

PERSPECTIVE

Proliferative vitreoretinopathy: pathobiology, surgical management, and adjunctive treatment

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Surgical repair of rhegmatogenous retinal detachment is currently successful in over 90% of cases.¹⁻⁴ Where there is a final failure to reattach the retina this is due to the development of proliferative vitreoretinopathy (PVR) in over 75% of cases.⁵⁻⁷ This process is characterised by cellular proliferation on both surfaces of the detached neuroretina, on the posterior vitreous face, and within the vitreous base resulting in the formation of contractile periretinal membranes. It is estimated to occur in 5-10% of all rhegmatogenous retinal detachments.⁷

Initial clinical observations emphasised cellular activity in, and retraction of, the vitreous together with the appearance of retinal folds. The condition was referred to as massive vitreous retraction (MVR) or massive preretinal retraction (MPR) on the premise of the primary pathology being centred in the vitreous gel.⁸ This was later modified to massive periretinal proliferation (MPP)⁹ to acknowledge the role of periretinal membrane formation.

A unifying classification was published by the Retina Society Terminology Committee in 1983.⁷ This used the term proliferative vitreoretinopathy and has served as the basis for subsequent clinical and laboratory studies. It subdivides PVR into four stages (A-D) of increasing severity based on clinical features: vitreous haze and pigment, retinal stiffness and wrinkling, rolled edges of retinal breaks, vascular tortuosity, and fixed retinal folds advancing to a funnel retinal detachment. A revised form of this classification further subdivides the proliferative process by location (anterior/posterior) and type (focal/diffuse/subretinal/circumferential and anterior displacement).¹⁰

While these classifications have served to standardise the terminology and clinical descriptions used in dealing with PVR they are essentially anatomical and do not address the biological activity of the PVR process. Furthermore, they do not record clinically important information such as the number, size, and location of retinal breaks, factors known to be of significance in the risk of development and progression of PVR.¹¹ The existing classifications therefore have limitations with respect to the comparison of the biological stage and the level of activity of the process between individual eyes in clinical or laboratory studies.

Pathophysiology

CELLULAR CONSTITUENTS

PVR can be viewed as a wound healing process in a specialised tissue. Various studies have addressed the question of the cellular composition of the periretinal membranes which are the central feature of the pathobiology. There is general agreement that four categories of cell can be identified (Table 1).

Retinal pigment epithelial (RPE) cells have been identified by light and electron microscopy¹²⁻¹⁴ and

immunohistochemically.¹⁵⁻¹⁷ Experimental work has demonstrated the presence of proliferating RPE cells in an animal model of PVR⁹ and also that RPE cells within the eye may undergo metaplastic change to a macrophage or fibroblast-like morphology.^{18,19} Clinical²⁰ and experimental²¹ studies have demonstrated that transscleral cryotherapy applied to eyes with retinal detachment enhances the dispersion of viable RPE cells into the vitreous cavity. Since there is a uniform presence of RPE cells in the contractile membranes formed in PVR this is potentially an important step in the pathogenesis of the condition.

Glial cells have been shown to be a part of PVR membranes.^{17,22-24} The cellular derivation of the glial component remains uncertain. Müller's cells, astrocytes, microglia, and perivascular glia have the potential to proliferate and contribute to periretinal membrane formation. It is notable that 'simple' glial epiretinal membranes may form in relation to retinal breaks and holes.^{12,25} These glial membranes can potentially provide a scaffold for the formation of the more complex membranes seen after retinal detachment.

Immunohistochemical study of epiretinal glia has shown that non-tractional membranes were purely glial, suggesting that other cellular components are necessary to produce the contractile and tractional properties of the periretinal membranes seen in PVR.²⁴

Subretinal membranes are a further constituent of PVR. These can form as diffuse cell sheets or as taut membranes or bands²⁶⁻²⁸ and may prevent surgical reattachment of the retina. Light and electron microscopic studies of subretinal membranes have demonstrated diffuse subretinal sheets to be purely glial,²⁹ whereas subretinal bands are formed by a mixed population of cells²⁹⁻³¹ including RPE, fibroblast-like cells, macrophages, and glia. Immunohistochemical analysis has shown that a high percentage of these cells are RPE and that glial cells are a minor component.³²

