likely to be present in all eyes with retinal detachment irrespective of whether they subsequently develop PVR, and in the report suggesting IL-1α associated with subsequent PVR risk, there was extensive overlap between levels in patients who did and did not subsequently develop PVR,[9] suggesting limited utility as a biomarker. However, when combined with other clinical and genetic markers, a single nucleotide polymorphism in IL-1 receptor antagonist was associated with PVR risk, supporting the role of IL-1 in PVR pathogenesis.[45]

TGFβ

The TGFβ superfamily are important modulators of cell growth, matrix synthesis and apoptosis.[67] TGFβ opposes the actions of many pro-inflammatory cytokines and TGFβ$_1$ and TGFβ$_2$ isoforms are found in the eye, with levels of TGFβ$_2$ being predominant in the posterior segment of human eyes.[93,94] Both in vitro and in vivo, TGFβ isoforms regulate the synthesis and degradation of ECM, causing increased collagen accumulation and fibrosis.[95] TGFβ is secreted as part of a latent complex, cleaved into its active form by RPE cell–derived thrombospondin-1.[96] Activated TGFβ transforms RPE cells into type 1 collagen producing fibroblast-like cells and myofibroblast-like cells; actions that are dependent on a lack of normal cell-cell or cell-matrix interactions in vitro.[97,98] There are separate receptors (R) for TGFβ$_1$ and TGFβ$_2$, although many of these cross-react and TGFβ$_2$R co-localizes with TGFβ$_1$ and fibronectin expression in myofibroblastic RPE cells,[99,100] although the relative roles of TGFβ$_1$ and TGFβ$_2$ in the fibrotic process of PVR have yet to be determined. TGFβ$_2$ is secreted by activated T lymphocytes and M2 macrophages, whose polarization it also induces.[28,95] TGFβ$_2$ regulates TGFβR and downstream signaling molecule expression, as well as the transcription of genes that encode for proinflammatory growth factors and IL-1R and IL-6R.[101,102] TGFβ$_2$ can also induce the proliferation of fibroblasts at low concentrations by modulating autocrine PDGF secretion.[103] TGFβ$_2$ maintains the immunosuppressive status of aqueous humor in mouse eyes afflicted with endotoxin-induced uveitis.[73] RPE cells secrete CTLA-2α, differentiating T cells into TGFβ-producing T$_{reg}$ cells.[104] In patients with RRD caused by PVR, variably elevated levels of TGF-β$_2$ are recorded in aqueous and vitreous samples and excised PVR fibrous membranes,[43,86,93,105,106] and single nucleotide polymorphisms in TGFβ$_{1\&2}$ associate with PVR risk.[45]

Because TGFβ isoforms regulate the synthesis and degradation of ECM proteins both in vitro and in vivo, causing increased collagen accumulation and fibrosis, they are obvious candidates as PVR predicative biomarkers.[95] However, in conflicting data, some articles record no difference in vitreous and aqueous levels of TGFβ isoforms in retinal detachment patients who do or do not go on to develop PVR, whereas others record elevated levels in vitreous of PVR patients.[107–109] Nonetheless, levels of decorin (a potent TGFβ antagonist and potential PVR treatment)[110] are higher in eyes with retinal detachment that did develop PVR supporting involvement of the decorin-TGFβ axis is the pathogenesis of PVR.[107] Decorin also has pro-inflammatory and pro-apoptotic effects, stimulating TNFα release and downregulating (anti-inflammatory) interleukin-10, although variability in decorin levels limits its utility as a biomarker to distinguish patients who will or will not go on to develop PVR.[107,111]

Chemokines

Chemokines are small proteins that regulate the migration of leukocytes into sites of inflammation.[112] Chemokines are divided into two groups depending on their chemotactic activity and the arrangement of cysteine residues. CC chemokines, named because of adjacent cysteine residues, attract monocytes, T lymphocytes, eosinophils and basophils. CXC chemokines, so-named because N-terminal cysteine residues are separated by another amino acid (represented by X), recruit neutrophils and activated T lymphocytes.[112] Chemokine R are integral membrane proteins that specifically bind and respond to chemokines. For example, CCR2 is found on the surface of monocytes and binds monocyte

chemo-attractant protein-1 (CCL-2), a chemokine that specifically mediates monocyte chemotaxis in experimental retinal detachment.[112,113] CCL2 levels are elevated in the vitreous of patients with PDR and in idiopathic epiretinal membranes.[114] Most chemokines tested for are elevated in the subretinal fluid of patients with primary RRD compared to vitreous from patients with macular hole.[86,115–117] One study finds higher CCL2 levels in established PVR than in primary RRD, suggesting a late role in the disease process.[118] Zandi et al.[86] record elevated levels of a multiplicity of chemokines (CCL8, 15, 19, 22, 23, 26, 27 and CXCL6, 9, 10, 12) in cases of PVR compared to primary RRD without PVR but find that only levels of CCL19 are associated with the grade of PVR.[86] Ricker et al.[115–117,119] find that CCL17, 19, 22, and CXCL9 to predict the development of postoperative PVR and CCL19 also correlated with postoperative visual acuity, and Hoerster et al.[108] find that aqueous CCL2 predicts the development of PVR.

CCL2 is produced locally by Müller glia and in cultured IL-1/TNF-α-stimulated CCL2^{+} RPE cells, contributing to photoreceptor apoptosis after retinal detachment.[120,121] Many cell types (including human microglia and astrocytes) express CXCL8 in response to inflammatory stimuli.[122] Müller glia resident in PVR membranes also express CXCL8, which chemoattracts neutrophils and probably promotes gliosis.[122,123] CXCL9 and CXCL10 are specific for T lymphocytes.[124,125] CXCR3 and CXCL9R and CXCL10R are preferentially expressed on T lymphocytes mediating intraocular inflammation.[126] Cultured RPE cells produce CXCL9 and CXCL10 in response to TNF-α, IL-1β, and IFN-γ, which is inhibited by IFN-β.[127] Although absent from the vitreous in PVR, IFN-β may protect against retinal inflammation.[127] The CC chemokines CCL17, CCL18 and CCL22 mediate cell trafficking and activation of T lymphocytes.[128–130] CCL19 is crucial for the development of adaptive immunity, mediating migration of naïve, T_{reg} and natural killer T cells and B cells, as well as macrophages within lymphoid tissue and stimulating macrophages and fibroblasts to secrete IL-8 and VEGF, respectively.[131,132]

During the development of PVR, locally generated chemo-attractive factors that direct both the migration and proliferation of RPE cells, fibrous astrocytes, fibroblasts and chemoattract macrophages, lymphocytes, and neutrophils are possible predictive PVR chemokine biomarkers.[91,120,133–135] However, levels of most of the above chemokines are raised in RRD irrespective of subsequent progression to PVR, and levels overlap significantly between patients who do and do not develop PVR. The approach of Ricker et al.,[116] who combine clinical predictors with levels of multiple cytokines including the presence of pre-existing PVR, CCL22 and IL-3 to improve predictive value, may hold promise.

