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Pathophysiology of Proliferative Vitreoretinopathy in Retinal Detachment

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Abstract. Because proliferative vitreoretinopathy cannot be effectively treated, its prevention is indispensable for the success of surgery for retinal detachment. The elaboration of preventive and therapeutic strategies depends upon the identification of patients who are genetically predisposed to develop the disease, as well as upon an understanding of the biological process involved and the role of local factors, such as the status of the uveovascular barrier. Detachment of the retina or vitreous activates glia to release cytokines and ATP, which not only protect the neuroretina but also promote inflammation, retinal ischemia, cell proliferation, and tissue remodeling. The vitreal microenvironment favors cellular de-differentiation and proliferation of cells with nonspecific nutritional requirements. This may render a pharmacological inhibition of their growth difficult without causing damage to the pharmacologically vulnerable neuroretina. Moreover, reattachment of the retina relies upon the local induction of a controlled wound-healing response involving macrophages and proliferating glia. Hence, the functional outcome of proliferative vitreoretinopathy will be determined by the equilibrium established between protective and destructive repair mechanisms, which will be influenced by the location and the degree of damage to the photoreceptor cells that is induced by periretinal gliosis. (**Surv Ophthalmol 58**:321–329, 2013.

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The success of retinal detachment (RD) surgery is dependent on the absence or control of proliferative vitreoretinopathy (PVR).[80,92] PVR is a nonspecific disorder that does not principally differ from other proliferative intraocular disorders, such as diabetic retinopathy, central retinal vein occlusion, or retinopathy of prematurity. For improvements in the surgical success rate, it is necessary to understand the risk factors for PVR in patients presenting with acute retinal detachments. These fall into three categories: preoperative eye- and patient-related risks, those related to surgical technique and management, and those related to the use of pharmacological adjuvants.[3] We review the current understanding of the pathophysiology of PVR and the underlying risk factors.

Causes

Attachment of the neuroretina to the retinal pigment epithelium (RPE) is far from strong, and the intervening space may be readily widened even under the influence of weak tractional forces or if the pumping function of the RPE is impaired. Once the

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retina has separated from the RPE and retinal detachment is evolving, increased distance to the choroidal blood supply and reduced oxygen flux from the choroid to the inner segments lead to a loss of photoreceptor outer segments and furthermore to a proliferation of Müller cells.[26,65] The deficiency of oxygen activates a cascade of processes leading to cell death.[71] Ultimately, the entire photoreceptor layer atrophies.[31,80,92,103] PVR is a complex process, involving not only ischemic tissue damage, but also inflammation and proliferation of several types of local cells and production of local factors.[3,43,51,64]

Cells and membranes may form on the inner and outer surface of the retina. Fibroblasts or fibroblast-like cells may be responsible for the contraction of epiretinal membranes.[26,40,65] Contraction of membranes is likely to be a cellular phenomenon.[37,71] The extracellular matrix (ECM) of the membranes does not have contractile properties. The fibroblast-like and de-differentiated cells do not have actin or myosin. Contraction thus may result from interaction of migrating cells and ECM. These membranes are similar to those formed traumatically or during the course of diabetic or ischemic retinopathy.[88]

PVR was first reported in 1934 by Gonin, who described the disease as a preretinal disorder, involving the formation of membranes that invade the inner retinal surface without modifying the retinal structure. Growing evidence, meanwhile, indicates a relevant role of genetic disposition for the development of PVR. Ongoing research focuses on the identification of candidate genes associated with a higher risk of PVR after retinal detachment,[84,85] and one of the most prominent candidate genes seems to be the tumor necrosis factor locus in the LTA gene.[84]

Pathological outcome of wound healing in PVR

The tissue trauma that is triggered by a separation of the neuroretina from the RPE sets the stage for the development of PVR.[99] If the process of cell proliferation and retinal wound healing could be pharmacologically controlled, then this would prevent PVR formation and optimize success of retinal detachment repair. Identification of high-risk cases could increase the success of such a pharmacological strategy. To this end, it will be necessary to fully understand the pathological processes that are implicated in retinal detachment and PVR.

HISTOPATHOLOGY

Histologically, PVR is evidenced by the presence of contracting cellular or fibrocellular membranes that interfere with retinal function by their progressive contraction (Fig. 1A and B).[56] Neuronal processes found in epi- and subretinal membranes have been linked to glial cell growth from the neuroretina (Fig. 1C).[61] This probably nonspecific tissue-repair response indicates a significant capacity for neuronal remodeling of the retina in response to different disease conditions.[60] Epiretinal membranes in association with PVR reveal a high amount of proliferating cells with a higher density of glial and immune cells (Fig. 1C and D) compared with membranes in proliferative diabetic retinopathy, whereas in membranes formed after successful repair of retinal detachment no glial cells and only a smaller number of

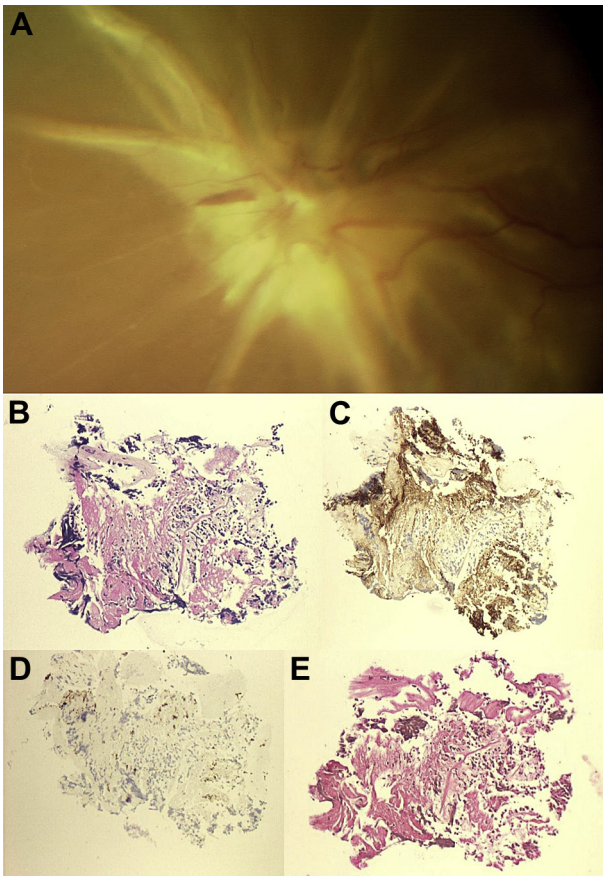

Fig. 1. *A:* Fundus photography of a contractile PVR starfold prior to its removal. The patient had reported floaters and flashes for almost one year and a complete vision loss of minimally three months prior to presentation. *B:* Light micrograph of a section through the excised tissue after staining with hematoxylin and eosin, revealing the presence of retinal pigmented epithelial (RPE) cells and fibroblasts within the predominantly avascular membrane. (Magnification ×150.) *C:* Staining for the glial fibrillary acidic protein reveals the PVR-membrane to harbor a profusion of glia. *D:* Tagging with a CD68-specific marker confirms the presence of macrophages and macrophage-like (e.g., transdifferentiated RPE) cells. *E:* Staining with elastica-van-Gieson discloses an abundance of collagenous (red) and elastic (purple) fibers.