Original article

A rat model of proliferative vitreoretinopathy induced by RPE-J cells and platelet-rich plasma

Xiaozhi Zheng, Hongli Li, Lianfang Du, Qing Gu, Huiping Wang

Department of Medical Ultrasound, Experimental Research Laboratory of Ophthalmology, Experimental Research Center, Shanghai Jiaotong University Affiliated First People’s Hospital, Shanghai 200080, China

Background: Proliferative vitreoretinopathy (PVR) is a serious complication of retinal detachment surgery or ocular trauma. Growth factors are believed to play an important role in promoting the events that contribute to PVR. It is important to study the pathogenesis of PVR and possible therapies.

Objective: To determine whether heterogenic differentiated retinal pigmented epithelial (RPE) cells and/or syngeneic platelet-rich plasma (PRP) injected into the vitreous cavity of Wistar rats could create a model for PVR, and to quantitatively detect the expression levels of transforming growth factor-β2 (TGF-β2), platelet-derived growth factor-AA and BB (PDGF-AA, PDGF-BB) in this rat model.

Methods: RPE-J cells and autogeneic PRP were injected separately (or in combination) into the vitreous cavity of adult Wistar rats (4.5x10^5 RPE-J cells /eye and 3.7x10^9 platelets/eye). Seven, 14, 21, and 28 days after cell injections, PVR was quantified using surgical microscopy and histopathologic examination. Three, seven, 14, 21, and 28 days after cell injections, the expression levels of TGF-β2, PDGF-AA and PDGF-BB were tested using enzyme-linked immunosorbent assay (ELISA).

Results: The intravitreal injection of RPE-J cells alone could not initiate a proliferative process in the eyes. However, PRP alone or in combination with RPE-J cells, induced a PVR-like process characterized by inflammatory cell infiltration, extracellular collagen production, and formation of epiretinal membranes. The strongest proliferative process was induced by the co-injection of RPE-J cells and PRP into the eyes of Wistar rats. In this process, the expression levels of TGF-β2, PDGF-AA and PDGF-BB were significantly up-regulated.

Conclusion: Intravitreal co-injection of RPE-J cells and PRP in Wistar rat eyes could effectively induce a model of PVR. PRP clearly promoted the proliferative process of PVR. TGF-β2 and PDGF-BB took part in the pathogenesis of this model.

Keywords: Platelet-rich plasma, proliferative vitreoretinopathy, PDGF, RPE-J cells, TGF-β, Wistar rat model.

Proliferative vitreoretinopathy (PVR) is a serious complication of retinal detachment surgery or ocular trauma. It is characterized by migration and proliferation of cells, fibroblastic transdifferentiation, formation of fibrocellular membranes, extracellular collagen production, formation of fixed folds, and tractional detachment of the retina [1-3]. This process often causes loss of vision as detachment progresses. To study the pathogenesis of PVR and various therapies for this disease, nearly 30 in vivo models have been developed. Each model has individual features and uses.

The Wistar rat is one of the most studied albino outbred rat stocks, sharing a common origin with Long-Evans rats. Although there are some disadvantages as an animal model for PVR due to large lens size and a smaller vitreous volume, the availability of this genetically modified species of rats is a significant advantage. In addition, a reproducible rat model allows testing of genetic backgrounds in the pathogenesis of PVR by comparing multiple inbred strains. This may facilitate testing of candidate drugs to treat this disease [4]. Moreover, Wistar rats are readily available and of
relatively low costs. However, Wistar rat models of PVR are still seldom reported. The methods employed in modeling of PVR include cell injection, surgical interventions, and others. Surgical interventions are relatively complicated, and require specialized skills. Injecting cells is easily performed, and the cells injected can be quantified to ensure reproducibility of every experiment. PVR-like membranes and tractional retinal detachments have been induced by intravitreal injection of RPE cells, Müller cells, blood, fibroblasts, and blood monocytes [4]. Retinal pigmented epithelial (RPE)-J cells are derived from primary cultures of RPE cells taken from pigmented Long-Evans rats. They are readily available and differentiate rapidly in culture into stable, polarized monolayers [5]. They retain many differentiated features of RPE including the ability to synthesize melanosomes [6]. Platelet-rich plasma (PRP) has been shown to be rich in growth factors, which are able to enhance endothelial cell migration and proliferation [7, 8]. PRP is readily available using established techniques. It is extensively used to accelerate bone repair. Using PRP to induce a model of PVR has been previously reported [9, 10].