Mitogenic Growth Factors

PDGF and VEGF

PDGF and VEGF are closely related members of a superfamily of signaling molecules, with a cysteine-knot structure formed by 8 cysteine residues.[136] Intravitreal injected (iviti) PDGF into traumatized rabbit eyes causes severe PVR, as do iviti PDGF and platelets into traumatized pig eyes.[137–139] PDGF displays a wide spectrum of chemo-attractive and mitogenic activities for mesenchymal cells and glia.[136] Proangiogenic VEGF is present in the developing PVR fibrotic membranes, as well as epiretinal and diabetic proliferative membranes. VEGF is synthesized and secreted by both retinal glia and RPE cells and levels may be raised in serum samples of patients with PVR, suggesting systemic levels confer disease susceptibility.[140–142] Levels average 2X higher in the subretinal fluid from eyes that go on to develop PVR compared to those that do not, although significant overlap between the vitreous VEGF levels in the two populations limits its utility as a biomarker in isolation.[9] RPE cells and retinal glia in epiretinal membranes express VEGF, PDGF and PDGFR and VEGFR,[143–145] suggesting an important role in epiretinal membrane growth, although iviti bevacizumab (monoclonal antibody against VEGF) does not seem to prevent and may worsen further membrane development in eyes with advanced PVR.[146,147] PDGFα, FGF-2, TGFβ, insulin-like growth factor–1 and epidermal growth factor are present in vitreous and SRF in PVR may promote RPE proliferation and fibrosis.[9,148]

FGF-2

In vitro, FGF-2 stimulates EMT production by RPE cells and is RPE-cell– but not Müller glia–protective (although it does stimulate migration of the latter cells).[144,149,150] In conflicting reports, vitreal and subretinal fluid FGF-2 levels are raised in both PDR,[151] established PVR,[109,152,153] and elevated in vitreous but not aqueous or subretinal fluid of RRD patients who subsequently develop PVR on follow-up.[9,108,109] Thus further evidence is required before FGF-2 is accepted as a predictive biomarker for PVR developing after retinal reattachment surgery.

Adipokines

Adipokines are a group of trophic mediators, originally identified in adipose tissue but now known

to be important in most inflammatory and immune responses and in wound healing in many tissues including the eye.[154,155] For example, in analyses of subretinal fluid sampled at the time of retinal reattachment surgery for primary RRD, high leptin, adiponectin and cathepsin S levels and low TIMP-1 levels are associated with the development of postoperative PVR.[156]

Leptin

Vitreal leptin levels are elevated in females and diabetics.[157] Mice defective in leptin and leptin-R have dysregulated immune and inflammatory responses and impaired wound healing.[158] High levels of serum leptin are associated with disease activity in Vogt-Koyanagi-Harada disease,[159] highlighting a possible ocular inflammatory role. In a rabbit model, successful treatment of PVR was associated with reduced vitreous leptin levels.[160] SRF leptin levels correlate significantly with body mass index,[156] but there is no consistent association with PVR.[156,161] Obese patients are at increased risk for development of RRD,[162] although this may be a mechanical effect and may or may not translate into a higher rate of PVR since the relationship between obesity and PVR remains unresolved.

Cathepsin S

The cysteine protease cathepsin S has a key role in antigen presentation[163] and is produced by RPE cells, where it is crucial for photoreceptor cell maintenance by regulating rhodopsin lysosomal digestion.[164,165] Cathepsin S is also upregulated in detached neuroretina as early as 24 hours after detachment and levels of cathepsin S are raised in the SRF of patients with retinal detachments that go on to develop PVR and correlate with the extent and duration of retinal detachment and this remains significant after correction for body mass index[50,156]; however, significant overlap between cathepsin S levels in patients who did and did not go on to develop PVR limits its utility as a biomarker in isolation.

TIMP and MMP

TIMP1 is a glycoprotein that inhibits MMP, a group of peptidases that degrade ECM and remodel collagen.[166] In addition, TIMP-1 promotes the proliferation of a wide range of cell types and may also have anti-apoptotic properties.[167,168] TIMP-1 regulates photoreceptor migration and expression is linked to retinal fibrosis,[169] and angiogenesis.[170–172] RPE cells produce TIMP-1 both in vitro and in excised epiretinal and subretinal membranes.[173,174] Protease/protease inhibitor imbalance within the detached retina and adjacent vitreous may therefore contribute to PVR membrane formation.

A number of MMP isoforms are normally present in the vitreous.[175] MMP-2 is constitutively expressed in normal vitreous and probably regulates collagen turnover and the degradation of gelatin (denatured collagen) and a number of cytokines, including TGFβ.[176,177] Multiple hormones, cytokines and growth factors regulate MMP expression and, in vitreal pathology such as diabetic retinopathy and retinal vein occlusion, increased expression is associated with VEGF expression.[176,178] MMP-12 is important for macrophage migration in murine retina and vitreous but has not been detected in human vitreous.[179] Low levels of MMP3 are protective against experimental uveitis,[180] whereas MMP9 levels correlate with the severity of wet (age-related macular degeneration) AMD.[181]

The most abundant protease inhibitor in human plasma in α1-antitrypsin, which is consistently elevated in the vitreous of patients with PVR.[182,183] Vitreous MMP-1, -2, -3, -8, -9 and TIMP-1 levels correlate with PVR grade.[177] Vitreous MMP, TIMP-1 and α-1 antitrypsin are therefore all consistently elevated in patients with PVR and single nucleotide polymorphisms in MMP-2 associate with PVR risk.[45] In patients with retinal detachment, increased vitreous MMP-2 and -9 activity associates with subsequent postoperative PVR, with a negative predictive value (for low activity) of 100% for MMP-2 and 97% for MMP-9 (positive predictive values for high activity 16% and 19%, respectively).[175]

Periostin

Periostin is a fibroblast-derived matricellular mitogenic protein that stimulates EMT in cancer cells, accelerates cutaneous wound healing by activating fibroblasts[184,185] and causes inflammatory chemotaxis of TH2 cells and M2 macrophages by inducing cytokine production.[186,187] In patients with PVR, vitreal periostin levels are elevated along with high periostin expression in PVR membranes,[27] and the protein is produced in vitro by RPE cells that undergo TGFβ_2-induced EMT.[106] These findings provide little support that periostin is likely to be useful as a predictive PVR molecular biomarker.

MicroRNA

Significant interest in the role of microRNA (miRNA), including exosomal miRNA,[188] in systemic and ophthalmic disease, including diabetic retinopathy and age-related macular degeneration, has been reflected in an exponential increase in the number of publications in recent years.[189] A single study has evaluated miRNA as predictive biomarkers of PVR and found that miR-21, a profibrotic miRNA, was

upregulated in the vitreous of eyes with PVR and was also upregulated in vitro by Human adult retinal pigment epithelial cells (ARPE-19) after TGFβ-induced EMT, regulating migration and proliferation.[190] The miR-21 transcription is induced by a number of proinflammatory and profibrotic stimuli including IL-6 and TGFβ and opposed by decorin, being post-transcriptionally activated through the actions of TGFβ.[111,191] The miR-21 production is associated with resolution of acute inflammation and the switch to a profibrotic phenotype,[191] making miR-21 a candidate biomarker requiring confirmation.

Validation of Molecular PVR Biomarkers

Predictive molecular biomarkers are agents present in tissues which forecast the risk of development of a specific pathology in which the biomarker may or may not persist.[192] The assessment of biomarker validity is critically dependent on reliability of the serial sampling technique and positive and negative predictive values. Serial consistency in harvesting SRF and vitreal fluid is difficult to achieve and can generate highly variable mean putative biomarker values and thus requires careful supervision and attention to detail. Serum samples would provide more reliable readings, but relevant biomarker titers are likely to be significantly lower than those from retina, where factors are locally produced; consequently few serum-based studies have been reported.[193] In addition, surgical techniques for the management of RRD can vary widely, with surgeon-dependent PVR-rates, meaning that the process of PVR may also vary between surgeons, suggesting that either surgical approach should be considered in detail in future biomarker studies or that sampling should include a range of surgeons or surgical techniques.

