Review Article

Comparison between Epiretinal Membrane Component in Proliferative Vitreoretinopathy and Other Fibroproliferative Diseases: A Scoping Review

PJO – Official Journal of Ophthalmological Society of Pakistan

Amanda Natalie Wijaya[1], Raihanny Andrea Zahra[2], Anggun Rama Yudantha[3]
[1-2]Faculty of Medicine University of Indonesia
[3]Vitreoretina division, Department of Ophthalmology, Dr. Cipto Mangunkusumo Hospital

ABSTRACT

The growth of proliferative vitreoretinopathy epiretinal membrane (PVR-ERM) is a major complication of rhegmatogenous retinal detachment (RRD). Despite surgery, adjunct treatment is necessary to control the aberrant wound healing response that occurs in PVR-ERM to prevent its recurrence. Existing studies on adjunct agents target pathways in the pathogenesis of PVR-ERM. We conducted a scoping review of composition of PVR-ERMs and other fibroproliferative ERMs. After literature search, 12 articles were included into the study. Outcome measured was gene expression, growth factors, extracellular matrix components, and enzymes. Among these studies, 9 compared PVR-ERM with PDR-ERM, 2 compared PVR-ERM with iERM, and 1 compared PVR-ERM with secondary ERM. Higher expression of certain genes or a higher concentration of particular factors can be observed throughout PVR, PDR, iERM, or secondary ERM.TGF-β, MALAT1 gene, and fibronectin are distinct factors that might play a bigger role on the pathogenesis of PVR compared to other fibroproliferative diseases.

Keywords: Gene expression, Fibrogenic factor, Angiogenic factor, Extracellular Matrix, Proliferative Vitreoretinopathy.

How to Cite this Article: Wijaya AN, Zahra RA, Yudantha AR. Comparison Between Epiretinal Membrane Component in Proliferative Vitreoretinopathy and Other Fibroproliferative Diseases: A Scoping Review. 2024;40(4):435-445. **Doi:10.36351/pjo.v40i4.1886**

Correspondence: Amanda Natalie Wijaya
University of Indonesia-Cipto Mangunkusumo Hospital
Email: amandanatwijaya@gmail.com

Received: July 04, 2024
Accepted: September 01, 2024

INTRODUCTION

The growth of PVR-ERM is a major complication of RRD, occurring in 5-10% cases and 95% of these appear within 45 days after retinal detachment.[1] It is caused by abnormal retinal wound healing which is characterised by formation of fibrous ERM.[2] This scar-like fibrous tissue can cause contractions on retina, thereby increasing the risk of retinal re-detachment after surgery. In fact, PVR-ERM was found to be the major cause of retinal re-detachment, which occurred in 50-75% cases. If left untreated, PVR-ERM can impair visual function significantly and even cause permanent visual loss.[3]

At present, the gold standard treatment of PVR-ERM is surgery. The anatomic success and functional success rates are variable. Not only is surgery often unsuccessful, the recurrence of PVR-ERM is also high. Adjunct treatments to supplement surgery in treating PVR-ERM is needed to prevent the formation of new or the progression of existing PVR-ERM lesions. These adjunctive agents are produced on the basis of PVR-ERM pathogenesis. They may specifically or non-specifically target growth factors, proteins, genes, or inflammatory cytokines that are known to play a role in PVR-ERM formation. The

effectiveness of these adjunct agents remains inconclusive.[1] Further investigation of PVR-ERM pathogenesis is crucial to identify the biological factors involved in order to achieve optimal strategies in PVR-ERM management.

