Molecular Biologic Milieu in Rhegmatogenous Retinal Detachment and Proliferative Vitreoretinopathy: A Literature Review

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Keywords
Rhegmatogenous retinal detachment · Proliferative vitreoretinopathy · Cytokines · Chemokines · Signaling molecules

Abstract
Multiple lines of evidence support an immunologic response along with inflammation to be implicated in the pathophysiology of primary rhegmatogenous retinal detachment (RRD) and the development of proliferative vitreoretinopathy (PVR). The purpose of this review is to provide an update on the signaling molecules in the vitreous and subretinal fluid (SRF) involved in these processes. A detailed literature search was performed in PubMed database until November 2021. We identified all papers referring to inflammatory and immunological mediators in the context of primary RRD and in cases complicated by PVR. We analyzed prospective and retrospective cohort studies and reference lists of the retrieved articles. A comprehensive investigation of immunological and inflammatory responses provides significant evidence for the implication of varying signaling molecules in the pathophysiology of RRD and the development of PVR. The reviewed series has revealed that disruption of the normal equilibrium during these processes may be present in the vitreous and SRF of these eyes. The precise role of cytokines, chemokines, and growth factors in the pathophysiology of these disorders remains to be clearly elucidated. Overall, immunological and inflammatory signaling molecules are widely implicated in both primary RRD and PVR. The reviewed literature indicates that precise knowledge concerning the pathological milieu sheds light on the underlying pathophysiology and potential therapeutic targets and highlights unmet needs to be addressed by future research.

Introduction
Retinal detachment (RD) is a severe vision-threatening condition with a variety of etiologies which occurs in approximately 12.4 in 100,000 people per year [1, 2]. Rhegmatogenous retinal detachment (RRD) is the most common type and constitutes an important cause of permanent visual impairment if left untreated. It is caused by
a retinal tear or hole through which vitreous fluid outflow into the subretinal space leads to separation of the neurosensory retina from the underlying retinal pigment epithelium (RPE). This condition exposes retinal cells, photoreceptors (PRs), and RPE to liquefied vitreous which forms a diffusional barrier to the influx of oxygen and nutrients from choroidal vasculature, occasionally leading to deficient functional recovery [3, 4].

Immunological and inflammatory signaling molecules consist a pathological biological milieu in various vitreoretinal disorders. In the process of RRD, there is an activation of both immune and inflammatory systems [5–9]. Immunoregulation may be stimulated by T lymphocyte helpers, both type 1 (TH1) and 2 (TH2) [9]. The analysis of experimental and human retinal tissue has notably indicated that expression of inflammatory genes dominated the response following RRD; increased cytokine expression, gliosis; and subretinal infiltration of monocytes and macrophages have been identified [5–12]. Indeed, a number of studies have demonstrated elevated levels of cytokines, chemokines, and growth factors in the vitreous cavity and the subretinal space of these eyes [5–23].

Abundant evidence is available showing that the innate immune responses and the presence of inflammatory mediators in ocular tissue may underlie the pathologic changes that ultimately lead to development of proliferative vitreoretinopathy (PVR) [24–46]. PVR is the most common cause for RRD recurrence and postoperative visual impairment. Despite multiple advances in the management of RRD, roughly 10% of eyes are ultimately complicated with a scarring intraocular process [28]. The biological processes involved in PVR show many similarities with the normal wound-healing response, in which inflammation plays a pivotal role. The main findings include changes in extracellular matrix (ECM) and formation of contractile tractional fibrocellular membranes on the epi-, intra-, and subretinal space of the detached or attached retina [25, 26], while mediating signaling molecules are present in the vitreous and subretinal fluid (SRF) [24, 25].

A literature search revealed several studies [5–45, 47–51] which focus on immunologic and inflammatory signaling molecules that are involved in the pathophysiology of RRD and PVR. This review article presents selected pertinent evidence on what is currently known about the most common mediators in the processes of RRD and PVR, discusses salient aspects of the related pathophysiology, and points to potentially fruitful directions for future research.

Methodology

This is a narrative review article for a comprehensive update on the signaling molecules involved in RRD and PVR. Articles published in PubMed without restriction on year of publication and until November 2021 were considered. Keywords with appropriate Boolean operators were used, using the terms “rhegmatogenous retinal detachment,” “proliferative vitreoretinopathy,” “cytokines,” “chemokines,” “growth factors,” and “signaling molecules.” In addition, the relevant reference list of all retrieved articles was carefully reviewed. The current article is based on previously published studies and does not include any studies performed by the authors.