The action of growth factors is thought to make a substantial contribution to induction of PVR. There are various growth factors involved in PVR described in the literature, among which, transforming growth factor (TGF) and platelet-derived growth factor (PDGF) play an important role [11-13].

At present, there are not satisfactory treatments available for PVR. Due to its easy accessibility, allowance for local application of therapeutic vectors with a reduced risk of systemic effects, and monitoring non-invasively after treatment, ocular gene therapy represents an attractive approach in dealing with this disease. Zheng et al. [14] reported that ultrasound-targeted microbubble destruction (UTMD) could enhance recombinant adeno-associated virus-mediated transgene expression in the retina, which is becoming the progenitor of some potentially major clinical breakthroughs.

This study is an effort to develop an albino rat model of PVR for further therapeutic studies. It was aimed at an experimental proof for attenuation of experimental PVR by inhibiting the action of TGF and PDGF at the level of gene transcription under the condition of UTMD. This was done by injecting RPE-J cells and PRP into the vitreous of Wistar rat eyes, and by quantitatively analyzing the expression levels of TGF-β2, PDGF-BB and PDGF-AA. The authors hoped to answer the following questions as: 1) Do heterogeneic differentiated RPE cells or syngeneic PRP injected separately into the vitreous cavity initiate a proliferative process, or do they have to be injected in combination? Does PRP promote the proliferative process of PVR? 2) Do TGF-β2, PDGF-BB, and PDGF-AA take part in the pathogenesis of this model of PVR?

Materials and methods

RPE-J cells preparation

RPE-J cells (CRL-2240, ATCC, Rockville, USA) were defrosted from -80°C liquid nitrogen and suspended in Dulbecco’s modified Eagle’s medium (DMEM) (Gibco, Grand Island, USA). Cell viability was controlled by trypan-blue counting. After defrosting, an average of 23% of RPE-J cells was observed dead. Then, the surviving RPE-J cells were seeded at a density of 2x10^4 cells/cm^2 in six-well culture plates, and maintained in DMEM with 4.5g/L glucose, 2mM L-glutamine, and 0.1mM non-essential amino acids supplemented with 4% (v/v) fetal bovine serum (FBS) (Gibco, Grand Island, USA) at 33°C, 5% CO₂/95% air. For subsequent passages, cells from confluent cultures were detached by 0.25% trypsin digestion and seeded as described above. Just before intravitreal injection, RPE-J cells were collected from six-well culture plates, centrifuged at 1000 rpm for 10 minutes, and resuspended in sterile pyrogen-free normal saline (NS) or platelet poor plasma (PPP) at a concentration of 3x10⁷/mL.

Preparation of PRP

Wistar rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (350 mg/kg body weight). Blood was collected into ethylene diamine tetraacetic acid vacuum tubes from the tail vein. The samples were centrifuged at 180g for five minutes to separate PRP from erythrocytes and leukocytes. PRP was transferred to a clean tube and centrifuged at 600g for 15 minutes to separate platelets from PPP [8, 15]. The platelet number in PRP was counted by an automatic hemocytometer and adjusted to 250x10⁹/mL with PPP. The PRP was conserved at 20-24°C for about 10 minutes until intravitreal injection.

Animal preparation

After obtaining the approval of the Shanghai Jiaotong University ethics committee, 84 normal adult
Wistar rats (male or female, age=8-10 weeks, weight=180-200g, SLACCAS, Shanghai, China) were enrolled in this experiment. All animals were bred, maintained, and sacrificed humanely in strict compliance with the policies stated in the statement of Association for Research in Vision and Ophthalmology for the use of animals in ophthalmic and vision research.