With the advancement of technology, investigation of molecular factors associated with PVR-ERM has become more and more popular. Several tests can be conducted to identify the composition of PVR-ERMs. This includes, but are not limited to, immunohistochemistry, Real Time - Polymerase Chain Reaction (RT-PCR), and Fluorescence in Situ Hybridization (FISH).[2] Besides PVR-ERM, other epiretinal fibroproliferative membranes, such as from proliferative diabetic retinopathy ERMs (PDR-ERM) and idiopathic ERM (iERM) have also been analysed in order to understand the differences and similarities between them. Compared to other fibroproliferative membranes, PVR-ERM is better known to cause more tractional retinal detachment.[2]

The purpose of this study is to analyse previous studies that have compared the composition of PVR-ERM and other fibroproliferative membranes in order to determine the potential biological components such as genes, growth factors, extracellular matrix, and enzymes, that are responsible for the more aggressive nature of PVR-ERMs. The identification of both similarities and differences can help provide new therapeutic strategies that can be used to inhibit the progression of PVR-ERMs.

METHODS

The literature search was conducted in August 2023 using several electronic databases such as PubMed, Cochrane, Scopus, and Embase. Boolean (AND and OR) operators were used to perform search with specific keywords including “Proliferative vitreoretinopathy” OR "Proliferative diabetic retinopathy" AND “Epiretinal membrane” AND “Gene expression” OR “Growth factors” OR “Angiogenic factors” OR “Fibrogenic factors” OR “Extracellular matrix”. The articles collected were imported into Rayyan, an artificial intelligence powered tool designed for systematic literature reviews. There are a total of 49 articles obtained from PubMed, 102 articles from Cochrane, 48 articles from Scopus, and 67 articles from Embase. Duplicates were removed by the software, resulting in 248 articles. These articles were further screened based on their titles and abstracts. The inclusion criteria were; studies with ERMs, specifically PVR-ERMs compared to other types of fibroproliferative diseases. Our main focus was to evaluate gene expression, growth factor, angiogenic, or fibrotic factors of the ERMs as outcomes. Articles with non-availability of full-text format, articles in languages other than English, and studies that included patients with coexisting eye diseases unrelated to ERMs within the study population were excluded. Finally, 12 articles were included in the review. The selection process of articles followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) diagram (Figure 1).

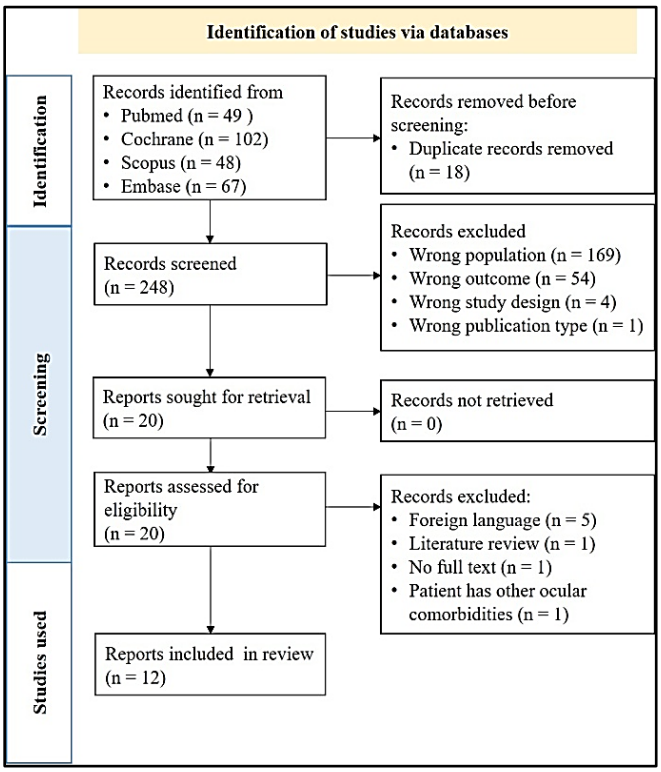

Figure 1: Search Strategy Flowchart.

All of the selected studies were considered as “cross-sectional study”, therefore the Newcastle-Ottawa scale adapted for Cross-Sectional Studies was used to assess the risk of bias (Table 1).

