


REVIEW

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Regulation of epithelial-mesenchymal transition in retinal pigment epithelium and its associated cellular signaling cascades: an updated review

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Abstract

Background The epithelial-mesenchymal transition (EMT) affects the retinal pigment epithelium's natural homeostasis. According to observations from around the world, numerous ophthalmopathies, including proliferative vitreoretinopathy (PVR), diabetic retinopathy (DR), and other macular degenerative illnesses such as age-related macular degeneration (AMD), have been linked to the epithelial-mesenchymal transition of retinal pigment epithelium (EMT of RPE). Retinopathy is referred to as an impairment in the retina, where AMD is characterized as an alteration in the macula region, DR as an impairment in the microvascular system, and PVR as an alteration in the subretinal bands, fibrovascular membranes, and fibrotic alteration in the detached retina. To find molecular targets and therapeutic drugs to protect and restore RPE function, a connection between EMT-related signaling pathways and RPE degeneration must be established.

Main body of abstract Studies conducted in vivo and in vitro indicate that several signaling pathways, including the Rho pathway, the transforming growth factor- β (TGF β) pathway, the Jagged/Notch pathway, mitogen-activated protein kinase (MAPK)-dependent pathway, and Wnt/ β -catenin pathway, are activated in RPE cells during PVR and AMD. In order to discover the most suitable candidate for retinopathy therapies, it is necessary to determine the relationship between the regulators of the EMT and the degeneration of the RPE. To treat retinopathies, particularly those that are brought on by the EMT of retinal pigment epithelial cells, it is necessary to investigate prospective pharmaceutical candidates.

Conclusion TGF β 's intracellular cascade, which comprises both canonical (SMAD-associated) and non-canonical (SMAD-nonassociated) pathways, is shown to be the most active signaling pathway in the degeneration of the RPE caused by EMT.

Keywords Proliferative vitreoretinopathy, Retinal pigment epithelium, Diabetic retinopathy, Age-related macular degeneration, Epithelial-mesenchymal transition

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1 Background

Cell signaling is being researched as a unique approach for better comprehending molecular processes, establishing intercellular signal network profiles, and finding biomarkers and therapeutic targets associated with cellular functions [1]. It is yet unknown exactly how these transcription factors contribute on a molecular level to the epithelial-mesenchymal transition of the retinal pigment epithelium (EMT of RPE) [2]. Growth factors and other biological agents cause RPE cells to lose their cell polarity and cell-to-cell contact, which triggers EMT through a variety of signaling pathways that encourage cell division, migration, and the synthesis of extracellular matrix (ECM). The ECM is a complex network made up of a number of multidomain macromolecules that are structured in a network and cell/tissue-specific configurations [3]. RPE cells begin to exhibit mesenchymal cell characteristics such as the ability to migrate and proliferate as they become less differentiated. This review focuses on current developments in the field of molecular understanding at the level of cell signaling and presents current thoughts on various approaches by focusing on retinal pigment epithelium-related retinopathies such as proliferative vitreoretinopathy (PVR) and age-related macular degeneration (AMD). The macula, the small region of the central retina that is important for high-acuity vision, breaks down in AMD [4]. One of the problems that poses a major threat to the health of diabetic patients is DR, a microvascular impairment that can result in loss of visual acuity [5, 6]. Proliferative vitreoretinopathy (PVR) is defined by subretinal bands, fibrovascular membranes, and fibrotic alterations in the detached retina [7].

2 Main text

2.1 The role of EMT in retinal pigment epithelium

The Bruch's membrane and photoreceptors are both supported by the retinal pigment epithelium, which plays an essential role in maintaining visual acuity. RPE is terminally differentiated, highly polarised, and located between photoreceptors and choroids [8]. The RPE controls the flow of molecules between the fenestrated choroid capillaries and the photoreceptor layer of the retina to create the outer blood-retinal barrier (BRB). BRB works in many different ways, such as membrane pumps, transporters, channels, passive but selective diffusion, transcytosis, metabolic alteration of solutes in transit, and metabolic modification of solutes after they have left the cell. A monolayered cuboidal epithelium is held together by adherens junctions and tight junctions, which regulate epithelial diffusion via spaces between neighboring cells [9, 10, 11, 12].