Most studies of PVR periretinal membranes have identified cells categorised as fibroblasts or fibrocytes.^{9,12-15,33} Cells of fibroblastic morphology or cells which demonstrate an inconsistent or negative immunohistochemical staining for intermediate filaments (specifically glial fibrillary acidic protein and cytokeratin) have been shown to be the predominant cell type in some studies^{14,15,34,35}; however, their derivation is not well established. It has been argued that they represent transformed RPE^{9,13} or that

Table 1 Cell types involved in proliferative vitreoretinopathy

Cell	References
Retinal pigment epithelium	12-17, 29-32
Glial	12, 17, 22-25, 29-32
Fibroblastic	9, 12-15, 33-36
Inflammatory:	
Macrophages	14, 16, 34, 35, 38, 39
Lymphocytes	40-42

Table 2 Extracellular matrix components of proliferative vitreoretinopathy membranes

	References
Collagen (types I, II, III, and IV)	16, 17, 43
Heparan sulphate	16, 17
Laminin	16, 17
Fibronectin	17, 34, 43, 44

they may originate from vascular epithelial cells, glia, or hyalocytes.^{14 15} Given the evidence that the cells involved in PVR can change both in morphology^{18 19} and immunohistochemical characteristics,^{35 36} the exact cellular derivation of all cells in PVR membranes is difficult to ascertain, and estimates of the relative numbers of each cell type may therefore be inaccurate. The fibroblastic cells may also contain myofibrils,^{13 14 33} notably in recurrent epiretinal membranes³⁷ and these cells may therefore be responsible for the contraction of PVR cellular membranes.

Inflammatory cells have consistently been identified as a component of PVR periretinal membranes. Initial morphological reports identified macrophages within membrane tissue.^{14 34} Since there is experimental evidence that RPE cells can assume a macrophage-like morphology¹⁸ the origin of these cells has been further investigated. Immunohistochemical studies have confirmed the presence of macrophages in PVR membranes^{16 36 38} and demonstrated that in more severe intraocular proliferation these tend to be of an acute inflammatory subtype.³⁹

Recent studies have shown the presence of a population of lymphocytes within PVR tissue.⁴⁰⁻⁴² Immunohistochemical analysis has shown that these are T lymphocytes of both CD4+ and CD8+ subsets, and that these cells may bear the IL-2 receptor activation marker.^{40 41}

EXTRACELLULAR MATRIX

The extracellular matrix composition of PVR periretinal membranes has also been analysed immunohistochemically^{16 17 43} (Table 2). These studies have demonstrated the consistent presence of interstitial collagens types I and III and a variable presence of type II (vitreous associated) collagen. It had been postulated that both RPE and glial cells may be responsible for the elaboration of the collagens present.¹⁷ The basal lamina proteins – type IV collagen, heparan sulphate, and laminin – have also been demonstrated,^{16 17} notably where internal limiting membrane fragments are associated with the membrane specimen.¹⁶ The cell attachment protein fibronectin has been identified as a significant component of PVR membranes.^{17 34 43} Fibronectin mRNA labelling and protein immunostaining have been demonstrated on retinal glia, RPE, and fibroblastic cells in PVR epiretinal membranes⁴⁴ suggesting an intrinsic production of fibronectin by PVR tissue.

Clinically it has been observed that eyes with PVR have an increased tendency to develop marked intraocular fibrin formation after vitrectomy surgery.^{45 46} Experimental work

has shown that fibrin contact causes RPE cells to dedifferentiate and migrate into a fibrin clot to form sheets of fibrocyte-like cells.⁴⁷ Based on these observations it has been proposed that postoperative intraocular fibrin may form a surface for the formation of complex vitreal and epiretinal membranes with the resultant development of PVR.

Membrane contraction

Analysis of the constituents of the periretinal membranes formed in PVR, together with clinical observations and experimental studies, has led to an understanding of the pathobiological process. Retinal breaks may be associated with 'simple' glial epiretinal membranes; following retinal detachment there is a release of RPE cells and an associated breakdown of the blood-retinal barrier,⁴⁸ effects which are accentuated by surgical intervention and in particular by cryotherapy.^{21 49 50} There follows the formation of the complex periretinal and vitreous membranes containing the mixed cell types and extracellular matrix described above. It is the subsequent contraction of these membranes that is responsible for the clinical picture seen in PVR and for the potential failure of retinal reattachment surgery.