In cases of retinal detachment which go on to the develop PVR, IFF molecules consistently present before PVR onset have potential positive predictive value (PPV) and those present in retinal detachment cases that do not develop PVR have negative predictive value (NPV). One conundrum of screening potential biomarkers is that IFF feature in the retinal detachment condition irrespective of whether PVR ensues, probably explaining why so few IFF have PPV status. Thus factors other than IFF may constitute more plausible biomarker candidates. Factors with PPV that persist into the predicted disease state may also be used as putative prognostic biomarkers with a potential for targeting and monitoring anti-PVR treatments.[194] PPV/NPV rarely reach 100% and values are commonly much lower posing a problem in setting a threshold for assessing the status of biomarker rigor. Meaningful statistical estimates of PPV and NPV are dependent on the prevalence of PVR after RRD and as many studies use matched rather than consecutive cases, PPV and NPV cannot be meaningfully calculated. Therefore few studies claiming biomarker potential for particular IFF have evaluated their PPV/NPV. The most promising approach so far is in the combination of multiple clinical and laboratory biomarkers to improve the sensitivity and specificity of PVR prediction.[13,45,116]

Conclusion

PVR remains the most common reason for failure of retinal detachment after re-attachment surgery. Biomarker profiling has the potential for better prediction of PVR risk after surgery to inform surgical technique and identify patients in whom novel prophylactic adjunctive anti-PVR therapies might be of use. The evidence presented here shows that numerous IFF are a feature of retinal detachment and also contribute to the development of PVR but, because individual IFF have limited PPV, the search for PVR predictive biomarkers should combine selected biomarkers and broaden screening methods to encompass molecules other than IFF.

Acknowledgments

Funded by the National Institute for Health Research (NIHR) Surgical Reconstruction and Microbiology Research Centre (SRMRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Each author is aware of the ARVO Commercial Relationships Policy. There is no commercial interest.

Disclosure: **R. Chaudhary,** None; **R.A.H. Scott,** None; **G. Wallace,** None; **M. Berry,** None; **A. Logan,** None; **R.J. Blanch,** None

References

1. Sadaka A, Giuliari GP. Proliferative vitreoretinopathy: current and emerging treatments. *Clin Ophthalmol*. 2012;6:1325–1333.

2. Pastor JC. Proliferative vitreoretinopathy: an overview. *Surv Ophthalmol*. 1998;43:3–18.
3. Ioachim E, Stefaniotou M, Gorezis S, Tsanou E, Psilas K, Agnantis NJ. Immunohistochemical study of extracellular matrix components in epiretinal membranes of vitreoproliferative retinopathy and proliferative diabetic retinopathy. *Eur J Ophthalmol*. 2005;15:384–391.
4. Oberstein SY, Byun J, Herrera D, Chapin EA, Fisher SK, Lewis GP. Cell proliferation in human epiretinal membranes: characterization of cell types and correlation with disease condition and duration. *Mol Vis*. 2011;17:1794–1805.
5. Bonnet M. The development of severe proliferative vitreoretinopathy after retinal detachment surgery. Grade B: a determining risk factor. *Graefes Arch Clin Exp Ophthalmol*. 1988;226:201–205.
6. Pournaras C, Tsika C, Brozou C, Tsilimbaris MK. Surgical and visual outcome for recurrent retinal detachment surgery. *J Ophthalmol*. 2014; 2014:810609.
7. Di Lauro S, Kadhim MR, Charteris DG, Pastor JC. Classifications for Proliferative Vitreoretinopathy (PVR): An Analysis of Their Use in Publications over the Last 15 Years. *J Ophthalmol*. 2016;2016:7807596.
8. Yang S, Li H, Li M, Wang F. Mechanisms of epithelial-mesenchymal transition in proliferative vitreoretinopathy. *Discov Med*. 2015;20:207–217.
9. Ricker LJ, Kijlstra A, Kessels AG, et al. Interleukin and growth factor levels in subretinal fluid in rhegmatogenous retinal detachment: a case-control study. *PloS one*. 2011;6:e19141.
10. Kiel JW. The ocular circulation. *Colloquium Series on Integrated Systems Physiology: From Molecule to Function*.: Morgan & Claypool Life Sciences; 2011:1–81.
11. Bali E, Feron EJ, Peperkamp E, Veckeneer M, Mulder PG, van Meurs JC. The effect of a preoperative subconjuntival injection of dexamethasone on blood-retinal barrier breakdown following scleral buckling retinal detachment surgery: a prospective randomized placebo-controlled double blind clinical trial. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:957–962.
12. Tolentino FI, Lapus JV, Novalis G, Trempe CL, Gutow GS, Ahmad A. Fluorescein angiography of degenerative lesions of the peripheral fundus and rhegmatogenous retinal detachment. *Int Ophthalmol Clin*. 1976;16:13–29.
13. Kon CH, Asaria RH, Occleston NL, Khaw PT, Aylward GW. Risk factors for proliferative vitreoretinopathy after primary vitrectomy: a prospective study. *Br J Ophthalmol*. 2000;84:506–511.
14. Cook B, Lewis GP, Fisher SK, Adler R. Apoptotic photoreceptor degeneration in experimental retinal detachment. *Invest Ophthalmol Vis Sci*. 1995;36:990–996.
15. Lewis GP, Charteris DG, Sethi CS, Leitner WP, Linberg KA, Fisher SK. The ability of rapid retinal reattachment to stop or reverse the cellular and molecular events initiated by detachment. *Invest Ophthalmol Vis Sci*. 2002;43:2412–2420.
16. Menke MN, Kowal JH, Dufour P, et al. Retinal layer measurements after successful macula-off retinal detachment repair using optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2014;55:6575–6579.
17. Schocket LS, Witkin AJ, Fujimoto JG, et al. Ultrahigh-resolution optical coherence tomography in patients with decreased visual acuity after retinal detachment repair. *Ophthalmology*. 2006;113:666–672.
18. Trichonas G, Murakami Y, Thanos A, et al. Receptor interacting protein kinases mediate retinal detachment-induced photoreceptor necrosis and compensate for inhibition of apoptosis. *Proc Natl Acad Sci USA*. 2010;107:21695–21700.
19. Pastor JC, Rojas J, Pastor-Idoate S, Di Lauro S, Gonzalez-Buendia L, Delgado-Tirado S. Proliferative vitreoretinopathy: A new concept of disease pathogenesis and practical consequences. *Prog Retin Eye Res*. 2016;51:125–155.
20. Geller SF, Lewis GP, Anderson DH, Fisher SK. Use of the MIB-1 antibody for detecting proliferating cells in the retina. *Invest Ophthalmol Vis Sci*. 1995;36:737–744.
21. Pollreisz A, Sacu S, Eibenberger K, et al. Extent of Detached Retina and Lens Status Influence Intravitreal Protein Expression in Rhegmatogenous Retinal Detachment. *Invest Ophthalmol Vis Sci*. 2015;56:5493–5502.
22. Sen HA, Robertson TJ, Conway BP, Campochiaro PA. The role of breakdown of the blood-retinal barrier in cell-injection models of proliferative vitreoretinopathy. *Arch Ophthalmol*. 1988;106:1291–1294.
23. Takahashi S, Adachi K, Suzuki Y, Maeno A, Nakazawa M. Profiles of Inflammatory Cytokines in the Vitreous Fluid from Patients with Rhegmatogenous Retinal Detachment and Their Correlations with Clinical Features. *Biomed Res Int*. 2016;2016:4256183.
24. Bastiaans J, van Meurs JC, Mulder VC, et al. The role of thrombin in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 2014;55:4659–4666.