EMT is the process through which healthy epithelial cells modify into mesenchymal cells [13]. At four to six

weeks of gestation, the human RPE cell undergoes terminal differentiation and thereafter remains mitotically inactive [2]. Additionally, it is a well-studied fact that EMT is highly involved in embryonic organization and re-organization. Furthermore, the EMT can be divided into three types [14] (Fig. 1). There are three basic types of EMT, depending on where the process starts and how it ends. EMTs are divided into three types: type I, which is linked to embryogenesis, type II, which is linked to pathology, and type III, which is linked to carcinogenesis [14, 15]. The study employed many markers to distinguish between epithelial and mesenchymal cells despite the fact that EMT is a dynamic process [16].

The zona-occludens-1 (ZO-1), epithelial cadherin (E-cadherin), and cytokeratin are epithelial markers. N-cadherin, fibronectin, and vimentin are mesenchymal markers [17]. EMT in RPE is considered a fundamental underlying mechanism for severe diseases as it is observed in retinopathies such as AMD and PVR [17, 18]. Additionally, the *in vitro*, *in vivo*, and clinical data suggest that RPE cells undergo EMT [19, 20, 21, 17]. EMT of the RPE is caused by a combination of mechanisms including oxidative stress, pathological inflammation, aging, infections, tight junction loss, ECM breakdown, altered growth factor synthesis, misfolded protein accumulation, and infections [22].

2.2 Cellular signaling of EMT specifically in retinal pigment epithelium

The transformation of epithelial cells into mesenchymal cells, which results in the emergence of new biochemical instructions, requires cellular reprogramming and highly complicated cellular rearrangement [23]. Extracellular signals alter the gene expression of proteins associated with epithelial and mesenchymal tissues during the EMT process in the retinal pigment epithelium. They also regulate a variety of related cellular behaviors, including cell proliferation, migration, and death. This results in the development of PVR and AMD through a network of interconnected signaling pathways [2]. Tight junctions also play a part in the regulation of signaling pathways that control cellular functions including migration, proliferation, and differentiation [2]. Current understanding suggests that the phosphoinositide-3-kinase/Protein kinase B (PI3K/Akt) pathway, TGF β , Wnt, and Notch are only a few of the regulatory signaling pathways that are associated with the EMT of the RPE, as well as significant interactions between them [24] (Fig. 2).

2.3 Rho signaling pathway

Ras homolog family member A (RhoA/Rho)-kinase is associated with ocular fibrosis. The control of cellular actomyosin cytoskeletal architecture and motility is

