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The roles of signaling pathways in epithelial-to-mesenchymal transition of PVR

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Proliferative vitreoretinopathy (PVR) is the major cause of failure in patients undergoing surgery for rhegmatogenous retinal detachment (RRD). Characterized by the formation of an abnormal contractile membrane within the eye, PVR can cause tractional retinal redetachment. Epithelial-to-mesenchymal transition (EMT), in which epithelial cells morphologically and phenotypically transdifferentiate into mesenchymal cells, is the major pathological process implicated in PVR. Among the various cell types involved in the process, retinal pigment epithelium cells are primary contributors although, after decades of research, the mechanisms underlying EMT have remained elusive. Recently, signaling pathways, some involving growth factors, have been demonstrated to contribute to EMT. In this article, we review research to date about the roles of such signaling, including including transforming growth factor-beta-, hepatocyte growth factor-, platelet-derived growth factor-, and Notch-, Wnt/β-catenin-, and Hippo-signaling pathways, in the EMT of PVR.

Proliferative vitreoretinopathy (PVR) is an ocular disease characterized by the formation of a dense fibrotic contractile membrane composed of extracellular matrix (ECM) and various cell types in the vitreous cavity and on the epiretinal surface of the retina [1]. PVR occurs mainly in patients after surgery for rhegmatogenous retinal detachment (RRD) and is one of the most common causes of surgical failure, causing tractional retinal redetachment. The incidence of this serious visual complication has remained unchanged, at approximately 5–10%, despite recent advancements in surgery [2,3]. In addition to undergoing surgery, retinal detachment that is untreated for a period of weeks to months, retinal trauma, and a long history of intraocular inflammation are additional risk factors for PVR. As the membrane formation progresses, PVR is categorized into four stages. Grade A is identified by the vitreous haze and/or pigment clumps in the vitreous cavity or on the inferior retina. Grades B to D are identified by retinal morphology, with Grade D further divided into three subclasses [4]. Previously, there were no proposed approaches for preventing the occurrence of PVR, until a growing body of evidence indicated an important role for the epithelial-to-mesenchymal transition (EMT).

EMT is an orchestrated series of events that can occur, for example, during normal embryonic development. In EMT, epithelial cells lose their characteristic epithelial morphology and phenotype and acquire a mesenchymal-like morphology and phenotype [1]. The transdifferentiation is characterized morphologically, for example, by decreased intercellular adhesion and increased cell migration and invasion. Phenotypic changes include decreased expression of epithelial markers such as zonula occludens-1 (ZO-1) and E-cadherin and increased expression of mesenchymal markers such as α-smooth muscle actin (α-SMA), vimentin, and fibronectin [5]. The essential polypeptide ZO-1 is found in tight junction (TJ) complexes and E-cadherin in another type of cell-cell adhesion, adherens junction (AJ). TJ and AJ structures are important in normal epithelial cell structure and function [5-7]. Of the mesenchymal markers, α-SMA is an intracellular cytoskeletal contractile protein involved in cell motility. Vimentin, another intracellular cytoskeletal protein, plays a pivotal role in stabilizing cell structure during migration [5]. Fibronectin, also a marker for fibrosis, is required for microfibril deposition.

EMT mediates the normal physiologic processes of embryogenesis, organ development, and wound healing. However, EMT is also implicated in such pathologic processes as fibrosis, cancer metastasis, and PVR. It has been suggested that various cell types including retinal pigment epithelium (RPE) cells, fibroblast cells, glial cells, and macrophages are components of PVR membranes. RPE cells, a monolayer of tightly connected pigmented cells, are the most important PVR constituents [8]. Normally, RPE cells remain quiescent, maintaining their characteristic morphology and function. The outer blood–retinal barrier (BRB) normally prevents fluid from choroidal vessels from entering the retina. During a pathological condition known as retinal break, the BRB breaks down, and RPE cells become exposed to the vitreous

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that contains various growth factors and cytokines. RPE cells that are activated by the growth factors and cytokines then undergo EMT, and the resulting dedifferentiated RPE cells migrate, proliferate, and transform into (myo)fibroblasts, leading to PVR [7,8]. This suggests that preventing RPE cells from differentiating into (myo)fibroblasts is likely to be an important therapeutic approach to preventing PVR. However, the mechanism of PVR, including the role of EMT signaling pathways, has been obscure. Therefore, we focus on these signaling pathways in this review.

TGF-β signaling: RPE cells secrete various growth factors and cytokines including transforming growth factor-beta (TGF-β), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), connective tissue growth factor (CTGF), and others. This secretory capacity enables RPE cells to regulate their own growth and that of other surrounding cell types. In recent years, these growth factors have also been implicated as being influential in the development of the PVR membrane [4,8].