**Intravitreal injection of RPE-J cells and PRP**

In the first experiment, 69 Wistar rats were divided into three groups (23 rats per group) for clinical observation and histopathologic examination, so as to investigate whether RPE-J cells and PRP could induce a rat model of PVR. Group 1, 2, and 3 respectively received an intravitreal injection of RPE-J cells, PRP, and RPE-J cells + PRP. In the second experiment, 15 Wistar rats received an intravitreal injection of RPE-J cells + PRP for quantitative analysis of the expression level of TGF-β2, PDGF-BB, and PDGF-AA in this rat model of PVR. The strongest proliferative process was induced by the co-injection of RPE-J cells and PRP in the eyes of Wistar rats. Before intravitreal injection, Wistar rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (350mg/kg body weight). Surgical procedures and post-surgery care were performed as described previously [16]. Briefly, eyes were gently protruded using a rubber circle and subsequently covered with 0.3% ofloxacin eye ointment (Xingqi, Shenyang, China) to simulate a preset lens. Then, a self-sealing wound tunnel was constructed using a 1.5-cm, 28-gauge needle one mm posterior to the corneal limbus. After the vitreous cavity collapsed because of the outflow of vitreous fluid, a blunt 32-gauge Hamilton syringe was introduced through the sclera into the vitreous cavity under a surgical microscope (SM-2000J, Eder, Shanghai, China). The right eye served as a control eye, and was injected with 15 μL NS.

**Clinical observation**

All injected eyes of Wistar rats were inspected by two blinded observers seven, 14, 21, and 28 days after intravitreal injection. Retinophotographs were taken using a surgical microscope (SM-2000J, Eder, Shanghai, China). The proliferative response was evaluated according to the grade scales as follows: 0: no proliferative response, 1: vitreous haze, vitreous strands, 2: retinal folds in a single or more quadrants, 3: epiretinal membrane formation in a single quadrant, 4: epiretinal membrane formation in two or more quadrants (see fundus picture A-F in Fig. 1).

In the strongest proliferative group, 35 days after intravitreal injection, four eyes were enucleated for dissection under a surgical microscope. The ocular globes were cut pre-equatorially and photographed to show the gross aspect of the retina in situ.

**Histopathologic examination**

Seven, 14, 21, and 28 days after intravitreal injection, the Wistar rats (three per time-point) were sacrificed with a fatal dose of 10% chloral hydrate. Their eyes were enucleated, and fixed in 10% formaldehyde solution at a room temperature. Thereafter, they were embedded in paraffin, and cut into 5 μm-thick sections. Subsequently, the sections were stained with hematoxylin-eosin to observe retinal architecture, inflammatory cell infiltration, and proliferative membrane using light microscopy (Zeiss Axiovert S 100, Jena, Germany). All the results by histopathologic examination were confirmed by two blinded experts with experience in ophthalmological pathology including PVR.

**Enzyme-linked immunosorbent assay (ELISA)**

Three, seven, 14, 21, and 28 days after intravitreal injection, the Wistar rats (three per time-point) were sacrificed with an overdose of 10% chloral hydrate. The retinas were extracted and grinded into homogenate after enucleation of the globe by removing the anterior segment with eye scissors. TGF-β2, PDGF-BB, and PDGF-AA were measured using a capture sandwich kit with biotinylated affinity purified mouse monoclonal antibodies to rat TGF-β2, PDGF-BB, and PDGF-AA (Senxiong, Shanghai, China). Briefly, a flat-bottom ELISA plate (Costar 96-well) was coated with mouse anti-rat TGF-β2, PDGF-BB, or PDGF-AA antibody, 100 μL of standard preparation (or sample) was added in the wells and incubated at 37° for two hours. After washing six times, 100 μL of biotinylated mouse anti-rat TGF-β2, PDGF-BB, or PDGF-AA was added and incubated at 37°C in the dark for one hour, washed, and 100 μL of horseradish peroxidase labeled streptavidin was added and incubated at 37°C for one hour. The wells were washed six times again, and incubated with 100 μL of
substrate solution for 5-10 minutes. Finally, 50 μL of stop buffer was added to each well. Absorbance at 492 nm was measured using a microplate reader (Molecular Devices, Sunnyvale, USA). The samples for the detection of TGF-β2 needed activation using HCl and NaOH just before the conventional procedure. Sensitivity by ELISA was 16 pg/mL with an intra-assay variability of 10%.

**Statistical analysis**

All data were expressed as mean±SD. Analysis of variance (ANOVA) test was used to determine the significance of the difference in a multiple comparison. The differences were considered significant at p-values less than 0.05. The software packages used were SPSS (version 13, Chicago, USA).