RESULTS

All the included articles were qualitatively analysed. We summarised the chosen articles based on the following characteristics: author (year), test method,

Table 1: *Risk of Bias Assessment with Newcastle-Ottawa Scale adapted for Cross-sectional Studies.*

Study	Selection				Comparability	Outcome		Total (max. 10 Points)
	Representativeness of the Sample	Sample size	Non-respondents	Ascertainment of the Exposure		Assessment of Outcome	Statistical Test	
El-Asar (2007)	*	*	*	*	**	**	*	9
Harada (2004)	*	*	*	*	*	**	*	8
Loachim (2005)	*	*	*	*	*	**	*	8
Salzmann (2000)	*	*	*	*	*	**	*	9
El-Asrar (2011)	*	*	*	*	*	**	*	8
Korhonen (2021)	*	*	*	*	*	**	*	9
Hollborn (2004)	*	*	*	*	**	**	*	9
Hueber (1997)	*	*	*	*	**	**		8
Nicoletti (2002)	*	*	*	*	**	**	*	9
Nam (2009)	*	*	*	*	*	**	*	9
Roldán-Pallarés (2005)	*	*	*	*	**	**	*	9
Asato (2013)	*	*	*	*	*	**	*	8

Interpretation:

- Very Good Studies: 9-10 points
- Good Studies: 7-8 points
- Satisfactory Studies: 5-6 points
- Unsatisfactory Studies: 0 to 4 points

Table 2: *Results.*

Author	Test method	Component	Groups		p-value	Additional notes
El-Asrar (2007)			**PVR-ERM n= 5**	**PDR-ERM n= 14**		
	Immunohistochemistry	CTGF	100%	100%	N/A	
		α-SMA	100%	100%	N/A	Fibrotic marker
		CD105	0%	100%	N/A	Expressed in vascular endothelial cells
		CD34	0%	100%	N/A	Angiogenic marker
		MMP-9	60%	42.85%	N/A	
Harada (2004)			**PVR-ERM n= 10**	**iERM n= 17**		
	RT-PCR	NF-κB p50	100%	53%	0.0119	
		GFRα1	40%	80%	0.0393	
		GFRα2	60%	12%	0.0248	
		Ret mRNA	30%	35%	>0.999*	
		NF-κB p50 & GFRα2 Co-expression	60%	6%	N/A	

			PVR-ERM n= 10	**PDR-ERM n= 10**		
	Immunohistochemistry	NF-κB p50	100%	80%	N/A	NF-κB protein is also co-expressed with glial cell markers, vimentin, glutamine synthase, and GFAP, as well as IL-8, an angiogenic factor
Ioachim (2005)	**Immunohistochemistry**		PVR-ERM n= 14	PDR-ERM n= 14		
		TN	None (0%) Weak (7.1%) Moderate (50%) Strong (42.9%)	None (0%) Weak (21.4%) Moderate (35.7%) Strong (42.9%)	>0.05*	
		FN	None (0%) Weak (0%) Moderate (36.4%) Strong (63.6%)	None (0%) Weak (50%) Moderate (33.3%) Strong (16.7%)	0.0035	
		CIV	None (0%) Weak (25%) Moderate (37.5%) Strong (37.5%)	None (0%) Weak (22.2%) Moderate (66.7%) Strong (11.1%)	0.0031	
		LN	None (7.1%) Weak (57.1%) Moderate (21.4%) Strong (14.3%)	None (11.1%) Weak (66.7%) Moderate (11.1%) Strong (11.1%)	>0.05*	
		MMP-3	None (29%) Weak (19%)	None (38%) Weak (14%)	>0.05*	
Salzmann (2000)			**PVR-ERM n= 21**	**PDR-ERM n= 24**		
		MMP-1	86%	66%	>0.05*	Present in normal retina
	Immunohistochemistry	MMP-2	81%	66%	>0.05*	Absent in normal retina
		MMP-3	52%	62%	>0.05*	Absent in normal retina
		MMP-9	48%	66%	>0.05*	Absent in normal retina
		TIMP-1	43%	71%	0.06*	Absent in normal retina
		TIMP-2	33%	62%	0.036	Present in normal retina
		TIMP-3	75%	66%	>0.05*	Absent in normal retina
El Asrar (2011)			**PVR-ERM n= 21**	**PDR-ERM n= 22**		
		HMGB1	95.1%	95.5%	N/A	

