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Review

Inflammatory and Fibrogenic Factors in Proliferative Vitreoretinopathy Development

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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

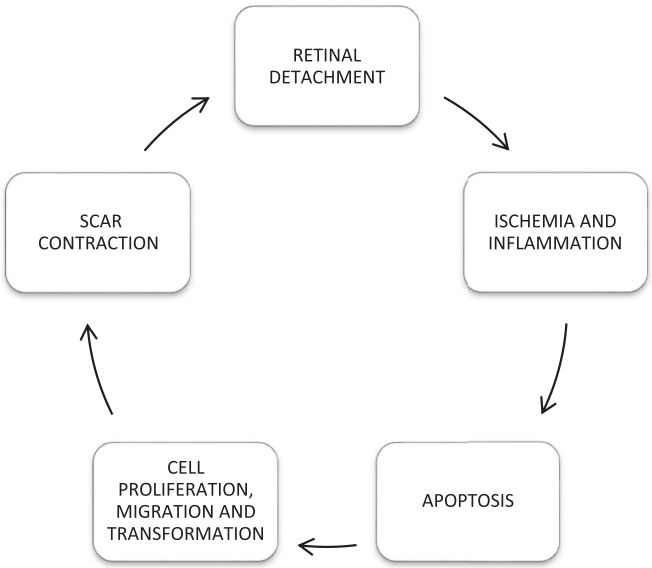

Figure. The key phases of PVR pathogenesis.

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.

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