25. Charteris DG, Hiscott P, Grierson I, Lightman SL. Proliferative vitreoretinopathy. Lymphocytes in epiretinal membranes. *Ophthalmology*. 1992;99:1364–1367.
26. Kobayashi Y, Yoshida S, Nakama T, et al. Overexpression of CD163 in vitreous and fibrovascular membranes of patients with proliferative diabetic retinopathy: possible involvement of periostin. *Br J Ophthalmol*. 2015;99:451–456.
27. Yoshida S, Nakama T, Ishikawa K, Nakao S, Sonoda KH, Ishibashi T. Periostin in vitreoretinal diseases. *Cell Mol Life Sci*. 2017;74:4329–4337.
28. Zhang J, Zhou Q, Yuan G, Dong M, Shi W. Notch signaling regulates M2 type macrophage polarization during the development of proliferative vitreoretinopathy. *Cell Immunol*. 2015;298:77–82.
29. Kiang L, Ross BX, Yao J, et al. Vitreous Cytokine Expression and a Murine Model Suggest a Key Role of Microglia in the Inflammatory Response to Retinal Detachment. *Invest Ophthalmol Vis Sci*. 2018;59:3767–3778.
30. Paschalis EI, Lei F, Zhou C, et al. Permanent neuroglial remodeling of the retina following infiltration of CSF1R inhibition-resistant peripheral monocytes. *Proc Natl Acad Sci USA*. 2018;115:E11359–E11368.
31. Hui YN, Sorgente N, Ryan SJ. Posterior vitreous separation and retinal detachment induced by macrophages. *Graefes Arch Clin Exp Ophthalmol*. 1987;225:279–284.
32. Li J, Wang JJ, Peng Q, et al. Macrophage metalloelastase (MMP-12) deficiency mitigates retinal inflammation and pathological angiogenesis in ischemic retinopathy. *PloS one*. 2012;7:e52699.
33. Wang LC, Hung KH, Hsu CC, Chen SJ, Li WY, Lin TC. Assessment of retinal pigment epithelial cells in epiretinal membrane formation. *J Chin Med Assoc*. 2015;78:370–373.
34. Kovacs EJ, Kelley J. Lymphokine regulation of macrophage-derived growth factor secretion following pulmonary injury. *Am J Pathol*. 1985;121:261–268.
35. Piguet PF, Collart MA, Grau GE, Sappino AP, Vassalli P. Requirement of tumour necrosis factor for development of silica-induced pulmonary fibrosis. *Nature*. 1990;344:245–247.
36. Trinchieri G. Interleukin-10 production by effector T cells: Th1 cells show self control. *J Exp Med*. 2007;204:239–243.
37. Nanes MS, McKoy WM, Marx SJ. Inhibitory effects of tumor necrosis factor-alpha and interferon-gamma on deoxyribonucleic acid and collagen synthesis by rat osteosarcoma cells (ROS 17/2.8). *Endocrinology*. 1989;124:339–345.
38. Roybal CN, Velez G, Toral MA, Tsang SH, Bassuk AG, Mahajan VB. Personalized Proteomics in Proliferative Vitreoretinopathy Implicate Hematopoietic Cell Recruitment and mTOR as a Therapeutic Target. *Am J Ophthalmol*. 2018;186:152–163.
39. Zhang W, Tan J, Liu Y, Li W, Gao Q, Lehmann PV. Assessment of the innate and adaptive immune system in proliferative vitreoretinopathy. *Eye*. 2012;26:872–881.
40. Galluzzi L, Vitale I, Abrams JM, et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. *Cell Death Differ*. 2012;19:107–120.
41. Genestier L, Kasibhatla S, Brunner T, Green DR. Transforming growth factor beta1 inhibits Fas ligand expression and subsequent activation-induced cell death in T cells via downregulation of c-Myc. *J Exp Med*. 1999;189:231–239.
42. Lee J, Choi JH, Joo CK. TGF-beta1 regulates cell fate during epithelial-mesenchymal transition by upregulating survivin. *Cell Death Dis*. 2013;4:e714.
43. El Ghrably I, Powe DG, Orr G, et al. Apoptosis in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 2004;45:1473–1479.
44. Rojas J, Fernandez I, Pastor JC, et al. Development of predictive models of proliferative vitreoretinopathy based on genetic variables: the Retina 4 project. *Invest Ophthalmol Vis Sci*. 2009;50:2384–2390.
45. Rojas J, Fernandez I, Pastor JC, et al. Predicting proliferative vitreoretinopathy: temporal and external validation of models based on genetic and clinical variables. *Br J Ophthalmol*. 2015;99:41–48.
46. Chang JH, Kang SW, Ham DI. Sensitivity of CD95-induced apoptosis in different proliferative status of human retinal pigment epithelial cells. *Korean J Ophthalmol*. 2001;15:74–80.
47. Cardier JE, Schulte T, Kammer H, Kwak J, Cardier M. Fas (CD95, APO-1) antigen expression and function in murine liver endothelial cells: implications for the regulation of apoptosis in liver endothelial cells. *FASEB J*. 1999;13:1950–1960.
48. Barile GR, Chang SS, Park LS, Reppucci VS, Schiff WM, Schmidt AM. Soluble cellular adhesion molecules in proliferative vitreoretinopathy and proliferative diabetic retinopathy. *Curr Eye Res*. 1999;19:219–227.