**Results**

**Clinical examination**

Clinically, findings on fundus examination were normal. Figure 1 shows various levels of proliferation in retinophotography. No apparent inflammation and proliferative response was detected at any time in group 1 or in the control eyes of the other groups (A). In group 2 and group 3, a limited intravitreal proliferation, such as vitreous haze, vitreous strands within the vitreous or along the retinal surface, arising from the retina could be observed but there were no retinal folds seven days after intravitreal injection (B). An intravitreal proliferation with retinal folds could be observed 14 days after intravitreal injection in group 2 and group 3 (C). Twenty-one days after intravitreal injection, among eyes injected only with PRP, 11 out of 14 eyes had no proliferative response, and three out of 14 eyes had intravitreal membrane formation arising from the retina. On the contrary, in the eyes injected with PRP+RPE-J cells, the level of membrane formation was significantly enhanced, i.e., six out of 14 eyes had no proliferative response, and eight of 14 eyes had a epiretinal membrane formation arising from the retina with or without localized retinal detachments (p <0.01, ANOVA) (D). At the grade-4 PVR, an irregular, white, dense tissue (some showing crumbly villous texture) extended into the vitreous and onto the retinal surface, apparently altering the visibility of the retina and the retinal vessels which appeared dilated at the periphery of the retina (E). This aspect was confirmed by direct examination of the retina at 35 days after the injection of PRP+RPE-J cells during the dissection. Multiple folds and localized detachments were observed, in comparison with the retina of rats in the control group (F).

**Figure 2** shows clinical examinations at 14 and 28 days after intravitreal injections. Fourteen days after intravitreal injection, a grade-2 PVR was observed in one out of 14 eyes in group 2, and five out of 14 eyes in group 3. Twenty-eight days after intravitreal injection, a grade-2, -3, and -4 PVR was observed in one out of 14 eyes when PRP were injected alone. However, a grade-3 PVR was observed in three out of 14 eyes and a grade-4 PVR was observed in five out of 14 eyes when PRP+RPE-J cells were injected.

**Histological observation**

Figure 3 shows histologic analysis of eyes seven, 14, 21, and 28 days after RPE-J cells or/and PRP injections. At any time after intravitreal injection in group 1 and the control group, all layers of retina were well preserved without inflammatory cell infiltration, retinal folds, retinal detachments, and proliferative membrane formation (A). Numerous cell phenotypes experienced a series of time-dependent changes in group 2 and 3. Seven days after intravitreal injection (B), there were numerous neutrophilic leukocytes, a small amount of fibroblasts distributed at the retinal surface in an extracellular matrix that could be fibrin and collagen fibrils. Meanwhile, some fibroblasts at the retinal surface had established connections with the inner retina. Fourteen days after (C), neutrophilic leukocytes conspicuously decreased, monocytes and leukomonocytes significantly increased, fibroblasts proliferated, and generated collagen. In the eyes that received the co-injection of PRP+RPE-J cells, the progressive intravitreal and epiretinal proliferation often led to localized folds and localized retinal detachments in most of the cases. Twenty-one days after (D), monocytes and fibroblasts proliferated, collagen significantly increased and transformed into proliferative membranes with or without localized retinal folds and detachments. Twenty-eight days after (E), an epiroetinal membrane covered the retina with extensive retinal folds or detachments, with or without localized posterior capsular cataract. This was observed in eight out of 14 eyes that received the co-injection of PRP+RPE-J cells and two out of 14 eyes that received the injection of PRP alone. Numerous fibroblasts were still seen in the proliferative membrane at the retinal surface or in the vitreous cavity. In group 3, normal architecture of the retina was completely disrupted in two out of 14 eyes (F).
**Fig. 1** Retinophotographies showing the level of proliferation. A: no proliferative response, B: vitreous haze, vitreous strands, C: retinal folds in a single or more quadrants, D: epiretinal membrane formation in a single quadrant, E: epiretinal membrane formation in two or more quadrants, F: Pictures of the epiretinal membrane in situ of grade-4 PVR during dissection of ocular globes. (A, B, C, D, E and F: 25x magnification).