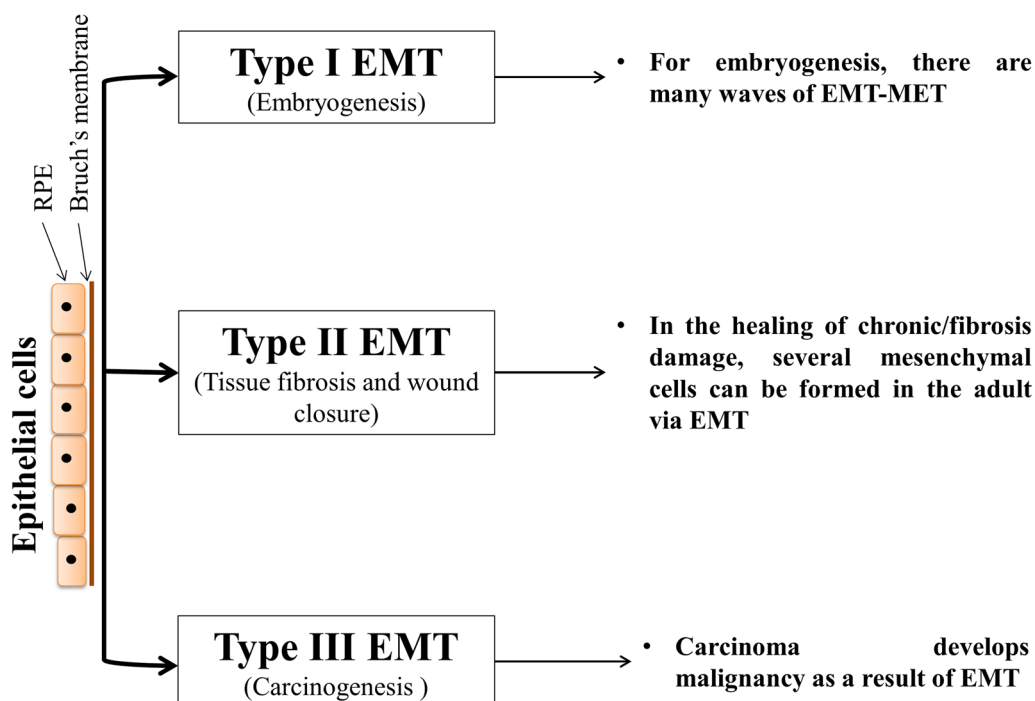


Fig. 1 Different categories of process of EMT. Based on the place of origin and end of the process, EMT may be classified into three fundamental categories. Type I: EMT (embryogenesis), Type II: pathological EMT, and Type III: cancer-related EMT. Diagrams developed with Microsoft PowerPoint

greatly influenced by two of RhoA's main downstream effectors, the Ras-related C3 botulinum toxin substrate 1 (Rac1) and Rho-associated, coiled-coil-containing kinases, Rho-associated kinase (ROCK) [25]. The Rho pathway has been found to control the assembly and structure of the actin cytoskeleton, as well as associated gene expression. It may be critical for RPE cell fibrotic response [26]. LIM domain kinase (LIMK), an actin-binding protein, phosphorylates cofilin, hence stabilizing actin filaments [3]. Activated RhoA or its downstream effector ROCK increases LIM-kinase activity, which then phosphorylates cofilin in TGFβ1-treated ARPE-19 cells. This phosphorylation reduces cofilin function, which promotes actin polymerization and cytoskeleton remodeling, ultimately leading to fibrosis [26].

TGFβ-induced RhoA activation stimulates cell motility and increases alpha-smooth muscle actin (α-SMA) expression in primary RPE cells [27]. The RhoA/Rho-kinase pathway has been demonstrated to mediate the synthesis of type I collagen by TGFβ2 in human RPE cells [19, 25]. In an in vivo PVR animal model, matrix stiffness enhanced ARPE-19 cell activation via the RhoA/(YAP) pathway, as well as retinal fibrogenesis [28]. Yes-associated protein 1 (YAP1) is a transcription coregulator that increases the expression of genes that regulate cell differentiation and proliferation [3]. Furthermore, thrombin stimulates ROCK and Rho, leading to phosphorylation

of the myosin light chain and the production of actin stress fibers in retinal pigment epithelial cells undergoing EMT [29]. Furthermore, recent research suggests that inhibiting RhoA upstream with C3 exoenzyme or inhibiting YAP downstream with verteporfin significantly reduced MMP production and collagen gel contraction in ARPE-19 cells. Blocking RhoA/YAP signaling inhibited the TGFβ/Smad pathway in vivo and reduced PVR-induced retinal fibrogenesis. This paper provides novel PVR treatment approaches that target the RhoA/YAP pathway [28]. Nicotinamide suppresses EMT in the RPE and increases RPE cell differentiation by downregulating ROCK and casein kinase 1 (CK1) [30]. The ROCK inhibitor Y27632 and the RhoA inhibitor simvastatin both decrease TGFβ2-induced type I collagen synthesis in ARPE-19 cells, demonstrating the existence of a connection between the Rho and SMAD pathways [11].