Pathophysiology

Cytokines comprise a group of signaling molecules that mediate various interactions between cells for physiologic and pathologic processes. They are secreted by specific cells that are elaborated by leukocytes and various cell types within tissues and may exert a broad range of pro- or anti-inflammatory effects. In particular, they regulate a spectrum of diverse biological functions including immunity, inflammation, proliferation, migration, fibrosis, tissue repair, and angiogenesis. The categories of the variable cytokines are defined based on their presumed function, cell of secretion, or target of action. They are divided into two main subcategories; type 1 predominantly includes immunoregulatory, hemopoietic, and cytokines related to cytokinesis and type 2 includes molecules that suppress inflammation [52, 53].

Chemokines consist of a group of secreted proteins within the cytokine family. These “chemotactic cytokines” are multifunctional mediators that are produced during the inflammatory reaction in response to cytokines. They seem to play a pivotal role in inducing and regulating inflammation and various immune responses. In addition, they contribute to the wound-healing process, angiogenesis, and fibrosis. Based on their chemotactic activity and structure of cysteine residues, chemokines can be divided into two major subfamilies; the inflammatory (CC and CXC) and the immune (C and CXC3) chemokines [54, 55].

Several cytokines, chemokines, and growth factors are involved in the process of vitreoretinal disorders, including RRD [5–23]. The pathophysiologic basis of RRD and that of cases complicated by PVR has been studied biologically and genetically [6, 56–60]. A number of sig-
naling molecules regulate various pathways and mediate PR apoptosis and retinal proliferative changes. Although their definite source is yet not clear, inflammatory cells, monocytes, retinal glial cells, and RPE cells contribute a major site of production [5–23]. The biological milieu during RRD derives from plasma cytokines through the impaired blood-retina barrier, while the signaling molecules contribute to triggering and enhancing the inflammatory and immune responses [5–23].

In recent years, matrix metalloproteinases (MMPs) have been associated with RRD since they are involved in ECM degradation and homeostasis, remodeling, and wound-healing process [61, 62]. The activity of MMPs is tightly regulated through pro-MMP expression and via tissue inhibitors of metalloproteinases (TIMPs). Loss of balance between MMPs and TIMPs has a negative effect on ECM homeostasis. Several cytokines (IL-4, -6, -10, -13) and growth factors (transforming growth factor-beta [TGF-β], platelet-derived growth factor [PDGF], epidermal growth factor [EGF], fibroblast growth factor [FGF]) have been shown to regulate MMPs expression and activity. MMPs have been reported to be present in the eye and are closely associated with the pathophysiology of several disorders, including PVR [47–51, 61, 62].

In response to RRD, the outer layers of the detached retina become ischemic leading to neuronal cell death. Apoptosis occurs almost exclusively in the PRs layer; it initially begins on the first day after RD, while the frequency of apoptotic cells peaks at 3 days and decreases rapidly after 7–14 days [22]. The progression, severity, and resolution of ocular inflammation during these processes are dependent on various mediating cytokines [5]. Since the presence and concentration of the molecules are also implicated in the pathogenesis of PVR, they may comprise useful biomarkers for development and severity of the disorder [24, 25, 41].

### Analysis of Inflammatory Immune Mediators

**IL-6**

Interleukin 6 (IL-6) is a pleiotropic cytokine that may function in a pro- and anti-inflammatory way. It constitutes a multifunctional cytokine with regulatory activity and is implicated in the induction of several chemokines. It is established as a trigger of the acute phase of inflammatory reaction, and it is involved in immune responses (leading to the recruitment of immune cells, such as leukocytes), wound-healing process, and angiogenesis [13, 52, 53]. In the posterior segment of the eye, IL-6 can be produced by RPE cells or by inflammatory cells in the subretinal space due to chemotactic signaling, while it notably stimulates the proliferation of fibroblasts and glial cells [13].

Several studies have supported that the levels of IL-6 in RRD eyes were significantly higher than in controls. IL-6 expression and activity has been detected in the SRF and vitreous during RRD of patients either with or without PVR. Of note, IL-6 concentration in RRD eyes complicated with PVR has been found significantly greater compared to uncomplicated cases of primary RRD, though the potential involvement of IL-6 in PVR pathophysiology has not been fully elucidated. Interestingly, La Heij et al. [20] supported that IL-6 levels were significantly higher in RRD eyes complicated by PVR, especially if more than one quadrant was detached. Additionally, most cellular components of PVR membranes have been shown to produce IL-6.