Based on the finding of fibroblastic cells, some of which have been demonstrated to contain cytoplasmic myofilaments,^{13 15 33} it has been proposed that membrane shortening is mediated by intrinsic contraction of these component cells, thus producing the tractional forces found clinically in PVR. An *in vitro* system has shown that both RPE and fibroblasts, but not retinal glia, are capable of mediating the contraction of a type I collagen matrix by cellular mobility and subsequent attachment of collagen fibres.⁵¹

Experimental work has suggested an alternative mechanism of membrane contraction involving the interaction of RPE cells and collagen.⁵² In this scheme collagen fibres are pulled by the RPE cells by alternating extension and retraction of their lamellipodia (fibronectin serving as a bridge between RPE and collagen), collagen is piled up adjacent to the RPE cell with subsequent tissue shortening.

The role of growth factors/cytokines

Recent studies on the pathogenesis of PVR have investigated the mediators of the cellular events outlined above. Growth factors have the potential to regulate the chemotaxis, proliferation, contraction, and extracellular matrix elaboration by the cells involved in PVR and hence are likely to be centrally involved in its pathobiology. Results of growth factor/cytokine studies are summarised in Table 3.

In vitro experimental work has demonstrated that RPE cells can respond by mitogenesis and chemotaxis to vitreous derived fluid obtained after blood-retinal barrier

Table 3 Growth factors/cytokines in proliferative vitreoretinopathy (PVR)

	PDGF	aFGF	bFGF	TGFβ	EGF	TNFα	IGF1	IL-1	IL-2	IL-6	INFγ
In vitro activity (refs 53, 55, 56, 58)											
RPE chemotaxis	+		-		-			+			
RPE proliferation	+	+	+	*	+		+				
Glial cell chemotaxis	+	-	-	-	-						
Vitreous (refs 59-61)											
Protein				++		++		++		++	++
PVR epiretinal membranes											
Protein (refs 63-65, 67)	+	+			+		+				+
mRNA (ref 66)						+		+		+	

RPE=retinal pigment epithelium; PDGF=platelet derived growth factor; a/bFGF=acidic/basic fibroblast growth factors; TGFβ=transforming growth factor β; EGF=epidermal growth factor; TNFα=tumour necrosis factor α; IGF1=insulin-like growth factor 1; IL-1, IL-2, IL-6=interleukin 1, 2, 6; INFγ=interferon γ. + = identified/upregulated; - = not found/absent; * = inhibition; ++ = increased; (blank = no data).

breakdown was induced⁵⁰ and that serum is an RPE chemoattractant.⁵³ It has been shown that PVR vitreous stimulates RPE chemotaxis and proliferation and that this effect is greater in more advanced PVR.⁵⁴ In vitro studies have also analysed the response of RPE and glial cells to individual growth factors. Interpretation of the results of these experiments is problematic since culture medium contents and cell culture density can affect the response of the target cell. In addition, the in vivo response of a given cell type will be modified by the interaction of growth factors and the type and amount of extracellular matrix.

RPE chemotaxis has been demonstrated in response to platelet derived growth factor (PDGF)⁵³ and interleukin 1 (IL-1)⁵⁵ but not to basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF).⁵³ Acidic and basic fibroblast growth factors (a/bFGF), EGF, PDGF, and insulin-like growth factor 1 (IGF-1) have been shown to stimulate DNA synthesis and cellular proliferation in cultured RPE and to be synergistic in this effect.⁵⁶ In contrast, this response is inhibited by transforming growth factor β (TGF- β) suggesting that growth factor effects on RPE are potentially a complex network of synergistic and antagonistic, positive and negative responses.⁵⁶ Cellular responses are further modified by the local microenvironment – for example, the nature of the extracellular matrix.⁵⁷ Retinal glial cells have also been shown to have a positive chemotactic response to PDGF but not to IL-1, IL-2, TGF- β , aFGF, bFGF, or EGF.^{55 58}