2.4 Signaling cascade Mitogen-activated protein kinase (MAPK)

MAPK is divided into three subfamilies: extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 mitogen-activated protein kinases (p38s). ERKs are activated by growth factors, whereas JNKs and p38 are activated by cellular stresses or inflammatory cytokines. These signaling pathways regulate several biological processes in the fibrotic process of

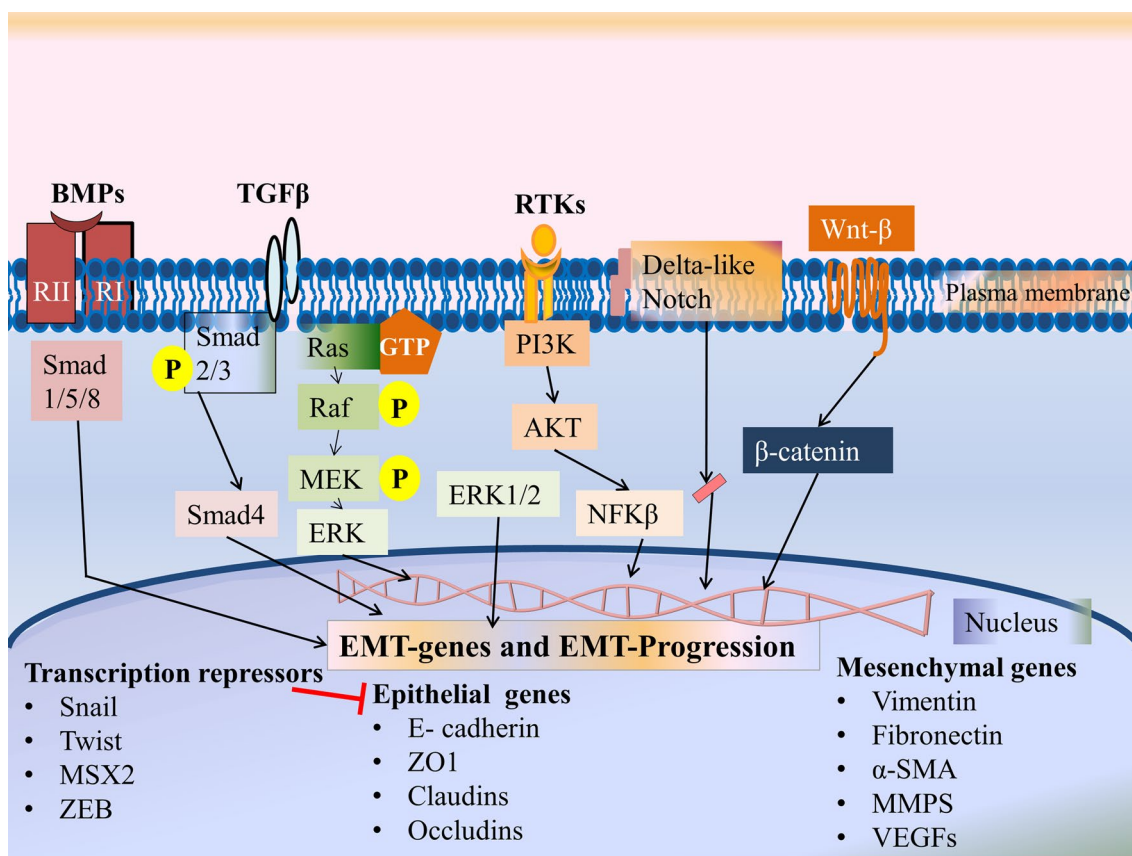


Fig. 2 Signaling cascades involved in EMT process. Many signaling pathways have been implicated in the retinal pigment EMT, either of canonical or non-canonical TGFβ signaling pathways are involved in the EMT of retinal pigment epithelium. Many additional signaling pathways, such as BMP signaling, RTK signaling, Wnt signaling, and jagged-Notch signaling, are implicated in the EMT process in retinal pigment epithelium. Furthermore, the interplay between these pathways is well documented. Diagrams developed with Microsoft PowerPoint