Studies have demonstrated an association between IL-6 and several chemokines in RRD indicating that a common pathway may be involved in these procedures. In the study by Ricker and colleagues [14], a multiplex immunoassay was used to determine levels of different chemokines and IL-6 in SRF samples obtained during scleral buckling for primary RRD. The levels of several cytokines were significantly higher in patients with RD due to postoperative PVR than in patients with uncomplicated detachment, while IL-6, with a threefold increase in the PVR patients, was positively correlated with several chemokines. Indeed, increased chemotactic signaling and upregulation of IL-6 after the onset of RRD may be the underlying phenomenon leading to wide influx of inflammatory cells and may cause a response that is associated with the future development of PVR. Furthermore, Symeonidis et al. [29] investigated the relationship between CXCL-1 (chemokine contributing to acute inflammatory reaction) and IL-6 in the context of RRD complicated by PVR. In particular, the authors aimed to report potential disparities concerning the CXCL-1/IL-6 ratio between SRF and vitreous fluid. They mentioned that CXCL-1/IL-6 ratio was markedly elevated in both the SRF and vitreous of RRD eyes compared to controls (vitreous samples from human organ donors) [29]. In addition, Ricker et al. [14] found a significant correlation between IL-6 and both CCL22 and CXCL8. Overall, whether IL-6 plays a role in the induction of chemokines or is secreted by cells invading the subretinal space after RRD remains to be elucidated.

Concerning the correlation of IL-6 levels with clinical severity and staging of PVR, the results of the studies have...
stirred controversy. Indeed, Kaufmann et al. [31] reported that IL-6 levels in vitreous humor may correlate with clinical severity in PVR patients, while Kojima et al. [34] could not support this hypothesis. In addition, La Heij et al. [20] did not notice any significant differences in IL-6 concentrations concerning PVR staging, though only patients up to C1 PVR stage were included in this analysis.

Finally, increased levels of inflammatory cytokines such as IL-6 and IL-8 postvitrectomy may accelerate the development of cataract and glaucoma [14, 63]. Nonetheless, IL-6 may also be part of self-protection mechanism and comprise a potential neuroprotectant of PR, as has been shown in experimental model of RRD.

IL-8

Interleukin 8 (IL-8) is considered a proinflammatory chemokine with various chemotactic properties. It belongs to the class of CXC chemokines and in addition to IL-6, may have a critical role in ocular inflammation through the effects of proliferation, differentiation, and activation of cells. In vitro and in vivo studies support that IL-8 is the major chemoattractant for neutrophils and T-lymphocytes, while it enhances vascular permeability and angiogenesis in ocular inflammation. The effects of IL-8 in ocular tissue may differ based on the source of production. The release of this cytokine is triggered by special inflammatory signals from different cell types, while it is mainly secreted by RPE cells, macrophages, and endothelial cells [8, 54, 55, 64].

Mechanical stress to RPE in various vitreoretinal disorders induces RPE cells to express IL-8 and other molecules. Indeed, IL-8 and monocyte chemotactic protein 1 (MCP-1) may be involved in the early stages of RD [16]. These chemoattractant molecules play major roles in proinflammatory RPE-derived chemotactic activity, while their expression may be upregulated by interactions between monocytes and vascular endothelial cells [11]. Hypoxia and oxidative stress during RRD may lead to increased IL-6 and IL-8 mRNA expression [65]. Furthermore, elevated levels of IL-8 along with NF-kappa B protein may contribute to the formation of fibrocellular membranes, evidently playing a potential role in the pathogenesis of PVR [32]. Lastly, high IL-8 vitreous levels during vitrectomy significantly increase the risk of recurrent vitreous hemorrhage, as IL-8 is implicated in angiogenesis [66].

TNF-α

Tumor necrosis factor (TNF)-α is a cytokine that is mainly used by the immune system for cell signaling during the inflammatory response. Concerning ophthalmic tissues, the expression of TNF-α after RD has been found to be biphasic (peaking at 1 and 6 h) in the neurosensory retina of experimental models. Notably, the vitreous samples from RD eyes have been found to contain significantly higher levels of TNF-α than eyes with macular hole or idiopathic premacular fibrosis. However, TNF-α may not play a significant role in acute noncomplicated RD [12, 18].