Various studies have addressed the question of growth factor presence in vitreous, subretinal fluid, and periretinal membranes from eyes with PVR. Analysis of vitreous has shown the presence of elevated levels of IL-1, IL-6, tumour necrosis factor α (TNF α), and interferon γ (IFN γ).⁵⁹ TGF β 2 has been reported to be elevated in the vitreous in PVR^{60 61} although subsequent studies have failed to confirm this result.⁵⁹ Cellular aspirates from PVR vitreous and subretinal fluid have demonstrated immunoreactivity to aFGF, EGF, IGF-1, and TGF β 1.⁶² It is, however, still uncertain whether the growth factor profile of vitreous reflects the growth factors active in the pathological processes in PVR membranes.

Immunohistochemical analysis of PVR epiretinal membranes has demonstrated the presence of aFGF, EGF, and IGF-1 protein localised to cells and extracellular matrix.^{63 64} PDGF and PDGF receptors have been localised immunohistochemically to cells in PVR tissues.⁶⁵ mRNA expression for the inflammatory growth factor TNF α , IL1 β , and IL-6 has been observed in cells in PVR membranes,⁶⁶ as has IFN γ protein.⁶⁷ The cellular localisation of growth factor protein and mRNA is notable since it suggests that the cells in these membranes are involved in local growth factor production.

The demonstration of growth factors known to play a role in fibrosis and wound healing (FGF, TGF β , PDGF, EGF) and in inflammation (IL-1, IL-6, TNF α) along with in vitro work showing an effect of these peptides on the possible target cells involved (although data on growth factor receptor expression in PVR tissues are limited) is suggestive of a role in the pathobiology of PVR. Potentially, growth factor mechanisms may hold the key to the imbalance of wound healing regulation seen in PVR. However, the exact roles of individual growth factors remain uncertain in what is likely to be a complex network of growth factor activity in the various stages of the evolution of PVR.

Immune system involvement in PVR

The demonstration of the presence of macrophages^{16 35 38 39} and lymphocytes^{40–42} and the observation of MHC class II

positive cells in PVR membranes^{38 40–42 68} (both inflammatory and non-inflammatory cell types) has produced an increasing interest in the role of the immune system in the development in PVR.

Deposits of immunoglobulins and complement components have also been demonstrated on PVR epiretinal membranes³⁸ and on pars plana biopsies taken from eyes with PVR.⁶⁹ The cellular adhesion molecules CD11a, CD11c, CD18, ICAM-1, and LFA-1, which mediate the interaction of leucocytes with other cells and extracellular matrices, have also been found on PVR tissues.^{42 70}

The observation of both cellular^{71 72} and humoral⁷² immune system responses to retinal antigens following retinal detachment and to the retinal antigens IRBP, S antigen, and opsin in an experimental model of PVR,⁷³ and of anti-S antigen antibodies in the sera of patients with PVR⁷⁴ has led to the view that an autoimmune reaction is involved in the ongoing pathobiology of PVR. In addition the finding of complement components in PVR vitreous⁷⁵ and the known interaction between T cells and RPE cells⁷⁶ is suggestive of an immune system response.

The evidence for an autoimmune response in PVR, however, remains incomplete. Several studies have demonstrated that healthy controls have humoral and cellular immune responses to retinal S antigen.^{77–79} Humoral and cellular responses to S antigen have also been shown in diabetic patients following panretinal photocoagulation^{80 81} without the development of an ongoing intraocular inflammatory or autoimmune response.

T lymphocytes and macrophages are fundamental cellular components of normal wound healing^{82 83} and have been shown to have a reciprocal interaction via growth factors in the wound healing process.^{84 85} Moreover, it has been shown that fibroblasts may produce a soluble factor which can prolong T cell survival⁸⁶ and hence potentiate the role of T cells at foci of fibrogenesis. The presence of cells involved in the immune response does not therefore imply an autoimmune mechanism as part of the pathogenesis of PVR. None the less, lymphocytes and macrophages have the potential to play a significant role in the development of PVR; mediating the pathobiology through growth factor secretion and the subsequent regulation of cellular chemotaxis and proliferation and the production of collagen, fibronectin, and other extracellular matrix components.^{87–91}

Surgical management of PVR

The basic principles of the surgical treatment of retinal detachments complicated by PVR are those of detachment surgery in general – that is, the closure and sealing of retinal breaks and the complete release of periretinal traction. To these can be added the prevention of recurrence of the proliferative process and its ensuing tractional forces.