	Immunohistochemistry	RAGE	85.7%	91%	N/A	
		OPN	100%	91%	N/A	
		Egr-1	94.1%	72.7%	N/A	
Korhonen (2021)			**PVR-ERM n= 2**	**PDR-ERM n= 11**		
	mRNA sequencing	DEGs in Epithelial-to-mesenchymal transition (EMT)	Upregulated genes: BMP7 FGFR2 SOX9 SFRP1 NOG IRMDA BAMBI	Upregulated genes: ZNF703 HEY1 COL1A1 DACTC S100A4 NOTCH1 TGFBR2 CTNNB1 SNAI2 ERG HEYL ACVRL1 LEF1 HEY2 HGF LIMS1 ENG EOMES TGFB3	FDR < 0.05 and absolute log2-fold change > 1	
Hollborn (2004)			**PVR-ERM n= 3**	**PDR-ERM n= 3**		
		HGF	100%	100%	N/A	Activation of the c-Met receptor by HGF caused increased cell migration with maximum and VEGF release by Müller cells
	Immunohistochemistry	c-Met	100%	100%	N/A	
		GFAP	100%	100%	N/A	Glial cell marker
Hueber (1996)			**PVR-ERM n= 8**	**PDR-ERM n= 12**		
	Immunohistochemistry	bFGF mRNA	75%	57,14%	N/A	
		bFGF peptide	100%	80%	N/A	
		FGFR-1	100%	40%	N/A	
Nicoletti (2003)			**PVR-ERM n= 10**	**PDR-ERM n= 37**		
	ELISA	VEGF	3.53 ng/mg	5.21 ng/mg	<0.05	

Nam (2009)			**PVR-ERM n= 10**	**PDR-ERM n= 37**		
	ELISA	VEGF	1.2 ± 3.0 pg/µg	9.2 ± 8.0 pg/µg	0.026	
		PEDF	7.5 ± 1.5 ng/µg	3.5 ± 1.5 ng/µg protein	0.002	
		PDGF	3.3 ± 4.9 ng/µg	3.9 ± 5.6 ng/µg	0.852*	
		TGF-β1	<0.15	<0.15	1.00*	
Roldán-Pallarés (2005)			**PVR-ERM n= 4**	**iERM n= 4**		
	Immunohistochemistry	ET-1	100%	100%	N/A	Protein analysis of vitreous humor, the amount of ET-1 was significantly higher ($p<0.003$) in PVR-ERM eyes compared to iERM or retinal detachment without PVR-ERM eyes.
		Cell population	Macrophages, glial cells, fibroblastic cells, RPE cells	Macrophages, glial cells, fibroblastic cells	N/A	
		ET-1 & GFAP (glial cell marker) coexpression	100%	100%	N/A	
		ET-1 & cytokeratin (RPE cell marker) co-expression	100%	0%	N/A	
	PCR	β-actin	100%	100%	N/A	
		ETA mRNA	100%	100%	N/A	
		ETB mRNA	100%	100%	N/A	
Asato (2013)			**PVR-ERM n= 3**	**Secondary ERM post cataract surgery n= 2**		
	Expressed sequence tag analysis	Top functional subsets of genes respectively in the order of most abundant	Metabolism, proliferation, cytoskeleton, cell adhesion, signalling	Metabolism, signalling, ribosome, proliferation, transport	N/A	
		Most abundant gene	MALAT1 FN1	ZNF713 FOXK1	N/A	
		Differentially expressed genes (DEGs)	MALAT1 FN1 PARP8	ZNF13	<B-H cutoff	

groups and, components tested, results, p-value, and additional notes (Table 2). We were able to obtain 12 studies.[2,4–14]Four studies showed moderate overall risk of bias, mostly due to lack of explanation regarding ethical approval and limitation of study.