Elevated levels of TNF-α in RD appear to play a neurodestructive role in PRs. Nakawaza and coworkers [12] investigated the role of the TNF-α pathway on PR apoptosis after RD in animal models deficient in TNF and TNF receptors (low-affinity TNFR1 and high-affinity TNFR2). The authors supported the hypothesis that TNF-α has a critical role in PR destruction following RD and indicated that treatment with intraperitoneal dexamethasone injection significantly suppressed RD-induced PR degeneration due to expression of TNF-α [12]. A recent experimental study demonstrated that TNF-α played significant role in the regulation of autophagy activity after RD and supported that control of autophagy to a proper level may provide new therapeutic approach to treat PR degeneration in retinal disorders [22].

An interesting point to be mentioned is that TNF-α is expressed in human retinas with proliferative disorders, and TNF-α mRNA vitreous levels are elevated under ischemic conditions in experimental models. TNF-α is considered to promote PVR as it has been identified in most epiretinal membranes of patients with PVR, with positive TNF-α staining both intracellularly and in the ECM. The identification of genetic polymorphism of the TNF locus implies that TNF-α may predispose to PRV development [12, 18, 22].

TGF-β

TGF-β describes a group of pleiotropic cytokine isoforms including TGF-β1, -β2, and -β3 [41]. In the eye, TGF-β is thought to be implicated in the maintenance of immune privilege through the inhibition of antigen-driven T cell activation and proliferation. TGF-β is known to stimulate the activity of PVR and is present in high concentrations in those eyes. It induces epithelial–mesenchymal transition as well as type I collagen and ECM production in RPE cells via a complex intracellular signaling cascade [41]. An interesting point to be mentioned is that hepatocyte growth factor seems to upregulate the expression of TGF-β and connective tissue growth factor, which in the presence of TGF-β may be major mediators of retinal fibrosis. Both hepatocyte growth factor and connective tissue growth factor may be increased in vitreous
from PVR eyes. Moreover, TGF-β is involved in contraction of epiretinal PVR-invoking macrophages and RPE-derived TGF-β2. TGF-β2 has been found to be directly proportional to the extent of fibrosis. The isoform TGF-β3 has been found significantly upregulated in the vitreous of RRD eyes compared with eyes with epiretinal membranes. Interestingly, a simultaneous increase of both TGF-β3 and IL-8 suggests that apoptotic processes as well as biological activities involved in ECM synthesis occur at the same time to a greater extent in cases where more retinal quadrants are involved [25, 37, 39, 67].

**VEGF**

Vascular endothelial growth factor (VEGF) is considered an endothelial cell mitogen and vasopermeability factor involved in cell proliferation, inflammation, and angiogenesis. Increased VEGF levels in the vitreous during inflammatory and oxidative conditions, along with the breakdown of the blood-retinal barrier and retinal hypoxia may contribute to increased levels of VEGF in primary uncomplicated RRD [18, 68, 69]. These events act as the initiating factors of the potential PVR cascade, therefore resulting in elevated concentration of VEGF in the vitreous, SRF, and epiretinal membranes in eyes with chronic RD and PVR [70]. An interesting aspect to be mentioned is that intravitreal levels of VEGF have been found to be lower in RRD eyes of patients under statin treatment due to their antioxidative, microvascular, and neuroprotective pleiotropic properties [19].

**bFGF**

Basic fibroblast growth factor (bFGF) may have neuroprotective effect on retinal tissue by preventing PR degeneration induced by RRD. Gene expression of bFGF has been demonstrated on cultured Muller cells. Notably, the neuroprotective properties of bFGF on PRs may be exerted utilizing two possible ways; either indirectly by activating Muller cells or by an increased expression in PRs during their degeneration. As shown in an experimental study, the induction of bFGF may be initiated at 24 h after RD suggesting a secondary, self-protective response of PR towards injury. On the other hand, bFGF seems to induce a reactive gliosis in the retina; however, the relation between retinal gliosis and PR degeneration remains unclear [7, 20, 37]. La Heij et al. [20] found increased levels of bFGF in SRF in patients with PVR. Of note, bFGF has been also found to be elevated in vitreous fluid of patients with RRD complicated by PVR [7, 37]. In this context, Cassidy et al. [7] detected elevated levels of bFGF in almost all RRD eyes with PVR but only in a lesser degree in eyes with RRD without PVR. A point to be mentioned is that the study by La Heij et al. [20] could not confirm the neuroprotective effect of bFGF on the PRs that was supported by former studies, as the authors did not find any significant relation between bFGF and visual outcomes or the duration of RRD. Other studies have confirmed more elevated levels of bFGF and an upregulation of bFGF mRNA in SRF than in vitreous samples. A potential explanation concerns the hypothesis that bFGF may be secreted by Muller cells and RPE cells to a higher degree into the subretinal space than into the vitreous. Besides, it has been demonstrated that human RPE cells have a polarized secretion of various mediators into the subretinal space [7, 20, 37].

