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Proliferative vitreoretinopathy: A new concept of disease pathogenesis and practical consequences

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ABSTRACT

During the last four decades, proliferative vitreoretinopathy (PVR) has defied the efforts of many researchers to prevent its occurrence or development. Thus, PVR is still the major complication following retinal detachment (RD) surgery and a bottle-neck for advances in cell therapy that require intraocular surgery. In this review we tried to combine basic and clinical knowledge, as an example of translational research, providing new and practical information for clinicians. PVR was defined as the proliferation of cells after RD. This idea was used for classifying PVR and also for designing experimental models used for testing many drugs, none of which were successful in humans. We summarize current information regarding the pathogenic events that follow any RD because this information may be the key for understanding and treating the earliest stages of PVR. A major focus is made on the intraretinal changes derived mainly from retinal glial cell reactivity. These responses can lead to intraretinal PVR, an entity that has not been clearly recognized. Inflammation is one of the major components of PVR, and we describe new genetic biomarkers that have the potential to predict its development. New treatment approaches are analyzed, especially those directed towards neuroprotection, which can also be useful for preventing visual loss after any RD. We also summarize the results of different surgical techniques and clinical information that is oriented toward the identification of high risk patients. Finally, we provide some recommendations for future classification of PVR and for designing comparable protocols for testing new drugs or techniques.

1. PVR: concept and pathogenesis

Proliferative vitreoretinopathy (PVR) is a term coined by the Retina Society Terminology Committee (Committee, 1983) for describing a complication that can follow rhegmatogenous retinal detachments (RD). It is still the major cause of failure after RD surgery, and no relevant advances in clinical management have been made since the initial description (Pennock et al., 2014a). PVR is estimated to occur in 5–10% of all RD cases. While it can occur before surgery, it more commonly occurs after any surgical intervention for RD (Pastor et al., 2002; Pennock et al., 2014a) (Fig. 1).

According to the original description, PVR was characterized by the growth of membranes on both surfaces of the detached retina and on the posterior hyaloids (Committee, 1983). Posterior contraction of these membranes causes distortion of the retina and keeps it detached, transforming a rhegmatogenous RD into a tractional one. The pathogenesis of this complication is divided into several steps: 1) migration of cells, mainly retinal pigment epithelial (RPE) and glial cells; 2) proliferation of the migrating cells; 3) membrane development; 4) contraction of the cellular membrane; 5) extracellular collagen production; and 6) creation of fixed folds in the retina. The authors emphasized that cellular proliferation was the essential point of this disorder.

Based on the idea that cellular proliferation is the main feature of PVR, many researchers have tried for more than 40 years to solve the problem by inhibiting the proliferation of cells. Nevertheless, the problem remains unsolved, and we believe it is time to revise

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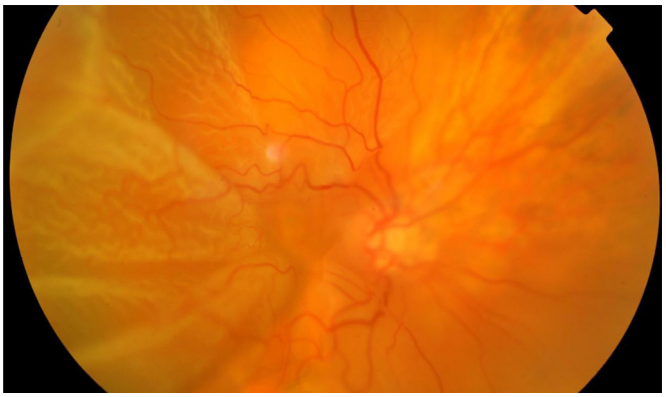

Fig. 1. Funduscopic image showing full-thickness retinal folds (star fold) and subtotal RD in a patient with history of chronic RD and PVR. Fold is created by an epiretinal membrane (epiretinal PVR). Patient was solved by simple 25G PPV and membrane peeling.

our understanding of the pathogenesis of PVR. In doing so, we can now focus on some other mechanisms involved in RD and in PVR with the aim of finding a useful prophylaxis or treatment for this complication.

Our personal approach is different from the original description of the pathogenic origins as it is based on several questions that we have asked during the last 15 years. First, if PVR appears after a RD, why are the events elicited in any RD, which include ischemia, photoreceptor death, astrocyte reactivity and others, not incorporated into the pathogenesis concept of PVR? Second, are RPE cells really the main effectors of PVR, or are there some other cell types that are more relevant for the characteristic tissue changes observed in this complication? Third, do the classification schemes in the literature have any real value for establishing the efficacy of the medical interventions? Fourth, because the pathogenesis of PVR is so poorly understood, what is the real value of experimental models that are mainly based on the original ideas of cell proliferation into the vitreous cavity?

We have structured this major review to provide updated information on all of these questions by using not only the reference databases, but also the vast experience of The Retina Group, IOBA (Eye Institute), University of Valladolid, Valladolid, Spain, both in clinical management and in PVR research (Pastor, 1998; Pastor et al., 2002; Rojas et al., 2015).

1.1. Mechanisms of tissue damage triggered by RD

Due to the scarcity of human tissue samples in the early stages of RD, most of our knowledge derives from experimental models. In the late 1960's, Machemer initiated a series of experimental RD studies in owl monkeys to understand the tissue changes (Machemer, 1978). Early alterations included intraretinal edema (mostly in the inner nuclear layer), disorganization of the photoreceptor outer segments, enlargement of some RPE cells that separate from Bruch's membrane, and reactivity of Müller and other glial cells (Geller et al., 2001; Ghazi and Green, 2002). These changes have been reproduced in other animal models (Fisher et al., 1995, 2005; Lewis et al., 1994; Lewis et al., 2005; Linberg et al., 2002). Our group has documented similar changes in organotypic cultures of pig and human neuroretinas (Fernandez-Bueno et al., 2012, 2008). These models have the potential to be useful in analyzing early changes after RD and to test some possible treatments (Fernandez-Bueno et al., 2012, 2008) (Figs. 2,3).

When the retina separates from the RPE, the outer retinal layers become ischemic. Surprisingly, despite the high metabolic demands of the neural retina, detachment from the choroidal vascular supply does not lead to immediate neuron death. Intrinsic protective mechanisms are activated during the early stages of RD. Specifically, stress-response genes and signaling pathways are activated that enable the photoreceptors to survive the acute phase of RD (Zacks et al., 2006). The breakdown of these protective mechanisms leads to the cell death, principally by apoptosis (Cook et al., 1995; Ghazi and Green, 2002).

Apoptosis has two major signaling cascades, the extrinsic and intrinsic pathways, both involving caspases, and leading to DNA fragmentation and cell death (Lo et al., 2011). Initiation of the apoptotic response may be mediated in part by the release of cytokines from the stressed and damaged tissues. The chemotactic properties of the cytokines can attract and activate macrophages and microglia. Activation of these cell types can then generate oxidative stress that could contribute to the cytotoxic effect on the photoreceptors after RD (Lo et al., 2011).

Although apoptosis is the principal mechanism of photoreceptor loss after RD, other cell-death mechanisms also exist (Lo et al., 2011). Programmed necrosis of photoreceptors also occurs after RD. Necroptosis, as this form of cell death is known, is mediated by a receptor-interacting protein (RIP) kinase (Lo et al., 2011; Murakami et al., 2011; Trichonas et al., 2010).

In this situation, programmed necrosis is less frequent than apoptosis, but it is enhanced when caspases are inhibited (Murakami et al., 2011). Another non-apoptotic pathway for cell death can be triggered by prolonged or excessive stress placed upon the endoplasmic reticulum. This programmed, endoplasmic reticulum stress-mediated pathway is important in neuronal death in neurodegenerative disorders and has been identified in experimental RD (Liu et al., 2010). Additionally, autophagy, a form of cellular recycling, is also upregulated in RD (Chinskey et al., 2014; Cook et al., 1995).

The pro-survival autophagy pathways inhibit apoptosis temporarily until the cell eventually dies (Besirli et al., 2011). An experimental model has demonstrated that photoreceptor necroptosis is associated with the activation of autophagy (Dong et al., 2014). This finding opens new possibilities for protection of these neurons by, for example, administration of necrostatin-1, which down-regulates RIP-1 phosphorylation and the autophagic biomarker LC-3ll (Dong et al., 2014).

Having a better understanding of the neuronal self-protective pathways and the self-destructive pathways is essential for developing new neuroprotective strategies as adjuncts for the surgical repair of RD (Lo et al., 2011). With careful management and innovative approaches, it may be possible to prevent the development of PVR altogether.

1.2. Initially, are there any differences between RD and PVR?

As mentioned, PVR is a complex process involving not only ischemic tissue damage, but also inflammation and proliferation of several types of cells and the production of local factors (Garweg et al., 2013; Pennock et al., 2014a). Tissue trauma, as in any RD, is triggered by the separation of the neuroretina from the RPE. According to our current knowledge on PVR, glial cells initiate the process as part of a nonspecific tissue repair response that leads to a remodeling of the retina (Garweg et al., 2013). Soon after RD, RPE cells de-differentiate into fibroblast- or macrophage-like cell morphology, driven by factors not yet fully understood. In the process, contractile cellular or fibrocellular membranes are created, preventing retinal reattachment. These membranes have been considered the most characteristic feature of PVR (Garweg et al.,

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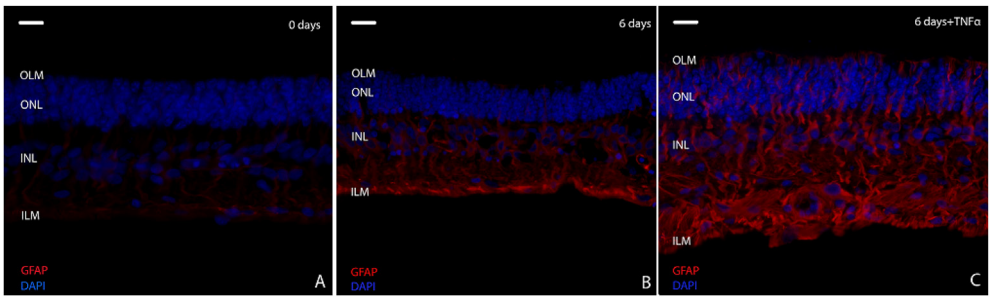

Fig. 2. Sections of porcine neuroretina organotypic culture immunostained for glial fibrillary acidic protein (GFAP). In fresh specimens (A), GFAP (glial fibrillary acidic protein) (red) expression was present in glial cells at the innermost retinal layers. Retinal structure and cellular organization were adequately preserved before culturing. In control cultures at 6 days (B) GFAP expression increased in the glial cells. Some Müller cell branches at the outer nuclear layer (ONL) expressed GFAP. In cultures with external added tumor necrosis factor alpha (TNFα; C) GFAP was markedly upregulated at 6 days culture. It appeared in Müller cell processes at the ONL and outer limiting membrane. Retinal tissue started to lose its characteristic organization. DAPI: 4′,6-diamino-2-phenylindole dihydrochloride staining (blue); ILM: inner limiting membrane INL: inner nuclear layer; OLM: outer limiting membrane; ONL: outer nuclear layer. Scale bars: 20 μm. Images courtesy of Dr. Ivan Fernandez-Bueno (IOBA, Spain).

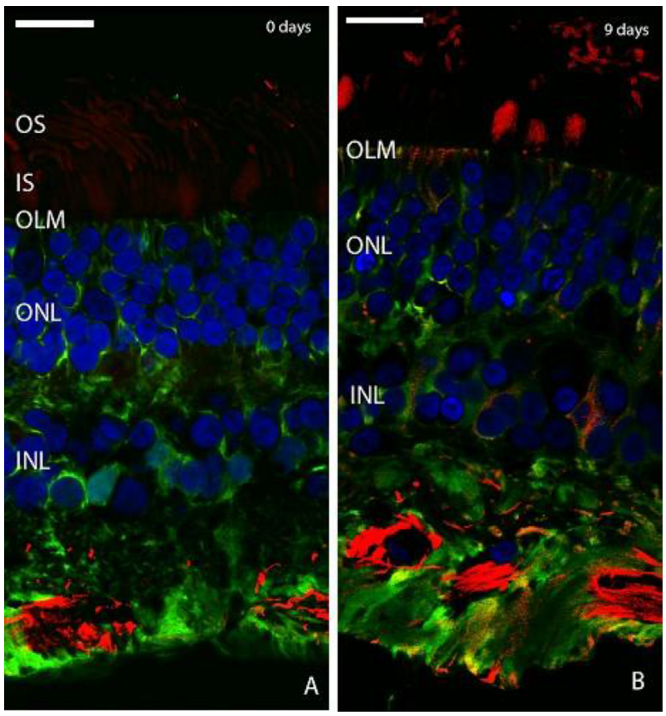

Fig. 3. Sections of human neuroretinas organotypic culture immunostained for glial fibrillary acidic protein (GFAP) and cellular retinaldehyde-binding protein (CRALBP). At day 0 (A) of culture immunostaining for CRALBP (green) showed Müller cells with normal morphology. The absence of Müller cell immunostaining for GFAP (red) indicates that these cells were not activated. At day 9 of culture (B) astrocytes had increased immunoreactivity to GFAP. Müller cells also expressed GFAP at the OLM level. OS: outer segments; IS: inner segments; OLM: outer limiting membrane; ONL: outer nuclear layer; INL: inner nuclear layer; ILM: inner limiting membrane. Scale bar: 20 μm. Images courtesy of Dr. Ivan Fernandez-Bueno (IOBA, Spain) and Dr. Nicolas Cuenca (University of Alicante, Spain).

2013). However, except for periretinal membrane formation, the glial hyper-reactivity is not different from the one elicited by any RD. Thus an as yet unidentified, critical distinctive difference must be present to direct these events towards a PVR.

Because early changes after RD are difficult to analyze in human samples, much of our current understanding of PVR development has been ascertained from experimental models. In some animal, the retinal architecture and vascularization is different from that in humans; therefore, some results could not be directly extrapolated. In cats after experimental RD, photoreceptors degenerate within 24 h (Fisher and Lewis, 2003; Lewis et al., 2003). The degeneration reaches a peak at 3 days and continues for as long as the retina is detached. In cats, 80% of photoreceptors are definitively altered after 3 months of detachment (Erickson et al., 1983); (de Souza et al., 2012) confirmed these changes in three samples of human retinal operculums or flaps. They also characterized functional changes, concluding that RD leads to alteration of the glutamate pathway.

Two days after RD in cats, rod synaptic terminals withdraw toward the cell bodies, leaving the outer plexiform layer disorganized (Lewis et al., 2003). At 7 days after DR, many ganglion cells become immunopositive for neurofilament protein and growth-associated protein 43. Furthermore, Müller cells quickly become activated. Fifteen minutes after the retina is detached, the Müller cells proliferate and hypertrophy, reaching a peak 3–4 days after RD, often extending their processes into the subretinal space.

RD also induces proliferation of some non-neuronal cells, including astrocytes, endothelial cells, pericytes, and microglia. The greatest period of proliferation for these cells is between 3 and 4 days after RD (Geller et al., 1995). Some of these changes, e.g., proliferation of endothelial cells and pericytes, are reversed by reattachment, especially if they occur within 1 day (Lewis et al., 2002). However, other changes are profound and may permanently affect the photoreceptors and glial cells. This could explain why in some cases the restoration of vision takes months or even years when the macula has been affected (Lewis et al., 2003).

Rod axon elongation towards the inner retina, formation of epiretinal membranes, Müller cell growth into the subretinal space, and stimulation of Müller cell growth into the vitreal surface of the retina after retina reattachment are events also identified in experimental models of RD.

While these events could be part of PVR pathogenesis (Lewis et al., 2003), they are also present after any RD, including those that do not have the distinctive characteristics of PVR.

1.3. The role of RPE cells

During the 1990's, many papers described the cellular types implicated in PVR by analyzing the vitreous and, more frequently, the removed epiretinal membranes (Campochiaro, 1997). RPE and glial cells were identified as the main participants. In cats, RPE cells initiate changes 24 h after RD (Anderson et al., 1981). They dedifferentiate, lose their polarity, and migrate into the subretinal space where they phagocytize outer-segment debris (Campochiaro, 1997). In RD, blood-retinal barriers are disrupted, and there is an increase of chemotactic and mitogenic activity in the vitreous

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cavity (Campochiaro, 1997). These factors stimulate the further migration and proliferation of RPE and glial cells (Campochiaro, 1997).

The RPE deserves more attention than it has previously received. Mature RPE cells are mitotically quiescent under physiological conditions, but when the neural retina suffers an injury, RPE cells start to proliferate while undergoing transformation (Chiba, 2014). After RD, RPE cells are exposed to serum factors because of the damage in the blood-retinal barriers. They become detached from Bruch's membrane, lose their epithelial morphology, and migrate into the vitreous through breaks in the neuroretina. There, they participate in the formation of epiretinal membranes (Chiba, 2014).

This process involves an epithelial-mesenchymal transition of the RPE cells, a biological process through which the detached polarized cells lose their epithelial characteristics. In doing so, the RPE cells acquire a mesenchymal phenotype that includes enhanced migratory capacity, invasiveness, resistance to apoptosis, and production of extracellular matrix (Chiba, 2014). In PVR, RPE cells become fibroblast-like cells. They can also transform into some other mesenchymal cells such as adipocytes, bone and cartilage cells, as well as reproduce RPE cells themselves, although their capability of producing neural retinal cells is very limited (Chiba, 2014).

The onset mechanism of proliferation is not fully understood although plenty of studies have been made (Campochiaro et al., 1985; Kirchhof et al., 1989; Osusky and Ryan, 1996). For instance, isolated RPE cells acquire responsiveness to proliferating factors such as platelet derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and transforming growth factor β (TGF-β) (Chiba, 2014). One of the important findings is that cell-to-cell contact seems to suppress the ability of cells to respond to mitotic factors. Thus the loss of cell-to-cell contact might be an important step in PVR development. Cadherin is a crucial adhesion protein, and its disruption results in the loss of cell-to-cell contact. In a rat RD model, Chen and Ma (2007) demonstrated that normal RPE cells do not express N-cadherin, but after RD, RPE cells, photoreceptors, and the outer limiting membrane exhibited intense immunolabeling for this protein. This type of cadherin is expressed in mesenchymal cells, and these changes were reversed by retinal reattachment.

Once RPE cells are trans-differentiated into fibroblast-like cells, they express alpha-smooth muscle actin, glial fibrillary acidic protein (GFAP), vimentin, etc. and become the main component of the epiretinal membranes (Chiba, 2014). This and other recent studies have confirmed the important role of RPE cells in one of the most characteristics findings of PVR: the membranes on the inner retinal layer and on the hyaloid.

1.4. Role of glial cells

As described above, PVR could be considered as an exaggerated response of the active remodeling process triggered by the injured retina (Garweg et al., 2013). In this process, glial cells have an important role, and tissue remodeling implicates Müller cell hypertrophy. Changes in Müller cells are observed 1 day after RD (Wickham and Charteris, 2009). Within 3 days, Müller cell bodies migrate to the outer nuclear and outer plexiform layers, occupying the spaces left by dying photoreceptors and extending their processes into the subretinal space (Wickham and Charteris, 2009). These cells, along with some RPE cells, microglia, and macrophages, contribute to create subretinal membranes, an uncommon finding in PVR. The presence of subretinal membranes is often seen after ocular trauma, and we propose to refer to this condition as subretinal PVR (Fig. 4).

In 1992, the hypertrophy of Müller cells was detected by our group in a rabbit model of PVR (Pinon et al., 1992). However, we were not able to recognize the importance of this finding, probably because we were under the influence of the pathogenesis ideas of the original description of PVR. Nevertheless in 2006, we detected these Müller cell changes in samples obtained from patients having PVR in which a retinectomy was necessary to reattach the retina (Pastor et al., 2006b). Although these changes are not specific to PVR, they lead to a shortening of the retina, a crucial point in PVR. Shortening of the retina constitutes, in our opinion, the most severe form of PVR (Pastor et al., 2003). Müller cells constitute only 20% of the retinal volume; therefore, even if they undergo hypertrophy, they cannot counteract the important loss of neurons after RD with PVR. Consequently, the retinal tissue becomes “shorter” (Pastor et al., 2003). The important role of the glial cells, especially Müller cells, of increasing PVR severity has been documented by other authors (Sethi et al., 2005). Thinning of the retina has also been demonstrated after 9 days in organotypic retina cultures (Fernandez-Bueno et al., 2012). These intraretinal changes were not described in the original pathogenesis description of this disease (Committee, 1983). But once again, most of these changes affecting glial cells are observed in any experimental model of RD as well as other retinal degenerative diseases. Therefore they cannot be considered specific for PVR.

Glial activity is very important for neuron survival (Fischer et al., 2015). Müller cells are crucial for photoreceptor survival and vascular integrity in the rodent retina. Nevertheless, glial cells can exacerbate neuronal death following excitotoxic injury (Fischer et al., 2015). For example, N- methyl-D-aspartate stimulates tumor necrosis factor alpha (TNF-α) production by Müller cells, and this cytokine diminishes neuron survival (Fischer et al., 2015). Conversely stimulation of the glia provides enhanced neuroprotection. In chickens, the elimination of microglia and macrophages prevented the development of RD and retinal folds (Fischer et al., 2015). In the central nervous system (CNS), the activation of microglia and macrophages can be detrimental to neuronal survival. In Parkinson's disease there is significant evidence that inflammation and microglial reactivity promotes neuronal degeneration (Tansey and Goldberg, 2010). Further, persistent changes in multiple sclerosis appear as the result of activated microglia and invading macrophages (Fischer et al., 2015).

Interestingly, in a porcine model of RD (Iandiev et al., 2006), the reactivity of Müller and microglial cells were not restricted to the detached areas, but were also observed in the intact regions of the

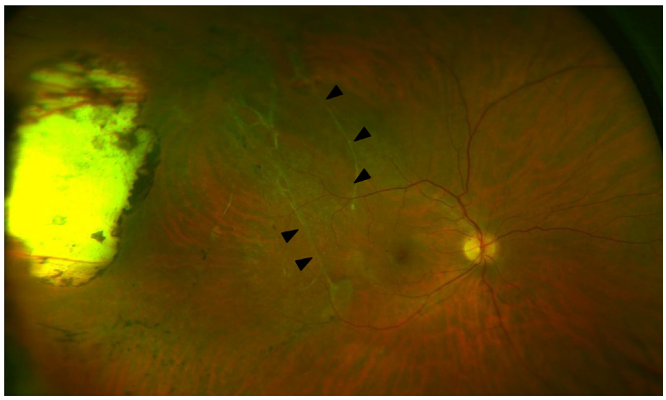

Fig. 4. Ultra-widefield fundus photograph showing subretinal PVR. Arrowheads showing subretinal bands. Courtesy of Prof. Stanga (Manchester Royal Eye Hospital).

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retina. This finding could have an implication in the loss of vision detected in some patients even after successful surgery for macula-on RD. It also might support the use of adjunctive treatments for preventing visual loss in most cases of RD.

Thus with regard to Müller and other glial cells, it is clear that they play an important role in the remodeling process elicited after RD. Hypertrophy of these cells and replacement of the lost retinal neurons causes the shortening of the retina in advanced cases of PVR (Figs. 5 and 6).

1.5. The role of macrophages

Macrophages are also considered important players in PVR (Campochiaro, 1997). Because of the breakdown of the blood-retinal barrier that follows any RD, they migrate into the sub-retinal space and to the vitreous cavity. The presence of macrophages in the vitreous is associated with a high risk of developing PVR. In 2003, our group demonstrated that they were more frequent in the vitreous of patients who developed PVR after surgery compared to RD patients that did not (Martin et al., 2003). These cells were also found around the retinal vessels and inside the retinal tissue in human PVR samples (Pastor et al., 2006b). Now it is recognized that macrophages not only release pro-inflammatory agents (Garweg et al., 2013), but they also mediate photoreceptor apoptosis through monocyte chemoattractant protein-1 (MCP-1) (Nakazawa et al., 2007).

In summary, three major cell types are implicated in RD and therefore in PVR: RPE, glial cells, and macrophages. The principal role of these cells in PVR is the remodeling of the retina after neuronal death caused by ischemia. However the unsolved question is why in some patients this mechanism exceeds the regular limits of this reparative process.

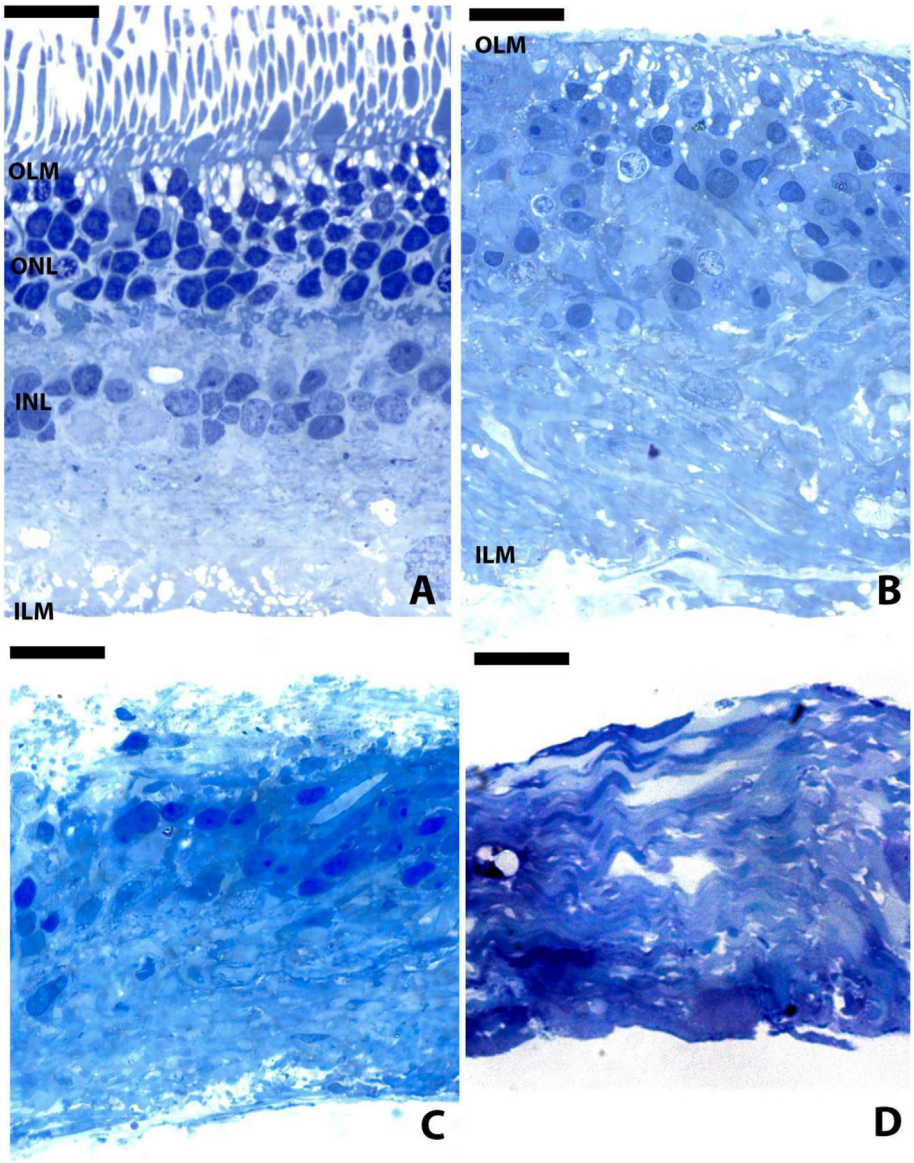

Fig. 5. Toluidine Blue staining of human retina specimens. Fresh human retina and retinal samples obtained from patients with intraretinal PVR where retinectomy was necessary to reattach the retina (100×). The images show progressive degenerative stages from a normal neuroretina in which retinal layers are perfectly organized (A) to a complete degenerate retina in which gliotic response dominate and the normal architecture is lost (D). Following retinal detachment, the photoreceptors are lost and there is a generalized loss of normal retinal architecture with progressive replacement for reactive gliosis (B and C). In the final stage, the neuroretina lacks of neurons and thick glial cells prolongations replace the normal retinal structure (D). Scale bar: 10 μ. Courtesy of Dr. M. Gayoso. University of Valladolid, Valladolid, Spain.