TGF-β is overexpressed in the vitreous humor, subretinal fluid, and proliferative membranes in patients with PVR [9,10] and is known to play a crucial role as a potent fibrotic factor. TGF-β signaling involves the canonical Smad signaling pathway and non-canonical pathways. These two types of pathways can interact with each other and contribute to EMT. In the Smad signaling pathway, TGF-β binds to its receptors, types I and II. The type I receptor can directly phosphorylate Smad2 and Smad3. The Smad proteins then associate with Smad4 and translocate to the nucleus where they exert their function. Non-canonical pathways include those of mitogen-activated kinase (MAPK), extracellular signal-regulated kinase 1/2(ERK1/2), and phosphatidyl inositol 3-kinase (PI3-K)/AKt (also named PKB, protein kinase B)/mTOR (mammalian target of rapamycin) [11,12]. The MAPK non-canonical signaling pathway involves three components—p38 MAP kinase, c-Jun N-terminal kinase (JNK), and p42/44 ERK; each exerts its own biologic function.

TGF-β has three isoforms: TGF-β1, TGF-β2, and TGF-β3. The major isoform is TGF-β2. TGF-β2 concentrations are higher than those of the other isoforms, and there is a strong correlation between TGF-β2 concentration and contractility [13-15]. In a model system that induces EMT in a human retinal pigment epithelial (ARPE-19) cell line with TGF-β2, there was decreased expression of epithelial markers such as E-cadherin and ZO-1 and upregulation of mesenchymal markers such as α-SMA and fibronectin [16,17]. Additional data suggested that TGF-β2 activates other growth factors that contribute to PVR [5,13]. TGF-β1, which was first described as regulating EMT in various epithelial cells [18], may also contribute to EMT, though the TGF-β1 concentration is low and induces a less effective EMT compared with that induced by TGF-β2.

Recently, various proposed approaches for inhibiting EMT of PVR have targeted the TGF-β signaling pathway. TricostatinA (TSA), a class I and II inhibitor of histone-deacetylases (HDACs), is one example [19-21]. HDAC inhibitors have been investigated in various therapeutic indications including inflammation and cancer [22,23] and have antifibrogenic effects in several cell lines. TSA suppresses TGF-β-induced EMT through not only the canonical TGF-β/Smad pathway but also the non-canonical pathways [11]. In addition, p38 MAP kinase, which phosphorylates the middle linker of Smads, also participates in the Smad signaling pathway [24]. Inhibitors of p38 MAP kinase are demonstrated to block TGF-β-induced EMT [9,25]. Taken together, approaches to blocking TGF-β signaling could, therefore, inhibit the process of EMT.

HGF signaling: HGF, a pleiotropic growth factor, contributes to the maintenance of retinal homeostasis and normal retinal function [26]. In a serum starvation model, a pathologic condition involving activation of HGF and its receptor c-Met, EMT was induced. This discovery implicated the HGF-signaling pathway as a potential contributor to EMT [27]. However, paradoxically, there were no HGF differences when interleukin and growth factor levels in RRD with or without PVR were compared [28]. Furthermore, some have hypothesized that HGF suppresses the transdifferentiation of RPE [3,29]. Taken together, these findings show that questions remain about the true function of HGF and the HGF/c-Met signaling pathway in PVR. It is possible that stage specificity of growth factor expression is a factor. The observation that HGF is expressed at the highest levels during the middle stage of PVR, probably by unidentified cell types other than RPE and glial cells, could bring a new perspective to the problem [4].

PDGF signaling: The PDGF family is composed of five ligands, PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD. These growth factors can each dimerize PDGF receptor (PDGFR) subunits into homodimers or heterodimers (PDGFRα, PDGFRβ, or PDGFRαβ). Many studies have shown an association between PDGF and PVR and reported the activated PDGFRs in membranes of human PVR [30,31]. Though PDGFs are the most abundant of all growth factors and cytokines measured in the vitreous, to date, neutralizing PDGF failed to prevent experimental PVR [3,32,33]. Recent data show that PDGFRα, which can be activated by a much larger spectrum of vitreal growth factors than can the other

receptor subtypes, is required in experimental PVR and inhibition of PDGFRα activation prevents the development of PVR [30,33,34]. The vitreal growth factors are suggested to be non-PDGFs capable of activating PDGFRα indirectly, thus driving PVR [3,33]. Regarding the nature of this indirect activation, evidence indicates that the non-PDGFs activate PDGFRα via an intracellular mechanism involving reactive oxygen species (ROS) and a Src family kinase (SFK) [3,35]. These findings suggest that inhibitors of PDGFRα and related pathways would be attractive as a potential target to prevent development of PVR.