Retinal detachments in eyes with only minimal PVR may be treated successfully by an external scleral buckling procedure.⁹² However, expansile gas should be used with caution in such cases since there is evidence to suggest that this may increase the incidence and progression of PVR.^{93–95} Successful surgical reattachment of recurrent retinal detachments in the absence of advanced PVR can be achieved by modification of the scleral buckle in selected cases.⁹⁶

In general, vitrectomy techniques are the basis of surgery for moderate to advanced PVR. Microsurgical manipulation allows the dissection and removal of epiretinal (and occasionally subretinal) membranes, thereby relieving tractional forces on the retina and permitting reattachment. Since cryotherapy is known to promote the dispersion of viable RPE cells and hence the progression of PVR,^{20 21} when possible laser photocoagulation is favoured to produce a chorioretinal adhesion around retinal breaks.

In eyes where there is advanced PVR, anterior proliferation in the region of the vitreous base and around the pre-equatorial retina is often a prominent feature.¹⁰ Lewis and Aaberg have described the evolution of their surgical approach to such cases⁹⁷ – initially vitreoretinal traction was relieved by a combination of vitrectomy and a high anterior scleral buckle, success rates were relatively low and a direct approach, dissecting and removing anterior PVR membranes was employed. Subsequently, anterior relaxing retinotomies were used to release traction. The use of retinotomy and retinectomy has now been extended to cases where there is very extensive epiretinal membrane formation, particularly strong membrane adhesions to retina or residual retinal traction following membrane dissection. Recent published series on PVR surgery have documented retinotomy rates of 2–40%^{98–101} with an increased use of retinotomy and retinectomy in more severe PVR cases. Extensive retinectomy, however, exposes large areas of RPE and there is evidence of high re-proliferation rates following this manoeuvre.¹⁰² Results from the Silicone Study Group suggest that in almost all cases eyes with severe PVR and without previous vitreous surgery can be managed without retinectomy.¹⁰¹

Perfluorocarbon liquids now provide a useful tool in the surgical management of PVR by allowing stabilisation of the retina to facilitate epiretinal membrane removal and the release of traction.¹⁰³ In addition, they have been shown to be effective in attaining retinal flattening and in the positioning of large retinal flaps following retinotomy and/or retinectomy.¹⁰⁴

Theoretically, since cells in PVR membranes have been demonstrated to be a source of extracellular matrix constituents and growth factors,^{44 66} membrane removal either by dissection or retinectomy can markedly decrease the intraocular production of these components. This 'debulking' of PVR tissue could potentially break the ongoing cycle of further membrane production and contraction and is an argument for this form of direct surgical approach.

The Silicone Study Group has addressed the question of the optimal type of intraocular tamponade following vitrectomy for eyes with severe PVR. Comparison of silicone oil with sulphur hexafluoride (SF₆) gas showed a statistically significant advantage of oil over gas both in terms of visual acuity and posterior retinal reattachment.¹⁰⁵ No such advantage was found in comparing silicone oil with perfluoropropane (C₃F₈)¹⁰⁶; indeed there was an advantage of borderline significance in favour of perfluoropropane in achieving anatomical reattachment. The rate of postoperative hypotony was lower in the silicone oil compared with the gas groups but it is notable that oil was removed in only 45% of cases in the recent report of this group.¹⁰⁷

The effect of intraocular tamponade on the proliferative process is as yet uncertain. Studies on the use of silicone oil after vitrectomy in eyes with PVR have reported a high rate of retro-oil epiretinal membrane re-proliferation,¹⁰⁸ particularly in association with large retinectomies.^{102 109} Histopathological study of the membranes formed has shown silicone oil droplets within membrane extracellular matrix^{109 110} which persists after oil removal. Potentially, silicone oil could downregulate membrane formation by limiting access of cells and growth factors to the retinal surface or may produce upregulation by compartmentalising these in contact with the retina. Experimental animal work has shown that silicone oil does not prevent epiretinal membrane formation.^{111–113} Moreover, one study has documented an increased incidence of membrane formation and tractional retinal detachment in oil filled compared with perfluoropropane or fluid filled eyes¹¹⁴ with a corresponding increased RPE mitogenic effect of silicone oil associated vitreous cavity fluid.