From 12 studies, 9 cross-sectional studies compared the differences between gene expression, ECM composition, and enzyme activity in PVR-ERM and PDR-ERM. It was found that PVR and PDR ERMs shared several similarities, which were; the expression of α-SMA and CTGF in myofibroblast,[4] gene transcription factor NF-κB in combination with GDNF receptors and IL-8,[5] and expression of ECM components such as TN, FN, MMP-1, -2, -3, and -9, TIMP-1, -2, and -3.[6,7] One study also demonstrated that PVR and PDR shared a common pathway which was the HMGB1/RAGE/OPN/EGR-1 pathway in ERM formation.[8]

Another study that did gene profiling comparing PDR and PVR membranes found that out of 26.621 genes, 1.447 were differentially expressed genes (DEGs FDR <0.05 and absolute $\log_2$-fold change > 1). According to the gene ontology enrichment analysis (GOEA) of the top principal compartment 1 (PC1) genes, presence/absence of vasculature-related biological processes (BP) differentiated the two membranes.[9] Other studies confirmed these differences, the expression of angiogenic factors such as CD34 and CD105, were expressed more in PDR-ERM than PVR-ERM.[4]

In the PDR membrane, several pathways were represented, one of them includes HGF/cMet. Hollborn et al,[10] found that both membranes expressed HGF and C-Met, its receptor, which was shown to increase cell migration and VEGF release by Müller cells. In another study by Korhonen et al,[9] co-expression of the two was found positive only in anti-VEGF treated PDR membranes, while in PVR membranes HGF was downregulated.

During the fibrotic process, myofibroblasts, which are the major contributors of fibrosis, undergo a transition called epithelial to mesenchymal transition (EMT). It was found that there were 26 DEGs responsible for EMT in both membranes. Some of them are BAMBI, BMP4, NOG, SFRP1, SOX9, FGFR2, and BMP7 that were found upregulated in PVR and downregulated in PDR. The TGF-β signalling pathway was also highly expressed in both membranes.[9]

Meanwhile in the ECM components, DEGs include 13 basement membrane genes 16 collagen genes, 19 ECM regulator genes, 12 proteoglycan genes, 23 ECM affiliated genes, and 30 secreted factor genes.[9] In another study, although both ERMs expressed FN, it was found that there was a statistically significant stronger expression (p=0.0035) in PVR compared to PDR, while CIV was found predominantly in PDR (p = 0.0031). Besides FN, there was also a difference in the expression of TN which was positively correlated with Ki-67, a proliferative index.[6]

Study by Hueber et al,[11] suggests that bFGF mRNA, bFGF peptide, and FGFR-1 are produced locally in the epiretinal membranes of PVR and PDR, but with higher immunoreactivity in PVR. Unfortunately, this study did not mention the statistical significance regarding the difference between PVR and PDR growth factor expression. The presence of both bFGF and its corresponding receptor suggests that they may contribute to the regulation of proliferative processes at the interface between the vitreous and the retina through autocrine and paracrine mechanisms.

Another study by Nicoletti et al,[12]reported that there was a statistically significant difference levels of VEGF in the proliferating ERMs between PDR (mean value 5.21 ng/mg proteins) and retinal detachment patients which half of them has a severe form of PVR (mean value 3.53 ng/mg proteins). The notable distinction observed between PDR and the other group provides strong evidence for the essential involvement of VEGF in the neovascularization and proliferation of the diabetic retina. The extent of growth factor production may correspond to the size of the ischemic area, influencing treatment decisions suggesting that photocoagulation may be effective in eliminating focal ischemic areas.

The research carried out by Nam[13] in 2009 adds more evidence to the idea that VEGF is produced in greater amounts in PDR (9.2 ± 8.0 pg/μg protein) than in PVR (1.2 ± 3.0 pg/μg protein; p = 0.026). On the other hand, the concentrations of PEDF in ERM were higher in PVR (7.5 ± 1.5 ng/μg protein) compared to PDR (3.5 ± 1.5 ng/μg protein; p = 0.002). The VEGF-to-PEDF ratio was higher in PDR (2.80 ± 1.83) compared to PVR (0.17 ± 0.09; p = 0.019). However, there were no differences in the concentrations of PDGF and TGF-β1 between PDR and PVR patients.