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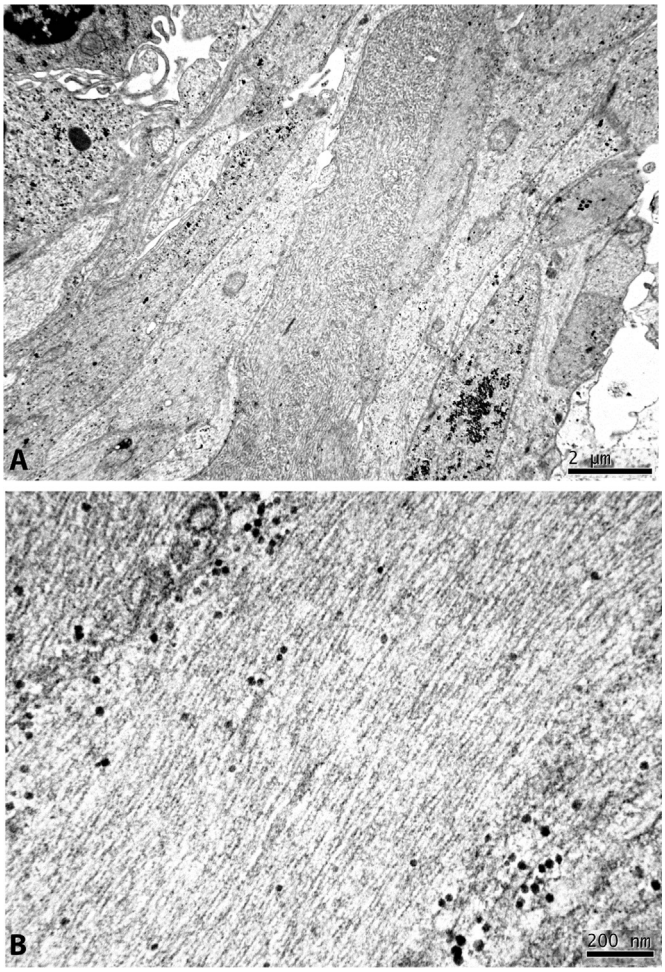

Fig. 6. Electron microscope images of intraretinal PVR samples obtained during surgery in which retinectomy was necessary to reattach the retina. Ultrastructural detail of a gliotic retinal area. (A) Most of the retina presents thick glial cells prolongations containing intermediate filaments (B). Courtesy of Dr. M. Gayoso. University of Valladolid, Valladolid, Spain.

1.6. Cytokines and other mediators

Many growth factors, signaling pathway mediators, and receptors have been described in patients suffering from PVR (Pennock et al., 2014a; Rouberol and Chiquet, 2014). Some of these have also been implicated in the stimulation of RPE and glial cells. Among them, PDGF, HGF, VEGF, EGF, transforming growth factor α (TGF α), TGF-β, granulocyte colony stimulating factor (G-CSF), acidic and basic FGF, insulin-like growth factor 1 (IGF-1), connective tissue growth factor (CTGF), and mothers against decapentaplegic homolog (SMADs) are the most important (Flanders, 2004; Saika et al., 2008, 2007). They are synthesized by a variety of cells and induce many actions. For example, PDGF is synthesized by glial cells and by RPE cells when they lose contact with photoreceptors. PDGF stimulates proliferation by its own receptor, and it is also a potent mitogen and chemoattractant for glial cells (Rouberol and Chiquet, 2014).

Other examples of molecular mediators found in PVR are TGF and the associated signaling pathway molecules SMAD3 and SMAD7. These are strongly implicated in apoptosis, the stimulation of epithelial-mesenchymal cells, fibroblast and myofibroblast conversions, and the enhanced expression of extracellular matrix proteins (Flanders, 2004; Saika et al., 2008, 2007). The following molecules have also been associated with this disease: interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), TNF-α and -β, interferon gamma (INF- γ) and MCP-1 (Pennock et al., 2014a; Rouberol and Chiquet, 2014).

The presence and concentration of cytokines have been proposed as biomarkers for predicting development and severity of PVR (Kon et al., 2000, 1999; Ricker et al., 2012; Rusnak et al., 2013). However once again, these cytokines are not specific for PVR and have been found in RD without PVR as well as in other intraocular disorders such as proliferative diabetic retinopathy (Pennock et al., 2014a; Rusnak et al., 2013).

1.7. Our ideas for the pathogenesis of PVR

To our knowledge, the initial mechanisms implicated in PVR are not different from those of any RD repair. After retinal separation, the retinal outer layers become ischemic and the photoreceptors start to die by several pathways, but mainly apoptosis. This loss of neurons stimulates the hypertrophy of retinal glial cells, mainly Müller cells, but also astrocytes and microglia, that begin the remodeling of the retina and perhaps the neuroprotection of the remaining neurons. However these intraretinal changes, if they are excessive, cause the substitution of neurons by glial tissue and the shortening of the retina. We propose to identify and name this phenomenon as intraretinal PVR (Fig. 7).

At the same time, and because of the breakdown of the blood-retinal barriers, microglia and macrophages migrate into the subretinal space and into the vitreous cavity where they release inflammatory products. RPE cells, after losing contact with photoreceptors and after being stimulated by growth factors produced by a variety of cells, including Müller cells, enter into a mesenchymal transformation. Through the retinal breaks or tears, the transformed cells migrate into the vitreous cavity. There they play an important role in the development of epiretinal PVR by the formation of contractile membranes at the inner surface of the retina and in the vitreous surface (Fig. 1). These activities are considered the most typical clinical feature of PVR (Committee, 1983; Pastor et al., 2002). Inflammation then plays an important role in PVR, but once again the mediators do not differ from those present in any RD. It is possible that the degree of inflammation is crucial for PVR development, and most of the identified clinical risk factors for PVR have an important inflammatory component (Moysidis et al., 2012; Rodriguez de la Rua et al., 2005; Tosi et al., 2014) as we will discuss further.

Our hypothesis is that when inflammation reaches a certain

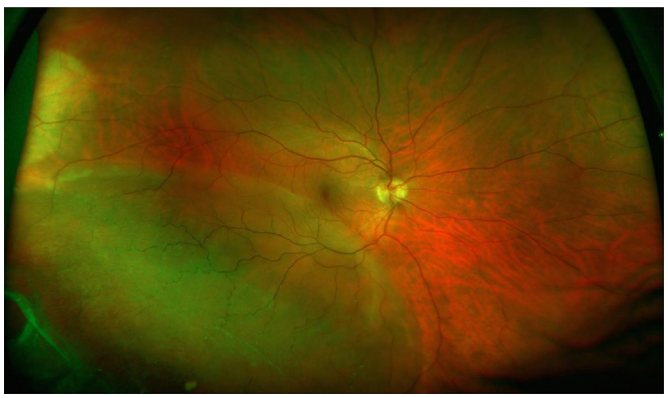

Fig. 7. Localized PVR in a RD. Whitish appearance of the surface and rolled edge of the tear suggest intraretinal changes (intraretinal PVR). Nevertheless, this finding should be confirmed during surgery (difficulties in flattening the retina). Courtesy of Prof. Stanga (Manchester Royal Eye Hospital).

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level, the remodeling mechanisms elicited by the detached retina are exaggerated and amplified, causing entry into the PVR process. There are two important questions regarding this hypothesis: "What is this level of inflammation beyond which PVR is initiated?" and "What compels the inflammatory process to exceed this level of inflammation?" Regulation of transcription factors, inhibition of kinases, stimulation of apoptosis, among others, are all processes involved in inflammation that are not perceived by the surgeon's eye. It is probable that all of these clinical factors that we evaluate in the office prior to surgery are telling us that parts of these mechanisms have been launched since the neuroretina and RPE lost contact with one another. The final outcome is played at a molecular level, which is probable determined by the genetic profile of the patient.

We have begun to explore the genetic profile of PVR patients (Pastor-Idoate et al., 2013a, 2013b; Rojas et al., 2009; Rojas et al., 2013; Sanabria Ruiz-Colmenares et al., 2006). We are convinced that genetics play an important role because the production of cytokines is a gene-regulated process (Zacks et al., 2006) and variations in these genes could be an important factor for PVR development. Additionally, the influence of gene composition probably extends further than the inflammatory process. Very recently, Matsumoto et al. (2014) demonstrated in mice that the genetic background affects the photoreceptor cell death rate in response to experimental RD. Modifying the expression of the SMAD7 gene in mice after RD suppresses fibrogenic responses to TGF-β2 by RPE cells (Saika et al., 2007).

In summary, pathogenic mechanisms implicated in PVR are not different from those elicited in any RD. If the response to RD occurs in a pro-inflammatory environment, whether by external situations or by the genetic profile of the patient, it is diverted from restoration of the injured retinal tissue. In those cases, the response is re-directed towards the onset of PVR. Obviously prophylactic measures or treatments based upon epiphenomena like intravitreal cell proliferation or extracellular matrix formation have had little success in solving the problem as has been demonstrated through the years. It now seems more likely that effective prophylaxis or treatment of PVR will be achieved by the regulation of mediators of inflammation such as transcription factors, receptors, cytokines, etc., or maybe even better, by a combination of both strategies.

2. Why should we investigate PVR in 2015?

Currently PVR management is basically restricted to the surgical repair of the detached retina. However, anatomical and functional success rates of surgical treatment remain unsatisfactory, although many efforts have been made to propose new pharmacological approaches to improve these results (Asaria and Charteris, 2006; Pennock et al., 2014a, 2011). Based on the original ideas of PVR pathology (Committee, 1983) and after testing them in experimental models, several medical treatments have been proposed. However, most of the strategies that showed positive results in animal models have failed to prove their efficacy in human clinical trials (Moysidis et al., 2012), and currently there is no other accepted treatment beside surgery. As we will discuss later, the discordant results obtained in experimental models and human clinical trials could be due to dissimilarities in the causes of PVR in the models and humans (Moysidis et al., 2012; Sadaka and Giuliari, 2012).

Without an appropriate comprehension of the biological processes involved in PVR, including the role of different mediators, it seems impossible to develop an efficient prophylaxis or treatment (Garweg et al., 2013). Therefore, to improve current outcomes in the treatment of PVR, a better understanding of its pathogenesis is mandatory and a greater cooperation between clinicians and basic scientists is needed.

2.1. There is not an appropriate treatment, yet

For the past 40 years, the pharmacologic agents proposed to prevent PVR have been mainly anti-inflammatory, anti-proliferative, anti-neoplastic, anti-growth factor, and antioxidant agents (Sadaka and Giuliari, 2012). However, none of them have been incorporated routinely into clinical treatments. Corticosteroids were the first drugs tested for PVR (Chandler et al., 1985). Experiments in animals found some efficacy with intravitreal administration of triamcinolone acetonide or topical and systemic corticosteroids (Pastor et al., 2000), but patients treated in clinical trials with these agents showed a poor response (Moysidis et al., 2012; Sadaka and Giuliari, 2012). In addition to the direct application of the corticosteroids, silicone oil was suggested as a reservoir for the drugs and some other substances with the aim of reducing the "re-proliferation". Unfortunately most of the drugs were not soluble in silicone oil (Pastor et al., 2008a).

The anti-neoplastic or anti-proliferative agents suggested for PVR prevention or treatment included compounds as 5-fluorouracil (5-FU), daunorubicin, taxol, colchicine, retinoic acid, ribozymes, vincristine and others. 5-FU is an antimetabolite that inhibits synthesis and fibroblast proliferation and has been one of the most tested agents for the treatment of PVR. In animal models it showed beneficial results, but in human clinical trials the results were poor with some important side effects (Moysidis et al., 2012). Also, a combination of this agent with low-molecular-weight heparin (LMWH), an anticoagulant that binds many growth factors, was proposed. However, in a large, randomized, controlled trial using this combination versus placebo, the combination did not improve anatomical or visual success rates after PVR (Wickham et al., 2007).

The principle for the use of anti-growth factors and antioxidant agents is to inhibit several growth factors and associated pathways. Many of them are currently being studied in experimental models, but currently there are no results from human clinical trials (Alex et al., 2010; Chan et al., 2013).

One of the latest approaches is the use of antiangiogenic drugs in PVR. Ranibizumab, an agent that neutralizes vascular endothelial growth factor A (VEGF-A) reduces vitreous bioactivity in patients and in experimental models of PVR (Pennock and Kazlauskas, 2012; Pennock et al., 2013). Similar results have been obtained with aflibercept (VEGF Trap-Eye) in animal models. These are interesting approaches but should be considered cautiously before transferring the results into the clinic. The rabbit model for these studies was based on the intravitreal injection of conjunctival fibroblasts (Pennock et al., 2014b, 2013). As we will discuss further, this model has little in common with the human disease.

One of the major drawbacks with many potential treatments, especially with the anti-proliferative agents, is the existence of undesirable side effects (Pastor, 1998; Scheer et al., 2004). In some cases these risks could be worth taking if there is a clear potential benefit. Such use could be justified only in patients with a high risk of developing PVR and with a high probability to respond to the treatment. This accurate identification is still a challenge, despite much research on the preoperative clinical risk factors, intraocular biomarkers, and genetic background. Unfortunately, there is still no accurate procedure to identify those RD patients (Rojas et al., 2009, 2015).

The early identification of at-risk patients is crucial for obtaining better outcomes because once PVR develops, the anatomical and functional results are very unsatisfactory. Currently PVR interventions are usually performed in an advanced stage of the disease, and there is no real prophylaxis (Pastor et al., 2002). Even

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more, many PVRs develop after RD surgery (Pennock et al., 2014a), and because in many cases clinical characteristics do not provide useful information, first surgeries are planned without having in mind the possibility of developing PVR. Thus, identifying patients with high susceptibility for PVR at RD presentation could also persuade the ophthalmic surgeon to decide in favor of a more conservative treatment, avoiding aggressive surgical trauma that is considered a clinical risk factor (Pastor et al., 2002).

2.2. There is little information on clinical outcomes, mainly functional

There is little information on the functional results after PVR, and this topic will be discussed later in the review. Most reports emphasize the anatomical reattachment of the retina, which is still a big challenge in most cases. Reattachment rates for RD cases that develop PVR are very low compared to those that do not develop PVR. The anatomical success rate after RD complicated with PVR is 60–80% in the most favorable cases, whereas the reattachment rate is up to 90% in RD without PVR (Mitry et al., 2010; Pastor et al., 2012, 2008b). Thus, it is not surprising that functional results are also very disappointing (Berker et al., 2007). The poor visual outcomes generate a huge burden in the quality of life of these patients (Asaria and Charteris, 2006; van de Put et al., 2014).

2.3. Multiple surgeries increase the cost of treatment

Another important aspect to be considered is the costs of treatment and current management of PVR. Patients who develop postoperative PVR (grade C or greater) double the costs of management in terms of higher number of surgical procedures and a more extensive follow-up period compared with patients without PVR (Patel et al., 2004). A recent study compared the outcomes of twenty-five gauge (25-G) surgery in RD complicated with grade C PVR with or without anterior PVR (Sato et al., 2014). The mean number of operations was 1.7 in patients with anterior PVR, classically associated with worse prognosis, and 1.3 in patients without anterior PVR. According to these results, this situation generates a heavy burden not only on these patients but also on the health care system.

2.4. PVR is not only important after RD but it also complicates other intraocular surgeries and prevents therapeutic advances

Finally, PVR is not only a complication of RD, but it also plays an important role in other ocular pathologies, such as penetrating globe trauma or RD after giant retinal tears. It can also appear after techniques such as 360-degree retinectomies that were used for macular translocation in wet AMD (Asaria and Charteris, 2006). Although these and others therapeutic attempts have been abandoned, possible new cell therapies that are already in development would require surgical approaches that could result in PVR (Fernandez-Bueno et al., 2013b).

In summary, to achieve more favorable cost-effective results that diminish the burden on health care systems and to decrease the vast impact on patient quality of life, efforts should be focused on obtaining a reliable method to identify patients at high risk for PVR and who could benefit from effective prophylactic treatment. Novel clinical strategies may require multimodal, combinatorial approaches targeting different signaling pathways involved in this disease (Moysidis et al., 2012; Rojas et al., 2009, 2015; Sadaka and Giuliari, 2012). Moreover, drugs proposed for treatment of PVR must be well considered because their application may be associated with potentially harmful side effects. Finally, correct optimization of dosing and administration of these drugs is needed. For all these reasons further investigation of this disease is still fully justified.

3. The problem of PVR classification and a new proposal

3.1. Historical review

The first widely recognized classification for PVR was published in 1983 (Committee, 1983). The Retina Society Terminology Committee based its work on the condition formerly called “massive vitreous traction” or “massive periretinal proliferation” (Havener, 1976; Machemer, 1978; Scott, 1975). This classification was based on the idea that cellular proliferation was the main feature of PVR. Thus the only clinical factors considered were the extent of fixed retinal folds and the overall configuration of the funnel shaped RD. Other important clinical features, such as the presence of visible subretinal membranes, vitreous mobility, location of trans-vitreous membranes, severity of traction on the anterior retina, equatorial retinal folds, and intraretinal membranes were not incorporated. This approach resulted in a simple classification, easy to use, but not useful in practice as has been demonstrated. In fact, this classification is not used currently by clinicians although there are still some papers dealing with medical treatments that use it (Ganekal and Dorairaj, 2014).

According to the revised classification scheme developed by The Retina Society Terminology Committee, a minimal PVR was designated Grade A and defined as the presence of vitreous haze and pigment clumps, a finding that is not unique of PVR. They can be present in many forms of granulomatous uveitis and in long standing RD without PVR (Rouberol and Chiquet, 2014). Grade B, or moderate PVR, included the presence of surface retinal wrinkling and/or rolled edges of the retinal break that could be accompanied by retinal stiffness and vessel tortuosity. However, these features can be present in some RDs that do not further develop an “extensive” PVR. In fact many surgeons obtained excellent results with the scleral techniques 10 years ago (Afrashi et al., 2005).

Grade C, or marked PVR, was defined as the presence of full thickness retinal folds in one (C-1), two (C-2), or three (C-3) quadrants. Grade D, or massive PVR, was defined as fixed retinal folds in four quadrants that result in a wide funnel shape (D-1), a narrow funnel shape (D-2), or a closed funnel without view of the optic disc (D-3).

These four stages also provided a false idea of the increasing severity of the disease. For example, a D grade PVR could be caused by a localized epiretinal membrane that would be easily managed with surgery. In contrast, a grade C PVR could be associated with intraretinal changes that have a worse prognosis (Pastor et al., 2002).

This classification missed many important clinical characteristics, such as the number and location of retinal breaks and the existence of pre-equatorial forms of PVR. With the idea of solving some of these problems, a new classification was proposed as part of the Silicone Study (Lean et al., 1989). Previous classifications emphasized the involvement of the post-equatorial retina (posterior PVR). The most important contribution of the new classification scheme was the inclusion of proliferative membranes in the pre-equatorial region and on the vitreous base (anterior PVR) that are more frequent after surgical attempts to reattach the retina. Furthermore, attention was paid to the quantitative assessment of PVR by recording the number of clock hours of the retina involved by membranes. In this classification, minimal (Grade A) and moderate (Grade B) classifications remained unchanged, but Grades C and D were replaced by Grades P and A (posterior and anterior forms). Moreover, Grades P and A were further defined by the presence of “types” of contraction. The extension of each grade was

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assessed by the number of clock hours, not necessarily contiguous, of the involved retina. As stated by the authors, this classification does not attempt to predict the PVR severity because factors that influence the results of surgical treatment were not fully understood (Lean et al., 1989).

To meet the need to incorporate changes proposed by the Silicone Study Group (Lean et al., 1989) and modifications proposed also by other authors (Heimann and Wiedemann, 1989), the Retina Society updated its classification in 1991 (Machemer et al., 1991). Three grades of increasing severity were described, emphasizing the posterior and anterior locations of proliferation. The new classification kept Grades A and B, modified Grade C, and eliminated Grade D (RD in funnel configuration). Following the Silicone Study classification, a more detailed description of Grade C (posterior and anterior) PVR was made by adding the types of contraction, the extent of which was detailed by using clock hours instead of quadrants.

In the classification revised by the Retina Society, Grade C was defined as full-thickness retinal folds and/or subretinal bands and pathologic changes that could be posterior, anterior, or both. Posterior grade C PVR was further divided into focal contractions resulting in starfold membrane formation (Type 1) and/or diffuse contractions resulting from confluent starfolds that can result in a closed-funnel configuration (Type 2). Grade C PVR also included anterior or posterior subretinal bands (Type 3). Anterior grade C was divided into circumferential contraction (Type 4) along the posterior margin of the vitreous base and anterior displacement (Type 5) of the peripheral retina (Machemer et al., 1991).

This classification may be too complex to be used in clinical practice and does not offer any indication for selecting the most appropriate management of the disease. Major drawbacks are found in its complexity and inability to be easily reproduced by different clinicians, therefore it has been rarely incorporated into the clinic.

Since the revision by the Retina Society, no other classification scheme has been popularized. Probably for all these reasons, most of clinicians do not use any classification or, alternatively, refer to the 1983 classification scheme (personal unpublished data). There are papers that still consider that the older classification is appropriate for defining the severity of the disease. This can cause controversial results that are, in part, attributable to the subjective assessments of PVR from surgeon to surgeon (Adelman et al., 2013).

3.2. Problems derived from the lack of an accepted classification

This lack of an appropriate and uniform grading system is a crucial point to resolve for evaluating new treatments. It is essential to uniformly evaluate similar cases and thereby facilitate proper comparison of alternative surgical or pharmacologic treatments and clinical results. Currently, efficient communication between clinicians and comparison of different studies are problematic.

One important problem is that all available classifications are purely a description of the ophthalmoscopic findings, and no attempts have been made to add new clinical information based on new imaging techniques. Only a few papers have tried to analyze the role of vitreous posterior detachment as a prognostic factor for PVR development. However, this type of analysis has not been incorporated into either routine examinations for PVR patients or any PVR classification (Capeans et al., 1998; Rezende et al., 2007). Even more, current classifications do not provide information on the activity of the disease, the prognosis, or the functional and/or anatomical outcome after successful treatment.

3.3. Some ideas for a possible new classification

PVR is a relatively acute process. Most of the cases are produced within one month after the retina is detached and surgically repaired. According to our experience, 77% of postoperative forms appear within one month after surgery and 95% in the first 45 days (Pastor, 1998; Pastor et al., 2002). Therefore it should be possible to find information on the stage of the disease, active or quiescent, which is important from the therapeutic point of view. During the 1990's, some surgeons recommended avoiding surgery at the early stages of the disease because it was demonstrated that after PVR was initiated, it could be stimulated by additional surgery (Campochiaro, 1997). The added degree of inflammatory activity could stimulate the so called “re-proliferation”, an important cause of failure after PVR surgery (Berker et al., 2007; Pastor, 1998; Pastor et al., 2002).

While cell proliferation in PVR peaks during the firsts 4 days after RD, it is reduced around day 7 and then continues thereafter at a lower rate (Fisher et al., 1991; Lewis et al., 2003). These events persist over the time in PVR, but currently we are not able to quantify the activity of these processes. The dynamics of retinal remodeling may have important practical implications if we were able to treat the disease at the right time. All this information is crucial when comparing different treatments and series, but currently our understanding of retinal remodeling dynamics and the forces that control it is very poor.

Finally, all of the classifications miss crucial aspects of the pathogenesis of the disease. For instance, they do not incorporate the presence and extension of intraretinal changes that are directly related to poor anatomical outcomes and functional prognoses (Pastor, 1998; Pastor et al., 2002, 2006b, 2003). The classification schemes also do not include the presence and importance of inflammation (Table 1) (Martin et al., 2003; Moysidis et al., 2012; Pastor et al., 2002; Rojas et al., 2010; Sanabria Ruiz-Colmenares et al., 2006; Symeonidis et al., 2012; Zhang et al., 2012).

3.4. Intraretinal changes are crucial

It is now clear that intraretinal PVR is the most severe form in which there are major changes in retinal architecture leading to significant dysfunction (Figs. 5, 6 and 8). Furthermore, these forms have a huge influence in the surgical complexity and in the anatomical and functional outcome, especially when the posterior pole is involved. In contrast, epiretinal or subretinal membranes can be relatively easily removed by surgery, and the prognosis of a macular epiretinal membrane is obviously better than an intraretinal one (Pastor et al., 2002, 2003). However until now, intraretinal changes have been detectable only during surgery when the surgeon could not appose the retina to the eyewall. Also, little attention has been paid to the identification of these changes before surgery or in the postoperative period. Even in recent papers these retinal changes have not been recognized (Rouberol and Chiquet, 2014). Nevertheless, there is hope that the use of new imaging technologies could add relevant information regarding the intraretinal changes (Boroomand et al., 2013).

Considering these facts, we believe that attention should be focused on changes in the retinal tissue rather than membrane extensions. We propose a simplified classification scheme with four major PVR forms: epiretinal, intraretinal, subretinal (rare) and mixed (most frequent). (Table 2) Further, we propose that the research efforts in the coming years focus on acquiring more information regarding the severity and extension of intraretinal changes. To achieve these goals, major components of these studies should include clinical information on intraretinal PVR extension, the role of intraocular inflammation, and the contribution of

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Table 1
Summary of the most relevant facts of the previous PVR classifications.

Classification	Most important features	Most critical disadvantages
1983[a]	Identifies PVR as an independent clinical entity	Based on ophthalmoscopic appearance Provides false idea of severity and progressiveness Does not recognize intraretinal changes
1989[b]	It added anterior forms and a detailed description of PVR extension an types of membranes and contraction	Too complex to be used in clinic Does not provide information of progressiveness Does not recognize intraretinal changes
1991[c]	Quite similar to the Silicone Study classification Simpler to use	Does not provide information of progressiveness Does not recognize intraretinal changes

Grades A and B are common in all classifications. They do not provide specific information on the further development of extensive PVR.
[a] Committee, T.R.S.T., 1983. The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90, 121–125.
[b] Lean, J.S., Stern, W.H., Irvine, A.R., Azen, S.P., 1989. Classification of proliferative vitreoretinopathy used in the silicone study. The Silicone Study Group. Ophthalmology 96, 765–771.
[c] Machemer, R., Aaberg, T.M., Freeman, H.M., Irvine, A.R., Lean, J.S., Michels, R.M., 1991. An updated classification of retinal detachment with proliferative vitreoretinopathy. Am J Ophthalmol 112, 159–165.