Table 4 Proliferative vitreoretinopathy: adjunctive treatment

	References
<i>Antiproliferative agents</i>	
5-Fluorouracil	118–122
Daunorubicin	123–125
Retinoids	131–134, 160
Taxol	135
Antitransferrin immunotoxin	137
Carmustine	159
Colchicine	152–154
Irradiation	128–130
<i>Anti-inflammatory agents</i>	
Corticosteroids	138–144
Non-steroidal	118, 138
Cyclosporin A	145
Heparin/low molecular weight heparin	45, 146–148
Tissue plasminogen activator	149
Growth factor regulators	150

The clinical significance of the re-proliferative effect of silicone oil remains unresolved although the results of the Silicone Study Group¹⁰⁶ would suggest that oil and perfluoropropane gas do not greatly differ in their potential to produce re-proliferation and subsequent surgical failure.

As vitreoretinal surgical techniques have advanced the anatomical success rate of retinal surgery in severe PVR has increased from around 60% to over 90% in recently reported series.^{98 99 115} Visual results, however, are often disappointing and the value of such surgery has been questioned. Analysis of the results of PVR surgery has shown that unilaterally aphakic eyes seldom achieve beneficial vision following complex PVR surgery and that subjective visual comfort is often poor owing to diplopia and photophobia.¹¹⁶ Despite this most patients report that surgery was worthwhile.^{116 117}

Adjunctive treatment

Studies on the pathobiology of PVR have identified the elements involved – fibrin deposition, cellular accumulation and proliferation, production of extracellular matrix, and contraction of the membranes formed. It has become possible to design pharmacological adjuncts to the surgical management of the condition which specifically target the cellular components and pathological processes of PVR (Table 4).

NON-SPECIFIC ANTIPROLIFERATIVE AGENTS

The proliferation of the cellular subtypes (RPE, glia, fibroblastic cells, and inflammatory cells) is a key stage in the progression of PVR. Various pharmacological agents are available which will inhibit the proliferation of the cells involved in PVR either through a general antiproliferative effect or via inhibition of a specific cellular type.

The antiproliferative agent 5-fluorouracil (5-FU) has been shown to be effective in reducing the incidence of PVR in animal models^{118 119} and appears to be relatively non-toxic at the levels required to be effective in experimental eyes.^{118 120} A prospective study in human eyes using a single intravitreal injection of a high dose of 5-FU (10 mg) at the completion of vitrectomy for PVR¹²¹ demonstrated that this dosage was well tolerated, a result also found in a previous study using 1 mg of intravitreal 5-FU¹²²; however, surgical success was not improved in the treated groups.

The efficacy of other antiproliferative agents in PVR has also been investigated. Daunorubicin (daunomycin) has been tested both experimentally and clinically. In an experimental animal model of PVR daunomycin prevented retinal detachment if injected at the time of PVR induction or in two doses 3 days later.¹²³ Uncontrolled clinical studies have been carried out using an infusion of daunomycin 7.5 mg/l for 10 minutes at the time of vitrectomy surgery on PVR following both trauma and

rhematogenous retinal detachment.^{124 125} Results indicate that this dosage appears to be well tolerated and produced surgical success rates which the authors felt improved on their previous work. A multicentre European trial is currently being conducted to investigate the potential role of daunomycin as an adjunct in PVR management.¹²⁶

The ocular toxicity of a range of antiproliferative agents has been investigated experimentally¹²⁷; however, data on the clinical efficacy and safety of the majority of antiproliferative drugs are limited at present.

Ocular irradiation has been proposed as a potential therapeutic option in the treatment of PVR. In vitro studies have shown that low dose irradiation can markedly inhibit RPE cell division¹²⁸ and animal work has demonstrated that low dose irradiation given early or late in the proliferative process can reduce the incidence of tractional retinal detachment.¹²⁹ A prospective clinical study, however, failed to demonstrate a significant beneficial effect of postoperative irradiation (with a relatively high dose of 3000 cGy).¹³⁰ No radiation retinopathy was reported after 3 years although this complication might develop at a later stage.