**Chemokines**

Elevated levels of chemokines are present during RRD, while a complex mix of these molecules may play a role in the pathogenesis of PVR [8, 54, 55]. It still remains unclear which cells are responsible for the secretion of chemokines after RRD. Contact with vitreous or monocytes, stimulation by proinflammatory cytokines, and mechanical injury have been shown to be a trigger for the production and secretion of chemokines by RPE cells and various inflammatory cell types [8, 54, 55]. Two of the most extensively studied chemokines are CCL2 and CXCL8 [8, 36, 71]. Several investigations have shown an upregulation of these chemokines in PVR patients. In particular, Ricker et al. [46] showed that various chemokines were significantly higher in patients who developed postoperative PVR after primary RRD repair than in patients with uncomplicated RD. In addition, they showed a slight but significant increase in CCL2 levels briefly after the onset of RRD. Besides, Elnet et al. [36] demonstrated a six-fold increase in CCL2 levels in PVR vitreous compared with that in samples from patients with uncomplicated RD. These results imply that CCL2 has a more profound role in later stages after RRD and when PVR membranes have already developed.

CXCL8 may be secreted by different cell types in response to inflammatory stimuli. Microglial cells may contribute to increased intraocular levels of CXCL8 in RD and PVR, thus CXCL8 receptor expression in glial cells of PVR retinas and PVR membranes suggests a role for CXCL8 in the initiation of reactive gliosis [46].

Studies have also focused on CXCL-1 levels that have been found to be significantly elevated in cases of RRD [29, 30, 33], while maximum concentration coincided with total RD, long duration, and late stage of PVR [30]. RPE cells have been shown to produce CXCL-1 as a result.
of PVR-related mediators. This fact may indicate a role of this chemokine in the onset and progression of the wound-healing process in the context of RRD and PVR [30]. Overall, increased chemotactic signaling after the onset of RRD may be the underlying phenomenon leading to a vast and immediate influx of inflammatory cells and may cause an inflammatory response that is associated with the future development of PVR.

MCP-1 is a CC chemokine that exhibits chemotactic activity and consists an important mediator for the inflammatory process. Interleukin-1, TNF-a, and interferon-γ are potent inducers of MCP-1 in fibroblasts, endothelial, and epithelial cells. Likewise, RPE cells may produce elevated levels of MCP-1 under the influence of TNF-a and IL-1. MCP-1 has been detected in 48% of RRD eyes with a significant association of MCP-1 and the severity of proliferation [38]. MCP-1 is present in a substantial percentage of vitreous samples from eyes with proliferative vitreoretinal disorders and may play an important role in stimulating the infiltration of monocytes and macrophages into affected eyes. In addition, MCP-1 is capable of inducing IL-6 production by monocytes. It is a hypothesis that increased levels of MCP-1 may activate monocytes through colony-stimulating factors, such as M-CSF, to promote PVR [38]. Activated phagocytes and lymphocytes may release inducers of cytokines such as IL-1 and TNF-a that further enhance levels of IL-8, MCP-1, M-CSF, and other leukocyte chemoattractants, such as transforming growth factor-beta (TGF-β), thereby recruiting additional leukocytes, amplifying inflammation, and leading to fibroproliferation. An interesting point to be mentioned is that the increased expression and release of MCP-1 may be an important cause of PR degeneration associated with RD [38].