**Fig. 2** Results of clinical examinations against grade scale of proliferation (A) 14 and (B) 28 days after intravitreal injections.
Fig. 3 Histologic images of eyes seven, 14, 21 and 28 days after RPE-J cells or/and PRP injections. (A) The retina shows a normal architecture of the retina without inflammatory cell infiltration, retinal folds, retinal detachments and proliferative membrane formation in the eyes that received the injection of RPE-J cells alone at any time after intravitreal injection. This specimen was prepared seven days after intravitreal injection. (B) The retina shows numerous neutrophilic leukocytes, a small amount of fibroblasts distributing at the retinal surface and some fibroblasts at the retinal surface had established connections with the inner retina (indicated by arrows) in the eyes that received the injection of PRP and PRP+RPE-J cells 7 days after intravitreal injection. (C) The retina shows neutrophilic leukocytes conspicuously decreased, fibroblasts proliferated and generated collagen (indicated by arrows) in the eyes that received the coinjection of PRP+RPE-J cells 14 days after intravitreal injection. (D) The retina shows collagen significantly increased and transformed into proliferative membrane (indicated by arrows) in the eyes that received the coinjection of PRP+RPE-J cells 21 days after intravitreal injection. (E) A villous epiretinal membrane covering the retina (indicated by arrows), (F) extensive retinal detachments or folds (indicated by arrows), and numerous fibroblasts (indicated by arrows) distributing in the detached proliferative membrane in vitreous cavity were seen in the eyes that received the coinjection of PRP+RPE-J cells 28 days after intravitreal injection. (A, B, C, D, E and F: 400x magnification).
**TGF-β2, PDGF-AA and PDGF-BB expression with RPE-J cells and PRP**

Table 1 shows growth factors expressed in the eyes of Wistar rats received the co-injection of RPE-J cells and PRP (Mean±SD). The levels of TGF-β2 expression were significantly higher (about 1.5-2.8 times) compared with the control levels measured three, seven, 14, and 21 days after intravitreal injection. The peak of the expression was achieved 21 days after intravitreal injection, decreasing down to the normal levels 28 days after. The levels of PDGF-BB were also significantly higher (about 1.2-1.4 times) than in the control group seven, 14, 21, and 28 days after intravitreal injection, showing a slight peak 21 days after. However, there was no significant difference in levels of PDGF-AA at each time-point after intravitreal injection. They were even lower than of the control group. In addition, it was found that the levels of TGF-β2 were far higher than of PDGF-AA and PDGF-BB, and the levels of PDGF-BB were significantly higher than of PDGF-AA. This indicates that TGF-β2 and PDGF-BB played a key role in the PVR-like proliferative process.

**Discussion**

The present observations show that intravitreal administration of PRP+RPE-J cells in Wistar rats successfully induced a PVR-like condition characterized by the sequential appearance of: 1) inflammatory cell infiltration, 2) extracellular collagen production, and 3) formation of epiretinal membranes with or without retinal folds or detachment. Quantitative detection of the expression level of TGF-β2, PDGF-AA, and PDGF-BB in this rat model of PVR indicates that TGF-β2 and PDGF-BB played an important role.

Previous studies tried several surgical interventions, such as lens extraction [17], retinal detachment with RPE scraping [18], and trauma [19]. None of them could successfully induce a Wistar rat model of PVR. Intravitreal injection of RPE can effectively induce a model of PVR in some animal species such as rabbits, but no Wistar rat model of PVR was successfully induced by means of intravitreal injection of RPE cells (from 1x10⁵ to 1x10⁹/eye). The present results also demonstrated that the injection of RPE-J cells into the vitreous of Wistar rats alone could not initiate a proliferative process in the eyes. All clinical and histological observations showed normal retinal architecture. RPE-J cells, injected into the vitreous cavity of rat eyes alone, may have already undergone earlier apoptosis, as it was confirmed by immunohistochemical analysis of anti-cytokeratin [2]. No or low expression of cytokines in the eye tissues could be the main reason for this result.

Although syngeneic PRP alone could induce a PVR-like condition, the model of PVR in this group was characterized by low ratio, slow advancement, and low severity. In 14 eyes, 11 eyes had no proliferative response. A grade-2, -3, and -4 PVR was observed in only one eye. However, the situation was changed when RPE-J cells were injected in combination with PRP. As shown in Fig. 2, in 14 eyes, a grade-3 PVR was observed in three eyes and a grade-4 PVR was observed in five eyes, while six eyes had no proliferative response. In this group, epiretinal membrane was usually accompanied with extensive retinal detachments and folds.