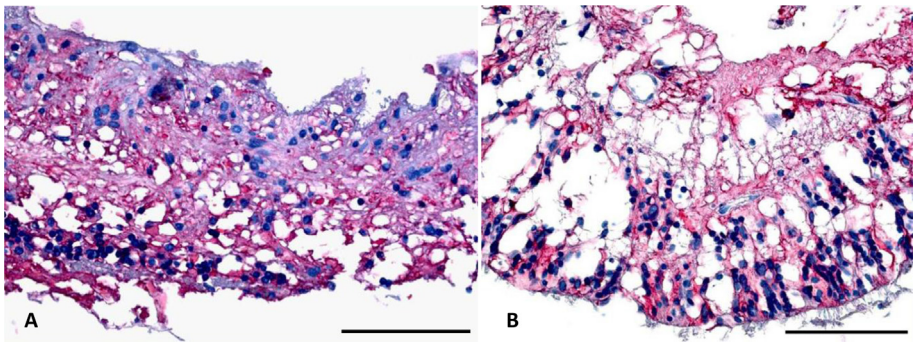

Fig. 8. Immunohistochemistry staining of PVR retinal samples obtained by retinectomy (A–B). The images show high glial fibrillary acidic protein (GFAP) immunoreactivity (red) resulting in gliotic retina (intraretinal PVR) with complete disorganization of the retinal tissue. (20× images. Scale bar: 100 μm).

Table 2
Critical elements for a new classification.

Type of morphologic changes	
Epiretinal	Membranes on retinal or vitreous surface
Intraretinal	Retinal shortening without epiretinal membranes
Subretinal	Any type of subretinal membrane, band, etc
Extension of changes	
By quadrants	
Retinal thickness by OCT	
Signs of severity and progressiveness	
Presence of SNP of risk	
Clinical risk factors clearly identified	
Time of evolution after onset	
Still unidentified signs	
New biomarkers able to determine presence of intraocular inflammation	

OCT: optic coherence tomography.
SNP: single nucleotide polymorphisms.

genetic profiles that influence the inflammatory response. Such information is critical to the ophthalmologist in deciding on the timing of surgical intervention and the use of adjuvant treatments.

4. Criticism of the current experimental models

From a theoretical point of view, experimental models should provide a systematic and controlled way to study cellular changes that occur in PVR. They can help to expand our knowledge of the pathobiological processes and also allow testing of new therapeutic agents. Unfortunately, most of the published models are based on the idea that pathogenic cellular proliferation into the vitreous cavity is the main feature in PVR, and the models have tried to reproduce this event.

Initially, models were created simply by injecting cells, mainly dermal fibroblasts, into the vitreous cavity. These efforts were followed by adding some other components such as inflammation, blood, cytokines, and so on, with or without cells (Agrawal et al., 2007). Obviously most of these models were used for testing anti-proliferative and anti-growth factor drugs. In some cases with positive results, these efforts stimulated researchers to transfer protocols into the clinic (Charteris et al., 2004). Unfortunately, these kinds of treatments failed, and the research was re-oriented towards other pathways. Nevertheless in some specific ways, these models could still have value, thus we have summarized them below.

4.1. *In vitro* models of PVR

In vitro systems can be used to analyze the behavior of defined cell populations under certain conditions. RPE cell culture has been widely used in the study of PVR, as they have been considered the major cell type involved in PVR pathogenesis (Bastiaans et al., 2014; Rouberol and Chiquet, 2014). Other *in vitro* models are based on vitreous explants and retinal organ cultures (Agrawal et al., 2007). However, the results of these studies are considered speculative and must be followed by *in vivo* studies.

A major criticism of *in vitro* model systems, mainly those based on cell culture, is that they do not adequately replicate a relatively complex tissue such as the retina, including the relationship with blood vessels. They also do not take into account the importance of the glial responses in RD and PVR, a common problem cited for organotypic cultures (Wickham and Charteris, 2009).

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4.2. In vivo models of PVR

Over 27 animal models of PVR have been described. For a recent review, see Agrawal et al. (2007). Intravitreal injections of different cell types or factors reported to play a role in this disease have been performed to reproduce the pathological processes that lead to PVR. The most common of these models consists of the injection of fibroblasts, which are not present in the healthy human retina but are present in PVR membranes (Moysidis et al., 2012; Pennock et al., 2011; Trese et al., 1985). However the fibroblast-like cells observed in human intravitreal membranes are now identified as the products of mesenchymal transformation of RPE cells (Chiba, 2014). Most of these experimental models used fibroblasts from dermal origin (Khawly et al., 1991). These cells are very different from the cells present in human PVR, although they may be somewhat similar to the intraocular proliferation of cells that occurs after ocular penetrating trauma (Hsu and Ryan, 1986). The problem with these models is that they depend on the type of cells that are chosen for injection into the vitreous rather than the cells that are actually present in PVR, i.e., RPE cells and glial cells that have transdifferentiated into fibroblasts.

Other models involve the intravitreal injection of different cell types such as RPE cells (Fastenberg et al., 1982; Radtke et al., 1981; Wong et al., 2002), macrophages (Hui et al., 1989), and platelets (Garcia-Layana et al., 1997; Pastor et al., 2000), among others. These models may have value for analyzing some specific features and for better understanding the pathogenesis of the disease. Unfortunately they have mostly been used for testing new proposed drugs, mainly anti-proliferative agents. As was the case for other studies of this type, positive results in animal models did not presage successful treatment for patients.

Other *in vivo* models have placed more emphasis on reproducing intraocular inflammation and the subsequent release of cytokines and growth factors (Pastor, 1998). These have included surgical manipulations such as lensectomy, vitrectomy, induction of RD, cryotherapy, and also penetrating trauma (Agrawal et al., 2007; Garcia-Layana et al., 1997; Goldaracena et al., 1997). These models could still have some value in terms of analyzing the preliminary changes occurring in PVR, but attention should be paid to the types of animals used for them. The retinal vascularization, glial components, and others elements of PVR are not identical among the different animal models, and the critical points in the development of experimental PVR could be unique to each species and different from that in humans.

Regarding the different animal species, rabbit is the most frequently used because rodents have a small eye and a relatively wide lens that interferes with the manipulation to induce PVR. In terms of retinal vasculature, ideally animal models should have a holoangiotic retina, which means the whole retina is vascularized like that of most mammals. The opposite retinal vascularization scheme is merangiotic, such as the rabbits, where blood vessels are present only in a smaller part of the retina. The disparate vascular patterns may play a critical role in the different behavioral responses to retinal trauma present in animal models and humans (Trivino et al., 1997).

Besides the vascular component, the presence and distribution of retinal glial cells is also an important factor for developing adequate PVR models. The retina contains Müller cells that are specialized radial glia that make extensive contacts with retinal neurons. As mentioned, in humans, Müller glial cells occupy up to 20 percent of the overall volume of the retina, and the density of these cells approaches 25,000 per mm^2 of the retinal surface area (Bringmann et al., 2006). Each Müller cell forms contacts with a clearly defined group of neurons organized in a columnar fashion. In humans, a single Müller cell supports approximately 16 neurons, while in rodents each one supports up to 30 neuronal cells (Bringmann et al., 2006).

Moreover, it is well known that biological responses differ among the species. For instance, post-transcriptional regulation of human NO synthetase 2 (NOS2) is very different from that in mouse. This simple step makes the resulting levels of NO produced by activation of human NOS2 lower than levels produced by mouse NOS2. This difference has very important implications in the tissue redox environment and immune responsiveness (Hoos et al., 2014).

Because PVR is a multifactorial disease and it results from the interaction of genetic and environmental factors, its pathogenesis may include many different events and signaling pathways (Pastor-Idoate et al., 2013b; Pennock et al., 2014a). Therefore, those experimental models that try to simulate a series of events that are not yet completely understood and which may involve pathways that are not present in human PVR pathogenesis, may in fact be very poor and misleading models of the human disease (Moysidis et al., 2012).

For all these reasons, the results of many of the above cited studies have limitations in their interpretation because there are important pathological differences between these animal model and human diseases. Nevertheless, despite these limitations, experimental models are especially important in complex diseases and in those with unknown pathogenesis like PVR, and they may provide crucial steps for the development of new therapeutic options if they are properly oriented. (Table 3).

5. Clinical risk factors

Clinical risk factors for developing PVR following a RD have been assessed since the early stages in the study of this process. Theoretically, identification of these factors could be useful for elucidating the mechanisms of pathogenesis, providing guidelines for the management of RD, and perhaps for making the decision of adding an adjuvant treatment (Cowley et al., 1989). Also, the aim of understanding the risk factors is to identify those patients at high risk and to avoid the preventable risks if possible, or to modify the surgical options (Bonnet, 1984, 1988; Chignell et al., 1973; Cowley et al., 1989; Tolentino et al., 1967; Yoshida et al., 1984). The identification of risk factors seems today very important because we are facing new therapeutic options. Thus it is necessary to identify the patients who may be prime candidates for pharmacologic treatments to prevent the occurrence and re-occurrence of PVR (Asaria and Gregor, 2002; Kon et al., 2000).

5.1. Types of clinical studies

Several attempts have been made to predict the risk of PVR development based on the clinical characteristics of RD patients (Asaria and Gregor, 2002; Kon et al., 2000; Rodriguez de la Rua et al., 2005). Unfortunately, the results so far have not been very consistent, and several formulas based on these factors have failed in demonstrating usefulness for routine clinical use (Asaria et al., 2001; Kon et al., 2000; Rodriguez de la Rua et al., 2005; Sala-Puigdollers et al., 2013; Wickham et al., 2011). However, the majority of these studies have been made retrospectively, and the results are often contradictory and inconclusive (Kon et al., 2000). It is worth noting that many differences in these studies exist in design, methodology, definitions, and statistical analysis, and therefore they cannot be directly compared (Asaria and Gregor, 2002). Other studies were oriented to discern the influence of a single specific factor or were focused on the identification of risk factors associated with specific circumstances such as aphakia, preoperative PVR, or subretinal PVR. However, these approaches are not appropriate for a multifactorial disease like PVR (Rodriguez

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Table 3
Experimental models of PVR used in recent studies. RPE: retinal pigment epithelium. EMT: epithelial mesenchymal transition. PDGF: platelet-derived growth factor. PDGFR: platelet-derived growth factor receptor.

Intervention		Animal species used	Advantages	Disadvantages
Injection	Fibroblasts + platelet rich plasma[a]	Pigmented rabbit	More rapid development, more consistent and severe compared to simple fibroblasts injection. Easy to perform, reproducible	Use of external fibroblasts. Exogenous influx of cells. Cells must be cultured to obtain sufficient number, which may cause lost of *in vivo* characteristics. No primary alteration of RPE. Too rapid time course may not be useful to test therapeutic agents
	RPE (Autologous, homologous)[b]	Pigmented rabbit	Use of RPE cells, which are primarily involved in PVR. Easy to perform, reproducible	Exogenous influx of cells. Cells must be cultured to obtain sufficient number, which may cause lost of *in vivo* characteristics. Cells may not suffer EMT
	RPE + Platelet rich plasma[c]	Wistar rat	Use of RPE cells, which are primarily involved in PVR. More rapid development, more consistent and severe compared to simple RPE injection. Easy to perform, reproducible. Suitable animal species for research	Exogenous influx of cells. Cells must be cultured to obtain sufficient number, which may cause lost of *in vivo* characteristics. Cells may not suffer EMT
	Dispase[d]	Mouse	Suitable animal species for genetic manipulation. Easy to perform, reproducible	Epiretinal membranes lack RPE-derived cells Small size of the animal limits surgical procedures
Surgical intervention + injection	RPE cell injection + gas vitreous compression	Albino rabbits[e] Pigmented rabbits[f]	Use of RPE cells, which are primarily involved in PVR. Gas compression provides a reliable technique to generate vitreous alteration, and seems easier than vitrectomy	Exogenous influx of cells. Cells must be cultured, which may cause lost of *in vivo* characteristics.
	RPE cell injection + Posterior vitreous detachment + Retinal detachment[g]	Pig	Use of RPE cells, which are primarily involved in PVR. Reproduces posterior vitreous detachment and retinal detachment, as it occurs in human disease. Animal species used more accurately resemble human retina	Absence of glial cell contribution in the membranes. Relative rapid time course may interfere with study of early stages of disease
	Blood (autologous) injection + Scleral incision + partial vitrectomy + wound closure, avoiding lens and retinal injury[h, i]	Pigmented rabbit	No need to culture cells. Reproduces posterior vitreous alteration and wound healing	Model resembles ocular trauma. Red blood cells impede ophthalmoscopic visualization. Total lack of pigmentation suggests glial origin of membranes rather than RPE
Surgical intervention	Lensectomy + vitrectomy + peripheral retinotomy through corneal incision[j]	Mouse	Reproduces vitreous alteration. Suitable animal species for genetic manipulation. Suitable for study early stages of PVR	Small size of the animal limits surgical procedures. No RPE migration into vitreous cavity
Growth factor model	Mouse fibroblasts expressing PDGFRs + Platelet rich plasma + partial vitrectomy + gas compression[k]	Pigmented rabbit	Allows the study of PDGF, which is supposed to play an important role in PVR. Gas compression provides a reliable technique to generate vitreous alteration	This factor of interest is the main one expressed, which may differ from human disease and may interfere with response of cells. Complex cell obtention

[a] Nakagawa, M., Refojo, M.F., Marin, J.F., Doi, M., Tolentino, F.I., 1995. Retinoic acid in silicone and silicone-fluorosilicone copolymer oils in a rabbit model of proliferative vitreoretinopathy. Investigative ophthalmology & visual science 36, 2388–2395.
[b] Radtke, N.D., Tano, Y., Chandler, D., Machemer, R., 1981. Simulation of massive periretinal proliferation by autotransplantation of retinal pigment epithelial cells in rabbits. American journal of ophthalmology 91, 76–87.
[c] Zhao, H.M., Sheng, M.J., Yu, J., 2014. Expression of IGFBP-6 in a proliferative vitreoretinopathy rat model and its effects on retinal pigment epithelial cell proliferation and migration. International journal of ophthalmology 7, 27–33.
[d] Canto Soler, M.V., Gallo, J.E., Dodds, R.A., Suburo, A.M., 2002. A mouse model of proliferative vitreoretinopathy induced by dispase. Experimental eye research 75, 491–504.
[e] Lee, J.J., Park, J.K., Kim, Y.T., Kwon, B.M., Kang, S.G., Yoo, Y.D., Yu, Y.S., Chung, H., 2002. Effect of 2'-benzoyl-oxycinnamaldehyde on RPE cells *in vitro* and in an experimental proliferative vitreoretinopathy model. Investigative ophthalmology & visual science 43, 3117–3124.
[f] Kuo, H.K., Chen, Y.H., Wu, P.C., Wu, Y.C., Huang, F., Kuo, C.W., Lo, L.H., Shiea, J., 2012. Attenuated glial reaction in experimental proliferative vitreoretinopathy treated with liposomal doxorubicin. Investigative ophthalmology & visual science 53, 3167–3174.
[g] Umazume, K., Barak, Y., McDonald, K., Liu, L., Kaplan, H.J., Tamiya, S., 2012. Proliferative vitreoretinopathy in the Swine-a new model. Investigative ophthalmology & visual science 53, 4910–4916.
[h] Cleary, P.E., Ryan, S.J., 1979a. Experimental posterior penetrating eye injury in the rabbit. I. Method of production and natural history. The British journal of ophthalmology 63, 306–311.
[i] Cleary, P.E., Ryan, S.J., 1979b. Experimental posterior penetrating eye injury in the rabbit. II. Histology of wound, vitreous, and retina. The British journal of ophthalmology 63, 312–321.
[j] Saika, S., Kono-Saika, S., Tanaka, T., Yamanaka, O., Ohnishi, Y., Sato, M., Muragaki, Y., Ooshima, A., Yoo, J., Flanders, K.C., Roberts, A.B., 2004. Smad3 is required for dedifferentiation of retinal pigment epithelium following retinal detachment in mice. Laboratory investigation; a journal of technical methods and pathology 84, 1245–1258.
[k] Andrews, A., Balciunaite, E., Leong, F.L., Tallquist, M., Soriano, P., Refojo, M., Kazlauskas, A., 1999. Platelet-derived growth factor plays a key role in proliferative vitreoretinopathy. Investigative ophthalmology & visual science 40, 2683–2689.

de la Rua et al., 2005). In addition, the high incidence of PVR found in some of these studies suggests that samples were composed of complex cases, and thus they are not representative of the population of non-complicated RD (Rodriguez de la Rua et al., 2005). Nevertheless, they have contributed valuable information because they have helped to unravel the complex nature of the disease. Most of the identified clinical risk factors are consistent with the inflammatory nature of PVR. While inflammation plays an important role in every case of PVR, it is not a unique factor (Pastor et al., 2002; Rodriguez de la Rua et al., 2005).

Some studies have been specifically designed to prove a particular hypothesis regarding the pathological origin of PVR, a decision that could implicate an important bias (Asaria and Charteris, 2006). For example, RPE cells are considered crucial in the development of PVR; therefore, many circumstances related to the high release of these cells have been investigated, such as the

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size of the retinal break, the use and intensity of cryo-application, the use of vitrectomy before or after the cryotherapy, etc. However, any risk factor should be identified as an independent parameter. Unfortunately most of the suspected risk factors are clearly related to each other, and it is not possible to isolate them from other circumstances (Rodriguez de la Rua et al., 2005).

5.2. Preoperative, intraoperative, and postoperative risk factors

Risk factors are classified as preoperative, intraoperative, or postoperative. Preoperative factors associated with a higher risk of PVR include ocular trauma (Girard et al., 1994), a history of prolonged intraocular inflammation (previous uveitis), prior infectious retinitis, and low intraocular pressure (IOP) secondary to intraocular inflammation (Girard et al., 1994; Pastor et al., 2002; Rodriguez de la Rua et al., 2005; Rodriguez de la Ruz Franch et al., 2000; Wickham et al., 2011; Yoshino et al., 1989). Retinal tear characteristics such as large size and number and RD extension are also some of the clinical factors almost constantly associated with the development of PVR (Rodriguez de la Rua et al., 2005; Rodriguez de la Ruz Franch et al., 2000; Wickham et al., 2011; Yoshino et al., 1989). Other preoperative risk factors include RD associated with vitreous hemorrhage (Duquesne et al., 1996), aphakia, previous intraocular surgery, previous choroidal detachment, and preoperative grade A or B PVR. All of these preoperative risk factors are in concordance with the inflammatory nature of PVR (Asaria et al., 2001; Bonnet, 1984, 1988; Yoshino et al., 1989).

Intraoperative risk factors include vitreous or subretinal bleedings, inability to fully close retinal tears, intraoperative choroidal detachments (Cowley et al., 1989), pigment release during endodrainage (Lleo Perez et al., 2000), and excessive cryotherapy (Bonnet, 1988; Cowley et al., 1989) or endolaser (Rodriguez de la Rua Franch et al., 2000). Both strategies of retinopexy induce a pro-inflammatory environment that could explain the high risk as shown in experimental models (Garcia-Layana et al., 1997; Goldaracena et al., 1997; Pinon et al., 1992). Indeed, in a prospective, randomized, placebo-controlled, double-blind clinical trial performed to determine if prolonged administration of systemic corticosteroids would attenuate early stages of PVR, the application of transcleral cryocoagulation was associated with more cases developing epiretinal membranes in the placebo than the steroid group (Koerner et al., 2012). These findings reinforce the idea that the anti-inflammatory strategy could be one of the best options for preventing PVR. While other clinical trials have not reported the same results (Dehghan et al., 2010), it is possible that the time of application or intraocular levels of steroid may not have been the most appropriate.

Postoperative risk factors for inducing PVR include prolonged inflammation or uveitis, new or persistent vitreous hemorrhage, postoperative choroidal detachment, the use or air or sulphur hexafluoride (SF_6), repeated surgical procedures, loss of vitreous during drainage of subretinal fluid, persistent traction of breaks, and the presence of unadverted or non-appropriated closed tears or holes. (Asaria et al., 2001; Pastor et al., 2002). Most of these are clearly related to inflammation. Table 4 summarizes some of the clinical risk factors identified by large clinical studies.

5.3. Some other problems and formulas

The design of many clinical retrospective studies for identifying clinical factors that predispose the onset of PVR is very weak. Often the many factors that contribute to PVR development are closely related to others and cannot be analyzed in an independent way. Nevertheless, there are a few studies with the appropriate methodology. One prospective study included 409 eyes and tested the influence of 14 categories of clinical variables (Duquesne et al., 1996). Using single and multiple logistic regression analysis, only four variables were found to independently and jointly be associated with the risk of postoperative PVR. Among them, two have been confirmed by further studies: 90° or greater circumferential extent of the retinal tears and the use of cryopexia (Sadaka and Giuliari, 2012).

In 2005, our group performed an observational case-controlled study among 335 patients (201 control and 134 cases) with non-complicated RD (Rodriguez de la Rua et al., 2005). Risk factors for PVR were identified by multivariate analysis, and the influence of variables was assayed according to the surgical approach. Once again, breaks larger than “1 clock hour” and extension of RD were found to be risk factors for PVR. Age and lower IOP, scleral surgical techniques, aphakia/pseudophakia when associated with scleral buckle and re-interventions were also risk factors. We proposed a statistical model that was independent of the surgical procedure employed for RD repair to estimate the probability of developing PVR for any patient. The best values of sensitivity and specificity obtained with this model were 78.0% and 75.6% respectively, which were higher than those obtained by previous studies (Asaria et al., 2001; Kon et al., 2000). The area under the receiver operating characteristic curve was 0.86. Nevertheless, those values were not sufficiently high for routine clinical use (Rodriguez de la Rua et al., 2005).

More recently, Wickham et al. (2011) devised a simplified formula that used preoperative clinical data to estimate the risk of PVR following primary RD repair by vitrectomy. Vitreous hemorrhage, grade C PVR, and the extent of detachment were related to failure due to PVR. There was good agreement between risk estimates produced by the point system and those calculated directly using a multivariate regression model. The area under the receiver operating characteristic (ROC) curve for the model was 0.84 (Wickham et al., 2011). Nevertheless, in general the low sensitivity and specificity of these formulas has rendered them unsuitable for routine clinical use (Asaria et al., 2001; Kon et al., 2000; Rodriguez de la Rua et al., 2005; Wickham et al., 2011).

There is another critical problem regarding the usefulness of the predictive formulas. These models tend to perform better with the data from which they were constructed rather than with new data (Bleeker et al., 2003). Predictive formulas require external validation with a new sample before being fully validated and implemented in clinical practice (Bleeker et al., 2003; Terrin et al., 2003). Our group performed an external validation of the four previously published formulas for predicting PVR development after RD surgery, each of which were developed with different criteria (Sala-Puigdollers et al., 2013). All four formulas (Asaria et al., 2001; Kon et al., 2000; Rodriguez de la Rua et al., 2005; Wickham et al., 2011) had limited ability to prospectively identify patients who would develop PVR, and therefore they are not reliable for general use in the clinic (Sala-Puigdollers et al., 2013). Thus, it is apparent that clinical factors alone do not provide sufficient predictive power to identify patients at high risk of PVR.

In fact, it is only when additional variables such as genetics or biochemical biomarkers are considered that performance of predictive models improves (Ricker et al., 2012; Rojas et al., 2015). These new formulas, after appropriate validation, could provide novel tools in our current clinical practice to identify those patients at high risk of developing PVR. This is a crucial step for designing new clinical trials. As we will discuss further, the inclusion in clinical trials of only those patients with a high risk of PVR will reduce the sample size and increase the power of the results.

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Table 4
"Risk factors for PVR". Main papers analyzing risk factors for developing PVR. "**X**" means that the variable evaluated in the study was significantly associated to PVR. RD. retinal detachment. SB: scleral buckle. PPV: pars plana vitrectomy. Pros: prospective study. Retrosp: tretrospective study. E: evaluated. NE: non evaluated.

Design of the study	Bonnet M. 1984	Bonnet M. 1988	Yoshida A. 1984	Cowley M. 1989	Malbran E. 1990	Girard P. 1994	Duquesne N. 1996	Kon CH. 1999
	354 eyes, complicated and non-complicated RD (included trauma), SB and/or PPV	Prosp. 70 eyes, SB	Retrosp. 521 eyes, complicated and non-complicated RD, SB	Retrosp. 607 eyes, complicated and non-complicated R (included trauma) D, SB and/or PPV	Retrosp. 1180 eyes, complicated and non-complicated RD	Retrosp. 1020 patients, complicated and non-complicated RD	Prosp. 409 eyes, RD	Prosp. 140 eyes, complicated RD, PPV
Preoperative PVR	X	X	X	X	E	X	X	NE
Tear/break characteristics	X	E	X	E	X	X	X	NE
Size of RD	NE	E	NE	E	NE	X	NE	NE
Aphakia/pseudophakia	NE	NE	NE	E	NE	E	E	NE
Genetic profile of patients	NE	NE	NE	NE	NE	NE	NE	NE
Vitreous cytokines/proteins	NE	NE	NE	NE	NE	NE	NE	X
Pre/intraoperative vitreous hemorrhage	NE	X	X	E	NE	X	E	NE
Reintervention	X	NE	E	E	NE	E	NE	NE
Postoperative choroidal hemorrhage	NE	NE	X	X	NE	X	NE	NE
Preoperative choroidal hemorrhage	NE	NE	E	X	NE	X	NE	NE
Technical procedure (PPV or SB)	NE	NE	NE	X	NE	E	E	NE
Tamponade	NE	NE	NE	NE	NE	X	E	NE
Cryopexy	NE	NE	NE	X	NE	NE	X	NE
Laser	NE	NE	NE	E	NE	E	E	NE
Uveitis	NE	NE	NE	E	NE	X	NE	NE
Age	NE	NE	NE	E	E	E	E	NE
Cytokines /proteins in subretinal fluid	NE	NE	NE	NE	NE	NE	NE	NE

Shading in Table 4 highlights PVR associated risk factors.

6. Designing new strategies for PVR treatment based upon genetics and biomarkers

6.1. Monogenic and complex diseases

The human genome contains an estimated 20,000–25,000 genes that encode all of our proteins (Consortium, 2004). Protein-coding sequences account for only a very small fraction of the genome, approximately 1.5%. The remainder includes non-coding sequences such as introns, short and long interspersed elements, and the rest of the genome for which no function has yet been elucidated (Lobo, 2008).

Inherited human diseases can be classified as monogenic or complex. Monogenic diseases are the result of a mutation in a single gene and are inherited in a Mendelian fashion. These diseases are relatively rare, but they have a high penetrance despite a very low allele frequency. In contrast, complex inherited diseases, which are relatively common, are multifactorial in nature. Most multifactorial diseases have low penetrance and a common allele frequency, occurring in at least 5% of the population (Lobo, 2008). Multifactorial diseases can occur in isolation but environmental influences can increase or decrease the risk of the disease. In this sense, a given *noxa* could induce different responses in different subjects. Thus, an individual's genetic profile could determine if he/she has a greater or lesser susceptibility to a disease under the influences of the same environment (Dempfle et al., 2008).

An important ocular example for the role of genetics is age-related macular degeneration (AMD). In this disease, the importance of the genetic profile in the development of the disease and the response to treatment has been demonstrated (Gemenetzi and Lotery, 2014; Horie-Inoue and Inoue, 2014; SanGiovanni and Chew, 2014; Schramm et al., 2014).