**MMPs**

MMPs expression is regulated by various cytokines. IL-6 mainly modulates the expression and in turn activity of MMPs and TIMPs, which have been both found to be implicated in the process of RRD [47–51]. MMP/TIMP-1 levels have been notably found to be elevated in SRF and vitreous during RRD. The family of MMPs consists of several proteolytic enzymes which are involved in ECM homeostasis and remodeling. The functions of different MMPs may be diverse and distinct during RRD. MMPs such as collagenases and stromelysin are mainly expressed at the onset of RRD and may be associated with wound initiation, matrix degradation, and edema. On the contrary, MMPs such as active gelatinases are expressed throughout RRD and may be associated with wound-healing process (including deposition of newly formed fibrous tissue in the inner and outer surface of the neural retina), angiogenesis, and proliferation. Especially elevated collagenase (MMP-1, MMP-8) activity has been associated with ECM degradation. Increased gelatinase A and B (MMP-2, MMP-9) activity has been reported in the vitreous and SRF during RRD. Collagens, in addition to gelatin and elastin, are the primary substrates of MMP-3 (stromelysin-1) and have been detected in a significant proportion of epiretinal membranes. Similarly, TIMP-1 has been detected in epiretinal PVR membranes, as well as in the vitreous and the SRF during RRD complicated by PVR. In the study by Symeonidis et al. [48], significant correlations between PVR grade and MMP-2 in SRF and proMMP-2, MMP-1, -2, -3, -8, -9, and TIMP-1 levels in vitreous were detected. Interestingly, this result highlighted the aspect that investigation of MMP activity in vitreous may provide more valid conclusions compared to SRF pertaining to the role of the MMPs during RRD. Of note, loss of balance between MMP and TIMP is considered to be an important aspect of the PVR pathophysiology. Overall, it appears that MMPs are differentially expressed during RRD and their exact role in the morphological manifestations associated with RRD and PVR remains to be clarified [47–51].

**Other Molecular Mediators**

The concentrations of the inflammatory mediators reflect the microenvironment in the eye following RRD. Analyzing these molecules may provide new insights relating to the biological mechanism of the disease. The three earliest responding cytokines within 1 h after experimental RD have been found to be TNF-a, IL-1β, and MCP-1 suggesting an immediate proinflammatory response. In particular, Nakawaza and colleagues [12] reported that TNF-a and IL-1β may increase the immediate inflammatory response following RD and influence the prolonged expression of MCP-1 and the subsequent retinal response including Müller cell hypertrophy, microglial cell activation, and monocyte recruitment. They were the first to mention that MCP-1 may have a toxic effect on PRRs [12]. Vitreous samples from RD eyes have been found to contain significantly higher levels of TNF-a, IL-1β, MCP-1, and bFGF as compared to eyes with macular hole or idiopathic premacular membranes. In addition, levels of IL-6, IL-16, IFN-γ, MCP-1, and MIF have been found significantly higher in RRD and PVR than in eyes with epiretinal membranes. IL-6, IL-8, and MCP-1 have also been found to be upregulated in the vitreous fluid in vitreoretinal disorders including RRD [38, 43], while...
strongly correlated with each other indicating a common pathway involved in inflammation process [5]. Interestingly, intravitreal injection of triamcinolone acetonide has been found to suppress elevated levels of intraocular MCP-1, MIP-1β, and IP-10 in eyes with RRD [43].

In an attempt to further examine the inflammatory responses to RRD in vitreous fluid, Kiang et al. [10] analyzed the concentrations of cytokines, growth factors, and soluble receptors in vitreous samples from patients with macula-off RRD. The authors used an experimental model to examine the effects of detachment on retinal cytokine mRNA expression, the attraction of leukocytes to the retina, and the response of retinal microglia to RRD. Based on their findings, RRD increased expression of several cytokines associated with microglial activation, as well as microglial proliferation and migration toward the distressed PR cells. The latter may suggest that an inflammatory response involving microglia is a component of the reaction to RRD [10].

A number of molecular mediators have been found to be increased in cases with PVR as compared to primary RRD; interleukins 4, 5, and 15; granulocyte-macrophage colony-stimulating factors; stem cell factor; stem cell growth factor; macrophage inflammatory protein 1α; and interferon γ-induced protein 10 [28]. Recently, vitreous levels of lipocalin-2 (LCN-2) have been found to play a potential role in the progression of PVR [72]. Banerjee et al. [73] demonstrated a complex pattern of vitreous cytokine concentrations in patients with PVR. Especially, IL-4 may stimulate enhanced chemokine secretion on RPE cells indicating that this molecule may play a pivotal role in the development of an inflammatory response in the cell population that ultimately elicits PVR. IL-5 has been reported to be associated with prolonged inflammation and aberrant wound healing in experimental models. IL-15 mRNA expression in RPE cells after interaction with proinflammatory molecules has been found to be upregulated. Furthermore, MCP-1, IL-8, and IP-10 have been found significantly upregulated in the vitreous of PVR eyes than in those without PVR [38]. Similarly, hepatocyte growth factor, TGF-β2, and platelet-derived growth factor (PDGF) are upregulated in the eyes of RRD patients complicated with PVR but not in those with primary RRD [25, 38, 39]. Finally, the presence of fibrocytes with stem cell-specific markers in PVR specimens suggests a possible role for stem cells and their attendant cytokines in the development of this disorder [38]. The signaling molecules which are commonly found in the vitreous and SRF of RRD and cases complicated by PVR are shown in Table 1.

