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Is neutralizing vitreal growth factors a viable strategy to prevent proliferative vitreoretinopathy?

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ABSTRACT

Proliferative vitreoretinopathy (PVR) is a blinding disorder that occurs in eyes with rhegmatogenous retinal detachment and in eyes that have recently undergone retinal detachment surgery. There are presently no treatment strategies to reduce the risk of developing PVR in eyes with retinal detachment, and surgical intervention is the only option for eyes with retinal detachment and established PVR. Given the poor visual outcome associated with the surgical treatment of PVR, considerable work has been done to identify pharmacologic agents that could antagonize the PVR process. Intensive efforts to identify molecular determinants of PVR implicate vitreal growth factors. A surprise that emerged in the course of testing the 'growth factor hypothesis' of PVR was the existence of a functional relationship amongst growth factors that engage platelet-derived growth factor (PDGF) receptor α (PDGFRα), a receptor tyrosine kinase that is key to pathogenesis of experimental PVR. Vascular endothelial cell growth factor A (VEGF), which is best known for its ability to activate VEGF receptors (VEGFRs) and induce permeability and/or angiogenesis, enables activation of PDGFRα by a wide spectrum of vitreal growth factors outside of the PDGF family (non-PDGFs) in a way that triggers signaling events that potently enhance the viability of cells displaced into vitreous. Targeting these growth factors or signaling events effectively neutralizes the bioactivity of PVR vitreous and prevents PVR in a number of preclinical models. In this review, we discuss recent conceptual advances in understanding the role of growth factors in PVR, and consider the tangible treatment strategies for clinical application.

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1. Clinical proliferative vitreoretinopathy

1.1. Introduction

Proliferative vitreoretinopathy (PVR) is a clinical syndrome that occurs after rhegmatogenous retinal detachment (caused by a break in the retina e.g. retinal tear or retinal hole) and its surgical repair. The pathogenesis involves the release of cells into the vitreous cavity where they thrive and organize into membranes on the inner and/or outer surfaces of the retina, creating wrinkling of the retina and retinal traction (Committee, 1983). PVR can occur in untreated eyes with retinal detachment or after retinal procedures including retinal cryopexy, laser retinopexy, pneumatic retinopexy, scleral buckle and/or pars plana vitrectomy. The prevalence of PVR ranges widely among different published series, but in general, it is estimated that PVR develops in approximately 5–10% of all rhegmatogenous retinal detachment cases (Cardillo et al., 1997; Tseng et al., 2004). PVR and its associated retinal traction is the main reason for failure (recurrent retinal detachment) of initially successful repair of retinal detachment. With modern surgical techniques most PVR cases can be surgically repaired; however, these cases often have limited visual recovery due to retinal damage from recurrent detachment and from the PVR process itself. Thus, one of the key goals of retinal detachment repair is to prevent the development of postoperative PVR with appropriate identification of pre-operative risk factors, prompt recognition of the early signs of PVR, modification of surgical techniques, and the development of adjuvant therapy that reduces the viability of the cells that cause PVR.

1.2. Clinical presentation and diagnosis

Proliferative vitreoretinopathy can develop in eyes with retinal detachment if the detachment remains untreated for a period of weeks to months. PVR more typically occurs in eyes that have undergone retinal reattachment surgery, and its onset is usually 4–12 weeks after surgery. The first clinical sign of PVR is the proliferation of cells in the vitreous cavity. This is followed by the proliferation of cells on the retinal surface as the cells create fibrocellular membranes which are adherent to the retina (epiretinal membranes). These membranes may eventually contract, leading to wrinkles and folds of the retina. PVR progresses when the membranes exert increasing retinal traction, resulting in larger retinal folds and increased retinal rigidity. This can re-open previously closed retinal breaks and/or create new breaks, which leads to recurrent retinal detachment. PVR-related retinal detachment can occur anywhere in the retina. A posterior retinal detachment can ultimately advance to a closed-funnel configuration, while anterior PVR can progress to form a cyclitic membrane and hypotony.

The diagnosis of PVR is made clinically by direct visualization of the retina with slit lamp biomicroscopy or indirect ophthalmoscopy. Ancillary testing such as ultrasonography and fundus photography are often helpful in delineating the extent and location of the retinal detachment, tractional membranes, and retinal folds. B-scan ultrasonography is especially helpful in cases where the media is hazy and does not allow visualization of the location and extent of the retinal detachment and fibrocellular membranes.

1.3. Classification of proliferative vitreoretinopathy

Classification schemes for PVR have been developed to help predict prognosis and guide in the surgical approach. The most commonly used classification is the Updated Proliferative Vitreoretinopathy Grade Classification (Machemer et al., 1991), which describes PVR in terms of its location, extent, and severity.

Grade A is characterized by vitreous haze and/or pigment clumps in the vitreous cavity or on the inferior retina (Fig. 1A). Grade B is characterized by wrinkling of the inner surface of the retina, retinal stiffness, vessel tortuosity, and/or rolled edges of retinal breaks (Fig. 1B). Grade C is characterized by full-thickness retinal folds and/or subretinal bands that are further classified according to the location of the contraction in relationship to the equator of the eye: posterior, anterior, or both. Posterior Grade C PVR is further divided into *focal* contraction resulting in starfold formation (Type 1) and *diffuse* contraction resulting from confluent starfolds, the most extreme example being a closed-funnel configuration (Type 2) (Fig. 1C). Grade C PVR is also characterized by *subretinal bands* (Type 3) that can be either posterior or anterior