SPECIFIC ANTI-PROLIFERATIVE AGENTS

The proliferation and phenotypic change seen in RPE cells after retinal detachment and in PVR may be due to the depletion of retinoid input to these cells. In vitro work has shown that retinoic acid produces a growth arrest in RPE cell cultures and prevents the dedifferentiation of individual RPE cells.¹³¹ In addition to the specific effects on RPE cells retinoids can also modulate the differentiation of other cell types.

The role of retinoids has been investigated in animal models of PVR and it has been shown that retinoic acid can reduce the rate of tractional retinal detachment when delivered to the vitreous cavity in silicone¹³² and loaded in microspheres of biodegradable polymer.¹³³ Oral retinoic acid is currently used in the treatment of skin disorders and is relatively non-toxic. An initial report on the use of oral 13-*cis* retinoic acid as an adjunct to surgery in PVR has shown a promising result¹³⁴ and further reports on the efficacy of this agent are awaited.

Taxol is an agent which stabilises microtubules and blocks the G2 and M phases of the cell cycle. It has been shown to inhibit fibroblast replication, migration, and contraction. An experimental study has shown that a single dose of taxol is effective in reducing the rate of tractional retinal detachment in PVR.¹³⁵ Drugs aimed specifically at fibroblast activity may have a role to play in PVR management.

Immunohistochemical analysis has shown that cells in PVR epiretinal membranes express transferrin receptors.¹³⁶ Proliferating cells are known to upregulate their transferrin receptor expression and in vitro experimental work has demonstrated that antitransferrin receptor monoclonal antibodies conjugated to an immunotoxin selectively inhibit proliferating RPE cells,¹³⁷ thus providing another selective antiproliferative treatment for PVR.

ANTI-INFLAMMATORY THERAPY

Corticosteroids are a potential adjunctive therapy for PVR since they modify both cellular proliferation and the inflammatory response, two major pathophysiological processes of PVR. In vitro studies have suggested that steroids may have a bimodal effect on ocular fibroblast proliferation with increased proliferation at low dosage and a reduction in proliferation at high dosage.¹³⁸ Studies on

RPE cell proliferation have shown a non-significant reduction in proliferation.¹³⁹ Animal studies, however, suggest that intravitreal injections of dexamethasone¹⁴⁰ or triamcinolone^{141 142} reduce intraocular cellular proliferation and tractional retinal detachment. This action may be largely mediated by a reduction in blood-retinal barrier breakdown and associated intraocular inflammation. A prospective, controlled study using high dose systemic steroids starting 5 days postoperatively has shown a benefit in mild but not advanced PVR¹⁴³ and dexamethasone has been reported to be non-toxic when injected into the vitreous cavity after vitrectomy.¹⁴⁴ Good data on the efficacy of perioperative steroid treatment in the clinical setting are awaited.

Other approaches to downregulate the inflammatory component of PVR may also be of value. Non-steroidal anti-inflammatory medications given perioperatively could limit the degree of blood-retinal barrier breakdown and have been shown to inhibit cellular proliferation in vitro.¹³⁸ Experimental work has additionally demonstrated an additive effect of indomethacin when given with 5-FU.¹¹⁸ Again clinical data are lacking at present. The demonstration of T lymphocytes and other immune components in PVR tissues^{38 40-42 68} suggests that immunomodulation might provide an adjunctive treatment for PVR. Preliminary results of animal work using dexamethasone and the specific T cell inhibitor cyclosporin A have shown a reduction in PVR progression with this combined treatment but no additive effect.¹⁴⁵