Jagged/Notch signaling: The Jagged/Notch signaling pathway participates in many physiologic and pathologic processes including embryonic development, cancer metastasis, and fibrotic diseases [14,16]. In recent years, this pathway has also been implicated in the EMT that occurs in RPE cells. Although this association is not yet certain, accumulating evidence indicates that components of the Jagged/Notch signaling pathway, including Jagged-1, Notch-3, and downstream target genes *Hes-1* and *Hey-1*, are upregulated in RPE cells during TGF-β2-activated EMT [11,14]. Studies modulating the Notch pathway, including through knockdown or overexpression of Jagged-1, showed that the EMT induced by TGF-β2 was closely linked to Jagged/Notch activation [14]. These data indicate that, in addition to the canonical Smad and non-Smad pathways, the Jagged/Notch signaling pathway may also mediate TGF-β2-activated EMT. To further elucidate the pathological mechanism, there is increasing evidence that crosstalk between Smad and Jagged/Notch signaling pathways contributes to TGF-β2-activated EMT [14,16].

Wnt/β-catenin signaling: The Wnt signaling pathway, which is pivotal in cell motility and differentiation, mediates various diseases including PVR. Wnt exerts its function in a paracrine fashion. The canonical Wnt-signaling pathway proceeds as a cascade reaction, initiated when Wnt protein ligands bind to Frizzled and low density lipoprotein receptor-related protein (LRP) receptors on the cell surface. This induces activation of the cytoplasmic phosphoprotein Dishevelled (Dvl) and inhibits the GSK-3/APC/Axin-degradation complex. Dvl activation transduces signals to downstream components, leading to β-catenin accumulation in the cytoplasm and its subsequent translocation to the nucleus. β-Catenin in the nucleus interacts with transcription factor T-cell factor (TCF) and/or lymphoid enhancer factor (LEF), promoting expression of specific genes. Therefore, β-catenin translocation is regarded as being a key molecular event leading to EMT [36].

The Wnt/β-catenin signaling pathway has been primarily studied because of its effects on cadherins, transmembrane glycoproteins that modulate tissue movement [37]. β-Catenin binds to the cytoplasmic domain of cadherins [38-40]. When cadherin binding is disrupted, the release and nuclear translocation of β-catenin results in signaling activation. In this regard, inhibitors of β-catenin signaling may be a promising approach to prevent PVR [38,39].

Hippo signaling: The Hippo-signaling pathway influences cell growth and proliferation as well as contact inhibition. Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are key downstream effectors of the Hippo pathway. TAZ, also referred as WW-domain containing transcriptional regulator 1 (WWTR1), was first reported as a 14–3-3 binding protein [41,42]. TAZ is regarded as a paralog of YAP, and the two share some overlapping functions. However, compared with YAP, TAZ interacts with more DNA-binding transcription factors, including polyomavirus T antigens, TTF-1, TBX5, and Pax3 because of the structural and characteristic differences between the two proteins. TAZ, therefore, can participate in a wide range of biologic processes such as cell proliferation and migration. TAZ can also contribute to human cancers, including breast, ovarian, colorectal, lung, and brain tumors [43]. In recent studies, overexpression of YAP/TAZ-induced EMT during metastatic progression of tumor cells. These reports discussed potential roles of growth factors such as CTGF and the EGFR ligand and speculated on further mechanisms yet to be unraveled [43,44]. Thus far, there has not been any research specifically addressing the role of Hippo signaling in PVR.

Conclusion: PVR, which is characterized by the formation of a fibrotic contractile membrane, still remains a significant post-surgical complication for patients with RRD. It is clear that research toward understanding the complex pathogenic mechanism of PVR is still in its infancy and faces many challenges. However, work in recent decades has led to achievements in understanding several key signaling pathways. These include those pathways activated by TGF-β-, HGF-, and PDGF- as well as Notch-, Wnt/β-catenin-, and Hippo-signaling pathways. Though each has its respective functions, these signaling pathways can also interact with one other, potentially contributing to the pathogenesis of PVR [16]. Among these, the TGF-β-signaling pathway, especially that of TGF-β2, has drawn the most attention in PVR. Inhibiting these signaling pathways would be a potential therapeutic strategy for blocking EMT, thus preventing PVR. However, because growth factors are multifunctional cytokines and their inhibition might cause considerable side effects, individual signaling pathways should be targeted with cautiousness. Clearly, increased understanding of these

complex pathways remains a priority for future prevention and treatment of PVR.

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