the eye [30]. The MAPKs cascade, which is regulated by a number of activators, is thought to be involved in the development of the epithelial-to-mesenchymal transition process. The Ras-MAPK pathway activates SNAIL1 and SNAIL2. The early growth response factor-1 (Egr-1) accelerates the transition from epithelial to mesenchymal [31]. TGFβ-induced EMT and fibrosis were mediated by ERK activation in ARPE-19 cells [32]. A recent study of induced pluripotent stem cell (hiPSC)-derived RPE cells found that inhibiting TGFβ and fibroblast growth factor (FGF/MAPK) pathways improved differentiation of RPE[33]. Furthermore, previous in vitro and in vivo studies indicate that the SNAIL is expressed at both the transcription and post-transcription levels in many complex signaling pathways such as integrin-linked kinase (ILK), phosphatidylinositol 3-kinase (PI3-K), MAPKs, glycogen synthase kinase 3-b (GSK-3b), and nuclear factor kappa B (NF-κB) [34].

Shukal and coworkers demonstrated using an in vitro study that, the anti-epithelial to mesenchymal transition in cells of RPE by a pyruvate analog, the dichloroacetate

(DCA) via (MAPK/Erk) and PI3K/Akt pathway [35]. Inhibiting keratin 8 (KRT8) phosphorylation suppresses oxidative stress-mediated epithelial to mesenchymal transition in RPE cells while avoiding potential cell death, indicating that autophagy-mediated KRT8 overexpression combined with MAPK1/3 pathway inhibition could be a potential AMD intervention strategy [18]. Saika and colleagues established the therapeutic efficacy of p38MAPK inhibitor (SB202190) in ARPE-19 cells, with reduced TGFβ2-mediated migration and extracellular matrix production via MAPK signaling [36].

2.5 Notch signaling cascade

It is believed that Notch signaling pathway may be significant in the onset and genesis of many illnesses because the Notch signaling cascade modulates the ratio of cell death to proliferation [37]. The transcriptional regulator retinol-binding proteins (RBP) is necessary for the conventional Notch cascade in the RPE. RBP-J performs a transcriptional factor role in Notch signaling [38, 39]. Throughout the development of the eye, the Notch

signaling system plays a role in the regulation of cell fate, differentiation, and patterning [39]. Notch signaling has also been connected to the control of cell proliferation, specification, and differentiation during the retinogenesis and formation of the mammalian ocular lens [39, 40].

In the study of the TGF β 2-induced EMT process in retinal pigment epithelium, it is discovered that the TGF β -dependent Smad signaling cascade initiates the Jagged/Notch pathway. Further, the blocked Notch pathway inhibited the EMT process effectively [41]. Zhang and coworkers reported that the notch inhibitor (LY411575) blocked the Notch signaling in the PVR model of ARPE-19 cells [42]. One study by Niessen and coworkers targets SNAIL2 as part of Notch signaling and it has been observed that during hypoxia conditions SNAIL1 is directly induced by Notch signaling [43]. The overexpression of Jagged-1 and Notch-3 was observed in the TGF β 2-induced EMT of RPE [44]. The Jagged-1 knockout suppressed TGF β 2-mediated EMT process in RPE via downregulation of SNAIL, SLUG, and zinc finger E-box binding homeobox 1 (ZEB1) [44]. The collagen-1 (COL1A1 and COL1A2) expression was found regulated by TGF β 2 treatment in cells (ARPE-19), as they are related to Notch/Jagged and MAPK signaling pathway [45]. Another research demonstrates the connection between the Notch/Jagged and MAPK signaling pathways in the EMT process in the RPE caused by the concomitant administration of TGF β 1 and tumor necrosis factor-alpha (TNF-alpha) [45].