6.2. Usefulness of genetic studies: unraveling the pathogenesis of diseases and biomarkers of risk

Single nucleotide polymorphisms (SNPs), variations at a single isolated nucleotide position, are the most frequent polymorphisms in nature. They are almost always biallelic, involving only one of two choices, such as A or T, at a given site within the population. SNPs have a wide variation in frequency in different populations and may occur anywhere in the genome: exons, introns, or intergenic regions. The SNPs that occur in exons are more likely to be important because they could alter the gene product and predispose a change in phenotype or susceptibility to a disease (functional SNP). However much more commonly, SNPs have no real functional significance but rather serve as markers that are co-inherited with a disease-associated gene as a result of physical proximity. In other words, the SNP and the causative genetic factor are in linkage disequilibrium, and the SNP can be an identifying character when looking for the causative gene (Kumar and Cotran, 1994).

The genetic study of any multifactorial disease can help to unravel the pathogenesis in different ways. For example, in the identification of causative genes, functional SNPs or SNPs in linkage disequilibrium with causative genes could point out genes that have never been implicated in the disease, or they could confirm the role of other genes previously identified (Rojas et al., 2013).

Groups of biomarkers such as SNPs can serve as indicators of risk for multigenic diseases. As such, they could be used to select high-risk patients for recruitment into clinical trials for assessing new procedures or therapeutic agents. This could reduce the required sample size in a dramatic way because it would enable the selection of a more homogenous population of subjects, as discussed below.

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Kon CH. 1998	Kon CH. 2000	Rodriguez de la Rua E. 2000	Rodriguez de la Rua E. 2005	Rojas J. 2009	Rojas J. 2010.	Wickham L. 2011	Ricker LJ. 2012	Rojas J. 2015.	Times found it as risk factor
Prosp. 140 eyes, complicated RD, PPV	Prosp. 136 eyes, complicated RD, PPV	Retrosp. 298 eyes, complicated and non-complicated RD, PPV and/or SB	Prosp. 335 eyes, non-complicated RD, PPV and/or SB	Retrosp. and prosp. 450 eyes, non-complicated RD, PPV and/or SB	Retrosp. and prosp. 450 eyes, non-complicated RD, PPV and/or SB	Prosp. 615 patients, complicated and non-complicated RD, PPV	Retrosp. 75 eyes, primary RD, SB.	Retrosp. and prosp. 546 eyes, non-complicated RD, PPV and/or SB	
NE	X	X	E	NE	NE	X	X	X	11
NE	NE	E	X	NE	NE	E	E	NE	6
NE	E	X	X	NE	NE	X	E	NE	4
NE	X	E	X	NE	NE	E	X	NE	3
NE	NE	NE	NE	X	X	NE	NE	X	3
X	X	NE	NE	NE	NE	NE	NE	NE	3
NE	E	E	E	NE	NE	E	E	NE	3
NE	NE	X	X	NE	NE	NE	NE	NE	3
NE	NE	E	E	NE	NE	NE	NE	NE	3
NE	NE	E	E	NE	NE	NE	NE	NE	2
NE	NE	E	X	NE	NE	NE	NE	NE	2
NE	E	X	E	NE	NE	NE	E	NE	2
NE	E	E	E	NE	NE	NE	E	NE	2
NE	E	X	E	NE	NE	NE	NE	NE	1
NE	E	E	E	NE	NE	E	NE	NE	1
NE	E	E	X	NE	NE	E	E	NE	1
NE	NE	NE	NE	NE	NE	NE	X	NE	1

Another advantage of studying the genetic component of any multifactorial disease is the possibility of identifying biomarkers of the response to treatment.

6.3. Genetics of PVR

With these concepts in mind and taking into consideration the weak ability of primary RD patient clinical characteristics to predict the risk for developing PVR, we thought that the genetic composition of these patients could have an important role. Our working hypothesis was that RD can evolve in different ways depending on the genetic profile of each patient (Sanabria Ruiz-Colmenares et al., 2006).

Most genetic studies of PVR have been performed by analyzing monogenic diseases such as Norrie disease and familial exudative vitreoretinopathy among others (Poulter et al., 2012; Robitaille et al., 2011; Yang et al., 2012). Because single genes are responsible for each of those diseases, the pathogenesis of these vitreoretinopathies has nothing in common with PVR secondary to a primary RD.

As mentioned, some years ago we performed a preliminary genetic study that reinforced the idea that the genetic component could have a role in the risk of PVR following RD (Sanabria Ruiz-Colmenares et al., 2006). Later, a replicated candidate gene association study confirmed the implication of the SMAD7 gene and the TNF locus in the pathogenesis of PVR (Rojas et al., 2010, 2013). In addition p53 and MDM2, genes that play roles in apoptosis, have been implicated in the development of PVR (Pastor-Idoate et al., 2013a, 2013b). All of these efforts have been made thanks to a collaborative study that we named “Retina 4 Project”.

6.4. Designing new strategies for PVR treatment guided by genetics

The findings of the Retina 4 Project have resulted in recognition of the importance of early inflammation mediators such as TNF-α in the development of PVR. This and other mediators of inflammation are potentially new targets for preventing PVR. Our group has demonstrated that adalimumab, a TNF-α blocker, reduced the reactive retinal glio
sis in organotypic cultures of porcine neuroretinas (Fernandez-Bueno et al., 2013a). Also, the genetic study of PVR pointed out the relevance of TGF-β mediators in the onset of fibrosis that occurs in PVR. Our group's results support the idea that anti-TNF-α could serve as a novel way to prevent or even treat the gliosis observed in PVR.

The TGF-β pathway is another potential target pointed out by our study (Rojas et al., 2013). SMAD7 is a mediator that acts as an inhibitor of the profibrotic action of TGF-β by blocking phosphorylation of SMAD2 and SMAD3. SMAD7 is a mediator in the TGF-β pathway, and it acts as an inhibitor of the pro-fibrotic action of TGF-β by blocking phosphorylation of SMAD2 and SMAD3 (Flanders, 2004; Saika et al., 2008). In mice, overexpression of SMAD7 inhibited the RPE transition to myofibroblasts elicited by the addition of TGF-β2 (Saika et al., 2007). As a result, the RPE fibrogenic response was inhibited. The replication genetic study highlighted the possible role of SMAD7 in the development of PVR in humans, and potentially opened a new therapeutic target (Rojas et al., 2013). Finally, a Korean research group has found that pirfenidone, a small compound with combined anti-inflammatory and antioxidative action, inhibits TGF-β1-induced fibrogenesis by blocking nuclear translocation of Smads in the human retinal pigment epithelial cell line ARPE-19 (Choi et al., 2012). The authors proposed this inhibitor of the TGF-β pathway as a potential treatment for preventing PVR.

The Retina 4 Project also revealed the importance of apoptosis in PVR by the involvement of both the p53 and MDM2 genes. The

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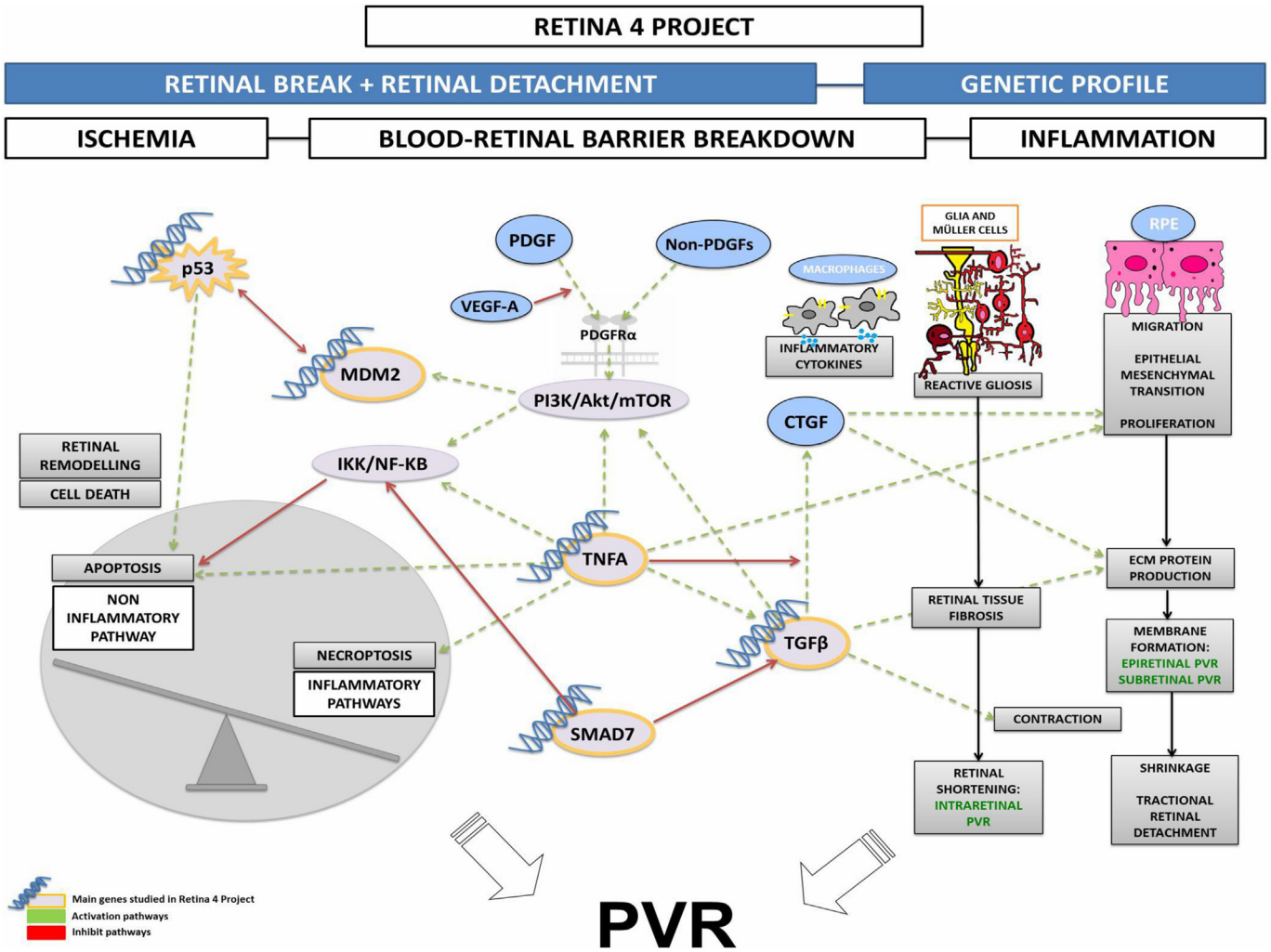

Fig. 9. This figure represents a summary of our ideas in the pathogenesis of PVR highlighting the genetic findings and their relations with the tissular changes and mechanisms of neuronal death.

tumor suppressor gene p53 is crucial for host defense against genomic mutations. It is well known for its ability to induce cell cycle arrest, apoptosis, senescence, and differentiation following cellular stress (Hede et al., 2011).

Our colleagues Gomez-Sanchez et al. from the University of Salamanca reported that the human Tp53 Arg72Pro SNP is responsible for worse functional prognoses in patients suffering stroke (Gomez-Sanchez et al., 2011). The basis for this observation was that the variant SNP was associated with an increase of apoptotic activity. The presence of neurons prone to apoptosis in the ischemic penumbra and perihematoma may account for poor prognosis (Gomez-Sanchez et al., 2011). Therefore with the assistance of the Salamanca group, the presence of this SNP was analyzed by our group for our sample of RD patients with and without PVR.

A SNP variant of the p53 gene associated with anti-apoptotic activity resulted in increased risk for developing PVR (Pastor-Idoate et al., 2013a). This suggests that the variant SNP could be associated with an enhanced inflammatory process after RD. We also found that a SNP variant of MDM2, one of several apoptosis mediators in the p53 signaling pathway, was related to a high risk of PVR (Pastor-Idoate et al., 2013b). Pro-apoptotic agents such as crocetin and other drugs currently being evaluated in early phases of clinical trials (Li et al., 2015) could be proposed in the near future as another strategy directed toward preventing PVR.

The identification of SMAD7, TNF-locus, p53, and MDM2 in PVR or any other gene associated with human diseases provides the rational for research of new drugs, or better, already developed drugs, in the treatment or prevention of these diseases (Fig. 9).

6.5. Designing new strategies for PVR prevention based upon genetic biomarkers

The identification of patients at high risk for developing PVR would help to diminish the required sample size to test more specific treatments or therapeutic strategies. Our group developed three predictive models of PVR based on the analysis of genetic variables (Rojas et al., 2009). One of these models withstood external validation, offering as good a predictive accuracy as obtained prior to the validation (Rojas et al., 2015). Also, the analysis of the relevant clinical and genetic variables significantly improved the discriminatory capability of the model (Rojas et al., 2015). Our model, which incorporated the genetic analysis along with clinical data and was validated by an external sample, had much better predictive power for the risk of PVR than did other studies that did not incorporate a genetic component (Asaria et al., 2001; Kon et al., 2000; Rodriguez de la Rua et al., 2005; Rojas et al., 2015; Sala-Puigdollers et al., 2013; Wickham et al., 2011).

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Table 5
Genetic contribution to PVR development.

Retina 4 project Genetic contribution to PVR development			
GEN	Polymorphisms		Reasons for analysis/potential contribution to PVR
CTGF	rs1931002	rs928501	- Participates in fundamental biologic processes including wound healing and fibrosis
	rs4897554	rs9399005	- Under the influence of TGF-β and CTGF, the RPE become myofibroblastic and fibrosis ensues
	rs6917644	rs9483364	- Reported CTGF expression in the human PVR membranes
			- Polymorphisms in CTGF predict the risk of PVR
EGF	rs1024600	rs2237051	- Promotes Müller glia proliferatio and RPE proliferation via activation of the β catenin signaling pathway
	rs11568943	rs4698803	- Contributes to cell-growth regulation in PVR
	rs17238095	rs6533485	- EGF receptor exists in the early stage of PVR
	rs9999824	rs718768	- EGF stimulates phosphorylation of the phosphatidylinositol 3'-kinase (PI3K)-dependent effector kinase Akt, MEK- Dependent
	rs1860129		mitogen- activated kinase (MAPK), and extracellular signal-regulated kinase (ERK)
			- Polymorphisms in EGF predict the risk of PVR
FGF2	rs1048201	rs308435	- Basic FGF (bFGF) in the vitreous of PVR is overexpressed
	rs1476217	rs3804158	- bFGF mRNA, bFGF peptide and FGF receptor are involved in epiretinal membrane formation in PVR
	rs167428	rs7683093	- Promotes RPE proliferation via activation of the β catenin signaling pathway and stimulates the production of interferon gamma
	rs1982569	rs9990554	- Participates in the activation of Smad/ZEB1/2 signaling responsible of proliferation and epithelial-mesenchymal transition (EMT)
	rs308417	rs308428	of RPE (hallmarks of PVR)
			- Polymorphisms in FGF2 predict the risk of PVR
HGF	rs1558001	rs17501080	- Exhibits pleiotropic biologic functions in its target cells as mitogenic, motogenic, morphogenic, and angiogenic factors
	rs2074724	rs5745687	- Has profound effects on growth and migration of RPE cells
	rs917183		- HGF and its receptor (HGFR) are strongly expressed in epiretinal membranes associated with PVR and in the vitreous of patients
			with PVR
			- Polymorphisms in HGF predict the risk of PVR
IFNG	rs12306852	rs2098395	- Inflammatory cytokine significantly increased in vitreous samples from patients with PVR
	rs2069718	rs2193049	- Mediates in cellular mechanisms of migration, proliferation, and differentiation, which are involved in PVR membrane formation
	rs2069727	rs2430561	- Participates in the induction of ICAM-1 by RPE cells
			- Polymorphisms in IFNG predict the risk of PVR
IGF1	rs1019731	rs5742629	- Are present in biologically active quantities in the vitreous fluids of patients with fibrocontractive diseases
	rs1520220	rs6214	- Increase the contraction stimulating effect of Müller cells and has a stimulating effect for traction on RPE cells
	rs2195240	rs7136446	- Have a significant physiopathological role in fibro-contractile disorders like PVR
	rs2971575	rs9308315	- Upregulated expression in vitreous of patients with PVR
	rs35767		- Involved in the progression, stimulation of epiretinal membrane contraction and inflammation process in PVR
IGF2	rs1003483	rs3213221	- Potent promoters of RPE cell tractional force generation
	rs2585	rs3741208	- IGF ligands and binding proteins are known to be present in the vitreous, and in the environment that drives RPE responses in PVR
	rs3213221	rs1003483	- The concentration of some IGF proteins are correlated with the severity and prognosis of PVR
	rs3741212		- Polymorphisms in IGF-IR predict the risk of PVR
IGF-IR	rs10794486	rs2684787	
	rs12899533	rs4305005	
	rs1568501	rs4966035	
	rs1879613	rs7166287	
	rs2048641	rs7173191	
	rs2229765	rs8038015	
IL1A	rs1304037	rs2856836	- Broad spectrum of activity in inflammation and wound healing
	rs17561	rs3783516	- Associated with the initiation of inflammatory mediators cascade and inflammatory reaction in PVR
	rs1800587	rs2048874	- Have the ability to activate T- lymphocytes, stimulate the secretion of immunoglobulin, induce neuronal differentiation, and
	rs3783550		trigger the release of acute phase proteins
IL1B	rs1143634	rs16944	- Are synthesize by a variety of cells, including monocytes, synoviocytes, fibroblasts and RPE cells
	rs3917368	rs4848306	- Stimulate the migration of RPE cells
	rs7596684		- Are increased in vitreous samples from patients with PVR
IL1RN	rs1688072	rs1794066	- Stimulate the proliferation of fibroblast and glial cells
	rs3087270	rs315946	- Stimulate the synthesis of collagen
	rs315949	rs315952	- Total levels of some ILs in the vitreous are predictive risk factors for postoperative PVR development
	rs315958	rs446433	- Reported ILs expression in the human PVR membranes
	rs973635		- The interaction between extracellular matrix- bound cytokine and inflammatory leucocytes or resident cells of the retina may
IL6	rs11766273	rs12700386	promote the development and perpetuation of PVR
	rs1474347	rs1800795	- Participate in the transdifferentiation, migration, proliferation, survival, and extracellular matrix formation in fibro-contractile
	rs2056576	rs2069840	disorders like PVR
	rs2140543	rs4719713	- IL-10 limits the inflammatory response by blocking IFNG, IL-2, TNFA and IL-4 production. IL1RN binds the IL-1 receptor, Inhibiting
IL8	rs2227306	rs2227543	its union to IL1A and B, neutralizing their action
	rs4073	rs4694178	- Polymorphisms in IL-10 and IL1RN predict the risk of PVR
IL10	rs10494879	rs17015767	
	rs1800871	rs1800872	
	rs1800890	rs2222202	
	rs3024493	rs3024498	
	rs4390174		
MCP1	rs1024611	rs2530797	- Potent chemotactic factor for monocytes
	rs2857653	rs3091316	- Is present in a substantial percent of vitreous samples from eyes with proliferative vitreoretinal disorders stimulating the
	rs3760396	rs4795893	infiltration of monocytes and macrophages
			- Is induced by TNF alpha in retinal glial cells during post- ischemic inflammation
			- Polymorphisms in MCP1 predict the risk of PVR

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Table 5 (*continued*)

Retina 4 project
Genetic contribution to PVR development

GEN	Polymorphisms		Reasons for analysis/potential contribution to PVR
MIF	rs1007888	rs1984309	- Involved in cell-mediated immunity, immunoregulation, and inflammation
	rs2096525	rs4820571	- Plays a role in the regulation of macrophage function in host Defense
	rs4820571	rs738806	- Increased levels in the vitreous samples of patients with PVR
	rs755622		- Polymorphisms in MIF predict the risk of PVR
MMP2	rs1561220	rs243864	- MMPs and their natural inhibitors (TIMPs) play an important role in matrix remodeling and their involvement in the formation of scar-like tissue in PVR
	rs2192853	rs243866	
	rs243840	rs7201	- Presence of MMPs and TIMPs in epiretinal and subretinal membranes in patients with PVR
	rs243845	rs9928731	- Significant correlations between PVR grade and MMPs in sub retinal fluid and proMMPs, MMPs-and TIMPs levels in vitreous
MMP9	rs2250889	rs3787268	- Polymorphisms in MMPs predict the risk of PVR
	rs2274756	rs3918241	
	rs3918253	rs4810482	
NFKB1	rs11722146	rs4648141	- NF-KB is a transcription factor that plays an important role in biological processes
	rs230540	rs4698858	- NF-KB can be activated by exposure of cells to pro-inflammatory cytokines such asTNF-a and IL-1/3 or by exposure to several other stimuli including bacteria, viral proteins, and hypoxia
	rs28362491	rs7674640	
	rs3774932	rs997476	- Induce the transcription of a variety of genes that bear KB- binding sites, including proinflammatory cytokine, chemokine, and cell adhesion molecule genes
	rs4648110		
NFKBIA	rs17103274	rs3138045	- NF-κB, in combination with GDNF receptors, are involved in the formation of the glial cell component of ERMs in PVR
	rs2007960	rs3138056	- NF-κB is expressed in human PVR membranes and vitreous samples
	rs3138045	rs696	- Polymorphisms in NFkBIA and NFkBIB predict the risk of PVR
	rs7152826		
NFKBIB	rs10410544	rs2241705	
	rs11879872	rs3136640	
	rs2053071	rs3136646	
	rs9403		
PDGFA	rs11764261	rs11768030	- Its expression is increased in RPE cells within the ERM of human patients
	rs4916944	rs7777705	- Are associated with PVR in humans and strongly promotes experimental PVR driven by multiple vitreal growth factors outside the PDGF family
	rs7806249		
PDGFRA	rs17739921	rs2114039	- Once activated, the PDGFR initiates signal relay cascades that drive biologic responses, such as chemotaxis and proliferation
	rs4289498	rs4864877	- Expression increase the ability of fibroblasts to induce experimental PVR
	rs6850748	rs7656613	- Vascular endothelial growth factor A and non- PDGFs are able to influence in the activation of PDGFRα
	rs7691129		- Polymorphisms in PDGF and PDGFR predict the risk of PVR
PIK3CG	rs3173908	rs4460309	- Important modulator of extracellular signals, including those elicited by E-cadherin-mediated cell–cell adhesion, which plays an important role in maintenance of the structural and functional integrity of epithelia
	rs4727666	rs4730204	
	rs6961244	rs757902	- Plays a pivotal role in the regulation of cytotoxicity in NK cells
	rs849380	rs849384	- Is highly activated in the RPE cells of PVR and is essential for PVR in a rabbit model of the disease
	rs849385	rs849387	- Influences in the activation of αPDGFR to mediate PVR
			- Polymorphisms in PIK3CG predict the risk of PVR
SMAD3	rs1866316	rs7169183	- SMAD3 mediates the signals from the TGF-β superfamily ligands that regulate cell proliferation, differentiation and death
	rs2033785	rs7177795	- SMAD3 is essential for EMT and fibrogenic responses by RPE cells induced by retinal detachment
	rs3743343	rs731874	- SMAD7 is a TGF-β type 1 receptor antagonist. It blocks TGF-β1 and activin associating with the receptor, blocking access to SMAD2. It is an inhibitory SMAD (I-SMAD) and is enhanced by SMURF2
	rs4776881	rs8031627	
	rs6494634	rs8032802	- Experimental PVR development after retinal detachment is inhibited by Smad7 overexpression
SMAD7	rs1873190	rs4939826	- Polymorphisms in SMAD3 and SMAD7 predict the risk of PVR
	rs2337143	rs6507877	- Genetic implication of SMAD7 in the development of PVR has been confirmed by genetic case–control studies
	rs2878889	rs7226855	
	rs9946510		
TGFB1	rs2241715	rs4803455	- Participates in the modulation of cell migration and proliferation, cell death, and protein synthesis during development, tissue repair, and other physiological or pathological processes.
	rs2241713	rs8179181	
	rs1800471		- Enhances extracellular matrix production and suppresses cell proliferation
TGFB2	rs1418556	rs2796821	- Capables of inducing several number of growth factors
	rs1891467	rs4846267	- TGFB1 induces cytoskeleton reorganization, alpha- SMA expression, increases the phosphorylation of ERK, Smad2/3, and AKT, and activates RhoA and Rac1 signaling pathways.
	rs2000220	rs4846476	
			- Concentration of TGFB2 in the vitreous humor of the eye correlates with the severity of the PVR
			- TGF-β2 contributes to transdifferentiation of hyalocytes into α-smooth muscle actin positive myofibroblast-like cells that cause collagen gel contraction
			- Are overexpressed in the vitreous of patients with PVR and are also detectable in the contractile membranes
			- Polymorphisms in TGFB1 and TGFB2 predict the risk of PVR
TNFA	rs1799964	rs2857602	- TNFA and TNFR2 play a pivotal role in inflammation, by activating endothelial cells to display leukocyte adhesion molecules such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1
	rs1800629	rs2857706	
	rs2229094	rs673	- High levels of these molecules are associated with inflammatory processes such as PVR
			- Are overexpressed in the vitreous of patients with PVR and are also detectable within the extracellular matrix
	rs2256965	rs909253	PVR membranes
	rs2256974	rs915654	- TNFα mRNA detected by RT-PCR in vitreous and Subretinal Fluid (SRF) samples of patients with PVR, indicating local production of these cytokines by vitreous and SRF cells
TNFR2	rs1061622	rs3397	
	rs1061624	rs542282	- TNFα, is able to bind to receptors on Müller cells and able to activate Müller cells, microglia and astrocytes
	rs1061628	rs590977	- TNF-induced Reactive oxygen species (ROS) production and other cell death pathways such as necroptosis
	rs652284		- Participate in the formation of fibrillar collagen and cellular proliferation in eyes with PVR
			- Genetic analysis from patients with post-rhegmatogenous retinal detachment PVR demonstrated a significant association with the nonsynonymous, SNP rs2229094(T→C) at the TNF locus
			- Polymorphisms in TNFA and TNFR2 predict the risk of PVR
			- Genetic implication of TNFA in the development of PVR has been confirmed by genetic case–control studies

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Table 5 (*continued*)

Retina 4 project Genetic contribution to PVR development		
GEN	Polymorphisms	Reasons for analysis/potential contribution to PVR
p53	rs1042522	- Is crucial for cell repair of genomic mutations and induces cell cycle arrest, apoptosis, senescence, or differentiation following cellular stress - The codon 72 polymorphism in p53 regulates the interaction with NF-kB and transactivation of genes involved in apoptosis, immunity and inflammation. It has been associated with several cancers and inflammatory processes - Is related to a poor functional prognosis in patients who have suffered from ischemic or hemorrhagic stroke - Seems to be a checkpoint of RD and how its local increase in the vitreous by using inhibitors of MDM2, seem to be a promising approach as a prophylaxis in experimental RD and also in experimental PVR - Pro allele of the p53 gene, associated with a decrease in apoptotic function of p53, has a higher risk of developing PVR after RD - Downregulation of p53 appeared to be a required event in PDGFRα-mediated contraction of cells in a collagen gel and retinal detachment in an animal model of PVR - The presence of soluble apoptotic molecules has been implicated in the development of PVR - Polymorphisms in P53 predict the risk of PVR
MDM2	rs2279744	- Key negative regulator of p53 and in humans - The G/G variant increases the binding affinity of the transcriptional activator Sp1 resulting in high levels of mdm2 protein; formation of transcriptionally inactive p53-MDM2 complexes and a consequent decreased activity of the p53 pathway - Carriers of the G allele of the MDM2 gene, associated with a decrease in apoptotic function of p53, have higher risk of PVR after RD - Polymorphisms in MDM2 predict the risk of PVR
BAX	rs4645878	- Pro-apoptotic members, triggers mitochondrial outer membrane permeabilization - A mediator of apoptosis that is also involved in retinal cell death after retinal ischemia - Is associated with a decrease in the apoptosis levels, being involved in the control life or death of a cell, and in the cellular proliferative response - A/A allele of rs4645878 could be a biomarker of high risk for developing PVR in patients undergoing RD surgery
BCL-2	rs2279115	- Anti-apoptotic members of Bcl-2 family able to neutralize BAX and block mitochondrial outer membrane permeabilization - The BCL-2-938 AA genotype is associated with an increase in Bcl-2 expression - Although an over-expression of bcl-2 is associated with a decreased apoptotic response, unlike bax, the over-expression in bcl-2 is able to induce an inhibitory effect in the programmed necrosis cell death and other non-apoptotic pathways like autophagy - It has been reported that increase expression of bcl-2 attenuates the TNFA induced necroptosis pathway

A total of 200 common SNPs with minor allelic frequencies >10% were selected for its analysis in the retina 4 project (Pastor-Idoate et al., 2013a, 2013b; Rojas et al., 2009; Rojas et al., 2013).