49. Ricker LJ, Altara R, Goezinne F, Hendrikse F, Kijlstra A, La Heij EC. Soluble apoptotic factors and adhesion molecules in rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci*. 2011; 52:4256–4262.
50. Zacks DN. Gene transcription profile of the detached retina (An AOS Thesis). *Trans Am Ophthalmol Soc*. 2009;107:343–382.
51. Besirli CG, Chinskey ND, Zheng QD, Zacks DN. Inhibition of retinal detachment-induced apoptosis in photoreceptors by a small peptide inhibitor of the fas receptor. *Invest Ophthalmol Vis Sci*. 2010;51:2177–2184.
52. Anderson DH, Stern WH, Fisher SK, Erickson PA, Borgula GA. The onset of pigment epithelial proliferation after retinal detachment. *Investigative ophthalmology & visual science*. 1981;21:10–16.
53. Kanda A, Noda K, Hirose I, Ishida S. TGF-beta-SNAIL axis induces Muller glial-mesenchymal transition in the pathogenesis of idiopathic epiretinal membrane. *Sci Rep*. 2019;9:673.
54. Abu El-Asrar AM, Struyf S, Van Damme J, Geboes K. Circulating fibrocytes contribute to the myofibroblast population in proliferative vitreoretinopathy epiretinal membranes. *Br J Ophthalmol*. 2008;92:699–704.
55. Charteris DG, Hiscott P, Robey HL, Gregor ZJ, Lightman SL, Grierson I. Inflammatory cells in proliferative vitreoretinopathy subretinal membranes. *Ophthalmology*. 1993;100:43–46.
56. Fisher SK, Lewis GP, Linberg KA, Verardo MR. Cellular remodeling in mammalian retina: results from studies of experimental retinal detachment. *Prog Retin Eye Res*. 2005;24:395–431.
57. Tosi GM, Marigliani D, Romeo N, Toti P. Disease pathways in proliferative vitreoretinopathy: an ongoing challenge. *J Cell Physiol*. 2014;229: 1577–1583.
58. Sheridan CM, Magee RM, Hiscott PS, et al. The role of matricellular proteins thrombospondin-1 and osteonectin during RPE cell migration in proliferative vitreoretinopathy. *Curr Eye Res*. 2002;25:279–285.
59. Rattner A, Toulabi L, Williams J, Yu H, Nathans J. The genomic response of the retinal pigment epithelium to light damage and retinal detachment. *J Neurosci*. 2008;28:9880–9889.
60. Eastlake K, Banerjee PJ, Angbohang A, Charteris DG, Khaw PT, Limb GA. Muller glia as an important source of cytokines and inflammatory factors present in the gliotic retina during proliferative vitreoretinopathy. *Glia*. 2016;64:495–506.
61. Geller SF, Lewis GP, Fisher SK. FGFR1, signaling, and AP-1 expression after retinal detachment: reactive Muller and RPE cells. *Invest Ophthalmol Vis Sci*. 2001;42:1363–1369.
62. Valapala M, Maji S, Borejdo J, Vishwanatha JK. Cell surface translocation of annexin A2 facilitates glutamate-induced extracellular proteolysis. *J Biol Chem*. 2014;289:15915–15926.
63. Choi KS, Fitzpatrick SL, Filipenko NR, et al. Regulation of plasmin-dependent fibrin clot lysis by annexin II heterotetramer. *J Biol Chem*. 2001; 276:25212–25221.
64. Hajjar KA. *Annexin A2 in Proliferative Vitreoretinopathy*.. Weill Medical College of Cornell University New York, United States; 2017.
65. Esser P, Heimann K, Bartz-Schmidt KU, Walter P, Krott R, Weller M. Plasminogen in proliferative vitreoretinal disorders. *Br J Ophthalmol*. 1997;81:590–594.
66. Elner SG. Human retinal pigment epithelial lysis of extracellular matrix: functional urokinase plasminogen activator receptor, collagenase, and elastase. *Trans Am Ophthalmol Soc*. 2002;100:273–299.
67. Schultz GS, Wysocki A. Interactions between extracellular matrix and growth factors in wound healing. *Wound Repair Regen*. 2009;17:153–162.
68. Grieve AG, Moss SE, Hayes MJ. Annexin A2 at the interface of actin and membrane dynamics: a focus on its roles in endocytosis and cell polarization. *Int J Cell Biol*. 2012;2012:852430.
69. Hardwick C, Morris R, Witherspoon D, et al. Pathologic human vitreous promotes contraction by fibroblasts. Implications for proliferative vitreoretinopathy. *Arch Ophthalmol*. 1995;113:1545–1553.
70. Mauer J, Denson JL, Brüning JC. Versatile functions for IL-6 in metabolism and cancer. *Trends in immunology*. 2015;36:92–101.
71. Liu X, Ye F, Xiong H, et al. IL-1beta induces IL-6 production in retinal Muller cells predominantly through the activation of p38 MAPK/NF-kappaB signaling pathway. *Exp Cell Res*. 2015;331:223–231.
72. Curnow SJ, Falciani F, Durrani OM, et al. Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. *Invest Ophthalmol Vis Sci*. 2005;46:4251–4259.
73. Ohta K, Yamagami S, Taylor AW, Streilein JW. IL-6 antagonizes TGF-beta and abolishes immune privilege in eyes with endotoxin-induced uveitis. *Invest Ophthalmol Vis Sci*. 2000;41:2591–2599.

74. Perez VL, Papaliodis GN, Chu D, Anzaar F, Christen W, Foster CS. Elevated levels of interleukin 6 in the vitreous fluid of patients with pars planitis and posterior uveitis: the Massachusetts eye & ear experience and review of previous studies. *Ocul Immunol Inflamm*. 2004;12:193–201.
75. Ghasemi H. Roles of IL-6 in Ocular Inflammation: A Review. *Ocul Immunol Inflamm*. 2018; 26:37–50.
76. Sato K, Takeda A, Hasegawa E, et al. Interleukin-6 plays a crucial role in the development of subretinal fibrosis in a mouse model. *Immunol Med*. 2018;41:23–29.
77. Yamamoto H, Hayashi H, Uchida H, Kato H, Oshima K. Increased soluble interleukin-6 receptor in vitreous fluid of proliferative vitreoretinopathy. *Curr Eye Res*. 2003;26:9–14.
78. Biswas PS, Banerjee K, Kinchington PR, Rouse BT. Involvement of IL-6 in the paracrine production of VEGF in ocular HSV-1 infection. *Exp Eye Res*. 2006;82:46–54.
79. Kauffmann DJ, van Meurs JC, Mertens DA, Peperkamp E, Master C, Gerritsen ME. Cytokines in vitreous humor: interleukin-6 is elevated in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 1994;35:900–906.
80. Limb GA, Little BC, Meager A, et al. Cytokines in proliferative vitreoretinopathy. *Eye*. 1991;5 (Pt 6):686–693.
81. Lin T, Zhang W, Fan Y, Mulholland M. Interleukin-1beta and interleukin-6 stimulate matrix metalloproteinase-9 secretion in cultured myenteric glia. *J Surg Res*. 2007;137:38–45.
82. Symeonidis C, Papakonstantinou E, Androudi S, et al. Interleukin-6 and the matrix metalloproteinase response in the vitreous during proliferative vitreoretinopathy. *Cytokine*. 2011;54:212–217.
83. Yao JS, Zhai W, Young WL, Yang GY. Interleukin-6 triggers human cerebral endothelial cells proliferation and migration: the role for KDR and MMP-9. *Biochem Biophys Res Commun*. 2006;342:1396–1404.
84. Dai Y, Wu Z, Sheng H, Zhang Z, Yu M, Zhang Q. Identification of inflammatory mediators in patients with rhegmatogenous retinal detachment associated with choroidal detachment. *Mol Vis*. 2015;21:417–427.
85. Garweg JG, Zandi S, Pfister I, Rieben R, Skowronska M, Tappeiner C. Cytokine profiles of phakic and pseudophakic eyes with primary retinal detachment. *Acta Ophthalmol*. 2019;97:e580–e588.
86. Zandi S, Pfister IB, Traine PG, et al. Biomarkers for PVR in rhegmatogenous retinal detachment. *PloS one*. 2019;14:e0214674.
87. Kaneko H, Takayama K, Asami T, et al. Cytokine profiling in the sub-silicone oil fluid after vitrectomy surgeries for refractory retinal diseases. *Sci Rep*. 2017;7:2640.
88. Dinarello CA. Introduction to the interleukin-1 family of cytokines and receptors: Drivers of innate inflammation and acquired immunity. *Immunol Rev*. 2018;281:5–7.
89. Kosnosky W, Li TH, Pakalnis VA, Fox A, Hunt RC. Interleukin-1-beta changes the expression of metalloproteinases in the vitreous humor and induces membrane formation in eyes containing preexisting retinal holes. *Invest Ophthalmol Vis Sci*. 1994;35:4260–4267.
90. Kataoka K, Matsumoto H, Kaneko H, et al. Macrophage- and RIP3-dependent inflammasome activation exacerbates retinal detachment-induced photoreceptor cell death. *Cell Death Dis*. 2015;6:e1731.
91. Jaffe GJ, Roberts WL, Wong HL, Yurochko AD, Cianciolo GJ. Monocyte-induced cytokine expression in cultured human retinal pigment epithelial cells. *Exp Eye Res*. 1995;60:533–543.
92. Hoerster R, Fauser S, Cursiefen C, Kirchhof B, Heindl LM. The influence of systemic renin-angiotensin-inhibition on ocular cytokines related to proliferative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:1721–1725.
93. Connor TB, Jr., Roberts AB, Sporn MB, et al. Correlation of fibrosis and transforming growth factor-beta type 2 levels in the eye. *J Clin Invest*. 1989;83:1661–1666.
94. Pfeffer BA, Flanders KC, Guerin CJ, Danielpour D, Anderson DH. Transforming growth factor beta 2 is the predominant isoform in the neural retina, retinal pigment epithelium-choroid and vitreous of the monkey eye. *Exp Eye Res*. 1994;59:323–333.
95. Verrecchia F, Mauviel A. Transforming growth factor-β signaling through the Smad pathway: role in extracellular matrix gene expression and regulation. *J Invest Dermatol*. 2002;118:211–215.
96. Sweetwyne MT, Murphy-Ullrich JE. Thrombospondin1 in tissue repair and fibrosis: TGF-β-dependent and independent mechanisms. *Matrix Biol*. 2012;31:178–186.
97. Dvashi Z, Goldberg M, Adir O, Shapira M, Pollack A. TGF-beta1 induced transdifferentiation of rpe cells is mediated by TAK1. *PloS One*. 2015;10:e0122229.