### Concluding Perspectives

Cytokines, chemokines, and growth factors play an important role in mediating inflammation and immune response in various vitreoretinal disorders [5–23]. Robust evidence suggests elevated levels of signaling molecules in RRD eyes complicated by PVR as compared to primary detachment [24–45]. Although a link has been established between the biological milieu of the SRF/vitreous and proliferation, the involved mechanisms are complex and require a balance between promoting cell survival, apoptosis, and inflammatory responses. Despite the association of the biological signaling molecules with RRD, PVR, and PR degeneration, the mechanisms that induce their release along with their roles remain largely unexplored [5–45].

Several inflammatory and immune mediators orchestrate the biological response during RRD [5–23]. In the

### Table 1. Cytokines, chemokines, and growth factors which are commonly found in the vitreous and SRF of RRD and PVR

| Molecular mediators | References |
|---------------------|------------|
| IL-1β, IL-4, IL-5, IL-6, IL-8, IL-15, IL-16 | [5, 11–16, 18, 20, 21, 23, 25, 28, 29, 31, 32, 34–38, 40–42, 44–46, 50, 51, 63, 65, 66, 73] |
| TNF-α | [12, 18, 22, 25] |
| TGF-β | [25, 37–39, 41, 67] |
| VEGF | [18, 19, 40, 68–70] |
| bFGF | [7, 12, 20, 37, 44] |
| CC/CXC chemokines (CXCL8, CCL2, CXCL8) | [8, 10, 14, 17, 25, 29, 30, 33, 36, 46, 71] |
| MMPs | [19, 42, 47–51] |
| MCP-1 | [5, 12, 21, 36, 38, 40, 43, 45] |
| IFN-γ | [25, 41, 45] |
| IP-10 | [21, 28, 38, 43] |
| LCN-2 | [72] |

Ophthalmic Res 2022;65:637–646
DOI: 10.1159/000525530
process of PVR, uncontrolled inflammation may result in detrimental outcomes via the production of neurotoxic and fibrogenic factors that exacerbate the proliferative pathology. Notably, anti-inflammatory responses are regulated by proteins that inhibit signal transduction pathways to help control excessive inflammation [24–45]. The conditions that may disrupt the normal equilibrium should be further elucidated. Besides, the recruitment of inflammatory cells via signaling molecules to the sites of injury is instrumental in the process of the damage cascade.

Given the mounting evidence for their role in the process of RRD, these molecules may receive considerable attention as therapeutic targets [25]. Considering that inflammation mediated by cytokines and chemokines is a common denominator in the PVR process, targeting the mechanisms that contribute to disease pathogenesis will be a challenge to design appropriate therapies. We should thoroughly understand that these molecular mediators may lead to protective or deleterious (when extensively upregulated) inflammatory response.

This study summarizes the most common immunological and inflammatory biomarkers that have been identified in the vitreous and SRF of RRD eyes. Future studies should aim at the detailed investigation of chemokine-cytokine networks that are involved in the process of RRD complicated by PVR to better understand the related pathophysiology. More precise knowledge concerning the biological milieu in these patients may contribute to the development of novel therapeutic targets in the management of these disorders.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding or sponsorship was received for this study.

Author Contributions

Konstantinos Ananikas has contributed to conception, design, drafting, and final approval of the work and is accountable for the accuracy and integrity of any part of this version. Panagiotis Stavrakas has contributed to conception, drafting, revision, and final approval of the work and is accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version. Christos Kroupis, Dimitrios Brouzas, and Petros Petrou have contributed to conception, design, drafting, and final approval of the work and are accountable for the accuracy and integrity of any part of this version.

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