The genetic implication of TNF locus and SMAD 7 in the development of PVR have been confirmed by subsequent genetic case–control replication studies within the retina 4 project.

- 196 common SNPs from 30 candidate genes associated with inflammation and known to be implicated in PVR pathways: CTGF, PDGF, PDGFRα, PI3KCG, EGF, FGF2, MIF, MMP2, MMP7, MCP1, IGF1, IGF2, IGF1R, TNF, TNFR2, TGF-β1, TGF-β2, SMAD3, SMAD7, IFNα, IL1α, IL1β, IL1RN, IL6, IL8, IL10, NFκB1, NFκBIA, NFκBIB, and HGF.
- 4 common SNPs from 4 genes related with apoptosis and diverse cell death pathways: p53, MDM2, BAX and BCL-2.

- CTGF: Connective Tissue Growth Factor.
- EGF: Epidermal Growth Factor.
- FGF-2: Fibroblast Growth Factor 2 (bFGF).
- HGF: Hepatocyte Growth Factor.
- IFNG: Interferon Gamma.
- IGF1: Insulin-like Growth Factor 1.
- IGF2: Insulin-like Growth Factor 2.
- IGF-IR: Insulin-like Growth Factor Receptor.
- IL1A: Interleukin-1 Alpha.
- IL1B: Interleukin-1 Beta.
- IL1RN: Interleukin 1 Receptor Antagonist.
- IL6: Interleukin-6.
- IL8: Interleukin-8.
- IL10: Interleukin-10.
- MCP1: Monocyte Chemoattractant Protein-1.
- MIF: Macrophage Migration Inhibitory Factor.
- MMP2: Matrix Metalloproteinase 2.
- MMP9: Matrix Metalloproteinase 9.
- NFKB1: Nuclear Factor NF-kappa-B 1 p105 subunit.
- NFKBIA: Nuclear Factor of Kappa Light Polypeptide Gene.
- NFKBIB: Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-cells Inhibitor, Beta.
- PDGFA: Platelet-Derived Growth Factor Subunit A.
- PDGFRA: Platelet-Derived Growth Factor Receptor Alpha.
- PIK3CG: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Gamma.
- SMAD3: Mothers Against Decapentaplegic Homolog 3.
- SMAD7: Mothers Against Decapentaplegic Homolog 7.
- TGFB1: Transforming Growth Factor, Beta 1.
- TGFB2: Transforming Growth Factor, Beta 2.
- TNFA: Tumor Necrosis Factor Alpha.
- TNFR2: Tumor Necrosis Factor Receptor 2.
- p53: Tumor Suppressor p53 Gene.
- MDM2: Mouse Double Minute 2 Homolog.
- BAX: BCL2-Associated X Protein Gene.
- BCL-2: B-Cell Lymphoma 2 Gene.

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Another interesting attempt to develop a predictive model for the onset of PVR was made by Ricker et al. (2012). They examined the combined predictive value of clinical risk factors and biomarkers in the subretinal fluid collected during surgery. Once again preoperative PVR was identified as the only variable that was an independent predictor of postoperative PVR. The addition of certain biomarkers improved the area under the ROC curve. However, this interesting approach has two limitations. First, the model should be externally validated before being fully accepted. Second, from a practical point of view, obtaining the information after surgery may delay the application of prophylactic measures.

It is clear then that analysis of the genetic component of any multifactorial disease, and particularly PVR, is probably one of the most innovative approaches to understanding this entity. Knowledge of the genetic contribution to this multifactorial disease could explain many of the obstacles that until now have obscured the path to prevention and treatment of PVR. Table 5 summarizes some of the most relevant findings of the genetic component of PVR.

7. Anatomical and functional results after surgery

Currently, treatment of PVR consists of surgical repair of the retina (Pastor et al., 2002; Sadaka and Giuliari, 2012). However, despite recent advances in vitreoretinal surgery that offer a wider range of surgical techniques, the improved anatomical and functional success rates remain unsatisfactory. But as it has mentioned, presently, it is widely accepted that there is no effective treatment for PVR (Coffee et al., 2014). The final goal of RD and PVR surgeries is to reattach the retina and to prevent future re-detachment. To do this, repair of retinal breaks, relief of traction forces, and stabilization of the retina are required (Coffee et al., 2014; Pastor, 1998).

Given the high variability of this process and wide diversity of surgical procedures currently available, it is very difficult to adequately estimate anatomical and visual outcomes of this condition (Pastor et al., 2002). This variability arises principally from the difficulty of classifying the severity of disease, the existence of different surgical techniques and timing of surgery, and the great variability of the PVR process itself (Pastor et al., 2002). Nevertheless, many studies have been performed to assess these results.

7.1. Anatomical results after surgery

Anatomical success has been reported to be 60–90% depending on the severity of the disease (Aaberg, 2010; Pastor et al., 2002; Sadaka and Giuliari, 2012). In the most complex cases, when heavy silicone oil was used as a tamponade, in only 39% of the cases did the retina remain attached during the entire follow-up period (Regler et al., 2009).

7.2. Functional results after surgery

The best visual acuity results are associated with the success of the first surgery (Abrams et al., 1997). However, anatomical success does not ensure visual improvement, as will be discussed later, and there are many factors in PVR that impede an appropriate recovery of best corrected visual acuity (BCVA).

The most commonly reported rates of functional success following RD surgery show that 40–80% of the patients recover at least ambulatory vision of 5/200 or better (Pastor et al., 2002; Sadaka and Giuliari, 2012). The poor results may be due to changes in the macula (Kiss et al., 2007), but they are also related to the number of procedures performed (Pastor et al., 2002). These results could also be derived from reactive gliosis secondary to an excessive scarring process generated in this condition. This scarring can be the result of microscopic changes such as Müller cell hypertrophy and transdifferentiation of RPE cells into fibroblasts that invade the retinal layers (Pastor et al., 2006b; Pennock et al., 2011). Alternatively, they could be due to macroscopic changes with the creation of epiretinal membranes, intraretinal changes, or subretinal bands (Pastor et al., 2006b). The sum of these factors leads to a severe visual loss despite a complete reattachment of the retina. With the implementation of 25-G surgery, BCVAs of >20/60 in 51.9% of the eyes at 12 months have been achieved (Iwahashi-Shima et al., 2013). The development of PVR with recurrent RD usually requires additional surgery, and it is associated with poor visual acuity (Pennock et al., 2014a). Classically, the prognosis of anterior PVR tends to be worse than posterior PVR (Diddie et al., 1996).

The problem of poor functional results is common with RD even when it is not complicated with PVR. Although reattachment is obtained in up to 94% of the cases (Pastor et al., 2008b), functional results at 3 months of follow-up show that less than 50% achieve a BCVA of 20/40 or higher. Further, in our experience almost 15% of patients with RD macula-on and no involvement of the macula experienced a visual loss (personal unpublished data).

This decrease in visual acuity can be attributable in some cases to structural changes, as has been reported with the use of new optical coherence tomography and adaptative optic retinal imaging instrumentation (Saleh et al., 2014). However, it is also possible that the release of factors by the detached retina may affect some other areas of the retina, even if the affected regions were not within the detached retinal area (Iandiev et al., 2006). For these reasons, we are convinced that neuroprotection must be a complement of RD surgery in the very near future. These factors, obviously, will be also present in PVR.

7.3. Timing for PVR surgery

As PVR is a dynamic process, the ideal time to perform surgery is difficult to choose, and it has been a matter of controversy among vitreoretinal surgeons (Coffee et al., 2014; Pastor et al., 2002). The judgment of surgical management remains subjective because decisions are based on the expected evolution of the disease and depend on preferences and surgical skills of the surgeon. According to some authors, the presence of clinical signs of activity may point out the need to delay surgical intervention for some weeks (Pastor et al., 2002) because the controlled trauma of a new surgery could generate an extra stimulus for cellular proliferation (Coffee et al., 2014). Besides, as epiretinal proliferation takes an average of 6–12 weeks to completely develop, delay of surgery would allow an easier removal of these membranes (Coffee et al., 2014).

However, another recent study showed that delay in surgery greater than 28 days is itself an independent risk factor associated with PVR (Feng et al., 2013).

Obviously the time of evolution is an important factor for functional results, but we have the impression that in some cases repeated surgeries lead the problem towards an intractable stage. Perhaps in these cases an adjuvant treatment would be a better solution.

7.4. Anatomical and visual results of different surgical techniques

Surgical approaches must be modified according to the preoperative characteristics of the each patient. Some characteristics that increase the risk of PVR are easily detectable, such as traumatic RD or the presence of giant tears. However others may be subtle, such as the extent of RD (Wickham et al., 2011), and yet others may require special diagnostic techniques such as the analysis of genetic predisposition. Light and moderate cases of PVR, according to the

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currently existing classifications, can be managed by conventional surgery, whereas severe cases may require complex interventions, including scleral buckling (SB), pars plana vitrectomy (PPV), membrane peeling, retinotomy, retinectomy, and retinal tamponade among others (Sadaka and Giuliari, 2012). However, once again the lack of a uniform classification prevents the adequate comparison between techniques and series.

7.4.1. Scleral buckling

Scleral buckling (SB) involves the placement of a silicone band that encircles the eye to indent it from the outside. This band helps to close retinal breaks, support the vitreous base, and reduce the anterior-posterior traction (Coffee et al., 2014; Pennock et al., 2014a). Light and moderate cases of PVR can be treated with this technique, but PPV is indicated in most cases (Pastor et al., 2002). Anatomical success reported with SB is 34–47% (Coffee et al., 2014). In those patients at high risk of suffering postoperative PVR, the combination of PPV with SB was associated with significantly higher single surgery anatomical success compared with PPV alone (Storey et al., 2014). Nevertheless, some authors suggested that there is no benefit regarding the anatomical success by adding SB to PPV (Oyagi and Emi, 2004).

7.4.2. Vitrectomy

The main goals of vitrectomy are to remove sources of traction, achieve retinal reattachment, and prevent re-detachment. Careful membrane peeling is needed to achieve these goals (Coffee et al., 2014). Vitrectomy eliminates transvitreal traction in PVR and must include elimination of the vitreous base. The vitreous base may play a key role in the pathogenesis of PVR because it hosts the RPE cells that accumulate and proliferate. These cells then produce collagen and generate membranes that subsequently contract and generate new breaks and extensions of the existing RD. Thus, an anterior vitrectomy reaching the vitreous base is highly recommended (Pennock et al., 2014a).

Historically, twenty-gauge (20-G) vitrectomy has been used for the treatment of PVR. However, new transconjunctival vitrectomies (23-G and 25-G) reduce the surgical trauma and postoperative inflammation, leading to a faster visual recovery (Iwahashi-Shima et al., 2013; Recchia et al., 2010). These advantages make the new surgical procedures especially valuable in diseases like PVR in which inflammation plays a major role (Iwahashi-Shima et al., 2013). Twenty-five gauge vitrectomy is effective in selected cases of PVR, although anatomical recovery rates are difficult to compare with previous reports due to the great variability in the severity of the cases and also in the surgical procedures performed in each case (Iwahashi-Shima et al., 2013).

In one study, anatomical success rates were similar between 20-G and 25-G surgeries (Iwahashi-Shima et al., 2013). However, visual recovery was faster in eyes after 25-G vitrectomy, with BCVA improving at one month after surgery. In contrast, eyes with 20-G vitrectomy required 3 months to regain visual acuity. The authors reported that sometimes it was necessary to perform an additional 20-G sclerotomy to use 20-G instruments for specific surgical manipulations (Iwahashi-Shima et al., 2013).

7.4.3. Retinotomy and retinectomy

If adequate mobilization or complete retinal reattachment is not achieved, it may be due to a contraction and foreshortening of the retina. The prudent use of a relaxing incision (retinotomy) or removal of tissue (retinectomy) should be considered (Williamson and Gupta, 2010). According to our data, up to 50% of patients with RD complicated with PVR showed intraoperative signs of "shortening" after a careful membrane peeling (Pastor et al., 2003). In 16% of these patients, it was necessary to perform a retinectomy to flatten the retina. Retinectomies are necessary in extensive cases of intraretinal PVR. Even a 360-degree retinectomy has been proposed in cases of severe PVR to obtain functional vision and prevent new surgeries (Garnier et al., 2013). These aggressive techniques are usually indicated in severe anterior PVR and may be beneficial for some cases. Nevertheless, the number and severity of complications are very high, including PVR recurrence (up to 50%), hypotony (up to 40%), and other complications. In some cases, the resulting complications can lead to enucleation of the blind and painful eye (Garnier et al., 2013).

In some series, after PPV and retinectomy in grade C PVR, reattachment rates of 51% and 72% at the end of the follow-up have been reported (Grigoropoulos et al., 2007). Nevertheless, cutting the retina does not seem like a good solution. After retinotomies, retinal edges may lift and scroll up with subsequent visual impairment. Additionally, aggressive surgical trauma produced by these techniques may exacerbate the process by increasing stimuli that lead to PVR (Williamson and Gupta, 2010). To avoid the increase in the breakdown of the blood-retinal barrier and the release of cytokines and growth factors, it has been recommended that surgeons avoid retinotomies and retinectomies when possible (Williamson and Gupta, 2010). If they are mandatory, the surgery should be delayed until the PVR is in a quiescent state.

7.4.4. Other procedures

7.4.4.1. Membrane peeling and internal limiting membrane (ILM) peeling. As described above, epiretinal proliferation takes an average of 6–12 weeks to completely develop. Thus delay of surgery would allow an easier removal of these membranes (Coffee et al., 2014). ILM peeling is another proposed approach in PVR surgery. This technique acts by reducing retinal tension in the posterior pole. It also reduces the recurrence of posterior epiretinal membrane formation and subsequent re-detachment (Minarcik and von Fricken, 2012). Nevertheless, neither the deleterious effect of removing of the ILM nor the possible beneficial effect on PVR has been clearly evaluated.

7.4.4.2. Lensectomy. When a RD and PVR occur in a patient with a cataract, removal of the lens is a routine procedure performed with the PPV. Removal of the clear lens by pars plana lensectomy improves the intraoperative visualization and helps to complete elimination of the anterior vitreous. In some cases this procedure has significantly better anatomical results (Quiram et al., 2006), and can be performed through a 25-G system (Kiss and Vavvas, 2008). This surgical maneuver might decrease the risk of suffering postoperative hypotony by reducing membrane formation on the ciliary body (Tseng et al., 2009).

7.4.4.3. Photocoagulation. The application of endolaser along the margins of the retinotomies, retinectomies, and retinal breaks is needed to seal these lesions and to reattach the retina (Coffee et al., 2014). It is considered less likely to stimulate RPE release and intraocular inflammation (Singh et al., 1986).

7.4.4.4. Retinal tamponade. When PVR traction has been eliminated and the retina has been reattached, retinal endotamponade is mandatory (Pennock et al., 2014a). The tamponade material provides time for retinal adhesions to form firmly around tears and incisions and avoids fluid flow into the breaks (Coffee et al., 2014). Endotamponade is usually performed with long-acting intraocular gas such as sulfur hexafluoride (SF6) or perfluoropropane (C3F8), or with silicone oil (SiO). Based on findings provided by the Silicone Oil Study, the retinal reattachment rate increased to 70–85% of macular attachments at 36 months, and there were better visual outcomes with SiO or C3F8 compared with SF6 (Abrams et al., 1997;

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Schwartz et al., 2014). However less than 50% of the eyes with reattached retinas reached visual acuity of 5/200 or better in severe cases of PVR (Abrams et al., 1997).

Silicone oil and C3F8 had similar rates of success regarding anatomical and visual outcomes (Abrams et al., 1997; Schwartz et al., 2014), suggesting that success in the first surgery is more important than the choice of tamponade in most of the cases. Nevertheless, the selection of the tamponade must be individualized for each patient. This was the conclusion of a Cochrane study (Schwartz et al., 2014). One of the disadvantages of SiO compared to C3F8 is the complications derived from the silicone oil removal (Coffee et al., 2014; Jonas et al., 2001). This maneuver can induce the formation of new retinal breaks, reopen previous breaks with insufficient scarring or incomplete retinopexy, and create unresolved tractions that produce retinal re-detachment affecting from 3.5% to 34% of the eyes (Al-Wadani et al., 2014; Jonas et al., 2001).

Some patients undergo a severe visual loss when the SiO is removed (Christensen and la Cour, 2012; Shalchi et al., 2015). Based on optical coherence tomography analysis, atrophy and a significant thinning of inner retinal layers in the macular region occurred with SiO tamponade but not with C3F8 (Christensen and la Cour, 2012). The reason of this loss remains unknown, but it is hypothesized that the thinning and atrophy may be due to a direct or indirect toxic effect of the SiO (Christensen and la Cour, 2012). Some explanations for this phenomenon deal with changes of ion concentrations derived from the collapse of Müller cells, increased levels of cytokines, or phototoxicity that lead to retinal cell death (Christensen and la Cour, 2012; Shalchi et al., 2015).

In 2006 we published an analysis of organic lipophilic compounds from silicone oil used in humans eyes for repairing RD. Among the compounds, cholesterol and α-tocopherol were present in high concentrations, and they were correlated with the intraocular permanence time. We concluded that silicone oil was able to extract lipophilic compounds from intraocular tissues, and therefore it may affect retinal and other intraocular cells. This may be an alternative explanation to the retinal atrophy that can occur after silicone oil use as a tamponade (Pastor et al., 2006a). This deleterious effect on the retina was observed by our group many years ago in experimental models (Nakamura et al., 1991; Pastor et al., 1992). At that time we attributed the changes to the presence of low molecular weight components, but the changes were also present when we used highly purified silicone oil (Pastor, 1998). For special cases where there are signs of PVR in the inferior retina, there is now the option of using “heavy silicone oils” (Williams et al., 2013). However the discussion on these substances is not within the scope of this major review (Khan et al., 2015).

Considering the poor anatomical and visual outcomes obtained after very aggressive surgeries, we can conclude that there is no effective treatment for PVR. As it is well recognized that PVR is an inflammatory condition, the implementation of new surgical approaches that avoid the inflammatory response triggered by surgical trauma may help improve these unsatisfactory results. Clearly, research must be focused in preventing these complications.

8. Adjuvant therapy for the treatment of PVR: present and future

As discussed earlier in this report, PVR is a complex process involving different risk factors for development. It is comprised of events that have been considered to be similar to those of the wound healing response with inflammation, migration, and proliferation of a variety of cells (Kauffmann et al., 1994; Kosnosky et al., 1994; Limb et al., 1991; Pastor, 1998). However the retina reacts in the same manner as the CNS, and more attention should be paid to the mechanisms of repairing the brain after an inflammatory insult. With respect to the cellular aspect of the CNS inflammatory response, microglia respond within minutes to hours by proliferating, activating, and migrating to the area of injury, where they essentially function as macrophages (Hauwel et al., 2005; Schmidt et al., 2005). Increased blood–brain barrier permeability allows leukocyte infiltration from the blood to the injury site, a process that is mediated by cytokines, chemokines, and complement proteins. Neutrophils are followed by monocytes. The oxidative burst of neutrophils and macrophages is harmful because of the release of oxygen free radicals and neurotoxic enzymes; however, both activated microglia and monocyte-derived macrophages aid in clearing debris from dead and damaged cells via phagocytosis.

Over the last 20 years, vitreoretinal surgical techniques have evolved, and greater emphasis has been placed on the success of primary RD surgery to prevent PVR. Case selection has been refined and the incidence of PVR might have been expected to decline. Yet the frequency of this condition remains largely unchanged, with a postoperative incidence of PVR ranging from 4% to 34% in prospective studies (Charteris et al., 2002; Heimann et al., 2007; Leiderman and Miller, 2009). These results show that there is a need for adjunctive pharmacologic treatment that could prevent or halt progression of PVR.

Laboratory and clinical studies have suggested that pharmacological adjuvant therapy can mitigate the proliferative disease process and improve surgical success. In general, these pharmacological strategies have included anti-inflammatory, anti-proliferative, anti-neoplastic, anti-growth factor, and antioxidant agents to either modify the inflammatory cascade or interfere with proliferation. Although most of these attempts have failed, we have summarized the results because of their valuable information.

8.1. Anti-inflammatory agents

Based on the hypothesis that PVR pathogenesis is due to inflammation, steroids such as triamcinolone acetonide or dexamethasone have been considered promising prophylaxis and/or treatment candidates (Ahmadieh et al., 2008; Garcia-Layana et al., 1997; Hui et al., 1993; Koerner et al., 1982; Rubsamen and Cousins, 1997; Tano et al., 1980a, 1981, 1980b; Weller et al., 1990). However, despite the success seen with steroids in animal experiments (Hui et al., 1993; Rubsamen and Cousins, 1997; Tano et al., 1980a), human studies failed to demonstrate the same beneficial effects in terms of reattachment rate, visual acuity, recurrence of PVR, or reoperation rate (Ahmadieh et al., 2008; Pastor, 1998; Sadaka and Giuliari, 2012). It is possible that these drugs have not been applied at the proper time or they have not reached the appropriate concentration in the eye (Nguyen and Lee, 1992). In fact some authors have recommended systemic postoperative use (Koerner et al., 1982) while others have advocated for the early administration of these drugs (Hui and Hu, 1999).

There is a huge variety in the route of steroid administration. Besides the systemic route, some authors recommend intravitreal application (Jonas et al., 2000) and others subconjunctival application (Bali et al., 2010), both of which are claimed to reduce PVR development. There are some papers that have tested the efficacy of low doses of intravitreal triamcinolone after silicone oil tamponade (Chen et al., 2011; Fernandes-Cunha et al., 2014; Kivilcim et al., 2000; Szurman et al., 2009). The authors reported that it is safe and effective, a result that is difficult to reconcile with our finding that triamcinolone is hardly soluble in silicone oil (Pastor et al., 2008a), a finding confirmed by others (Spitzer et al., 2009). Further, it seems that relatively high intraocular levels of steroids would be required. In cell culture, only concentrations of dexamethasone over 200 μg/ml had an additive effect with 5-FU on the inhibition of human RPE

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proliferation (Tung et al., 2001).

8.2. Anti-neoplastic/anti-proliferative agents

To interfere with proliferative events in PVR, anti-neoplastic agents, which inhibit the cell cycle and cellular proliferation, have been extensively explored, including compounds like 5-FU, daunorubicin, taxol, colchicine, retinoic acid, ribozymes, vincristine, cisplatin, adriamycin, mitomycin, dactomycin, and others. 5-FU is one of the most tested compounds for the treatment of PVR because it is frequently used to reduce scarring in glaucoma-filtering surgeries (Sadaka and Giuliari, 2012).

Several clinical trials have tested the efficacy of heparin and its fragment, low molecular weight heparin (LMWH), in PVR by using them in combination with steroids or anti-metabolite drugs such as 5-FU (Asaria et al., 2001; Charteris et al., 2004; Wickham et al., 2007; Williams et al., 1996). The use of heparin in the vitrectomy-infusion fluid during PVR vitrectomy not only did not reduce the rate of proliferation, but it did increase the rate of postoperative hemorrhage (Williams et al., 1996). Most of the clinical trials with LMWH showed no significant or only minimal differences in anatomical and functional outcomes (Asaria et al., 2001; Charteris et al., 2004; Wickham et al., 2007). Furthermore, the combined use of 5-FU and LMWH resulted in worse visual acuity (Wickham et al., 2007), raising some toxicity concerns about this adjuvant therapy. A recent Cochrane review has concluded that there is not enough evidence to recommend the use of 5-FU and LMWH to prevent PVR (Sundaram et al., 2013).

Daunorubicin, a topoisomerase inhibitor that acts on cell proliferation and migration, has also been used to treat PVR (Wiedemann et al., 1998, 1987). The Daunomycin Study Group assessed the efficacy and safety of daunorubicin during vitrectomy in eyes with PVR and found that it produced a small reduction in the number of re-operations in patients undergoing retinal surgery with established PVR (Wiedemann et al., 1998). Although there are only a few clinical trials that have analyzed the efficacy of daunorubicin in preventing PVR, it appears to be ineffective when used as a single agent (Moysidis et al., 2012). Thus this drug has not been incorporated into the clinical routine.

Agents like taxol and colchicine that respectively stabilize and inhibit microtubule formation have the potential to reduce migration and proliferation of cells (Lemor et al., 1986a) and therefore have been tested in models for efficacy in PVR (Lemor et al., 1986b; van Bockxmeer et al., 1985). Retinoic acid, which promotes growth arrest of RPE cells *in vitro* (Campochiaro et al., 1991), increased the rate of retinal attachment (Campochiaro et al., 1991; Chang et al., 2008; Fekrat et al., 1995; Verstraeten et al., 1992). It also significantly lowered rates of macular pucker formation and produced higher rates of ambulatory vision in the treated groups (Chang et al., 2008).

In addition to these agents, there are a large number of studies that show potential benefits from a variety of pharmacological interventions to prevent the occurrence of PVR. One of these is glucosamine, an inhibitor of N-linked oligosaccharide biosynthesis and processing. It effectively suppresses RPE cell proliferation *in vitro* (Liang et al., 2010) and interferes with the TGF-β signaling pathway in RPE cells (Liang et al., 2011). DNA-RNA chimeric ribozymes that target proliferating cell nuclear antigen (PCNA) have been tested in preclinical and multicenter clinical trials for PVR (Mandava et al., 2002; Schiff et al., 2007). Unfortunately this drug was not effective in preventing PVR recurrence in patients with established grade C or worse PVR (Schiff et al., 2007). Agents such as etoposide and tacrolimus have also been tested and shown to significantly decrease the severity of experimental PVR (Kuo et al., 2007; Turgut et al., 2012).

8.3. Anti-growth factor pathway inhibitors

With our improved knowledge regarding the role that growth factors play in the pathogenesis of PVR, there has been a movement towards blocking growth factors and the respective pathways as a prophylaxis or as a treatment. These strategies include kinase inhibitors such as hypericin or herbimycin, which have both shown positive results in preclinical PVR studies (Imai et al., 2000; Machado et al., 2009; Tahara et al., 1999). Alkylphosphocholine, an inhibitor of protein kinase C, was effective against RPE cell attachment, spreading, migration, and proliferation *in vitro* (Eibl et al., 2007). It was also identified as a promising agent in reducing the number of dividing Müller cells following RD *in vivo*. AG1295, an inhibitor of PDGF receptor (PDGFR) kinase, also significantly attenuated development of RD without apparent histologic or functional damage to the retina (Zheng et al., 2003).