2.6 Wnt- β -catenin and Hippo-YAP signaling pathway

An essential component of the Wnt-beta-catenin pathway, beta-catenin is activated by dissociating from its complex and translocating into the nucleus, where it further activates the genes SNAIL and other EMT-related genes [16]. The Wnt signaling mechanism is crucial for cancer, aging, and post-natal stem cell regeneration in addition to regulating tissue differentiation during embryogenesis [46]. Beta-catenin binds to the cytoplasmic domain of cadherins, illustrating a point at which the Wnt pathway and the cadherin adhesion mechanism converge [46, 47]. Important for the EMT, the phosphorylation statuses of beta-catenin, a key Wnt mediator, and GSK-3, which is positioned upstream of beta-catenin, are altered. By changing the expression or active status of its transcriptional regulators Snail and Smads, the Wnt/beta-catenin pathway, as well as the pathways started by FGF and TGF β , govern the EMT process in RPE. The junction of many pathways is where GSK-3 is found [46, 48].

The Wnt-beta-catenin pathway is activated by laser-mediated coagulation, and this furthers the EMT process in RPE outcomes, according to an earlier investigation

by Han and colleagues [49]. The overexpression of beta-catenin was prevented in one in vitro experiment using ARPE-19 cells by the XAV939 (Wnt-beta downregulator). The increased expression of EMT markers is caused by the overexpression of beta-catenin [50]. The stimulation of EMT by the Wnt-beta-catenin signaling pathway was also demonstrated by further excessive light exposure on the retina [51]. Pentraxin 3 (HC-HA/PTX3) is a potent, non-toxic inhibitor that, in a dose-dependent manner, inhibits Wnt signaling to suppress the EMT process in RPE [52]. So, as already established, laser photocoagulation triggers a Wnt/beta-catenin signal transduction pathway, which in turn encourages the proliferation and conversion of the epithelial cells of the retinal pigment epithelium into mesenchymal cells. It may be favorable for the regeneration of the RPE to therapeutically regulate Wnt/beta-catenin signaling.

Contact inhibition and EMT, which govern organ size, are regulated by the Hippo signaling system [50]. The Hippo signaling cascade controls the transcription factors YAP and TAZ, which link the EMT process to cell proliferation [53, 54]. Hippo-YAP was shown to be associated with cadherin and the phosphorylation of Src family members [56]. The in vitro investigation demonstrated the role of EMT in RPE suppression by reducing tight junction disintegration [17]. The Hippo-YAP pathway, whose activity is mostly dependent on tight and adherens junctions, maintains RPE differentiation [16]. The Yap, on the other hand, was not found in the primary cells (RPE) of mice [17]. More research is needed to completely understand the facts surrounding the Hippo-YAP pathway, which is linked to the EMT process in the RPE.

2.7 Transforming growth factor-beta (TGF β) signaling pathway

TGF β and its intracellular cascade are particularly important in the EMT process in RPE [2]. TGF β is a crucial cytokine as an anti-inflammatory compound. Its production is associated with wound injury and inflammation [16]. TGF β showed a role in both normal physiological as well as abnormal pathological conditions [17]. The presence of TGF β 1, TGF β 2, and TGF β 3 are reported in the human eye [55]. In general, the concentration of TGF β cytokine is increased as an inflammatory response but if this condition remains for a prolonged period then it leads to EMT [56]. The drastic increased TGF β 2 favors a significant loss of cell-cell attachment in RPE [57]. The expression of TGF β , epidermal growth factor (EGF), insulin-like growth factor (IGF-II), or FGF-2 initiates the process of digesting the basement membrane by binding with epithelial receptors and starts kinase activities [58]. Among these factors, the most interesting cytokine is the EGF and its receptor, epidermal growth factor (EGFR).