From 12 studies, 2 cross-sectional studies compared the differences between gene expression of transcription factors, proteins and receptors in PVR-ERM and iERM. Gene expression, especially in transcription factor NF-κB and GDNF receptors, were significantly different between both membranes.[5] Co-expression of ET-1 and GFAP, a glial cell marker, were identified in both membranes, however only PVR-ERMs also positively stained for cytokeratin, a Retinal Pigment Epithelium (RPE) cell marker. It was also found that the amount of ET-1 was significantly higher in PVR eyes compared to iERM eyes ($p < 0.003$). The similarities shared between them were expression of β-actin, ETA and ETB mRNA.[14]

There was only 1 study out of 12 studies that compared PVR-ERM and secondary ERM post cataract surgery. The study analysed the gene expression using expressed sequence tag (EST) analysis on the two membrane samples. Whilst they shared 52 genes, among them, 23 genes were expressed higher in PVR-ERMs and 29 genes were expressed higher in secondary ERMs. Most of the genes that were matched with the human cDNA database showed that PVR-ERMs had genes most abundantly functioning for metabolism, proliferation, cytoskeleton, cell adhesion, and signalling, respectively, while secondary ERM had genes most abundantly functioning for metabolism, signalling, ribosome, proliferation and transport, respectively. With that said, PVR-ERMs are considered to be more aggressive, while secondary ERMs are more resting, expressing more housekeeping genes. It was also found that MALAT1 and FN1 were the most abundant in PVR-ERM.[2]

DISCUSSION

Despite numerous efforts to identify the factors involved in PVR, the exact pathogenesis of the disease still remains uncertain due to its complex nature.[1] The comparison of gene expression profiles between PVR and other fibroproliferative diseases may be useful for the identification of crucial genes involved in PVR formation.

Although both PVR and PDR undergo fibrosis, the driving forces behind the inflammatory process are different. The formation of PDR membranes is likely to be driven by the presence of neovascularization, which is not the case in PVR. Angiogenic factors, such as VEGF, are more highly expressed in PDR membranes than in PVR. The presence of VEGF in PDR membranes is essential for both neovascularization and proliferation.[12,13] This VEGF ligand – dependent angiogenic pathway is one of the multiple angiogenic pathways that are involved. There are other pathways that are VEGF – ligand independent, some examples are HGF/cMet and HMGB1/RAGE/OPN/Egr-1 pathway.[9,10] It is suggested that these pathways are responsible for some patients being unresponsive to treatment with anti-VEGF or photocoagulation. This is why combination therapies are highly recommended.[9]

In PVR, despite being an avascular membrane, and therefore is lacking of neovascularization, gene profiling results also reported an upregulation of VEGFA gene.[9] VEGF is thought to play a role in the pathogenesis of PVR through the activation of PDGFRα. Activation of the receptor is associated with the decline of p53, a tetrameric transcription factor that functions to trigger cell arrest. Decline of p53 is associated with the induction of PVR.[13] Pennock et al,[15]tested this theory with an anti-VEGF, ranibizumab, to an experimental PVR rabbit model. Intravitreal anti-VEGF injection was shown to protect the rabbits from developing PVR. PDGFRα can be activated by PDGFs and non PDGFs, such as VEGF. It was found that neutralisation of PDGFs was not found to be as effective as neutralisation of non PDGFs, such as VEGF, in preventing PVR. From this study, it can be said that despite being an angiogenic factor in other diseases, VEGF works differently in PVR. Understanding the role of VEGF in PVR might be a potential target for future therapies to come.

