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REVIEW

THE PATHOGENY OF PROLIFERATIVE VITREORETINOPATHY

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Abstract
Proliferative vitreoretinopathy (PVR) is the most important complication of rhegmatogenous retinal detachment (RRD) and the main cause of RRD surgery failure. This is a review of recent literature data, which concerns PVR pathogeny and risk factors.
The occurrence of pre- and subretinal membranes is a consequence of retinal pigment epithelial cells activation and migration, with concomitant participation of inflammatory cells. The newly synthesized extracellular matrix interacts with cells promoting membrane contraction.
Photoreceptor apoptosis limits functional recovery – but there is ongoing research for neuroprotective mechanisms.
A lot of evidence has been accumulated about the role of growth factors (PDGF, VEGF, HGF, EGF, TGF α and β, G-CSF, FGF, IGF-1,CTGF), cytokines (interleukins IL-1, -6, -8, -10 and interferon γ), matrix metalloproteinases and chemokines, by measuring their concentrations in the vitreous or the subretinal fluid of PVR patients.
A list of risk factors (common or more controversial) may help the surgeon make the best approach for the management of individual cases.
Adjuvant therapies tested for PVR prevention (steroids, heparin, 5 fluorouracil, daunomycin, colchicine and 13-cis retinoic acid) did not enter current practice, but there are numerous research directions currently being developed.
Keywords: proliferative vitreoretinopathy, pathogeny

Proliferative vitreoretinopathy (PVR) is a complex reaction that represents a healing path for vitreoretinal pathology, with typical clinical aspect: fibrocellular pre- or subretinal membranes, opposing the retinal reattachment [**1**]. It may occur after rhegmatogenous retinal detachment (RRD), surgical interventions or trauma.

The incidence of PVR in RRD is estimated at 5-11% - but it is much higher in the case of giant retinal breaks (16-41%). After perforating trauma, the incidence is largely variable, between 10 and 45% [**2**].

PVR is a major cause for the failure of RRD surgery (with 50-75% of failures attributable) [**3**].

The next pages are trying to provide an update on the current knowledge concerning the etiopathogenesis, physiopathology, and current directions of research with therapeutic purposes in this important complication.

Pathology

The evolution of PVR is the result of a balance (or disruption of balance) between destructive and protective mechanisms that are triggered by the occurrence of a retinal break.

The clinical aspect of PVR is correspondent to the histopathological appearance, represented by fibrocellular (and, in evolution, contractile) membranes on the anterior or posterior retinal surface [**4**].

The primordial element seems to be partial de-differentiation, migration, and proliferation of retinal pigment epithelial (RPE) cells, creating areas of hyperplasia, first at the limit between detached and attached retina and at the margins of retinal breaks. This process may start in the third day of retinal detachment evolution. The next step is the activation of glial cells, with proliferation of astrocytes, Muller cells, microglia, and capillary endothelial cells [**2**].

De-differentiated RPE cells acquire fibroblast-like (predominant in contractile membranes) or macrophage-like morphology. Since the extracellular matrix of PVR membranes does not have a contractile ability, and de-differentiated cells do not possess actin or myosin, it is believed that contraction is a result of interaction between cells and extracellular matrix.

Neuronal processes found in membranes extracted during surgery were considered an evidence for glial proliferation inside retina. Fragments of internal limiting membrane are also frequently found in PVR membranes, explaining the difficulty of peeling certain membranes (and the capacity of PVR membranes to induce new breaks) [**4**]. An intraretinal invasion of fibrotic tissue is being discussed.

In contrast, membranes found after successful retinal reattachment contain a small number of immune cells and no glial cells.

The surgical technique (especially the use of silicon oil) seems to favor attraction of macrophages that will subsequently produce cytokines and growth factors, further influencing PVR development.

The proliferation and metamorphosis of the main cells involved (RPE and glial cells) is accompanied to a lesser extent by the presence of polymorphonuclear leucocytes, macrophages, lymphocytes and platelets. A progressive cellular invasion of vitreous (mirrored in the first clinical sign of PVR stage A, the presence of cells and pigment particles in the vitreous, "tobacco dust") starts from the level of the retinal break. Subsequently, the margins of retinal breaks will present a rolled appearance (PVR stage B). In stages C and D collagen synthesis is obvious by the presence of clearly demarcated membranes that promote tractions on the retina.

Apoptosis and neuroprotection

The loss of retinal viability by apoptosis of photoreceptors that have lost contact with subjacent pigment epithelium starts the next day after the occurrence of a RRD. In an animal model, 80% of photoreceptors are definitively lost in a retina that has been detached for 3 months [**5**]. Lactic acidosis (caused by hypoxia) seems to be an important trigger for both cellular migration and cellular death [**6**]. Surgical reattachment of retina can be followed by a (slow and incomplete) structural recovery that takes several months [**7**].