8.4. Antioxidants and other agents

N-acetylcysteine (NAC), an antioxidant used in a variety of clinical entities, protected rabbits from PVR by blocking the activation of PDGFR-α. It also protected rabbits from developing RD, although it did not prevent formation of epiretinal membranes (Lei et al., 2010). Also in this group of anti-oxidants, three polyphenolic agents from vegetal origin, epigallocatechin gallate (from green tea), resveratrol (from red wine), and curcumin (from turmeric), were tested *in vitro* to analyze their effects on proliferation of human RPE cells (Alex et al., 2010). Of these, resveratrol was the most potent, but we have not found further studies on this agent.

Other agents such as genistein, an isoflavone (Yoon et al., 2000), calcium antagonists (Smith-Thomas et al., 2000), and neutralizing antibodies against PDGF, TGF-beta2, and IL-10 (Carrington et al., 2000) have also been tested against PVR. However, none of these agents has been incorporated routinely into clinical practice owing to concerns about retinal toxicity and because only a few have been assessed in clinical trials (Asaria and Gregor, 2002; Pastor, 1998; Pastor et al., 2002).

Another interesting approach is based on the inhibition of Rho-kinase (ROCK) because of the effect this kinase has on retinal cell survival and glial reactivity. In a retina culture, inhibition of ROCK had neuroprotective properties by attenuating the glial cell reactivity (Tura et al., 2009). Finally, Palomid 529 (Paloma Pharmaceuticals, Jamaica Plain, MA, USA), an inhibitor of the Akt/mTOR pathway that regulates intracellular signaling important for control of cell cycle, suppressed Müller cell proliferation, glial scar formation, and photoreceptor death in an experimental model of RD in rabbits (Lewis et al., 2009).

8.5. Neuroprotection

Although neuroprotection has the primary goal of improving the functional outcome after RD surgery by preventing photoreceptor death, (Lo et al., 2011; Murakami et al., 2011), it could be also useful in PVR. One of the possibilities is the use of caspase inhibitors, of which a large number of synthetic agents exist. However, despite extensive experimental efforts, there are few clinical trials using these compounds in human diseases (Murakami et al., 2013).

8.6. Multimodal approaches

Clinical strategies to prevent PVR would probably require a multimodal, combinatorial approach (Moysidis et al., 2012) because this is a multifactorial disease. Surprisingly, aside from the combination of 5-FU and LMWH, few reports have been published using

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combinations of drugs. Most of the existing studies were made many years ago and usually combined an anti-proliferative agent and a corticosteroid (Chen et al., 1992; Hui and Hu, 1999; Pastor et al., 2000; Salah-Eldin et al., 1994; Tung et al., 2001). There is also one study that combined a protein kinase C inhibitor and melatonin in an experimental model of PVR in rabbits, using grades A and B of the original classification of PVR (Er et al., 2006).

8.7. A look into the future

The most effective treatment option currently available for PVR remains vitrectomy. However the recent elucidation of pathways important in the pathogenesis of PVR and the increased understanding of its pathobiology has led to the identification of new potential targets to prevent it or to be used in adjunctive prophylaxis. One of these approaches is the interference or the modulation of integrin activity. Integrins are transmembrane protein receptors that act as bridges for cell-to-cell and cell-to-extracellular matrix interactions. Besides their importance for keeping RPE cells attached to their basal membranes and preventing migration into the vitreous cavity, these proteins could have a potential role in the final contraction process that affects existing epi- and/or subretinal membranes. Thus it may be possible to use antagonists to endogenous integrin mediators or reagents designed to inhibit integrin activity to prevent or treat PVR. Recent preclinical studies have shown that decreasing the expression of epithelial membrane protein 2, a RPE cell integrin, or inhibition of it by directed antibodies reduces the onset of PVR formation (Morales et al., 2012; Telander et al., 2011). The applicability of these *in vitro* results to human disease is not yet known.

Other insights have emerged from studies with drugs such as fasudil or simvastatin, generally used for other systemic disorders such as diabetes or pulmonary arterial hypertension. These agents have shown protection against PVR by interfering in the Rho activated kinase pathway (Kawahara et al., 2008; Kita et al., 2008). Anti-allergic drugs such as tranilast have also shown the ability to reduce experimental PVR (Ito et al., 1999).

Recently, in multiple preclinical models, strong evidence has shown that interfering with the PDGFR-α and p53 signaling pathways by using different targets such as VEGF or mdm2 may attenuate PVR. Therefore this could be another future approach (Lei et al., 2011; Murakami et al., 2013; Pennock et al., 2014b; Pennock and Kazlauskas, 2012; Pennock et al., 2013, 2011; Rosenkranz et al., 2002).

Perhaps, one of the most promising strategies for halting PVR development could emerge from studies of other retinal diseases or of the CNS. These studies involve neuroprotection and controlling reactive gliosis, one of the major intraretinal changes in PVR. Agents such as melatonin (Iribarne et al., 2007), aspirin (Bazan et al., 2010), tauroursodeoxycholic acid (TUDCA) (Fernandez-Sanchez et al., 2011; Mantopoulos et al., 2011), lutein (Woo et al., 2013), and especially anti-TNF-α (Nakazawa et al., 2011) may provide new therapeutic neuroprotective avenues to treat photoreceptor degeneration after a RD. They may also interfere at the same time with the glial processes that occur after an ischemic event in the retina (Fernandez-Bueno et al., 2013a), much like that which occurs in the CNS (Alonso-Alconada et al., 2013; Bae et al., 2006).

We believe that neuroprotection could play an important role in not only preventing PVR but also for improving the visual results after successful RD surgery. Many drugs are being investigated along with natural products such as resveratrol. This naturally occurring polyphenol, mainly found in grapes and red wine, has shown *in vitro* and *in vivo* neuroprotective effects for a variety of experimental models of neurodegenerative diseases (Zhang et al., 2015). This and other natural products such as TUDCA (Fernandez-Sanchez et al., 2011) or safranal deserve further investigation (Fernandez-Sanchez et al., 2012). Stem cells have also demonstrated neuroprotective properties *in vitro*, and our personal approach is that some of these factors released by cells, with or without some other drugs, should be investigated (Rodriguez-Crespo et al., 2014).

Apoptosis is another approach that should be taken into consideration for preventing PVR. Although some pro-apoptotic agents have failed to demonstrate any ability to inhibit progression of CNS tumors (Bedikian et al., 2014; Hu et al., 2013), they could still be an adequate option for PVR. Crocetin, which induces apoptosis through increased expression of pro-apoptotic Bax and activated caspase 3, has demonstrated promising results with esophageal carcinoma cells and could be another potential strategy for preventing PVR (Li et al., 2015).

As mentioned previously, another interesting target is TNF-α. It is a pleiotropic cytokine that plays an important role in inflammation by prompting various responses in different cell types, such as cell survival, proliferation, differentiation, and cell death by apoptosis or necroptosis among others (Vandenabeele et al., 2010). However, very little is known about the mechanisms by which TNF-α may mediate neuroprotection (Figiel, 2008). These mechanisms should be investigated. There are currently many anti-TNF-α drugs already approved for human disease, although none for PVR. Experience has shown that in recent years, many of the most interesting drugs were not specifically developed for eyes diseases but rather they were transferred from other purposes. Thus this and other similar approaches must be investigated.

A final point that deserves attention is the duration of the treatments. Although PVR is a relatively acute complication, it can last between 30 and 45 days in most cases (Pastor et al., 2002). Proposed treatments should guarantee efficient levels of therapeutic agents at the right target during this time. There are a few older reports that propose sustained delivery systems for treating PVR (Enyedi et al., 1996; Yang et al., 1998; Zhou et al., 1998). Currently we have gained more clinical experience with drug delivery systems, and there are new possibilities that should be explored.

For those agents that in preclinical studies have been demonstrated to be safe and effective in preventing PVR, clinical trials are the logical next step. Based on the identification of new key PVR mediators, the clinical trials could address the main complication after RD surgery.

9. Coming back to the classification: improving future clinical trials

One of the functions of any system of classification is to allow the comparison of new techniques and treatments, a clear necessity for PVR. In thinking about clinical trials, it is clear that the use of any of the existent classification schemes does not guarantee uniform results, and thus makes comparisons of techniques and treatments difficult or impossible. We are not sure if a new classification could be developed, but in the meantime we have a proposal for increasing the uniformity of the clinical trials.

Patients entering clinical trials could be classified in three categories. The first category would be composed of those patients with a RD and who do not exhibit any clinical sign of PVR. We do not consider the pigmented clumps as a definitive sign of this disease, so these patients could be included within this first category. This group could be used for testing prophylactic measures. To reduce the sample size necessary for these studies and to enhance the efficiency, it would be especially important to determine the genetic profile of the patients and select only those with a high risk of developing the disease.

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The second category of patients entering the clinical trials would be those with a frank preoperative PVR, a clear postoperative PVR, and those for whom the goal is to prevent the further development or re-proliferation of membranes that occur after long term tamponade with silicone oil. In these patients, emphasis should be made on the identification of intraretinal changes. The existence of epiretinal membranes can be solved in most of the cases by surgery. Patients in this second category, especially those with tamponade, could be an appropriate population to test anti-proliferative agents, drugs that inhibit collagen deposition and drugs that inhibit contraction of the membranes, and so on. Patients with intraretinal PVR, which could be detected by incorporating new imaging techniques into the routine examination, would be excluded from this second category of patients participating the clinical trials.

Finally, the third category of patients entering the clinical trials would be composed of those with extensive intraretinal PVR. At the time of surgery, the "shortening" of the retina is pathognomonic, but it would be very important to identify them before surgery. A careful clinical examination can add valuable information pertaining to intraretinal changes such as those that modify the color and transparency of the retina and the loss of mobility of the detached retina as detected by B-ultrasound. However these techniques have serious limitations and more reliable information can probably be gained by the application of new image-analysis techniques.

For patients in the third category of clinical trials, a severity scale should be added to indicate the extension of the intraretinal changes. If the extension affects more than one quadrant, it will be difficult to reattach without a retinectomy. The activity of the disease could also be evaluated. As described above, patients with RD and PVR of less than one week duration are likely to be in an almost pure inflammatory phase. In those patients, the measure of some biomarkers could add relevant information. For patients in whom the PVR is more than one week old, we can assume that mesenchymal transformation of RPE cells towards fibroblast-like cells plays an important role. Finally, in patients with PVRs of more than two weeks duration, membrane formation and contraction would be probably the most relevant facts. Obviously, a genetic profile should be mandatory to estimate the risk in this group.

According to these ideas, different families of compounds should be tested in patients placed into each of the three categories. We still believe that most of the effort must be made in avoiding the onset of PVR, and therefore the priority of designing clinical trials should be that of patients in the first category.

10. Conclusions and outlook (future directions)

Despite our best efforts over the past 40 years, we have thus far been unable to develop effective methods to prevent and treat PVR. It is still the most frequent and severe complication of RD surgery. Because of this, it also is a bottleneck for the development of new surgeries needed for advanced treatments, mainly cell therapy. The explanation for this failure for such a long period can be attributed to several causes. With the initial focus almost exclusively on cell proliferation and formation of membranes on the surface of the retina, not enough thought was given towards the development of objective and effective schemes for classification of PVR. This is an essential development that is needed to set the appropriate framework for further research. Furthermore, our lack of understanding of the existence and timing of developmental changes within the retina, lack of appropriate animal models, and lack of information regarding the cellular, molecular, and genetic origins of PVR pathogenesis have all contributed to the slow pace of clinical advances for this disease. Thus the historical focus on cell proliferation and membrane formation, which are relatively late events in the development of PVR, has led to inappropriate experimental models that have offered positive results for some drugs, but most of which have failed in the clinic.

Now we have a better idea regarding PVR pathogenesis and how it induces the remodeling of the retina that occurs after any RD. These changes, mainly intraretinal, are probably excessively amplified by inflammation and/or by a genetic pro-inflammatory profile. New advances in understanding the pathogenesis should drive the development of new and more appropriate models, if they are needed. Older classifications of PVR should be abandoned because they do not provide useful information from the clinical point of view. Even more, they do not contribute to uniformity in the samples for comparing new treatments and/or techniques. A broad consensus from clinicians would be required to collect samples in a more uniform way. The early identification of high risk patients through appropriate biomarkers, preferably before surgery, is mandatory to reduce the sample size of new clinical trials to a manageable number.

New treatments could be directed toward other factors besides cell proliferation such as immunomodulation or genetic therapy. In this sense we believe that retinal changes in RD, PVR, and some other retinal diseases will benefit from translational research currently taking place for CNS diseases. Thus it is highly probable that this disease cannot resist prevention and treatment for other 40 years.

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References

Aaberg Sr., T.M., 2010. Surgery as the primary management of proliferative vitreoretinopathy: a history reflecting my experiences and biases. Arch. Ophthalmol. 128, 1068–1070.

Abrams, G.W., Azen, S.P., McCuen 2nd, B.W., Flynn Jr., H.W., Lai, M.Y., Ryan, S.J., 1997. Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. Silicone study report 11. Arch. Ophthalmol. 115, 335–344.

Adelman, R.A., Parnes, A.J., Sipperley, J.O., Ducournau, D., 2013. Strategy for the management of complex retinal detachments: the European vitreo-retinal society retinal detachment study report 2. Ophthalmology 120, 1809–1813.

Afrashi, F., Akkin, C., Egrilmez, S., Erakgun, T., Mentes, J., 2005. Anatomic outcome of scleral buckling surgery in primary rhegmatogenous retinal detachment. Int. Ophthalmol. 26, 77–81.

Agrawal, R.N., He, S., Spee, C., Cui, J.Z., Ryan, S.J., Hinton, D.R., 2007. In vivo models of proliferative vitreoretinopathy. Nat. Protoc. 2, 67–77.

Ahmadieh, H., Feghhi, M., Tabatabaei, H., Shoeibi, N., Ramezani, A., Mohebbi, M.R., 2008. Triamcinolone acetonide in silicone-filled eyes as adjunctive treatment for proliferative vitreoretinopathy: a randomized clinical trial. Ophthalmology 115, 1938–1943.

Al-Wadani, S.F., Abouammoh, M.A., Abu El-Asrar, A.M., 2014. Visual and anatomical outcomes after silicone oil removal in patients with complex retinal detachment. Int. Ophthalmol. 34, 549–556.

Alex, A.F., Spitznas, M., Tittel, A.P., Kurts, C., Eter, N., 2010. Inhibitory effect of

epigallocatechin gallate (EGCG), resveratrol, and curcumin on proliferation of human retinal pigment epithelial cells in vitro. Curr. Eye Res. 35, 1021–1033.
Alonso-Alconada, D., Alvarez, A., Arteaga, O., Martinez-Ibarguen, A., Hilario, E., 2013. Neuroprotective effect of melatonin: a novel therapy against perinatal hypoxia-ischemia. Int. J. Mol. Sci. 14, 9379–9395.
Anderson, D.H., Stern, W.H., Fisher, S.K., Erickson, P.A., Borgula, G.A., 1981. The onset of pigment epithelial proliferation after retinal detachment. Invest. Ophthalmol. Vis. Sci. 21, 10–16.
Asaria, R.H., Charteris, D.G., 2006. Proliferative vitreoretinopathy: developments in pathogenesis and treatment. Compr. Ophthalmol. Update 7, 179–185.
Asaria, R.H., Gregor, Z.J., 2002. Simple retinal detachments: identifying the at-risk case. Eye (Lond.) 16, 404–410.
Asaria, R.H., Kon, C.H., Bunce, C., Charteris, D.G., Wong, D., Luthert, P.J., Khaw, P.T., Aylward, G.W., 2001. How to predict proliferative vitreoretinopathy: a prospective study. Ophthalmology 108, 1184–1186.
Bae, M.K., Kim, S.R., Lee, H.J., Wee, H.J., Yoo, M.A., Ock Oh, S., Baek, S.Y., Kim, B.S., Kim, J.B., Sik, Y., Bae, S.K., 2006. Aspirin-induced blockade of NF-kappaB activity restrains up-regulation of glial fibrillary acidic protein in human astroglial cells. Biochim. Biophys. Acta 1763, 282–289.
Bali, E., Feron, E.J., Peperkamp, E., Veckeneer, M., Mulder, P.G., van Meurs, J.C., 2010. 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. 248, 957–962.
Bastiaans, J., van Meurs, J.C., Mulder, V.C., Nagtzaam, N.M., Smits-te Nijenhuis, M., Dufour-van den Goorbergh, D.C., van Hagen, P.M., Hooijkaas, H., Dik, W.A., 2014. The role of thrombin in proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 55, 4659–4666.
Bazan, N.G., Calandria, J.M., Serhan, C.N., 2010. Rescue and repair during photoreceptor cell renewal mediated by docosahexaenoic acid-derived neuroprotectin D1. J. Lipid Res. 51, 2018–2031.
Bedikian, A.Y., Garbe, C., Conry, R., Lebbe, C., Grob, J.J., 2014. Dacarbazine with or without oblimersen (a Bcl-2 antisense oligonucleotide) in chemotherapy-naive patients with advanced melanoma and low-normal serum lactate dehydrogenase: the AGENDA trial. Melanoma Res. 24, 237–243.
Berker, N., Batman, C., Ozdamar, Y., Eranil, S., Aslan, O., Zilelioglu, O., 2007. Long-term outcomes of heavy silicone oil tamponade for complicated retinal detachment. Eur. J. Ophthalmol. 17, 797–803.
Besirli, C.G., Chinskey, N.D., Zheng, Q.D., Zacks, D.N., 2011. Autophagy activation in the injured photoreceptor inhibits fas-mediated apoptosis. Invest. Ophthalmol. Vis. Sci. 52, 4193–4199.
Bleeker, S.E., Moll, H.A., Steyerberg, E.W., Donders, A.R., Derksen-Lubsen, G., Grobbee, D.E., Moons, K.G., 2003. External validation is necessary in prediction research: a clinical example. J. Clin. Epidemiol. 56, 826–832.
Bonnet, M., 1984. Clinical factors predisposing to massive proliferative vitreoretinopathy in rhegmatogenous retinal detachment. Ophthalmologica 188, 148–152.
Bonnet, M., 1988. The development of severe proliferative vitreoretinopathy after retinal detachment surgery. Grade B: a determining risk factor. Graefes Arch. Clin. Exp. Ophthalmol. 226, 201–205.
Boroomand, A., Wong, A., Li, E., Cho, D.S., Ni, B., Bizheva, K., 2013. Multi-penalty conditional random field approach to super-resolved reconstruction of optical coherence tomography images. Biomed. Opt. Express 4, 2032–2050.
Bringmann, A., Pannicke, T., Grosche, J., Francke, M., Wiedemann, P., Skatchkov, S.N., Osborne, N.N., Reichenbach, A., 2006. Muller cells in the healthy and diseased retina. Prog. Retin. Eye Res. 25, 397–424.
Campochiaro, P.A., 1997. Pathogenic mechanisms in proliferative vitreoretinopathy. Arch. Ophthalmol. 115, 237–241.
Campochiaro, P.A., Hackett, S.F., Conway, B.P., 1991. Retinoic acid promotes density-dependent growth arrest in human retinal pigment epithelial cells. Invest. Ophthalmol. Vis. Sci. 32, 65–72.
Campochiaro, P.A., Jerdan, J.A., Glaser, B.M., Cardin, A., Michels, R.G., 1985. Vitreous aspirates from patients with proliferative vitreoretinopathy stimulate retinal pigment epithelial cell migration. Arch. Ophthalmol. 103, 1403–1405.
Capeans, C., Lorenzo, J., Santos, L., Suarez, A., Copena, M.J., Blanco, M.J., Sanchez-Salorio, M., 1998. Comparative study of incomplete posterior vitreous detachment as a risk factor for proliferative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 236, 481–485.
Carrington, L., McLeod, D., Boulton, M., 2000. IL-10 and antibodies to TGF-beta2 and PDGF inhibit RPE-mediated retinal contraction. Invest. Ophthalmol. Vis. Sci. 41, 1210–1216.
Chan, C.M., Chang, H.H., Wang, V.C., Huang, C.L., Hung, C.F., 2013. Inhibitory effects of resveratrol on PDGF-BB-induced retinal pigment epithelial cell migration via PDGFRbeta, PI3K/Akt and MAPK pathways. PLoS One 8, e56819.
Chandler, D.B., Rozakis, G., de Juan Jr., E., Machemer, R., 1985. The effect of triamcinolone acetonide on a refined experimental model of proliferative vitreoretinopathy. Am. J. Ophthalmol. 99, 686–690.
Chang, Y.C., Hu, D.N., Wu, W.C., 2008. Effect of oral 13-cis-retinoic acid treatment on postoperative clinical outcome of eyes with proliferative vitreoretinopathy. Am. J. Ophthalmol. 146, 440–446.
Charteris, D.G., Aylward, G.W., Wong, D., Groenewald, C., Asaria, R.H., Bunce, C., Group, P.V.R.S., 2004. A randomized controlled trial of combined 5-fluorouracil and low-molecular-weight heparin in management of established proliferative vitreoretinopathy. Ophthalmology 111, 2240–2245.
Charteris, D.G., Sethi, C.S., Lewis, G.P., Fisher, S.K., 2002. Proliferative vitreoretinopathy-developments in adjunctive treatment and retinal pathology. Eye (Lond.) 16, 369–374.
Chen, E.P., Steinhorst, U.H., Samsa, G.P., Saloupis, P.T., Hatchell, D.L., 1992. The effect of combined daunorubicin and triamcinolone acetonide treatment on a refined experimental model of proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 33, 2160–2164.
Chen, H.J., Ma, Z.Z., 2007. N-cadherin expression in a rat model of retinal detachment and reattachment. Invest. Ophthalmol. Vis. Sci. 48, 1832–1838.
Chen, W., Chen, H., Hou, P., Fok, A., Hu, Y., Lam, D.S., 2011. Midterm results of low-dose intravitreal triamcinolone as adjunctive treatment for proliferative vitreoretinopathy. Retina 31, 1137–1142.
Chiba, C., 2014. The retinal pigment epithelium: an important player of retinal disorders and regeneration. Exp. Eye Res. 123, 107–114.
Chignell, A.H., Fison, L.G., Davies, E.W., Hartley, R.E., Gundry, M.F., 1973. Failure in retinal detachment surgery. Br. J. Ophthalmol. 57, 525–530.
Chinskey, N.D., Zheng, Q.D., Zacks, D.N., 2014. Control of photoreceptor autophagy after retinal detachment: the switch from survival to death. Invest. Ophthalmol. Vis. Sci. 55, 688–695.
Choi, K., Lee, K., Ryu, S.W., Im, M., Kook, K.H., Choi, C., 2012. Pirfenidone inhibits transforming growth factor-beta1-induced fibrogenesis by blocking nuclear translocation of Smads in human retinal pigment epithelial cell line ARPE-19. Mol. Vis. 18, 1010–1020.
Christensen, U.C., la Cour, M., 2012. Visual loss after use of intraocular silicone oil associated with thinning of inner retinal layers. Acta Ophthalmol. 90, 733–737.
Coffee, R.E., Jiang, L., Rahman, S.A., 2014. Proliferative vitreoretinopathy: advances in surgical management. Int. Ophthalmol. Clin. 54, 91–109.
Committee, T.R.S.T., 1983. The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90, 121–125.
Consortium, I.H.G.S., 2004. Finishing the euchromatic sequence of the human genome. Nature 431, 931–945.
Cook, B., Lewis, G.P., Fisher, S.K., Adler, R., 1995. Apoptotic photoreceptor degeneration in experimental retinal detachment. Invest. Ophthalmol. Vis. Sci. 36, 990–996.
Cowley, M., Conway, B.P., Campochiaro, P.A., Kaiser, D., Gaskin, H., 1989. Clinical risk factors for proliferative vitreoretinopathy. Arch. Ophthalmol. 107, 1147–1151.
de Souza, C.F., Kalloniatis, M., Polkinghorne, P.J., McGhee, C.N., Acosta, M.L., 2012. Functional and anatomical remodeling in human retinal detachment. Exp. Eye Res. 97, 73–89.
Dehghan, M.H., Ahmadieh, H., Soheilian, M., Azarmina, M., Moradian, S., Ramezani, A.R., Tavallal, A., Naghibozakerin, J., 2010. Effect of oral prednisolone on visual outcomes and complications after scleral buckling. Eur. J. Ophthalmol. 20, 419–423.
Dempfle, A., Scherag, A., Hein, R., Beckmann, L., Chang-Claude, J., Schafer, H., 2008. Gene-environment interactions for complex traits: definitions, methodological requirements and challenges. Eur. J. Hum. Genet. EJHG 16, 1164–1172.
Diddie, K.R., Azen, S.P., Freeman, H.M., Boone, D.C., Aaberg, T.M., Lewis, H., Radtke, N.D., Ryan, S.J., 1996. Anterior proliferative vitreoretinopathy in the silicone study. Silicone study report number 10. Ophthalmology 103, 1092–1099.
Dong, K., Zhu, Z.C., Wang, F.H., Ke, G.J., Yu, Z., Xu, X., 2014. Activation of autophagy in photoreceptor necroptosis after experimental retinal detachment. Int. J. Ophthalmol. 7, 745–752.
Duquesne, N., Bonnet, M., Adeleine, P., 1996. Preoperative vitreous hemorrhage associated with rhegmatogenous retinal detachment: a risk factor for post-operative proliferative vitreoretinopathy? Graefes Arch. Clin. Exp. Ophthalmol. 234, 677–682.
Eibl, K.H., Lewis, G.P., Betts, K., Linberg, K.A., Gandorfer, A., Kampik, A., Fisher, S.K., 2007. The effect of alkylphosphocholines on intraretinal proliferation initiated by experimental retinal detachment. Invest. Ophthalmol. Vis. Sci. 48, 1305–1311.
Enyedi, L.B., Pearson, P.A., Ashton, P., Jaffe, G.J., 1996. An intravitreal device providing sustained release of cyclosporine and dexamethasone. Curr. Eye Res. 15, 549–557.
Er, H., Turkoz, Y., Mizrak, B., Parlakpinar, H., 2006. Inhibition of experimental proliferative vitreoretinopathy with protein kinase C inhibitor (chelerythrine chloride) and melatonin. Ophthalmologica 220, 17–22.
Erickson, P.A., Fisher, S.K., Anderson, D.H., Stern, W.H., Borgula, G.A., 1983. Retinal detachment in the cat: the outer nuclear and outer plexiform layers. Invest. Ophthalmol. Vis. Sci. 24, 927–942.
Fastenberg, D.M., Diddie, K.R., Sorgente, N., Ryan, S.J., 1982. A comparison of different cellular inocula in an experimental model of massive periretinal proliferation. Am. J. Ophthalmol. 93, 559–564.
Fekrat, S., de Juan Jr., E., Campochiaro, P.A., 1995. The effect of oral 13-cis-retinoic acid on retinal redetachment after surgical repair in eyes with proliferative vitreoretinopathy. Ophthalmology 102, 412–418.
Feng, K., Hu, Y., Wang, C., Shen, L., Pang, X., Jiang, Y., Nie, H., Wang, Z., Ma, Z., 2013. Risk factors, anatomical, and visual outcomes of injured eyes with proliferative vitreoretinopathy: eye injury vitrectomy Study. Retina 33, 1512–1518.
Fernandes-Cunha, G.M., Saliba, J.B., Siqueira, R.C., Jorge, R., Silva-Cunha, A., 2014. Determination of triamcinolone acetonide in silicone oil and aqueous humor of vitrectomized rabbits' eyes: application for a pharmacokinetic study with intravitreal triamcinolone acetonide injections (Kenalog(R) 40). J. Pharm. Biomed. Anal. 89, 24–27.
Fernandez-Bueno, I., Fernandez-Sanchez, L., Gayoso, M.J., Garcia-Gutierrez, M.T., Pastor, J.C., Cuenca, N., 2012. Time course modifications in organotypic culture