The key to PVR formation is said to be due to exposure of RPE cells to the profibrotic cytokines and growth factors such as bFGF, TGF-β, and PDGF, in the vitreous during RRD which in turn activates the EMT process.[1,3] There are several differences in EMT regulatory gene found between PVR and PDR. The genes that were upregulated in PVR, such as BAMBI, BMP4, BMP7, SFRP1, SOX9, GFGR2, and FGFR2, was downregulated in PDR. Most of these genes play a role in eye development by promoting cell proliferation, differentiation, and migration. BMP4 and BMP7 belong to the TGF-β superfamily which is a group of multifunctional proteins that control cell proliferation, differentiation and many other functions. BAMBI gene is also found to encode transmembrane glycoprotein related to the type 1 receptors of the TGF-β family.[13]

TGF-β signalling pathway was highly expressed in both PVR and PDR membranes. Nam et al,[13] detected TGF-β1 in both PVR and PDR membranes. Although it did not show any significant statistical difference, TGF-β1 is known to be the key driver of EMT in fibrosis.[16] In fact, it is one of the most upregulated genes found in PDR-ERM. In PDR, it also served as a modulator for neovascularization.[13] The effect of TGF-β in fibrosis is very variable depending on its environment. That aside, targeting TGF-β has been shown to reduce the formation of PVR. Mirza et al,[17] used a human monoclonal TGF-β antibody that targets both TGF-β1 and TGF-β2 on experimental PVR rabbit models. It was shown to reduce the clinical stage of PVR in a dose and time-dependent manner. Many other studies also have shown promising results in the use of TGF-β lowering agents, such as intravitreal injection of corticosteroids, decorin, resveratrol, etc. in preventing EMT of RPE cells, which will hopefully prevent PVR formation.[16]

One of TGF-β's downstream mediator is CTGF, which is predicted to be a key determinant in progressive tissue scarring.[4] It is secreted by RPE cells and is known to play an important role in wound repair, angiogenesis, tumour growth, etc. In PVR, CTGF mediates EMT through activation of the PI3K/AKT pathway. Besides EMT, it also plays a role in ECM components secretion such as collagen type III, fibronectin, and α-SMA.[18] Daftarian et al,[19] presented the use of intravitreal anti-CTGF injection in a PVR rabbit model. It was shown to decrease membrane thickness, collagen fibres, and myofibroblast density in the PVR model. It can be suggested that targeting CTGF signalling may have a therapeutic effect on PVR.

Asato et al,[2] found MALAT1, a long noncoding RNA (IncRNA), to be the most expressed gene in the PVR-ERM compared to iERM. It is associated with metastasis and regulated cell motility. As it turns out, MALAT1 also plays an important role in regulating EMT of RPE cells induced by TGF-β1. Yang et al,[20] observed that MALAT1 expression significantly increased in RPE cells that were incubated with TGF-β1. Silencing the gene attenuates TGF-β1-induced EMT, migration, and proliferation of RPE cells. This discovery reveals the important role that MALAT1 gene plays in RPE cells when induced by TGF-β1, providing new insight to understanding the pathogenesis of PVR.

Besides RPE cells, glial cells are also responsible for the formation of ERMs. During the inflammatory process, glial cells are able to secrete growth factors, ECM components, as well as undergo transition into myofibroblasts. Harada et al,[5] suggested that the fibroglial component of PVR and PDR was due to activation of GFRα2 by GDNF, which induces NF-κB activation, a protein complex that controls DNA transcription, and finally initiate PVR membrane formation through activation of other fibrogenic and angiogenic factors, one example is IL-8. GDNF is structurally related and a distant member of TGF-β superfamily, which means it has the ability to regulate its own gene expression and other growth factors. In Müller glial cells, GDNF is seen to increase production of bFGF and its self, GDNF. Interestingly, in iERM, GFRα1 was more dominant than GFRα2, it is predicted that a different route and different condition of trophic factors may activate different GFR receptor subtypes.[21]