MODULATION OF FIBRIN PRODUCTION

Another possible target for adjunctive treatment is the prevention of fibrin formation associated with blood-retinal barrier breakdown seen after vitreoretinal surgery. A clinical trial of the use of heparin to prevent postoperative fibrin formation demonstrated a reduction following intravitreal infusion of heparin 10 IU/ml, but an associated increased incidence of intraoperative bleeding,⁴⁵ 5 IU/ml infusion, and intravenous heparin had no significant effect. Low molecular weight heparin is thought to produce fewer haematological complications for an equal antithrombotic effect¹⁴⁶ and has been shown experimentally to reduce fibrin formation after vitrectomy.¹⁴⁷ In addition, heparin interferes with cell-substrate adhesion by binding fibronectin, binds growth factors including FGFs, EGF, and PDGF, and inhibits cellular proliferation including scleral fibroblasts and RPE cells.¹⁴⁶ These combined activities make heparin (ideally low molecular weight heparin) a potential multifunctional drug for use in the prevention of the development of PVR. Preliminary reports on animal studies suggest that low molecular weight heparin does reduce the rate of tractional retinal detachment caused by PVR.¹⁴⁸

Clinical work has shown that formed intraocular fibrin can be effectively dissolved by tissue plasminogen activator (tPA)¹⁴⁹ without significant side effects. As yet there are no data on whether treatment with tPA influences the subsequent development of PVR.

Growth factor regulation

Growth factors are likely to play a central role in the pathological processes of PVR as described above. The inhibition or blocking of growth factor mediated cellular activity is a treatment with the potential to selectively target the aberrant cellular proliferation seen in PVR while sparing physiological ocular wound healing. At present growth factor blocking agents are of limited availability but in vitro work has demonstrated the ability of protamine,

histone IIB, pentosan polysulphate, and polylysine as well as heparin to block growth factor mediated RPE cell chemotaxis and DNA synthesis.¹⁵⁰

Prevention of membrane contraction

PVR periretinal membrane contraction is responsible for retinal traction and shortening and consequent surgical failure, and is an additional possible target for pharmacological intervention. As described above heparin blocks cell substrate adhesion (via fibronectin) and can therefore prevent membrane contraction.¹⁴⁶ An *in vitro* study has demonstrated the inhibition of fibroblast mediated contraction of collagen gels by vitamin A, retinoic acid, and n-butyrate.¹⁵¹ The potential of these and other agents to modulate the progression of PVR via inhibition of membrane contraction has not yet been fully investigated. The antiproliferative agent colchicine has been shown to be effective in inhibiting RPE cell contractility *in vitro*¹⁵² and to reduce experimental retinal detachment and PVR.¹⁵³ A prospective clinical study using low dose oral colchicine as an adjunct to surgery for PVR failed, however, to show any benefit of colchicine treatment.¹⁵⁴

Drug delivery

A major limitation to the successful treatment of PVR using pharmacological adjuncts is the difficulty in achieving therapeutic drug levels in the microenvironment of the retinal surfaces over a sufficiently long period to adequately inhibit periretinal membrane formation. Single intravitreal injections of antiproliferative agents have a relatively short half life (further shortened by vitrectomy, aphakia, and postoperative inflammation)¹³⁹ which is unlikely to be sufficient for an adequate therapeutic effect.

Recently sustained drug-delivery systems have been used in trials both experimentally and clinically. Biodegradable polymers^{155 156} and slow release reservoirs^{157 158} have provided adequate drug levels and appear to be relatively non-toxic. An additional possibility in PVR surgery is the use of silicone oil (or other future tamponade agents) as a vehicle for drug delivery and the lipophilic antiproliferative agent carmustine has been shown to reduce experimental PVR when delivered in this way.¹⁵⁹ Preliminary data on the experimental use of retinoic acid in a silicone oil/fluorosilicone copolymer (to produce an even drug delivery within the eye) have been encouraging.¹⁶⁰

Conclusion

The management of PVR is time consuming and resource intensive. Although surgical success rates have improved dramatically in the past 15 years visual results are often disappointing. Despite this, vitreoretinal surgeons feel justified in continuing to operate on this complex surgical problem and patients with PVR view their attempts as worthwhile.

Future resources must be aimed, firstly, at the prevention of this vexed complication of retinal detachment by appropriate surgical repair. Additionally, the identification of high risk cases, whether untreated primary detachments or failed primary repairs, will have increasing importance as pharmacological adjuncts become available both for prophylaxis and as an addition to vitreoretinal surgery. A range of adjunctive agents is currently available and data on the efficacy of these drugs are urgently needed. Investigation of the optimal mechanisms of delivery for such agents will also advance the future management of PVR.

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