Many research efforts have established its significance in the induction, maintenance, and control of cell proliferation, differentiation, and migration [59]. Further, it should be noted that TGF β is a known inducer of EMT, and that EGFR has been observed to rise in EMT-affected cellular microenvironment where EGF-assisted cell plasticity occurs [60].

In previous studies, it has been found that the galactose-binding lectin family protein (Galactin-1) is cross-talk with TGF β signaling, in a knockout mouse it shows decreased choroidal neovascularization (CNV) severity and suppression of EMT process in RPE [61] (Table 1). Some other studies also represent the crosstalk between Smad-dependent signaling and ERK1/2 molecular interaction in RPE [41]. Troglitazone and pioglitazone, peroxisome proliferator-activated receptor-gamma (PPAR- γ) suppresses phosphorylation of Smad and thus inhibit TGF β 2-mediated EMT process in RPE [62, 63]. Inhibition of sub-retinal fibrosis is shown by the retinoic acid receptor gamma (RAR- γ) agonist through the TGF β pathway [64].

Additionally, there are many agents such as bradykinin (BK) [65], fucoidan [13], bone morphogenic protein (BMP7) [66], BMP4 [67], LY-364947 (TGF β RI- inhibitor) [68], Baicalein [69], LYTAK1 (TAK1 inhibitors) [70], salinomycin [71], protein kinase-A inhibitor (H89) [72], and resveratrol [73] showed suppression of EMT process in RPE either in vivo or in vitro investigations. Recent studies on induced pluripotent stem cell (hiPSC)-derived retinal cells discovered that suppressing the protein kinase C or BMP signaling pathways, as well as reducing FGF/MAPK signaling, improved RPE differentiation [33]. Additionally, in the Smad3-mutated mouse PVR model, TGF β signaling triggered the downregulation of the EMT process [74].

Some other therapeutic agents are involved in the inhibition of the EMT process in RPE but by interacting with multiple signaling such as curcumin suppressing the Akt, MAPK, and TGF β pathways in RPE cells (Table 1). The mammalian target of rapamycin (mTOR) suppressor (Trichostatin A) hindered the EMT process in RPE by down-regulating the Jagged/Notch pathway,

Table 1 List of regulators of EMT process in RPE targeting via different signaling cascades

EMT-regulating agent	Involved signaling pathway	Effects on EMT process in RPE	References
Nicotinamide (NAM)	Rho-ROCK signaling	↓ EMT	[78, 79]
SB202190 (p38MAPK chemical inhibitor)	MAPK signaling	↓ EMT	[36]
Y27632 (ROCK inhibitor) and Simvastatin (RhoA inhibitor)	Rho signaling SMAD signaling	↓ EMT	[11]
BMP7	BMP7/ SMAD2/5/9 signaling TGF β 2/SMAD2/3 signaling	↓ EMT	[66]
LYTAK1 (TAK1 inhibitors)	ERK/AKT signaling	↓ EMT	[70]
Troglitazone and pioglitazone (PPAR- γ agonist)	TGF β signaling	↓ EMT	[62, 63]
Trichostatin A	Jagged/Notch signaling Smad signaling MAPK/ERK1/2 signaling	↓ EMT	[75]
BMP4	TGF β signaling		[67]
Curcumin	AKT signaling MAPK signaling TGF β signaling	↓ EMT	[80]
Sodium iodate (NAI)	–	Oxidative stress-mediated → EMT	[81]
Glucosamine (Glc-N)	TGF β signaling	↓ EMT	[82]
Fucoidan	TGF β signaling	↓ EMT	[13]
Erlotinib (EGFR inhibitors)	TGF β signaling	↓ EMT	[83]
Baicalein (inhibitors of 12/15 lipoxygenase)	TGF β signaling	↓ EMT	[69]
Bradykinin (BK)	TGF β signaling	↓ EMT	[65]
Proteasome inhibitor (MG132)	TGF β signaling	↓ EMT	[84]
Salinomycin (SNC)	TGF β signaling	↓ EMT	[71]
Resveratrol	TGF β signaling	↓ EMT	[85]
Protein kinase-A inhibitor (H89)	TGF β signaling	↓ EMT	[72]
Heavy chain-hyaluronan/pentraxin3	Wnt signaling and TGF β signaling	↓ EMT	[52]