An association between certain cytokines and protection of neural cells from ischemia consequences has been suggested. In an experimental model (obtained by deprivation of glucose and oxygen), leptin and interleukin 1-beta seem to have a protective action for neurons [**8**]. Neuroprotective mechanisms based on Bax inhibitor-1, a protein situated in the membrane of the endoplasmic reticulum, have been identified in the brain. Consequently, promoting the expression or activation of BI-1 may offer hope for countering the neuronal ischemic injuries in the first fazes of a retinal detachment [**4**].

The role of growth factors, cytokines, and chemokines

Is highlighted by an ever-growing body of literature, the sampling of vitreous and subretinal fluid being relatively easy during modern vitreoretinal surgery. The measuring of different factors is also made easier by tests that use minute quantities of biological material.

Under these circumstances, the main growth factors being studied are the following: platelet derived growth factor (PDGF), vascular

endothelial growth factor (VEGF), hepatocytes growth factor (HGF), epidermal growth factor (EGF), transforming growth factor (TGF α and β), granulocyte colony stimulating factor (G-CSF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1) and connective tissue growth factor (CTGF).

PDGF and its receptor (PDGFR) seem to be synthesized by RPE cells and glial cells when separation between photoreceptors and RPE occurs. In turn, PDGF is a chemotactic and mitogen factor for glial cells [**9**]. After the retinal reattachment, the concentration of PDGF diminishes.

Variations of growth factor levels might be genetically individualized, since it has been shown that the polymorphism of the tumor necrosis factor (TNF) locus is associated with biological media being modified in a manner that is also present in PVR [**10**].

The infiltration of polymorphonuclear leucocytes starts in the first hours after a retinal detachment, and they release growth factors like FGF – which in turn continue to stimulate the influx of monocytes and their differentiation to macrophages. In the next (proliferative) phase, the macrophages stimulate the proliferation of fibroblasts [**4**].

TGF β is responsible for the increased production of extracellular matrix [**11**].

RPE, glial and inflammatory cells communicate through an array of cytokines, but the relationships are difficult to individualize and understand. The vitreous of PVR eyes contains increased levels of interleukins IL-1, -6, -8, -10 and interferon (IFN) γ. Most studies have used as controls, patients who were subject to pars plana vitrectomy for macular conditions like idiopathic epiretinal membranes or macula holes.

The intravitreal presence of messenger RNA for IL-1, -6, -8 and TNF α is an evidence of local production of these cytokines [**12**]. In vitro, the growth of RPE cells is promoted by IL-1, IFN γ and TNF α [**13**].

The role of IL-6 in the expression of matrix metalloproteinases (MMP) is well known. A significant correlation was demonstrated between IL-6 and an increased MMP/ TIMP ratio in the subretinal fluid from RRD patients. The tissue inhibitor of metalloproteinase (TIMP) is considered the physiological response to a significant increase of MMP activity. In the pathological circumstance of a retinal detachment, the degradation of extracellular matrix was associated with an increased activity of MMP-1 and -8, and with the presence of latent forms proMMP-2 and proMMP-9. MMP-3 (stromelysin 1) is present in most membranes found in PVR patients [**14**]. A degradation of extracellular matrix by collagenases activation is an important step in any proliferative reaction.

The chemokines are small proteins that regulate the migration of leucocytes to inflammation sites. A study that investigated the levels of 15 chemokines in subretinal fluid has shown increased values of MIF (macrophage migration inhibitory factor), CCL2, CCL11, CCL17, CCL18, CCL19, CCL22, CXCL8, CXCL9 and CXCL10. CC type chemokines attract monocytes, macrophages, T lymphocytes, eosinophils, and basophiles, while CXC chemokines recruit the neutrophils and activated T lymphocytes [**15**].

The subretinal fluid of RRD patients has a high procoagulant activity, due to the presence of tissular factor, the major factor that initiates normal haemostasis. The tissular factor may also induce an array of cellular responses, including inflammation and cellular migration. This has been illustrated by the up-regulation of IL-6 and IL-8 in macrophages after formation of tissular factor-VIIa factor complex [**16**].

A personal research in cases of RRD targets the gradients of vitreal concentrations of cytokines and growth factors – together with possible correlations with the clinical evolution- since the late presentation is a frequent occurrence in our patients.

Risk factors

Retinal detachments caused by atrophic holes or retinal dialyses do not develop PVR, thus confirming the role of vitreoretinal interface in the occurrence of this complication [**2**].