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of human neuroretina. Exp. Eye Res. 104, 26–38.
Fernandez-Bueno, I., Garcia-Gutierrez, M.T., Srivastava, G.K., Gayoso, M.J., Gonzalo-Orden, J.M., Pastor, J.C., 2013a. Adalimumab (tumor necrosis factor-blocker) reduces the expression of glial fibrillary acidic protein immunoreactivity increased by exogenous tumor necrosis factor alpha in an organotypic culture of porcine neuroretina. Mol. Vis. 19, 894–903.
Fernandez-Bueno, I., Pastor, J.C., Gayoso, M.J., Alcalde, I., Garcia, M.T., 2008. Muller and macrophage-like cell interactions in an organotypic culture of porcine neuroretina. Mol. Vis. 14, 2148–2156.
Fernandez-Bueno, I., Rodriguez de la Rua, E., Hileeto, D., Parrado, M.L., Regueiro-Purrinos, M., Sala-Puigdollers, A., Srivastava, G.K., Gonzalo-Orden, J.M., Pastor, J.C., 2013b. Histology and immunochemistry evaluation of autologous translocation of retinal pigment epithelium-choroid graft in porcine eyes. Acta Ophthalmol. 91, e125–132.
Fernandez-Sanchez, L., Lax, P., Esquiva, G., Martin-Nieto, J., Pinilla, I., Cuenca, N., 2012. Safranal, a saffron constituent, attenuates retinal degeneration in P23H rats. PLoS One 7, e43074.
Fernandez-Sanchez, L., Lax, P., Pinilla, I., Martin-Nieto, J., Cuenca, N., 2011. Tauroursodeoxycholic acid prevents retinal degeneration in transgenic P23H rats. Invest. Ophthalmol. Vis. Sci. 52, 4998–5008.
Figiel, I., 2008. Pro-inflammatory cytokine TNF-alpha as a neuroprotective agent in the brain. Acta Neurobiol. Exp. 68, 526–534.
Fischer, A.J., Zelinka, C., Milani-Nejad, N., 2015. Reactive retinal microglia, neuronal survival, and the formation of retinal folds and detachments. Glia 63, 313–327.
Fisher, S.K., Erickson, P.A., Lewis, G.P., Anderson, D.H., 1991. Intraretinal proliferation induced by retinal detachment. Invest. Ophthalmol. Vis. Sci. 32, 1739–1748.
Fisher, S.K., Lewis, G.P., 2003. Müller cell and neuronal remodeling in retinal detachment and reattachment and their potential consequences for visual recovery: a review and reconsideration of recent data. Vis. Res. 43, 887–897.
Fisher, S.K., Lewis, G.P., Linberg, K.A., Barawid, E., Verardo, M.R., 1995. Cellular remodeling in mammalian retina induced by retinal detachment. In: Kolb, H., Fernandez, E., Nelson, R. (Eds.), Webvision: the Organization of the Retina and Visual System, Salt Lake City (UT).
Fisher, S.K., Lewis, G.P., Linberg, K.A., Verardo, M.R., 2005. Cellular remodeling in mammalian retina: results from studies of experimental retinal detachment. Prog. Retin Eye Res. 24, 395–431.
Flanders, K.C., 2004. Smad3 as a mediator of the fibrotic response. Int. J. Exp. Pathol. 85, 47–64.
Ganekal, S., Dorairaj, S., 2014. Effect of intraoperative 5-fluorouracil and low molecular weight heparin on the outcome of high-risk proliferative vitreoretinopathy. Saudi J. Ophthalmol. Off. J. Saudi Ophthalmol. Soc. 28, 257–261.
Garcia-Layana, A., Pastor, J.C., Saornil, M.A., Gonzalez, G., 1997. Porcine model of proliferative vitreoretinopathy with platelets. Curr. Eye Res. 16, 556–563.
Garnier, S., Rahmi, A., Grasswil, C., Kodjikian, L., 2013. Three hundred and sixty degree retinotomy for retinal detachments with severe proliferative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 251, 2081–2085.
Garweg, J.G., Tappeiner, C., Halberstadt, M., 2013. Pathophysiology of proliferative vitreoretinopathy in retinal detachment. Surv. Ophthalmol. 58, 321–329.
Geller, S.F., Lewis, G.P., Anderson, D.H., Fisher, S.K., 1995. Use of the MIB-1 antibody for detecting proliferating cells in the retina. Invest. Ophthalmol. Vis. Sci. 36, 737–744.
Geller, S.F., Lewis, G.P., Fisher, S.K., 2001. FGFR1, signaling, and AP-1 expression after retinal detachment: reactive muller and RPE cells. Invest. Ophthalmol. Vis. Sci. 42, 1363–1369.
Gemenetzi, M., Lotery, A.J., 2014. The role of epigenetics in age-related macular degeneration. Eye (Lond.) 28, 1407–1417.
Ghazi, N.G., Green, W.R., 2002. Pathology and pathogenesis of retinal detachment. Eye (Lond.) 16, 411–421.
Girard, P., Mimoun, G., Karpouzas, I., Montefiore, G., 1994. Clinical risk factors for proliferative vitreoretinopathy after retinal detachment surgery. Retina 14, 417–424.
Goldaracena, M.B., Garcia-Layana, A., Pastor, J.C., Saornil, M.A., de la Fuente, F., Gayoso, M.J., 1997. The role of retinotomy in an experimental rabbit model of proliferative vitreoretinopathy. Curr. Eye Res. 16, 422–427.
Gomez-Sanchez, J.C., Delgado-Esteban, M., Rodriguez-Hernandez, I., Sobrino, T., Perez de la Ossa, N., Reverte, S., Bolanos, J.P., Gonzalez-Sarmiento, R., Castillo, J., Almeida, A., 2011. The human Tp53 Arg72Pro polymorphism explains different functional prognosis in stroke. J. Exp. Med. 208, 429–437.
Grigoropoulos, V.G., Benson, S., Bunce, C., Charteris, D.G., 2007. Functional outcome and prognostic factors in 304 eyes managed by retinectomy. Graefes Arch. Clin. Exp. Ophthalmol. 245, 641–649.
Hauwel, M., Furon, E., Canova, C., Griffiths, M., Neal, J., Gasque, P., 2005. Innate (inherent) control of brain infection, brain inflammation and brain repair: the role of microglia, astrocytes, “protective” glial stem cells and stromal ependymal cells. Brain Res. Brain Res. Rev. 48, 220–233.
Havener, W.H., 1976. Massive vitreous retraction. Int. Ophthalmol. Clin. 16, 135–155.
Hede, S.M., Nazarenko, I., Nister, M., Lindstrom, M.S., 2011. Novel perspectives on p53 function in neural stem cells and brain tumors. J. Oncol. 2011, 852970.
Heimann, H., Bartz-Schmidt, K.U., Bornfeld, N., Weiss, C., Hilgers, R.D., Foerster, M.H., 2007. Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment: a prospective randomized multicenter clinical study. Ophthalmology 114, 2142–2154.
Heimann, K., Wiedemann, P., 1989. Cologne classification of proliferative vitreoretinopathy. In: Heimann, K., Wiedemann, P. (Eds.), Proliferative Vitreoretinopathy. Kaden Verlag, Heidelberg, pp. 148–149.
Hoos, M.D., Vitek, M.P., Ridnour, L.A., Wilson, J., Jansen, M., Everhart, A., Wink, D.A., Colton, C.A., 2014. The impact of human and mouse differences in NOS2 gene expression on the brain's redox and immune environment. Mol. Neurodegener. 9, 50.
Horie-Inoue, K., Inoue, S., 2014. Genomic aspects of age-related macular degeneration. Biochem. Biophys. Res. Commun. 452, 263–275.
Hsu, H.T., Ryan, S.J., 1986. Experimental retinal detachment in the rabbit. Penetrating ocular injury with retinal laceration. Retina 6, 66–69.
Hu, J., Wen, P.Y., Abrey, L.E., Fadul, C.E., Drappatz, J., Salem, N., Supko, J.G., Hochberg, F., 2013. A phase II trial of oral gimatecan for recurrent glioblastoma. J. Neuro Oncol. 111, 347–353.
Hui, Y.N., Goodnight, R., Sorgente, N., Ryan, S.J., 1989. Fibrovascular proliferation and retinal detachment after intravitreal injection of activated macrophages in the rabbit eye. Am. J. Ophthalmol. 108, 176–184.
Hui, Y.N., Hu, D., 1999. Prevention of experimental proliferative vitreoretinopathy with daunomycin and triamcinolone based on the time course of the disease. Graefes Arch. Clin. Exp. Ophthalmol. 237, 601–605.
Hui, Y.N., Liang, H.C., Cai, Y.S., Kirchhof, B., Heimann, K., 1993. Corticosteroids and daunomycin in the prevention of experimental proliferative vitreoretinopathy induced by macrophages. Graefes Arch. Clin. Exp. Ophthalmol. 231, 109–114.
Iandiev, I., Uckermann, O., Pannicke, T., Wurm, A., Tenckhoff, S., Pietsch, U.C., Reichenbach, A., Wiedemann, P., Bringmann, A., Uhlmann, S., 2006. Glial cell reactivity in a porcine model of retinal detachment. Invest. Ophthalmol. Vis. Sci. 47, 2161–2171.
Imai, K., Loewenstein, A., Koroma, B., Grebe, R., de Juan Jr., E., 2000. Herbimycin A in the treatment of experimental proliferative vitreoretinopathy: toxicity and efficacy study. Graefes Arch. Clin. Exp. Ophthalmol. 238, 440–447.
Iribarne, M., Canto-Soler, M.V., Torbidoni, V., Suburo, A.M., 2007. Controlling retinal pigment epithelium injury after experimental detachment of the retina. Invest. Ophthalmol. Vis. Sci. 48, 1348–1354.
Ito, S., Sakamoto, T., Tahara, Y., Goto, Y., Akazawa, K., Ishibashi, T., Inomata, H., 1999. The effect of tranilast on experimental proliferative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 237, 691–696.
Iwahashi-Shima, C., Sato, T., Bando, H., Ikeda, T., Emi, K., 2013. Anatomic and functional outcomes of 25-gauge vitrectomy for repair of eyes with rhegmatogenous retinal detachment complicated by proliferative vitreoretinopathy. Clin. Ophthalmol. 7, 2043–2049.
Jonas, J.B., Hayler, J.K., Panda-Jonas, S., 2000. Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy. Br. J. Ophthalmol. 84, 1064–1067.
Jonas, J.B., Knorr, H.L., Rank, R.M., Budde, W.M., 2001. Retinal redetachment after removal of intraocular silicone oil tamponade. Br. J. Ophthalmol. 85, 1203–1207.
Kauffmann, D.J., van Meurs, J.C., Mertens, D.A., Peperkamp, E., Master, C., Gerritsen, M.E., 1994. Cytokines in vitreous humor: interleukin-6 is elevated in proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 35, 900–906.
Kawahara, S., Hata, Y., Kita, T., Arita, R., Miura, M., Nakao, S., Mochizuki, Y., Enaida, H., Kagimoto, T., Goto, Y., Hafezi-Moghadam, A., Ishibashi, T., 2008. Potent inhibition of cicatricial contraction in proliferative vitreoretinal diseases by statins. Diabetes 57, 2784–2793.
Khan, M.A., Brady, C.J., Kaiser, R.S., 2015. Clinical management of proliferative vitreoretinopathy: an update. Retina 35, 165–175.
Khawly, J.A., Saloupis, P., Hatchell, D.L., Machemer, R., 1991. Daunorubicin treatment in a refined experimental model of proliferative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 229, 464–467.
Kirchhof, B., Kirchhof, E., Ryan, S.J., Sorgente, N., 1989. Vitreous modulation of migration and proliferation of retinal pigment epithelial cells in vitro. Invest. Ophthalmol. Vis. Sci. 30, 1951–1957.
Kiss, C.G., Richter-Muksch, S., Sacu, S., Benesch, T., Velikay-Parel, M., 2007. Anatomy and function of the macula after surgery for retinal detachment complicated by proliferative vitreoretinopathy. Am. J. Ophthalmol. 144, 872–877.
Kiss, S., Vavvas, D., 2008. 25-gauge transconjunctival sutureless pars plana vitrectomy for the removal of retained lens fragments and intraocular foreign bodies. Retina 28, 1346–1351.
Kita, T., Hata, Y., Arita, R., Kawahara, S., Miura, M., Nakao, S., Mochizuki, Y., Enaida, H., Goto, Y., Shimokawa, H., Hafezi-Moghadam, A., Ishibashi, T., 2008. Role of TGF-beta in proliferative vitreoretinal diseases and ROCK as a therapeutic target. Proc. Natl. Acad. Sci. U. S. A. 105, 17504–17509.
Kivilcim, M., Peyman, G.A., El-Dessouky, E.S., Kazi, A.A., Cheema, R., Hegazy, H., 2000. Retinal toxicity of triamcinolone acetonide in silicone-filled eyes. Ophthalmic Surg. Lasers 31, 474–478.
Koerner, F., Koerner-Stiefbold, U., Garweg, J.G., 2012. Systemic corticosteroids reduce the risk of cellophane membranes after retinal detachment surgery: a prospective randomized placebo-controlled double-blind clinical trial. Graefes Arch. Clin. Exp. Ophthalmol. 250, 981–987.
Koerner, F., Merz, A., Gloor, B., Wagner, E., 1982. Postoperative retinal fibrosis–a controlled clinical study of systemic steroid therapy. Graefes Arch. Clin. Exp. Ophthalmol. 219, 268–271.
Kon, C.H., Asaria, R.H., Occleston, N.L., Khaw, P.T., Aylward, G.W., 2000. Risk factors for proliferative vitreoretinopathy after primary vitrectomy: a prospective study. Br. J. Ophthalmol. 84, 506–511.
Kon, C.H., Occleston, N.L., Aylward, G.W., Khaw, P.T., 1999. Expression of vitreous cytokines in proliferative vitreoretinopathy: a prospective study. Invest. Ophthalmol. Vis. Sci. 40, 705–712.
Kosnosky, W., Li, T.H., Pakalnis, V.A., Fox, A., Hunt, R.C., 1994. Interleukin-1-beta changes the expression of metalloproteinases in the vitreous humor and

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induces membrane formation in eyes containing preexisting retinal holes. Invest. Ophthalmol. Vis. Sci. 35, 4260–4267.
Kumar, V., Cotran, R.S., 1994. Robbins' basic pathology. Arch. Pathol. Lab. Med. 118, 203–203.
Kuo, H.K., Wu, P.C., Yang, P.M., Chen, Y.H., Wu, Y.C., Hu, D.N., 2007. Effects of topoisomerase II inhibitors on retinal pigment epithelium and experimental proliferative vitreoretinopathy. J. Ocular Pharmacol. Ther. Off. J. Assoc. Ocular Pharmacol. Ther. 23, 14–20.
Lean, J.S., Stern, W.H., Irvine, A.R., Azen, S.P., 1989. Classification of proliferative vitreoretinopathy used in the silicone study. The silicone study group. Ophthalmology 96, 765–771.
Lei, H., Velez, G., Cui, J., Samad, A., Maberley, D., Matsubara, J., Kazlauskas, A., 2010. N-acetylcysteine suppresses retinal detachment in an experimental model of proliferative vitreoretinopathy. Am. J. Pathol. 177, 132–140.
Lei, H., Velez, G., Kazlauskas, A., 2011. Pathological signaling via platelet-derived growth factor receptor {alpha} involves chronic activation of Akt and suppression of p53. Mol. Cell. Biol. 31, 1788–1799.
Leiderman, Y.I., Miller, J.W., 2009. Proliferative vitreoretinopathy: pathobiology and therapeutic targets. Semin. Ophthalmol. 24, 62–69.
Lemor, M., de Bustros, S., Glaser, B.M., 1986a. Low-dose colchicine inhibits astrocyte, fibroblast, and retinal pigment epithelial cell migration and proliferation. Arch. Ophthalmol. 104, 1223–1225.
Lemor, M., Yeo, J.H., Glaser, B.M., 1986b. Oral colchicine for the treatment of experimental traction retinal detachment. Arch. Ophthalmol. 104, 1226–1229.
Lewis, G.P., Chapin, E.A., Byun, J., Luna, G., Sherris, D., Fisher, S.K., 2009. Muller cell reactivity and photoreceptor cell death are reduced after experimental retinal detachment using an inhibitor of the Akt/mTOR pathway. Invest. Ophthalmol. Vis. Sci. 50, 4429–4435.
Lewis, G.P., Charteris, D.G., Sethi, C.S., Leitner, W.P., Linberg, K.A., Fisher, S.K., 2002. The ability of rapid retinal reattachment to stop or reverse the cellular and molecular events initiated by detachment. Invest. Ophthalmol. Vis. Sci. 43, 2412–2420.
Lewis, G.P., Guerin, C.J., Anderson, D.H., Matsumoto, B., Fisher, S.K., 1994. Rapid changes in the expression of glial cell proteins caused by experimental retinal detachment. Am. J. Ophthalmol. 118, 368–376.
Lewis, G.P., Sethi, C.S., Carter, K.M., Charteris, D.G., Fisher, S.K., 2005. Microglial cell activation following retinal detachment: a comparison between species. Mol. Vis. 11, 491–500.
Lewis, G.P., Sethi, C.S., Linberg, K.A., Charteris, D.G., Fisher, S.K., 2003. Experimental retinal reattachment: a new perspective. Mol. Neurobiol. 28, 159–175.
Li, S., Jiang, S., Jiang, W., Zhou, Y., Shen, X.Y., Luo, T., Kong, L.P., Wang, H.Q., 2015. Anticancer effects of crocetin in human esophageal squamous cell carcinoma KYSE-150 cells. Oncol. Lett. 9, 1254–1260.
Liang, C.M., Tai, M.C., Chang, Y.H., Chen, Y.H., Chen, C.L., Chien, M.W., Chen, J.T., 2010. Glucosamine inhibits epidermal growth factor-induced proliferation and cell-cycle progression in retinal pigment epithelial cells. Mol. Vis. 16, 2559–2571.
Liang, C.M., Tai, M.C., Chang, Y.H., Chen, Y.H., Chen, C.L., Lu, D.W., Chen, J.T., 2011. Glucosamine inhibits epithelial-to-mesenchymal transition and migration of retinal pigment epithelium cells in culture and morphologic changes in a mouse model of proliferative vitreoretinopathy. Acta Ophthalmol. 89, e505–514.
Limb, G.A., Little, B.C., Meager, A., Ogilvie, J.A., Wolstencroft, R.A., Franks, W.A., Chignell, A.H., Dumonde, D.C., 1991. Cytokines in proliferative vitreoretinopathy. Eye (Lond.) 5 (Pt 6), 686–693.
Linberg, K.A., Sakai, T., Lewis, G.P., Fisher, S.K., 2002. Experimental retinal detachment in the cone-dominant ground squirrel retina: morphology and basic immunocytochemistry. Vis. Neurosci. 19, 603–619.
Liu, H., Qian, J., Wang, F., Sun, X., Xu, X., Xu, W., Zhang, X., Zhang, X., 2010. Expression of two endoplasmic reticulum stress markers, GRP78 and GADD153, in rat retinal detachment model and its implication. Eye (Lond.) 24, 137–144.
Lleo Perez, A., Campos Fernandez, R., Lopez Santovena, F., Sanchez Lorente, G., Hernandez Martinez, F.J., Navarro Palop, C., 2000. Clinical risk factors for proliferative vitreoretinopathy after retinal detachment surgery. Arch. la Soc. Espanola Oftalmol. 75, 741–750.
Lo, A.C., Woo, T.T., Wong, R.L., Wong, D., 2011. Apoptosis and other cell death mechanisms after retinal detachment: implications for photoreceptor rescue. Ophthalmologica 226 (Suppl. 1), 10–17.
Lobo, I., 2008. Multifactorial inheritance and genetic disease. Nat. Educ. 1.
Machado, R.A., Casella, A.M., Malaguido, M.R., Oguido, A.P., 2009. Experimental study of vitreoretinal proliferation inhibition by the use of hypericin. Arq. Bras. Oftalmol. 72, 650–654.
Machemer, R., 1978. Pathogenesis and classification of massive periretinal proliferation. Br. J. Ophthalmol. 62, 737–747.
Machemer, R., Aaberg, T.M., Freeman, H.M., Irvine, A.R., Lean, J.S., Michels, R.M., 1991. An updated classification of retinal detachment with proliferative vitreoretinopathy. Am. J. Ophthalmol. 112, 159–165.
Mandava, N., Blackburn, P., Paul, D.B., Wilson, M.W., Read, S.B., Alspaugh, E., Tritz, R., Barber, J.R., Robbins, J.M., Kruse, C.A., 2002. Ribozyme to proliferating cell nuclear antigen to treat proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 43, 3338–3348.
Mantopoulos, D., Murakami, Y., Comander, J., Thanos, A., Roh, M., Miller, J.W., Vavvas, D.G., 2011. Tauroursodeoxycholic acid (TUDCA) protects photoreceptors from cell death after experimental retinal detachment. PLoS One 6, e24245.
Martin, F., Pastor, J.C., De La Rua, E.R., Mayo-Iscar, A., Garcia-Arumi, J., Martinez, V., Fernandez, N., Saornil, M.A., 2003. Proliferative vitreoretinopathy: cytologic findings in vitreous samples. Ophthalmic Res. 35, 232–238.
Matsumoto, H., Kataoka, K., Tsoka, P., Connor, K.M., Miller, J.W., Vavvas, D.G., 2014. Strain difference in photoreceptor cell death after retinal detachment in mice. Invest. Ophthalmol. Vis. Sci. 55, 4165–4174.
Minarcik, J.R., von Fricken, M.A., 2012. Virtual retinectomy: indocyanine green-assisted internal limiting membrane peeling as a surgical adjunct in repair of recurrent rhegmatogenous retinal detachment due to PVR. Clin. Ophthalmol. 6, 631–636.
Mitry, D., Charteris, D.G., Fleck, B.W., Campbell, H., Singh, J., 2010. The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. Br. J. Ophthalmol. 94, 678–684.
Morales, S.A., Telander, D.G., Mareninov, S., Nagy, A., Wadehra, M., Braun, J., Gordon, L.K., 2012. Anti-EMP2 diabody blocks epithelial membrane protein 2 (EMP2) and FAK mediated collagen gel contraction in ARPE-19 cells. Exp. Eye Res. 102, 10–16.
Moysidis, S.N., Thanos, A., Vavvas, D.G., 2012. Mechanisms of inflammation in proliferative vitreoretinopathy: from bench to bedside. Mediat. Inflamm. 2012, 815937.
Murakami, Y., Miller, J.W., Vavvas, D.G., 2011. RIP kinase-mediated necrosis as an alternative mechanisms of photoreceptor death. Oncotarget 2, 497–509.
Murakami, Y., Notomi, S., Hisatomi, T., Nakazawa, T., Ishibashi, T., Miller, J.W., Vavvas, D.G., 2013. Photoreceptor cell death and rescue in retinal detachment and degenerations. Prog. Retin. Eye Res. 37, 114–140.
Nakamura, K., Refojo, M.F., Crabtree, D.V., Pastor, J., Leong, F.L., 1991. Ocular toxicity of low-molecular-weight components of silicone and fluorosilicone oils. Invest. Ophthalmol. Vis. Sci. 32, 3007–3020.
Nakazawa, T., Hisatomi, T., Nakazawa, C., Noda, K., Maruyama, K., She, H., Matsubara, A., Miyahara, S., Nakao, S., Yin, Y., Benowitz, L., Hafezi-Moghadam, A., Miller, J.W., 2007. Monocyte chemoattractant protein 1 mediates retinal detachment-induced photoreceptor apoptosis. Proc. Natl. Acad. Sci. U. S. A. 104, 2425–2430.
Nakazawa, T., Kayama, M., Ryu, M., Kunikata, H., Watanabe, R., Yasuda, M., Kinugawa, J., Vavvas, D., Miller, J.W., 2011. Tumor necrosis factor-alpha mediates photoreceptor death in a rodent model of retinal detachment. Invest. Ophthalmol. Vis. Sci. 52, 1384–1391.
Nguyen, K.D., Lee, D.A., 1992. Effect of steroids and nonsteroidal antiinflammatory agents on human ocular fibroblast. Invest. Ophthalmol. Vis. Sci. 33, 2693–2701.
Osusky, R., Ryan, S.J., 1996. Retinal pigment epithelial cell proliferation: potentiation by monocytes and serum. Graefes Arch. Clin. Exp. Ophthalmol. 234 (Suppl. 1), S76–S82.
Oyagi, T., Emi, K., 2004. Vitrectomy without scleral buckling for proliferative vitreoretinopathy. Retina 24, 215–218.
Pastor-Idoate, S., Rodriguez-Hernandez, I., Rojas, J., Fernandez, I., Garcia-Gutierrez, M.T., Ruiz-Moreno, J.M., Rocha-Sousa, A., Ramkissoon, Y., Harsum, S., Maclaren, R.E., Charteris, D., van Meurs, J., Gonzalez-Sarmiento, R., Pastor, J.C., 2013a. The p53 codon 72 polymorphism (rs1042522) is associated with proliferative vitreoretinopathy: the retina 4 Project. Ophthalmology 120, 623–628.
Pastor-Idoate, S., Rodriguez-Hernandez, I., Rojas, J., Fernandez, I., Garcia-Gutierrez, M.T., Ruiz-Moreno, J.M., Rocha-Sousa, A., Ramkissoon, Y., Harsum, S., Maclaren, R.E., Charteris, D., Vanmeurs, J.C., Gonzalez-Sarmiento, R., Pastor, J.C., 2013b. The T309G MDM2 gene polymorphism is a novel risk factor for proliferative vitreoretinopathy. PLoS One 8, e82283.
Pastor, J.C., 1998. Proliferative vitreoretinopathy: an overview. Surv. Ophthalmol. 43, 3–18.
Pastor, J.C., de la Rua, E.R., Martin, F., 2002. Proliferative vitreoretinopathy: risk factors and pathobiology. Prog. Retin Eye Res. 21, 127–144.
Pastor, J.C., Del Nozal, M.J., Marinero, P., Diez, O., 2006a. Cholesterol, alpha-tocopherol, and retinoid concentrations in silicone oil used as a vitreous substitute. Arch. la Soc. Espanola Oftalmol. 81, 13–19.
Pastor, J.C., Del Nozal, M.J., Zamarron, E., Garcia, M., 2008a. Solubility of triamcinolone acetonide and other anti-inflammatory drugs in silicone oil: implications for therapeutic Efficacy. Retina 28, 1247–1250.
Pastor, J.C., Fernández, I., Coco, R.M., Sanabria, M.R., Rodríguez de la Rúa, E., Piñon, R.M., Martinez, V., Sala-Puigdollers, A., Gallardo, J.M., Velilla, S., 2012. Variations in functional and anatomical outcomes and in proliferative vitreoretinopathy rate along a prospective collaborative study on primary rhegmatogenous retinal detachments: the retina 1 project—report 4. ISRN Ophthalmol. 2012, 1–7.
Pastor, J.C., Fernandez, I., Rodriguez de la Rua, E., Coco, R., Sanabria-Ruiz Colmenares, M.R., Sanchez-Chicharro, D., Martinho, R., Ruiz Moreno, J.M., Garcia Arumi, J., Suarez de Figueroa, M., Giraldo, A., Manzanas, L., 2008b. Surgical outcomes for primary rhegmatogenous retinal detachments in phakic and pseudophakic patients: the retina 1 project–report 2. Br. J. Ophthalmol. 92, 378–382.
Pastor, J.C., Lopez, M.I., Saornil, M.A., Refojo, M.F., 1992. Intravitreal silicone and fluorosilicone oils: pathologic findings in rabbit eyes. Acta Ophthalmol. (Copenh) 70, 651–658.
Pastor, J.C., Mendez, M.C., de la Fuente, M.A., Coco, R.M., Garcia-Arumi, J., Rodriguez de la Rua, E., Fernandez, N., Saornil, M.A., Gayoso, M.J., 2006b. Intraretinal immunohistochemistry findings in proliferative vitreoretinopathy with retinal shortening. Ophthalmic Res. 38, 193–200.
Pastor, J.C., Rodriguez de la Rua, E., Martin, F., Mayo-Iscar, A., de la Fuente, M.A., Coco, R., Bailez, C., Mahave, S., 2003. Retinal shortening: the most severe form of proliferative vitreoretinopathy (PVR). Arch. la Soc. Espanola Oftalmol. 78, 653–657.