98. Tamiya S, Liu L, Kaplan HJ. Epithelial-mesenchymal transition and proliferation of retinal pigment epithelial cells initiated upon loss of cell-cell contact. *Invest Ophthalmol Vis Sci*. 2010;51:2755–2763.
99. Bochaton-Piallat ML, Kapetanios AD, Donati G, Redard M, Gabbiani G, Pournaras CJ. TGF-beta1, TGF-beta receptor II and ED-A fibronectin expression in myofibroblast of vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 2000;41:2336–2342.
100. Memon MA, Anway MD, Covert TR, Uzumcu M, Skinner MK. Transforming growth factor beta (TGFbeta1, TGFbeta2 and TGFbeta3) null-mutant phenotypes in embryonic gonadal development. *Mol Cell Endocrinol*. 2008;294:70–80.
101. Bauge C, Cauvard O, Leclercq S, Galera P, Boumediene K. Modulation of transforming growth factor beta signalling pathway genes by transforming growth factor beta in human osteoarthritic chondrocytes: involvement of Sp1 in both early and late response cells to transforming growth factor beta. *Arthritis Res Ther*. 2011;13:R23.
102. Lee YS, Kim JH, Kim S-T, et al. Smad7 and Smad6 bind to discrete regions of Pellino-1 via their MH2 domains to mediate TGF-β1-induced negative regulation of IL-1R/TLR signaling. *Biochem Biophys Res Commun*. 2010;393:836–843.
103. Battegay EJ, Raines EW, Seifert RA, Bowen-Pope DF, Ross R. TGF-beta induces bimodal proliferation of connective tissue cells via complex control of an autocrine PDGF loop. *Cell*. 1990;63:515–524.
104. Sugita S, Horie S, Nakamura O, et al. Retinal pigment epithelium-derived CTLA-2alpha induces TGFbeta-producing T regulatory cells. *J Immunol*. 2008;181:7525–7536.
105. Hinton DR, He S, Jin ML, Barron E, Ryan SJ. Novel growth factors involved in the pathogenesis of proliferative vitreoretinopathy. *Eye*. 2002;16:422–428.
106. Ishikawa K, Yoshida S, Nakao S, et al. Periostin promotes the generation of fibrous membranes in proliferative vitreoretinopathy. *FASEB J*. 2014;28:131–142.
107. Begum G, O'Neill J, Chaudhary R, et al. Altered decorin biology in proliferative vitreoretinopathy: a mechanistic and cohort study. *Invest Ophthalmol Vis Sci*. 2018;59:4929–4936.
108. Hoerster R, Hermann MM, Rosentreter A, Muether PS, Kirchhof B, Fauser S. Profibrotic cytokines in aqueous humour correlate with aqueous flare in patients with rhegmatogenous retinal detachment. *Br J Ophthalmol*. 2013;97:450–453.
109. Kon CH, Occleston NL, Aylward GW, Khaw PT. Expression of vitreous cytokines in proliferative vitreoretinopathy: a prospective study. *Invest Ophthalmol Vis Sci*. 1999;40:705–712.
110. Abdullatif AM, Macky TA, Abdullatif MM, et al. Intravitreal decorin preventing proliferative vitreoretinopathy in perforating injuries: a pilot study. *Graefes Arch Clin Exp Ophthalmol*. 2018;256:2473–2481.
111. Merline R, Moreth K, Beckmann J, et al. Signaling by the matrix proteoglycan decorin controls inflammation and cancer through PDCD4 and MicroRNA-21. *Sci Signal*. 2011;4:ra75.
112. Martins-Green M, Petreaca M, Wang L. Chemokines and their receptors are key players in the orchestra that regulates wound healing. *Adv Wound Care*. 2013;2:327–347.
113. Nakazawa T, Hisatomi T, Nakazawa C, et al. Monocyte chemoattractant protein 1 mediates retinal detachment-induced photoreceptor apoptosis. *Proc Natl Acad Sci USA*. 2007;104:2425–2430.
114. Banerjee S, Savant V, Scott RA, Curnow SJ, Wallace GR, Murray PI. Multiplex bead analysis of vitreous humor of patients with vitreoretinal disorders. *Invest Ophthalmol Vis Sci*. 2007;48:2203–2207.
115. Ricker L, Kijlstra A, de Jager W, Liem A, Hendrikse F, La Heij E. The Role of CCL17, CCL19, CCL22, and CXCL10 in the development of proliferative vitreoretinopathy following rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci*. 2010;51:839–839.
116. Ricker LJ, Kessels AG, de Jager W, Hendrikse F, Kijlstra A, la Heij EC. Prediction of proliferative vitreoretinopathy after retinal detachment surgery: potential of biomarker profiling. *Am J Ophthalmol*. 2012;154:347–354e342.
117. Ricker LJ, Kijlstra A, de Jager W, Liem AT, Hendrikse F, La Heij EC. Chemokine levels in subretinal fluid obtained during scleral buckling surgery after rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci*. 2010;51:4143–4150.
118. Elner SG, Elner VM, Jaffe GJ, Stuart A, Kunkel SL, Strieter RM. Cytokines in proliferative diabetic retinopathy and proliferative vitreoretinopathy. *Curr Eye Res*. 1995;14:1045–1053.
119. Ricker L, Kessels A, de Jager W, et al. Prediction of PVR development in rhegmatogenous retinal

detachment by multiplex bead cytokine analysis. *Invest Ophthalmol Vis Sci*. 2009;50:3586–3586.

