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Epithelial and endothelial mesenchymal transition and their role in diabetic kidney disease

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ABSTRACT

Diabetic nephropathy (DN) is the main cause of end-stage renal disease. On the other hand, there are a couple of evidences, including human studies, which prove the role of epithelial mesenchymal transition (EMT) in pathophysiology of DN. EMT is characterized by loss of epithelial proteins and gain of mesenchymal markers. EMT is induced via three main conduit; TGFβ/Smad, integrin /ILK as well as Wnt/β-catenin pathways. Besides, numerous studies illustrated how drugs and agents can modify this phenomenon. On the other hand, endothelial mesenchymal transition (EndoMT) has a well-known role in pathophysiology of diabetic nephropathy which has been studied in animal and human. Here, several drugs and modifiers which have been studied to figure out if they can amend nature of EMT or EndoMT are reported briefly.

Mini-Review

Implication for health policy/practice/research/medical education:
Diabetes and its complications including diabetic nephropathy are spreading worldwide. On the other hand, pathophysiology of diabetic kidney disease and its modifiers have been studied broadly. This mini-review presents a couple of them, allocated to EMT and Endomt, briefly and to the point.
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Introduction

Diabetic kidney disease (DKD) is a major complication of diabetes and is the single largest cause of end-stage kidney failure (1). During the clinically silent stage, structural lesions include glomerular basement membrane thickening build up and extreme deposition of extracellular matrix (ECM) in the glomerulus and interstitial area. It, finally, leads to glomerulosclerosis and tubulointerstitial fibrosis as well (2,3). Pathophysiology of diabetic nephropathy (DN) has intensively been studied. Two of them i.e. epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndoMT) are discussed here. Furthermore, a couple of drugs and agents which modify these phenomena are listed.

Materials and Methods

For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following keywords and or their equivalents; epithelial mesenchymal transition, diabetic nephropathy, TGFβ/Smad, integrin /ILK, Wnt/β-catenin, diabetic kidney disease and endothelial mesenchymal transition. Manuscripts published in English as full-text articles and or as abstracts were included in the study.

Epithelial-mesenchymal transition

Epithelial cells are connected exteriorly to basement membrane and interiorly cover the lumen of tubules.

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Sideways, they interrelate with adjacent epithelial cells (4). Epithelial-mesenchymal transition (EMT) comprises loss of intercellular connections, their detachment from a basement membrane, loss of epithelial phenotype markers and attain mesenchymal markers and cell progression (5). The transition is characterized by loss of epithelial proteins such as cytokeratin, and E-cadherin and take mesenchymal markers including α-smooth muscle actin (α-SMA) and vimentin (6). However, the possession of EMT markers *in vivo*, is often variable, perhaps reflecting limited EMT (also termed pre-EMT) (7).

EMT might be an adaptive reaction of epithelial cells to an aggressive milieu. The chemokine slope made about tubular sections draw inflammatory cells to the tubulointerstitial space. They, in turn, generate matrix metalloproteinases (MMPs) and pro-fibrotic cytokines, accordingly (8).

MMPs, especially MMP-2 and MMP-9, secreted by macrophages and up-regulated by TGF-β1 in kidney tubular epithelial cells, have been shown to be pro-fibrotic by induction of tubular cells EMT (9).

MMP-9 decays normal basement membrane collagen and postpones degradation and endorses gathering of extracellular matrix (10). There is disordered ratio of MMP-9 and tissue inhibitor of metalloproteinase in EMT (11), including the EMT which takes place in DKD (12). Glomerular podocytes and endothelial cells also experience transition after damage. Phenotypic modification of podocytes leads to proteinuria and glomerulosclerosis (13). EMT is induced via three main conduits, three main converging signaling pathways, which they are TGFβ/Smad, integrin/ILK, and Wnt/β-catenin pathways (Figure 1).

TGFβ signaling

Tian et al explained that the cytoskeleton of proximal tubular epithelial cells undertakes notable restructuring in reaction to TGF-β (14). They lose their cobblestone morphology and become spindle shaped.