↓ = Suppression or Downregulation

non-canonical TGF/Akt, MAPK, and ERK1/2, as well as the standard Smad signaling pathways [75]. It has been demonstrated that several intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications can diminish retinal fibrosis in patients with active neovascular AMD (n-AMD) [19, 76, 77]. Choroidal neovascularization, which results in exudation, leakage, and finally fibrosis with photoreceptor loss, can be used to characterize n-AMD [3]. In recent safety phase II research, subretinal fibrosis in n-AMD patients receiving the combination of platelet-derived growth factor [Fovista®(E10030)] and an anti-VEGF drug was investigated. Additionally, a controlled phase II trial in n-AMD is now being conducted to examine the impact of either the FGF2 antagonist RBM-007 alone or in conjunction with the anti-VEGF drug on subretinal fibrosis [19].

3 Conclusions

Age-related macular degeneration and proliferative vitreoretinopathy activate several signaling cascades in RPE cells, including the SMAD, the Rho, the MAPK, the Jagged/Notch, and the Wnt/-catenin pathways, according to studies done in vitro and in vivo. The most active signaling cascade in the process of the retinal pigment epithelium's epithelial to mesenchymal conversion is discovered to be TGF β , namely its intracellular cascade and both SMAD and non-SMAD pathways. There are no medications on the market right now that aim to treat the EMT of the retinal pigment epithelium. Retinopathies, in particular those caused by the epithelial to the mesenchymal conversion of retinal pigment epithelium cells, may only be treated with antimetabolite pharmaceuticals, however, these drugs have severe, occasionally blinding side effects.

A link between the molecular targets and the regulators of the EMT of RPE must be established in order to choose the best candidate for retinopathy therapy. To treat retinopathies, especially those brought on by the epithelial-mesenchymal transition of retinal pigment epithelium cells, it is critical to investigate to explore potential pharmaceutical treatments.

Abbreviations

AMD	Age-Related Macular Degeneration
BK	Bradykinin
BMP-7	Bone Morphogenic Protein 7
CK1	Casein Kinase 1
CNV	Choroidal Neovascularization
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
EGFR	Epidermal growth factor (EGF) and its receptor
EMT	Epithelial-mesenchymal transition
Erks	Extracellular Signal-Regulated Kinases
Glc-N	Glucosamine
GSK-3	Glycogen synthase kinase 3
hiPSC	Human Induced Pluripotent Stem Cell

ILK	Integrin-Linked Kinase
JNKs	C-Jun N-Terminal Kinases
KRT8	Keratin 8
MAPKs	Mitogen-activated protein kinases
mTOR	Mammalian Target of Rapamycin
n-AMD	Neovascular-Age-Related Macular Degeneration
PPAR- γ	Peroxisome proliferator-activated receptor-gamma
PVR	Proliferative Vitreoretinopathy
RAR- γ	Retinoic Acid Receptor Gamma
ROCK	Rho-Associated Protein Kinase
RPE	Retinal pigment epithelium
Shh	Sonic hedgehog
TGF β	Transforming growth factor- β
VEGF	Vascular endothelial growth factor
YAP	Yes-Associated Protein

Acknowledgements

Not applicable.

Author contributions

BG and PM took part in the acquisition, analysis and interpretation, manuscript preparation and reviewing. PR, BP, KT, PC and KJ commented on previous version of manuscript. All authors have read and approved the final manuscript.

Funding

No funding was obtained for this study.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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Received: 3 November 2022 Accepted: 19 October 2023

Published online: 26 October 2023

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