Another significant component of ERMs is the ECM. The outer layer of ERMs, the ECM, is made up of abundant structural proteins that are secreted by surrounding cells. ECM functions to provide scaffold for the tissue and afford tensile strength. It is constantly being renewed and remodelled. Some examples of these proteins are laminin, fibronectin, tenascin, glycoproteins, and collagen. The producers of ECM in ERMs include glial cells, RPE cells, fibroblasts, and myofibroblasts. Myofibroblasts produce α-SMA that gives an ERM its contractile nature. When these ECM producers are exposed to upstream mediators such as TGF-β, CTGF, FGF, and PDGF, deposition of ECM increases, contributing to the size of the ERM.[1,3,16] Another way ERM can increase in size is through ECM remodelling, which proteolytic enzymes such as matrix metalloproteinases (MMPs) are responsible for. During the remodelling of ECMs, MMPs degrade the proteins which leads to previously dormant growth factors being released and activated. This surge of newly released growth factors then causes another cascade of ECM deposition.[16] In PVR and PDR, MMP-2, 3, and 9 are expressed differently from normal retina, indicating a certain role they play in ERM formation.[14]

Composition of ECM differs from each type of ERM. According to Asato et al, the top 10 ECM or cell adhesion genes in PVR-ERMs are FN1, COL1A1, COL1A2, COL3A1, POSTN, THBS1, LGALS1, SPARC, TIMP3, and DCN.[2] It was discovered that FN1, a fibronectin precursor, is the most expressed

gene in PVR.[2] Ioachim et al,[6] also found FN to be one of the ECM components that significantly differentiated PVR-ERM from PDR-ERM. Cellular FN is a glycoprotein that can stimulate migration of fibroblast toward the wound. The fibroblasts will then secrete more FN that make up the ECM. It is found to be a significant component in the early stages of membranes. Luthra-Guptasarma et al,[22] created an antibody that targets FN specifically and tested it on cultured RPE cells and a collagen gel fibrotic tissue model. The antibody was shown to inhibit features of fibrosis such as proliferation, migration, adhesion, MMP expression, fibronectin polymerization, and reduced collagen gel contraction. Sharma et al,[23] also demonstrated a similar result using antibody to a cryptic epitope on the n-terminal 30kDa fragment of FN on RPE cells and a fibrotic collagen gel model. These data suggest that antibodies towards FN can serve as a novel-antifibrotic candidate.

Limitations to our study is that patient demographics and the clinical stage of PVR-ERM was not included in the eligibility criteria. Limited studies were available and even more scarce studies that included information regarding patient characteristics and PVR staging when acquiring samples. PVR is mainly caused by an excessive inflammatory response. At different stages of wound healing, the factors involved may vary depending on stage. Different patient characteristics, such as age, might also affect wound healing abilities. Hence, composition of PVR may vary depending on the situation. Future studies are recommended to include PVR staging and patient characteristics as another factor to consider.

CONCLUSION

There are several factors that differentiate PVR-ERM and other fibroproliferative diseases, especially PDR and iERM. Differences can be found in gene expression, fibrotic factors, angiogenic factors, and extracellular matrix composition expressed on the ERMs. Although oftentimes they share several similar characteristics, the process or driving forces of the disease might not be the same. PVR is an avascular disease that relies more on fibroglial proliferation, while PDR-ERMs are fibrovascular membranes and involve neovascularization. PVR-ERMs compared to iERM are more aggressive in nature which is why a more aggressive approach to PVR, such as combination therapies, might be recommended in the future. From our study, it is worth noting that several factors have a bigger role on the pathogenesis of PVR. Among them are TGF-β, MALAT1 gene, and fibronectin. Our findings on these differences will hopefully open new avenues for future therapies to prevent PVR progression.

Funding: This study was not funded by any organization.

Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

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Authors Designation and Contribution

Amanda Natalie Wijaya; Medical Doctor: *Concepts, Design, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Raihanny Andrea Zahra; Medical Doctor: *Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation.*

Anggun Rama Yudantha; Medical Doctor: *Concepts, Design, Manuscript review.*