120. Elner VM, Burnstine MA, Strieter RM, Kunkel SL, Elner SG. Cell-associated human retinal pigment epithelium interleukin-8 and monocyte chemotactic protein-1: immunochemical and in-situ hybridization analyses. *Exp Eye Res*. 1997; 65:781–789.
121. Rutar M, Natoli R, Provis JM. Small interfering RNA-mediated suppression of Ccl2 in Muller cells attenuates microglial recruitment and photoreceptor death following retinal degeneration. *J Neuroinflammation*. 2012;9:221.
122. Russo RC, Garcia CC, Teixeira MM, Amaral FA. The CXCL8/IL-8 chemokine family and its receptors in inflammatory diseases. *Expert Rev Clin Immunol*. 2014;10:593–619.
123. Goczalik I, Ulbricht E, Hollborn M, et al. Expression of CXCL8, CXCR1, and CXCR2 in neurons and glial cells of the human and rabbit retina. *Invest Ophthalmol Vis Sci*. 2008;49:4578–4589.
124. Dufour JH, Dziejman M, Liu MT, Leung JH, Lane TE, Luster AD. IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T cell generation and trafficking. *J Immunol*. 2002;168:3195–3204.
125. Park MK, Amichay D, Love P, et al. The CXC chemokine murine monokine induced by IFN-gamma (CXC chemokine ligand 9) is made by APCs, targets lymphocytes including activated B cells, and supports antibody responses to a bacterial pathogen in vivo. *J Immunol*. 2002;169:1433–1443.
126. Norose K, Kikumura A, Luster AD, Hunter CA, Harris TH. CXCL10 is required to maintain T-cell populations and to control parasite replication during chronic ocular toxoplasmosis. *Invest Ophthalmol Vis Sci*. 2011;52:389–398.
127. Hooks JJ, Nagineni CN, Hooper LC, Hayashi K, Detrick B. IFN-β provides immuno-protection in the retina by inhibiting ICAM-1 and CXCL9 in retinal pigment epithelial cells. *J Immunol*. 2008;180:3789–3796.
128. Iellem A, Mariani M, Lang R, et al. Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. *J Exp Med*. 2001;194:847–853.
129. Kang S, Xie J, Ma S, Liao W, Zhang J, Luo R. Targeted knock down of CCL22 and CCL17 by siRNA during DC differentiation and maturation affects the recruitment of T subsets. *Immunobiology*. 2010;215:153–162.
130. Luzina IG, Papadimitriou JC, Anderson R, Pochetuhen K, Atamas SP. Induction of prolonged infiltration of T lymphocytes and transient T lymphocyte-dependent collagen deposition in mouse lungs following adenoviral gene transfer of CCL18. *Arthritis Rheum*. 2006;54:2643–2655.
131. Hauser MA, Legler DF. Common and biased signaling pathways of the chemokine receptor CCR7 elicited by its ligands CCL19 and CCL21 in leukocytes. *J Leukoc Biol*. 2016;99:869–882.
132. Pickens SR, Chamberlain ND, Volin MV, Pope RM, Shahrara S. Characterization of CCL19 and CCL21 in rheumatoid arthritis. *Arthritis Rheum*. 2011;63:914–922.
133. Planck SR, Huang XN, Robertson JE, Rosenbaum JT. Retinal pigment epithelial cells produce interleukin-1 beta and granulocyte-macrophage colony-stimulating factor in response to interleukin-1 alpha. *Curr Eye Res*. 1993;12:205–212.
134. Roberge FG, Caspi RR, Nussenblatt RB. Glial retinal Muller cells produce IL-1 activity and have a dual effect on autoimmune T helper lymphocytes. Antigen presentation manifested after removal of suppressive activity. *J Immunol*. 1988;140:2193–2196.
135. Vinores SA, Campochiaro PA, Conway BP. Ultrastructural and electron-immunocytochemical characterization of cells in epiretinal membranes. *Invest Ophthalmol Vis Sci*. 1990;31:14–28.
136. Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol*. 2005;6: 209.
137. Cleary PE, Ryan SJ. Experimental posterior penetrating eye injury in the rabbit. I. Method of production and natural history. *Br J Ophthalmol*. 1979;63:306–311.
138. Garcia-Layana A, Pastor JC, Saornil MA, Gonzalez G. Porcine model of proliferative vitreoretinopathy with platelets. *Curr Eye Res*. 1997; 16:556–563.
139. Yeo JH, Sadeghi J, Campochiaro PA, Green WR, Glaser BM. Intravitreous fibronectin and platelet-derived growth factor. New model for traction retinal detachment. *Arch Ophthalmol*. 1986;104:417–421.
140. Adamis AP, Shima DT, Yeo KT, et al. Synthesis and secretion of vascular permeability factor/vascular endothelial growth factor by human retinal pigment epithelial cells.

Biochem Biophys Res Commun. 1993;193:631–638.

141. Hata Y, Nakagawa K, Ishibashi T, Inomata H, Ueno H, Sueishi K. Hypoxia-induced expression of vascular endothelial growth factor by retinal glial cells promotes in vitro angiogenesis. *Virchows Arch*. 1995;426:479–486.
142. Sydorova M, Lee MS. Vascular endothelial growth factor levels in vitreous and serum of patients with either proliferative diabetic retinopathy or proliferative vitreoretinopathy. *Ophthalmic Res*. 2005;37:188–190.
143. Armstrong D, Augustin AJ, Spengler R, et al. Detection of vascular endothelial growth factor and tumor necrosis factor alpha in epiretinal membranes of proliferative diabetic retinopathy, proliferative vitreoretinopathy and macular pucker. *Ophthalmologica*. 1998;212:410–414.
144. Chen YS, Hackett SF, Schoenfeld CL, Vinores MA, Vinores SA, Campochiaro PA. Localisation of vascular endothelial growth factor and its receptors to cells of vascular and avascular epiretinal membranes. *Br J Ophthalmol*. 1997; 81:919–926.
145. Robbins SG, Mixon RN, Wilson DJ, et al. Platelet-derived growth factor ligands and receptors immunolocalized in proliferative retinal diseases. *Invest Ophthalmol Vis Sci*. 1994;35:3649–3663.
146. Zhang Q, Qi Y, Chen L, et al. The relationship between anti-vascular endothelial growth factor and fibrosis in proliferative retinopathy: clinical and laboratory evidence. *Br J Ophthalmol*. 2016;100:1443–1450.
147. Zhao XY, Xia S, Wang EQ, Chen YX. Efficacy of intravitreal injection of bevacizumab in vitrectomy for patients with proliferative vitreoretinopathy retinal detachment: A Meta-analysis of Prospective Studies. *Retina*. 2018;38:462–470.
148. Andrews A, Balciunaite E, Leong FL, et al. Platelet-derived growth factor plays a key role in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 1999;40:2683–2689.
149. Bryckaert M, Guillonneau X, Hecquet C, Perani P, Courtois Y, Mascarelli F. Regulation of proliferation-survival decisions is controlled by FGF1 secretion in retinal pigmented epithelial cells. *Oncogene*. 2000;19:4917–4929.
150. Romo P, Madigan MC, Provis JM, Cullen KM. Differential effects of TGF-beta and FGF-2 on in vitro proliferation and migration of primate retinal endothelial and Muller cells. *Acta Ophthalmol*. 2011;89:e263–268.
151. Sivalingam A, Kenney J, Brown GC, Benson WE, Donoso L. Basic fibroblast growth factor levels in the vitreous of patients with proliferative diabetic retinopathy. *Arch Ophthalmol*. 1990;108:869–872.
152. Cassidy L, Barry P, Shaw C, Duffy J, Kennedy S. Platelet derived growth factor and fibroblast growth factor basic levels in the vitreous of patients with vitreoretinal disorders. *Br J Ophthalmol*. 1998;82:181–185.
153. Hueber A, Wiedemann P, Esser P, Heimann K. Basic fibroblast growth factor mRNA, bFGF peptide and FGF receptor in epiretinal membranes of intraocular proliferative disorders (PVR and PDR). *Int Ophthalmol*. 1996;20:345–350.
154. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002;110:1093–1103.
155. Lago F, Dieguez C, Gomez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. *Nat Clin Pract Rheumatol*. 2007;3:716–724.
156. Ricker LJ, Kijlstra A, Kessels AG, de Jager W, Hendrikse F, La Heij EC. Adipokine levels in subretinal fluid from patients with rhegmatogenous retinal detachment. *Exp Eye Res*. 2012; 94:56–62.
157. Gariano RF, Nath AK, D'Amico DJ, Lee T, Sierra-Honigmann MR. Elevation of vitreous leptin in diabetic retinopathy and retinal detachment. *Invest Ophthalmol Vis Sci*. 2000;41:3576–3581.
158. Busso N, So A, Chobaz-Peclat V, et al. Leptin signaling deficiency impairs humoral and cellular immune responses and attenuates experimental arthritis. *J Immunol*. 2002;168:875–882.
159. Liu L, Yang P, He H, et al. Leptin increases in Vogt-Koyanagi-Harada (VKH) disease and promotes cell proliferation and inflammatory cytokine secretion. *Br J Ophthalmol*. 2008;92:557–561.
160. Zhang J, Zhou N, Zhang B, Ma J. Effect of Biodegradable Scleral Plugs Containing Curcumin on Proliferative Vitreoretinopathy. *Ophthalmic Res*. 2018;59:30–36.
161. Maberley D, Cui JZ, Matsubara JA. Vitreous leptin levels in retinal disease. *Eye*. 2006;20:801–804.
162. Farioli A, Hemmingsson T, Kriebel D. Vascular risk factors and rhegmatogenous retinal detachment: a follow-up of a national cohort of Swedish men. *Br J Ophthalmol*. 2016;100:907–913.