Several studies have indicated that PRP plays the dominant role in cell migration and proliferation through the growth factors released by platelets and pro-angiogenic molecules contained in plasma, such as TGF-β and PDGF [8, 9]. Our results have also demonstrated that the expression levels of TGF-β2 and PDGF-BB was significantly up-regulated in the proliferative process induced by the co-injection of RPE-J cells and PRP in the eyes of Wistar rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>TGF-β2 (pg/mL)</th>
<th>PDGF-AA (pg/mL)</th>
<th>PDGF-BB (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>280.82±14.17</td>
<td>46.85±4.28</td>
<td>78.69±18.17</td>
</tr>
<tr>
<td>3 day</td>
<td>454.43±20.65*</td>
<td>31.75±6.87*</td>
<td>70.57±7.29</td>
</tr>
<tr>
<td>7 day</td>
<td>416.52±13.26*</td>
<td>34.26±5.22*</td>
<td>96.68±10.15*</td>
</tr>
<tr>
<td>14 day</td>
<td>422.97±16.89*</td>
<td>33.96±7.37*</td>
<td>97.41±12.63*</td>
</tr>
<tr>
<td>21 day</td>
<td>794.87±26.79**</td>
<td>34.78±3.89*</td>
<td>111.66±14.32*</td>
</tr>
<tr>
<td>28 day</td>
<td>289.18±11.57</td>
<td>25.14±5.23*</td>
<td>100.69±11.54*</td>
</tr>
</tbody>
</table>

*p<0.05, significantly different compared to control. **p<0.01, significantly different compared to control.
TGF-β is considered to be the main inducer of the myofibroblastic phenotype. It up-regulates α-smooth muscle actin as well as extracellular matrix protein expression (e.g. collagen type I and fibronectin) in fibroblasts. TGF-β is also able to control cell adhesion and migration by modulating adhesion molecules on the cell surface [20]. In the eye, TGF-β2 is the main isoform of TGF-β. It has been shown to promote migration of cultured RPE cells [21], and activate RPE cells to produce PDGF that may act on fibroblasts and other mesenchyme derived cells which express PDGF receptors [11]. In PVR, vitreous TGF-β2 levels increase in proportion to disease severity [22].

PDGF plays a vital role in angiogenesis and wound healing by promoting proliferation and migration of mesenchyme derived cells such as fibroblasts, smooth muscle cells, and pericytes [11, 23]. PDGF-AA is selective more than PDGF-BB because PDGFR-β binds both PDGF-AA and -BB, while PDGFR-α binds only PDGF-BB. Theoretically, it might affect fewer cell types in a given tissue than PDGF-BB depending on the expression of α and β receptors on various cell types [23]. Andrews et al. [12] reported that PDGF makes an important contribution to the development of PVR in a rabbit model. Furthermore, there is a marked difference between the two receptors for PDGF. It is the PDGF-α receptor that is capable of driving events leading to PVR.

There are other growth factors such as hepatocyte growth factor, basic fibroblast growth factor, or interleukin-6 that are also implicated in PVR [13]. The increase of growth factors favor the recruitment of effector cells, such as RPE, glial cells, macrophages, and fibroblast, so as to promote the inflammatory reaction during the first phases of PVR. This is followed by a proliferative process. Thus, it is more likely that PRP more effectively contributed to the development of an experimental model of rat PVR than RPE-J cells but their co-injection may have synergistic effects.

In summary, our study is the first description of an albino rat model for PVR induced by heterogeneic differentiated RPE-J cells and syngeneic PRP intravitreal injection and the expression levels of TGF-β2, PDGF-AA and PDGF-BB. In this injection models, RPE cultures and PRP were utilized. This model is more relevant to the human disease, especially human PVR associated with intraocular bleeding [1]. The presence of PRP implies presence of more infiltrating leukocytes and their associated cytokines in this model. The subtle cellular and molecular mechanisms underlying this PVR-like process requires further characterization.

Future studies are needed to investigate the exact cell subtypes, the components of extracellular matrix, and the growth factors or cytokines involved in this model. Nevertheless, this new rat model of PVR could be of use in further study of the pathogenesis of PVR and possible therapies for this disease, including gene therapy targeted at growth factors-TGF-β2 and PDGF-BB.

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References