Several preoperative risk factors are known:

- duration of retinal detachment – especially in cases of RD that have been present for over one month, RPE cells migration and glial proliferation are to be expected.
- choroidal detachment.
- aphakia – more frequently associates multiple small size retinal breaks and a disruption of hemato-ocular barrier.

Pseudophakia is not considered a risk factor for PVR [**2**].

- vitreal haemorrage is a controversial risk factor – obvious for some authors [**17**], insignificant for others [**2**] – our personal experience leaning towards the first category.

- the type, shape and extension of retinal breaks: an extension of breaks over 90˚ (either a giant break, or as multiple breaks) would increase the risk for PVR. It has been postulated that the risk is in fact due to the tissue trauma represented by these breaks, that stimulate the release of cytokines in the periretinal space, followed by a break of hemato-ocular barrier, resulting in a new influx of cells, cytokines and growth factors.

- although vitreous levels of IL-1, -6, -8,- TNF α, VEGF and IFN γ are increased, there is no clear correlation to the severity of the disease [**4**].

- vitreous levels of MMP-2 and -9 and intercellular adhesion molecule (ICAM-1) [**2**].

- genetic profile (the gene of α lymphotoxin situated on the locus that also codes TNF).

- although literature is scarce on this subject, we should add on the list of risk factors the young age (children with RRD are extremely susceptible to PVR formation, but one can argue that the detachment was most probably caused by a trauma or by the presence of a congenital condition).

- the inflammation that pre-existed in patients with uveitis complicated with RD is also a strong promoter of PVR.

Intraoperative risk factors:

- incomplete vitrectomy.

- cryotherapy – responsible for freeing RPE cells in the vitreous cavity and aggravating the disruption of hemato-ocular barrier. Excessive photocoagulation may have the same effect [**4**].

- intraoperative complications: hyphema, subretinal hemorrhage, choroidal hematoma, choroidal detachment, posterior retinal breaks [**2**]. A legitimate question that remains unanswered is if drainage retinotomies placed outside temporal arcades may enhance the risk of posterior PVR – we support the idea of subretinal fluid drainage through the initial causative break whenever possible.

- an association between the type of tamponade and the subsequent development of PVR is also questionable. It is obvious that long acting tamponade (C3F8) or silicone oil is applied when preoperative PVR had existed or the surgeon has identified obvious risk factors for postoperative PVR. The use of air or SF6 (usual in recent, uncomplicated detachments) would influence the rate of PVR development only in cases with incomplete vitrectomy [**18**].

Most of the presented factors were discussed in the research published by the European Vitreoretinal Society, a retrospective analysis of 7678 surgical interventions. The presence of choroidal detachment, significant hypotony, preoperative presence of stage C1 PVR (more advanced PVR cases were not included), the presence of 4-quadrant retinal detachment and giant retinal breaks were identified as independent predictors for the failure of primary surgery. The predictive role of aphakia was not confirmed [**19**].

Prophylaxis

The first step in PVR prevention is to identify the patients at risk, using clinical (and perhaps biological) risk factors that were presented.

The main adjuvants tested for the purpose of PVR prevention are the following: corticosteroids, heparin, 5 fluorouracil, daunomycin, colchicine and 13-cis retinoic acid. It is enough to remember that the results of different studies, although sometimes have proven mild efficacy, did not prompt the use of these strategies by the vitreoretinal surgeons.

We can present a list of substances that might be validated in the future as adjuvants for PVR prevention: N-acetylcysteine, mitomycin C, prinomastat, anti PDGF agents (already intensively tested for neovascular AMD), silicone oil as vector for active substances (like retinoic acid or dexamethasone). Liposomes and microspheres might act as vectors for 5 fluorouracil or daunomycin [**20**]. For instance, an experimental study on a PVR model in rabbits has reported a reduction of PVR incidence from 89% to 11% by the use of an implant that delivered 1 mg of 5 fluorouracil [**21**].

Since we still lack a pharmaceutical approach with a proven efficacy, prompt surgical treatment of RRD with closure of all breaks and retinal reattachment is undoubtedly the most important action that we may take for preventing future PVR development [**20**].

Reviewing the literature in order to update our knowledge about proliferative vitreoretinopathy is a challenging enterprise

because new papers in this area emerge continuously. As a vitreoretinal surgeon, I am fascinated by the interest shown for this subject in the researchers' world, but much of the literature makes use of notions and methods that are beyond the comprehension of a clinician. This abundance of papers gives us hope that not far into the future our patients will benefit from an effective pharmaceutical adjuvant that will significantly improve the surgical outcomes in this important complication: proliferative vitreoretinopathy.

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