163. Saegusa K, Ishimaru N, Yanagi K, et al. Cathepsin S inhibitor prevents autoantigen presentation and autoimmunity. *J Clin Invest*. 2002;110:361–369.
164. Mazzoni F, Safa H, Finnemann SC. Understanding photoreceptor outer segment phagocytosis: use and utility of RPE cells in culture. *Exp Eye Res*. 2014;126:51–60.
165. Rakoczy PE, Lai MC, Baines MG, Spilsbury K, Constable IJ. Expression of cathepsin S antisense transcripts by adenovirus in retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci*. 1998;39:2095–2104.
166. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harb Perspect Biol*. 2011;3:a005058.
167. Ashutosh Chao C, Borgmann K, Brew K, Ghorpade A. Tissue inhibitor of metalloproteinases-1 protects human neurons from staurosporine and HIV-1-induced apoptosis: mechanisms and relevance to HIV-1-associated dementia. *Cell Death Dis*. 2012;3:e332.
168. Nalluri S, Ghoshal-Gupta S, Kutiyanawalla A, et al. TIMP-1 Inhibits Apoptosis in Lung Adenocarcinoma Cells via Interaction with Bcl-2. *PloS one*. 2015;10:e0137673.
169. Yu-Wai-Man C, Treisman R, Bailly M, Khaw PT. The role of the MRTF-A/SRF pathway in ocular fibrosis. *Invest Ophthalmol Vis Sci*. 2014;55:4560–4567.
170. Ji Y, Yu WQ, Eom YS, et al. The effect of TIMP-1 on the cone mosaic in the retina of the rat model of retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2014;56:352–364.
171. Kim B, Abdel-Rahman MH, Wang T, Pouly S, Mahmoud AM, Cebulla CM. Retinal MMP-12, MMP-13, TIMP-1, and TIMP-2 expression in murine experimental retinal detachment. *Invest Ophthalmol Vis Sci*. 2014;55:2031–2040.
172. Yamada E, Tobe T, Yamada H, et al. TIMP-1 promotes VEGF-induced neovascularization in the retina. *Histol Histopathol*. 2001;16:87–97.
173. Alexander JP, Bradley JM, Gabourel JD, Acott TS. Expression of matrix metalloproteinases and inhibitor by human retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. 1990;31:2520–2528.
174. Webster L, Chignell AH, Limb GA. Predominance of MMP-1 and MMP-2 in epiretinal and subretinal membranes of proliferative vitreoretinopathy. *Exp Eye Res*. 1999;68:91–98.
175. Kon CH, Occleston NL, Charteris D, Daniels J, Aylward GW, Khaw PT. A prospective study of matrix metalloproteinases in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 1998;39:1524–1529.
176. Abu El-Asrar AM, Mohammad G, Nawaz MI, et al. Relationship between vitreous levels of matrix metalloproteinases and vascular endothelial growth factor in proliferative diabetic retinopathy. *PloS one*. 2013;8:e85857.
177. Symeonidis C, Papakonstantinou E, Souliou E, Karakiulakis G, Dimitrakos SA, Diza E. Correlation of matrix metalloproteinase levels with the grade of proliferative vitreoretinopathy in the subretinal fluid and vitreous during rhegmatogenous retinal detachment. *Acta Ophthalmol*. 2011;89:339–345.
178. Tuuminen R, Loukovaara S. High intravitreal TGF-beta1 and MMP-9 levels in eyes with retinal vein occlusion. *Eye*. 2014;28:1095–1099.
179. Plantner JJ, Smine A, Quinn TA. Matrix metalloproteinases and metalloproteinase inhibitors in human interphotoreceptor matrix and vitreous. *Curr Eye Res*. 1998;17:132–140.
180. Van Hove I, Lefevere E, De Groef L, et al. MMP-3 Deficiency Alleviates Endotoxin-Induced Acute Inflammation in the Posterior Eye Segment. *Int J Mol Sci*. 2016;17: pii: E1825.
181. Ecker SM, Pfahler SM, Hines JC, Lovelace AS, Glaser BM. Sequential in-office vitreous aspirates demonstrate vitreous matrix metalloproteinase 9 levels correlate with the amount of subretinal fluid in eyes with wet age-related macular degeneration. *Mol Vis*. 2012;18:1658–1667.
182. Shitama T, Hayashi H, Noge S, et al. Proteome Profiling of Vitreoretinal Diseases by Cluster Analysis. *Proteomics Clin Appl*. 2008;2:1265–1280.
183. Yu J, Peng R, Chen H, Cui C, Ba J. Elucidation of the pathogenic mechanism of rhegmatogenous retinal detachment with proliferative vitreoretinopathy by proteomic analysis. *Invest Ophthalmol Vis Sci*. 2012;53:8146–8153.
184. Ontsuka K, Kotobuki Y, Shiraishi H, et al. Periostin, a matricellular protein, accelerates cutaneous wound repair by activating dermal fibroblasts. *Exp Dermatol*. 2012;21:331–336.
185. Wang X, Liu J, Wang Z, et al. Periostin contributes to the acquisition of multipotent stem cell-like properties in human mammary epithelial cells and breast cancer cells. *PloS one*. 2013;8:e72962.
186. Uchida M, Shiraishi H, Ohta S, et al. Periostin, a matricellular protein, plays a role in the induction of chemokines in pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2012;46:677–686.

187. Zhou W, Ke SQ, Huang Z, et al. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. *Nat Cell Biol*. 2015;17:170–182.
188. Lin J, Li J, Huang B, et al. Exosomes: novel biomarkers for clinical diagnosis. *ScientificWorldJournal*. 2015;2015:657086.
189. Kaneko H, Terasaki H. Biological Involvement of MicroRNAs in Proliferative Vitreoretinopathy. *Transl Vis Sci Technol*. 2017;6:5.
190. Usui-Ouchi A, Ouchi Y, Kiyokawa M, Sakuma T, Ito R, Ebihara N. Upregulation of Mir-21 levels in the vitreous humor is associated with development of proliferative vitreoretinal disease. *PloS one*. 2016;11:e0158043.
191. Sheedy FJ. Turning 21: induction of miR-21 as a key switch in the inflammatory response. *Front Immunol*. 2015;6:19.
192. Burke HB. Predicting clinical outcomes using molecular biomarkers. *Biomark Cancer*. 2016;8:89–99.
193. Abu El-Asrar AM, Struyf S, Kangave D, Geboes K, Van Damme J. Chemokines in proliferative diabetic retinopathy and proliferative vitreoretinopathy. *Eur Cytokine Netw*. 2006;17:155–165.
194. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. *Per Med*. 2010;7:33–47.