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Pastor, J.C., Rodriguez, E., Marcos, M.A., Lopez, M.I., 2000. Combined pharmacologic therapy in a rabbit model of proliferative vitreoretinopathy (PVR). Ophthalmic Res. 32, 25–29.

Patel, N.N., Bunce, C., Asaria, R.H., Charteris, D.G., 2004. Resources involved in managing retinal detachment complicated by proliferative vitreoretinopathy. Retina 24, 883–887.

Pennock, S., Haddock, L.J., Eliott, D., Mukai, S., Kazlauskas, A., 2014a. Is neutralizing vitreal growth factors a viable strategy to prevent proliferative vitreoretinopathy? Prog. Retin Eye Res. 40, 16–34.

Pennock, S., Haddock, L.J., Mukai, S., Kazlauskas, A., 2014b. Vascular endothelial growth factor acts primarily via platelet-derived growth factor receptor alpha to promote proliferative vitreoretinopathy. Am. J. Pathol. 184, 3052–3068.

Pennock, S., Kazlauskas, A., 2012. Vascular endothelial growth factor A competitively inhibits platelet-derived growth factor (PDGF)-dependent activation of PDGF receptor and subsequent signaling events and cellular responses. Mol. Cell. Biol. 32, 1955–1966.

Pennock, S., Kim, D., Mukai, S., Kuhnle, M., Chun, D.W., Matsubara, J., Cui, J., Ma, P., Maberley, D., Samad, A., Van Geest, R.J., Oberstein, S.L., Schlingemann, R.O., Kazlauskas, A., 2013. Ranibizumab is a potential prophylaxis for proliferative vitreoretinopathy, a nonangiogenic blinding disease. Am. J. Pathol. 182, 1659–1670.

Pennock, S., Rheaume, M.A., Mukai, S., Kazlauskas, A., 2011. A novel strategy to develop therapeutic approaches to prevent proliferative vitreoretinopathy. Am. J. Pathol. 179, 2931–2940.

Pinon, R.M., Pastor, J.C., Saornil, M.A., Goldaracena, M.B., Layana, A.G., Gayoso, M.J., Guisasola, J., 1992. Intravitreal and subretinal proliferation induced by platelet-rich plasma injection in rabbits. Curr. Eye Res. 11, 1047–1055.

Poulter, J.A., Davidson, A.E., Ali, M., Gilmour, D.F., Parry, D.A., Mintz-Hittner, H.A., Carr, I.M., Bottomley, H.M., Long, V.W., Downey, L.M., Sergouniotis, P.I., Wright, G.A., MacLaren, R.E., Moore, A.T., Webster, A.R., Inglehearn, C.F., Toomes, C., 2012. Recessive mutations in TSPAN12 cause retinal dysplasia and severe familial exudative vitreoretinopathy (FEVR). Invest. Ophthalmol. Vis. Sci. 53, 2873–2879.

Quiram, P.A., Gonzales, C.R., Hu, W., Gupta, A., Yoshizumi, M.O., Kreiger, A.E., Schwartz, S.D., 2006. Outcomes of vitrectomy with inferior retinectomy in patients with recurrent rhegmatogenous retinal detachments and proliferative vitreoretinopathy. Ophthalmology 113, 2041–2047.

Radtke, N.D., Tano, Y., Chandler, D., Machemer, R., 1981. Simulation of massive periretinal proliferation by autotransplantation of retinal pigment epithelial cells in rabbits. Am. J. Ophthalmol. 91, 76–87.

Recchia, F.M., Scott, I.U., Brown, G.C., Brown, M.M., Ho, A.C., Ip, M.S., 2010. Small-gauge pars plana vitrectomy: a report by the American academy of ophthalmology. Ophthalmology 117, 1851–1857.

Regler, R., Sachs, H.G., Hillenkamp, J., Helbig, H., Framme, C., 2009. Long-term evaluation of anatomic and functional results after complicated retinal detachment treated with pars plana vitrectomy and heavy silicone oil tamponade. Klin. Monatsblatter fur Augenheilkd. 226, 707–712.

Rezende, F.A., Kapusta, M.A., Burnier Jr., M.N., Costa, R.A., Scott, I.U., 2007. Preoperative B-scan ultrasonography of the vitreoretinal interface in phakic patients undergoing rhegmatogenous retinal detachment repair and its prognostic significance. Graefes Arch. Clin. Exp. Ophthalmol. 245, 1295–1301.

Ricker, L.J., Kessels, A.G., de Jager, W., Hendrikse, F., Kijlstra, A., la Heij, E.C., 2012. Prediction of proliferative vitreoretinopathy after retinal detachment surgery: potential of biomarker profiling. Am. J. Ophthalmol. 154, 347–354 e342.

Robitaille, J.M., Zheng, B., Wallace, K., Beis, M.J., Tatlidil, C., Yang, J., Sheidow, T.G., Siebert, L., Levin, A.V., Lam, W.C., Arthur, B.W., Lyons, C.J., Jaakkola, E., Tsilou, E., Williams, C.A., Weaver Jr., R.G., Shields, C.L., Guernsey, D.L., 2011. The role of Frizzled-4 mutations in familial exudative vitreoretinopathy and coats disease. Br. J. Ophthalmol. 95, 574–579.

Rodriguez-Crespo, D., Di Lauro, S., Singh, A., Garcia-Gutierrez, M.T., Garrosa García, M., Pastor, J.C., Fernandez-Bueno, I., Srivastava, G.K., 2014. Triple-layered mixed co-culture model of RPE cells with neuroretina for evaluating the neuroprotective effects of adipose-MSCs. Cell Tissue Res. 358, 705–716.

Rodriguez de la Rua, E., Pastor, J.C., Aragon, J., Mayo-Iscar, A., Martinez, V., Garcia-Arumi, J., Giraldo, A., Sanabria-Ruiz Colmenares, M.R., Miranda, I., 2005. Interaction between surgical procedure for repairing retinal detachment and clinical risk factors for proliferative vitreoretinopathy. Curr. Eye Res. 30, 147–153.

Rodriguez de la Ruz Franch, E., Aragon Roca, J.A., Pastor Jimeno, J.C., Carrasco Herrero, B., Gonzalez Rodriguez, J.C., Alvarez Requejo, A., Martin De Diego, I., Giraldo Arguello, A., 2000. Potential to predict the risk of developing proliferative vitreoretinopathy with the analysis of clinical factors of regmatogenous retinal detachments. Arch. la Soc. Espanola Oftalmol. 75, 807–812.

Rojas, J., Fernandez, I., Pastor, J.C., Garcia-Gutierrez, M.T., Sanabria, M.R., Brion, M., Coco, R.M., Ruiz-Moreno, J.M., Garcia-Arumi, J., Elizalde, J., Ruiz-Miguel, M., Gallardo, J.M., Corrales, R.M., Carracedo, A., 2010. A strong genetic association between the tumor necrosis factor locus and proliferative vitreoretinopathy: the retina 4 project. Ophthalmology 117, 2417–2423 e2411–2412.

Rojas, J., Fernandez, I., Pastor, J.C., Garcia-Gutierrez, M.T., Sanabria, R.M., Brion, M., Sobrino, B., Manzanas, L., Giraldo, A., Rodriguez-de la Rua, E., Carracedo, A., 2009. Development of predictive models of proliferative vitreoretinopathy based on genetic variables: the retina 4 project. Invest. Ophthalmol. Vis. Sci. 50, 2384–2390.

Rojas, J., Fernandez, I., Pastor, J.C., MacLaren, R.E., Ramkissoon, Y., Harsum, S., Charteris, D.G., Van Meurs, J.C., Amarakoon, S., Garcia-Arumi, J., Ruiz-Moreno, J.M., Rocha-Sousa, A., Brion, M., Carracedo, A., 2015 Jan. Predicting proliferative vitreoretinopathy: temporal and external validation of models based on genetic and clinical variables. Br. J. Ophthalmol. 99, 41–48.

Rojas, J., Fernandez, I., Pastor, J.C., Maclaren, R.E., Ramkissoon, Y., Harsum, S., Charteris, D.G., Van Meurs, J.C., Amarakoon, S., Ruiz-Moreno, J.M., Rocha-Sousa, A., Brion, M., Carracedo, A., 2013. A genetic case-control study confirms the implication of SMAD7 and TNF locus in the development of proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 54, 1665–1678.

Rosenkranz, S., Knirel, D., Dietrich, H., Flesch, M., Erdmann, E., Bohm, M., 2002. Inhibition of the PDGF receptor by red wine flavonoids provides a molecular explanation for the "French paradox". FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 16, 1958–1960.

Rouberol, F., Chiquet, C., 2014. Proliferative vitreoretinopathy: pathophysiology and clinical diagnosis. J. francais d'ophtalmologie 37, 557–565.

Rubsamen, P.E., Cousins, S.W., 1997. Therapeutic effect of periocular corticosteroids in experimental proliferative vitreoretinopathy. Retina 17, 44–50.

Rusnak, S., Vrzalova, J., Hecova, L., Kozova, M., Topolcan, O., Ricarova, R., 2013. Defining the seriousness of proliferative vitreoretinopathy by aspiration of cytokines from the anterior chamber. Biomarker. Med. 7, 759–767.

Sadaka, A., Giuliari, G.P., 2012. Proliferative vitreoretinopathy: current and emerging treatments. Clin. Ophthalmol. 6, 1325–1333.

Saika, S., Yamanaka, O., Flanders, K.C., Okada, Y., Miyamoto, T., Sumioka, T., Shirai, K., Kitano, A., Miyazaki, K., Tanaka, S., Ikeda, K., 2008. Epithelial-mesenchymal transition as a therapeutic target for prevention of ocular tissue fibrosis. Endocr. Metab. Immune Disord. Drug Targets 8, 69–76.

Saika, S., Yamanaka, O., Nishikawa-Ishida, I., Kitano, A., Flanders, K.C., Okada, Y., Ohnishi, Y., Nakajima, Y., Ikeda, K., 2007. Effect of Smad7 gene overexpression on transforming growth factor beta-induced retinal pigment fibrosis in a proliferative vitreoretinopathy mouse model. Arch. Ophthalmol. 125, 647–654.

Sala-Puigdollers, A., Fernandez, I., Coco, R.M., Sanabria, M.R., Rodriguez de la Rua, E., Ruiz-Moreno, J.M., Navea, A., Suarez de Figueroa, M., Pastor, J.C., 2013. External validation of existing formulas to predict the risk of developing proliferative vitreoretinopathy: the retina 1 Project; report 5. Retina 33, 1519–1527.

Salah-Eldin, M., Peyman, G.A., el-Aswad, M., Bandok, B., Bahgat, M.M., Niesman, M.R., 1994. Evaluation of toxicity and efficacy of a combination of antineoplastic agents in the prevention of PVR. Int. Ophthalmol. 18, 53–60.

Saleh, M., Debellemaniere, G., Meillat, M., Tumahai, P., Bidaut Garnier, M., Flores, M., Schwartz, C., Delbosc, B., 2014. Quantification of cone loss after surgery for retinal detachment involving the macula using adaptive optics. Br. J. Ophthalmol. 98, 1343–1348.

Sanabria Ruiz-Colmenares, M.R., Pastor Jimeno, J.C., Garrote Adrados, J.A., Telleria Orriols, J.J., Yugueros Fernandez, M.I., 2006. Cytokine gene polymorphisms in retinal detachment patients with and without proliferative vitreoretinopathy: a preliminary study. Acta Ophthalmol. Scand. 84, 309–313.

SanGiovanni, J.P., Chew, E.Y., 2014. Clinical applications of age-related macular degeneration genetics. Cold Spring Harb. Perspect. Med. 4.

Sato, T., Emi, K., Bando, H., Ikeda, T., 2014. Retrospective comparison of 25-gauge vitrectomy for repair of proliferative vitreoretinopathy with or without anterior proliferation. Graefes Arch. Clin. Exp. Ophthalmol. 252, 1895–1902.

Scheer, S., Morel, C., Touzeau, O., Sahel, J.A., Laroche, L., 2004. Pharmacological adjuvants for surgical treatment of proliferative vitreoretinopathy. J. francais d'ophtalmologie 27, 1051–1059.

Schiff, W.M., Hwang, J.C., Ober, M.D., Olson, J.L., Dhrami-Gavazi, E., Barile, G.R., Chang, S., Mandava, N., 2007. Safety and efficacy assessment of chimeric ribozyme to proliferating cell nuclear antigen to prevent recurrence of proliferative vitreoretinopathy. Arch. Ophthalmol. 125, 1161–1167.

Schmidt, O.I., Heyde, C.E., Ertel, W., Stahel, P.F., 2005. Closed head injury–an inflammatory disease? Brain Res. Brain Res. Rev. 48, 388–399.

Schramm, E.C., Clark, S.J., Triebwasser, M.P., Raychaudhuri, S., Seddon, J.M., Atkinson, J.P., 2014. Genetic variants in the complement system predisposing to age-related macular degeneration: a review. Mol. Immunol. 61, 118–125.

Schwartz, S.G., Flynn Jr., H.W., Lee, W.H., Wang, X., 2014. Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy. Cochrane Database Syst. Rev. 2. CD006126.

Scott, J.D., 1975. The treatment of massive vitreous retraction by the separation of pre-retinal membranes using liquid silicone. Mod. Probl. Ophthalmol. 15, 185–190.

Sethi, C.S., Lewis, G.P., Fisher, S.K., Leitner, W.P., Mann, D.L., Luthert, P.J., Charteris, D.G., 2005. Glial remodeling and neural plasticity in human retinal detachment with proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 46, 329–342.

Shalchi, Z., Mahroo, O.A., Shunmugam, M., Mohamed, M., Sullivan, P.M., Williamson, T.H., 2015. Spectral domain optical coherence tomography findings in long-term silicone oil-related visual loss. Retina 35, 555–563.

Singh, A.K., Michels, R.G., Glaser, B.M., 1986. Scleral indentation following cryotherapy and repeat cryotherapy enhance release of viable retinal pigment epithelial cells. Retina 6, 176–178.

Smith-Thomas, L.C., Richardson, P.S., Rennie, I.G., Palmer, I., Boulton, M., Sheridan, C., MacNeil, S., 2000. Influence of pigment content, intracellular calcium and cyclic AMP on the ability of human retinal pigment epithelial cells to contract collagen gels. Curr. Eye Res. 21, 518–529.

Spitzer, M.S., Kaczmarek, R.T., Yoeruek, E., Petermeier, K., Wong, D., Heimann, H., Jaissle, G.B., Bartz-Schmidt, K.U., Szurman, P., 2009. The distribution, release kinetics, and biocompatibility of triamcinolone injected and dispersed in silicone oil. Invest. Ophthalmol. Vis. Sci. 50, 2337–2343.

Storey, P., Alshareef, R., Khuthaila, M., London, N., Leiby, B., DeCroos, C., Kaiser, R.,

Please cite this article in press as: Pastor, J.C., et al., Proliferative vitreoretinopathy: A new concept of disease pathogenesis and practical consequences, Progress in Retinal and Eye Research (2015), http://dx.doi.org/10.1016/j.preteyeres.2015.07.005

2014. Pars plana vitrectomy and scleral buckle versus pars plana vitrectomy alone for patients with rhegmatogenous retinal detachment at high risk for proliferative vitreoretinopathy. Retina 34, 1945–1951.
Sundaram, V., Barsam, A., Virgili, G., 2013. Intravitreal low molecular weight heparin and 5-Fluorouracil for the prevention of proliferative vitreoretinopathy following retinal reattachment surgery. Cochrane Database Syst. Rev. 1. CD006421.
Symeonidis, C., Papakonstantinou, E., Androudi, S., Tsaousis, K.T., Tsinopoulos, I., Brazitikos, P., Karakiulakis, G., Diza, E., Dimitrakos, S.A., 2012. Interleukin-6 and matrix metalloproteinase expression in the subretinal fluid during proliferative vitreoretinopathy: correlation with extent, duration of RRD and PVR grade. Cytokine 59, 184–190.
Szurman, P., Frank, C., Kaczmarek, R.T., Spitzer, M.S., 2009. Vitreous substitutes as drug release systems. Klin. Monatsblatter fur Augenheilkd. 226, 718–724.
Tahara, Y.R., Sakamoto, T.R., Oshima, Y.R., Ishibashi, T.R., Inomata, H.R., Murata, T.R., Hinton, D.R., Ryan, S.J., 1999. The antidepressant hypericin inhibits progression of experimental proliferative vitreoretinopathy. Curr. Eye Res. 19, 323–329.
Tano, Y., Chandler, D., Machemer, R., 1980a. Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide. Am. J. Ophthalmol. 90, 810–816.
Tano, Y., Chandler, D.B., McCuen, B.W., Machemer, R., 1981. Glucocorticosteroid inhibition of intraocular proliferation after injury. Am. J. Ophthalmol. 91, 184–189.
Tano, Y., Sugita, G., Abrams, G., Machemer, R., 1980b. Inhibition of intraocular proliferations with intravitreal corticosteroids. Am. J. Ophthalmol. 89, 131–136.
Tansey, M.G., Goldberg, M.S., 2010. Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. Neurobiol. Dis. 37, 510–518.
Telander, D.G., Morales, S.A., Mareninov, S., Forward, K., Gordon, L.K., 2011. Epithelial membrane protein-2 (EMP2) and experimental proliferative vitreoretinopathy (PVR). Curr. Eye Res. 36, 546–552.
Terrin, N., Schmid, C.H., Griffith, J.L., D'Agostino, R.B., Selker, H.P., 2003. External validity of predictive models: a comparison of logistic regression, classification trees, and neural networks. J. Clin. Epidemiol. 56, 721–729.
Tolentino, F.I., Schepens, C.L., Freeman, H.M., 1967. Massive preretinal retraction. A biomicroscopic study. Arch. Ophthalmol. 78, 16–22.
Tosi, G.M., Marigliani, D., Romeo, N., Toti, P., 2014. Disease pathways in proliferative vitreoretinopathy: an ongoing challenge. J. Cell. Physiol. 229, 1577–1583.
Trese, M.T., Chandler, D.B., Machemer, R., 1985. Subretinal strands: ultrastructural features. Graefes Arch. Clin. Exp. Ophthalmol. 223, 35–40.
Trichonas, G., Murakami, Y., Thanos, A., Morizane, Y., Kayama, M., Debouck, C.M., Hisatomi, T., Miller, J.W., Vavvas, D.G., 2010. Receptor interacting protein kinases mediate retinal detachment-induced photoreceptor necrosis and compensate for inhibition of apoptosis. Proc. Natl. Acad. Sci. U. S. A. 107, 21695–21700.
Trivino, A., Ramirez, J.M., Ramirez, A.I., Salazar, J.J., Garcia-Sanchez, J., 1997. Comparative study of astrocytes in human and rabbit retinae. Vis. Res. 37, 1707–1711.
Tseng, J.J., Schiff, W.M., Barile, G.R., Biscette, O., Williams, S.L., Cekic, O., Dhrami-Gavazi, E., Chang, S., 2009. Influence of postoperative lens status on intraocular pressure in proliferative vitreoretinopathy. Am. J. Ophthalmol. 147, 875-885, 885 e871–872.
Tung, I.C., Wu, W.C., Kao, Y.H., Chang, Y.C., Chung, C.H., Hu, D.N., 2001. The effect of combined 5-fluorouracil and dexamethasone on cultured human retinal pigment epithelial cells. Kaohsiung J. Med. Sci. 17, 524–529.
Tura, A., Schuettauf, F., Monnier, P.P., Bartz-Schmidt, K.U., Henke-Fahle, S., 2009. Efficacy of rho-kinase inhibition in promoting cell survival and reducing reactive gliosis in the rodent retina. Invest. Ophthalmol. Vis. Sci. 50, 452–461.
Turgut, B., Uyar, F., Ustundag, B., Celiker, U., Akpolat, N., Demir, T., 2012. The impact of tacrolimus on growth factors in experimental proliferative vitreoretinopathy. Retina 32, 232–241.
van Bockxmeer, F.M., Martin, C.E., Thompson, D.E., Constable, I.J., 1985. Taxol for the treatment of proliferative vitreoretinopathy. Invest. Ophthalmol. Vis. Sci. 26, 1140–1147.
van de Put, M.A., Hoeksema, L., Wanders, W., Nolte, I.M., Hooymans, J.M., Los, L.I., 2014. Postoperative vision-related quality of life in macula-off rhegmatogenous retinal detachment patients and its relation to visual function. PLoS One 9, e114489.
Vandenabeele, P., Declercq, W., Van Herreweghe, F., Vanden Berghe, T., 2010. The role of the kinases RIP1 and RIP3 in TNF-induced necrosis. Sci. Signal. 3, re4.
Verstraeten, T., Hartzer, M., Wilcox, D.K., Cheng, M., 1992. Effects of vitamin A on retinal pigment epithelial cells in vitro. Invest. Ophthalmol. Vis. Sci. 33, 2830–2838.
Weller, M., Wiedemann, P., Heimann, K., 1990. Proliferative vitreoretinopathy—is it anything more than wound healing at the wrong place? Int. Ophthalmol. 14, 105–117.
Wickham, L., Bunce, C., Wong, D., Charteris, D.G., 2011. Retinal detachment repair by vitrectomy: simplified formulae to estimate the risk of failure. Br. J. Ophthalmol. 95, 1239–1244.
Wickham, L., Bunce, C., Wong, D., McGurn, D., Charteris, D.G., 2007. Randomized controlled trial of combined 5-Fluorouracil and low-molecular-weight heparin in the management of unselected rhegmatogenous retinal detachments undergoing primary vitrectomy. Ophthalmology 114, 698–704.
Wickham, L., Charteris, D.G., 2009. Glial cell changes of the human retina in proliferative vitreoretinopathy. Dev. Ophthalmol. 44, 37–45.
Wiedemann, P., Hilgers, R.D., Bauer, P., Heimann, K., 1998. Adjunctive daunorubicin in the treatment of proliferative vitreoretinopathy: results of a multicenter clinical trial. Daunomycin study Group. Am. J. Ophthalmol. 126, 550–559.
Wiedemann, P., Lemmen, K., Schmiedl, R., Heimann, K., 1987. Intraocular daunorubicin for the treatment and prophylaxis of traumatic proliferative vitreoretinopathy. Am. J. Ophthalmol. 104, 10–14.
Williams, R.G., Chang, S., Comaratta, M.R., Simoni, G., 1996. Does the presence of heparin and dexamethasone in the vitrectomy infusate reduce reproliferation in proliferative vitreoretinopathy? Graefes Arch. Clin. Exp. Ophthalmol. 234, 496–503.
Williams, R.L., Kearns, V.R., Lo, A.C., Day, M., Garvey, M.J., Krishna, Y., Ma, D., Stappler, T., Wong, D., 2013. Novel heavy tamponade for vitreoretinal surgery. Invest. Ophthalmol. Vis. Sci. 54, 7284–7292.
Williamson, T.H., Gupta, B., 2010. Planned delayed relaxing retinotomy for proliferative vitreoretinopathy. Ophthalmic Surg. Lasers Imaging 41, 31–34.
Wong, C.A., Potter, M.J., Cui, J.Z., Chang, T.S., Ma, P., Maberley, A.L., Ross, W.H., White, V.A., Samad, A., Jia, W., Hornan, D., Matsubara, J.A., 2002. Induction of proliferative vitreoretinopathy by a unique line of human retinal pigment epithelial cells. Can. J. Ophthalmol. J. Can. d'ophtalmologie 37, 211–220.
Woo, T.T., Li, S.Y., Lai, W.W., Wong, D., Lo, A.C., 2013. Neuroprotective effects of lutein in a rat model of retinal detachment. Graefes Arch. Clin. Exp. Ophthalmol. 251, 41–51.
Yang, C.S., Khawly, J.A., Hainsworth, D.P., Chen, S.N., Ashton, P., Guo, H., Jaffe, G.J., 1998. An intravitreal sustained-release triamcinolone and 5-fluorouracil codrug in the treatment of experimental proliferative vitreoretinopathy. Arch. Ophthalmol. 116, 69–77.
Yang, H., Li, S., Xiao, X., Guo, X., Zhang, Q., 2012. Screening for NDP mutations in 44 unrelated patients with familial exudative vitreoretinopathy or norrie disease. Curr. Eye Res. 37, 726–729.
Yoon, H.S., Moon, S.C., Kim, N.D., Park, B.S., Jeong, M.H., Yoo, Y.H., 2000. Genistein induces apoptosis of RPE-J cells by opening mitochondrial PTP. Biochem. Biophys. Res. Commun. 276, 151–156.
Yoshida, A., Ho, P.C., Schepens, C.L., McMeel, J.W., Duncan, J.E., 1984. Severe proliferative vitreoretinopathy and retinal detachment. II. Surgical results with scleral buckling. Ophthalmology 91, 1538–1543.
Yoshino, Y., Ideta, H., Nagasaki, H., Uemura, A., 1989. Comparative study of clinical factors predisposing patients to proliferative vitreoretinopathy. Retina 9, 97–100.
Zacks, D.N., Han, Y., Zeng, Y., Swaroop, A., 2006. Activation of signaling pathways and stress-response genes in an experimental model of retinal detachment. Invest. Ophthalmol. Vis. Sci. 47, 1691–1695.
Zhang, L.N., Hao, L., Wang, H.Y., Su, H.N., Sun, Y.J., Yang, X.Y., Che, B., Xue, J., Gao, Z.B., 2015. Neuroprotective effect of resveratrol against glutamate-induced excitotoxicity. Adv. Clin. Exp. Med. Off. Organ Wroclaw Med. Univ. 24, 161–165.
Zhang, W., Tan, J., Liu, Y., Li, W., Gao, Q., Lehmann, P.V., 2012. Assessment of the innate and adaptive immune system in proliferative vitreoretinopathy. Eye (Lond.) 26, 872–881.
Zheng, Y., Ikuno, Y., Ohj, M., Kusaka, S., Jiang, R., Cekic, O., Sawa, M., Tano, Y., 2003. Platelet-derived growth factor receptor kinase inhibitor AG1295 and inhibition of experimental proliferative vitreoretinopathy. Jpn. J. Ophthalmol. 47, 158–165.
Zhou, T., Lewis, H., Foster, R.E., Schwendeman, S.P., 1998. Development of a multiple-drug delivery implant for intraocular management of proliferative vitreoretinopathy. J. Control. Release 55, 281–295.

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