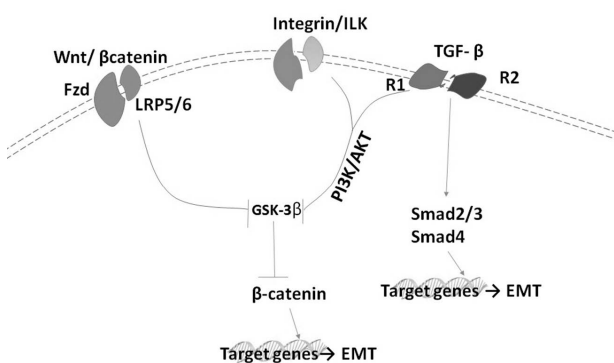This is accompanied by downregulation of expression of E-cadherin, a key constituent of adherents junctions, de novo expression of α-SMA and reformation of the actin microfibrillar which is characteristic of myofibroblasts. Smad proteins principally mediate the signals of TGF-β. Non-Smad pathways of TGF-β signaling complicated in EMT comprise RhoA, p38 mitogen-activated protein kinase (MAPK), and phosphatidyl-3-kinase(PI3K)/AKT. Rho kinase, on the other hand, can be motivated by sphingosine-1-phosphate (S1P) through its receptor, S1P2. Thus, S1P-S1P2 signaling takes part in EMT through Rho kinase activation in renal tubules (15).

Integrin/ILK signaling

Integrin linked kinase (ILK) obtains its biologic actions by two major characteristics; as a protein kinase and as a scaffolding protein (16). As a protein kinase, the catalytic activity of ILK renders it to directly phosphorylate a number of downstream kinases including GSK-3-β causes stabilization of β-catenin (17). This sequentially organizes the presentation of a cluster of genes that are fundamental for the EMT phenomenon.

Wnt/βcatenin signaling

In the lead of fastening to their receptors, Wnt proteins provoke a successive signaling, involving GSK-3-β. It, in turn, consequences in β-catenin escaping from ubiquitin-mediated degradation. As a result β-catenin accumulates in the cytoplasm and translocates into the nuclei, where it stimulates the transcription of Wnt target genes (18).

Endothelial mesenchymal transition (EndoMT)

For the first time, Karasek suggested that endothelial cells (EC) are a source of myofibroblasts in fibrotic diseases (19). During EndoMT, endothelial cells (EC) lose their molecular markers such as VE-cadherin, detach from endothelial layer and begin the expression of mesenchymal cell products (e.g. α-SMA) (20).

Molecular mechanisms of EndoMT

TGF-β-binding activates Smad-dependent and Smad-independent signaling. Consequently, inception of NOX4 emergence results in Snail1 provocation of EndoMT. Endothelin-1 wields strong collaboration with TGF-β effects on EndoMT, as well. Snail1 levels are modulated by GSK3-mediated phosphorylation.

Caveolins, on the other hand, are a family of essential membrane proteins that are involved in receptor-independent endocytosis. Caveolin-1 is most prominently expressed in endothelial, fibrous, and adipose tissue (21). It causes TGF-β receptors internalization and successive deprivation (22) (Figure 2).

Evidence of EMT in diabetic nephropathy

Stimulation of the Wnt/β-catenin signaling pathway has been verified to play a role in the pathogenesis and progression of DN, and multiple cells are considered to be involved in this process, including mesangial cells,
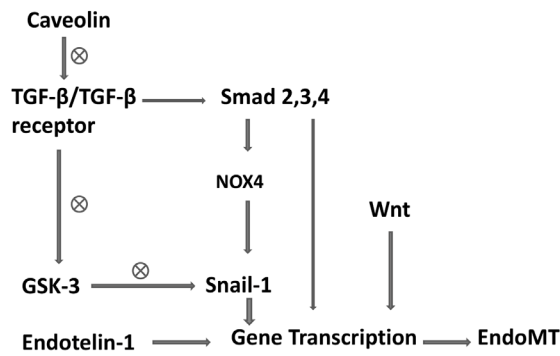

Figure 1. Three main signaling pathways which lead to expression of EMT genes

Figure 2. Molecular factors which induce EndoMT.

endothelial cells, podocytes and tubular cells (23). Zhou et al showed that levels of β-catenin and WNT proteins are upregulated in the kidney tissues of diabetic animal models. Furthermore, activated WNT signaling in cultured human renal proximal tubular epithelial cells and proteinuria induced by hyperglycemic milieu, could be ameliorated by using the antibody (24).

MicroRNAs
Micro (mi)RNAs are small noncoding endogenous RNA strands that regulate gene expression. For instance expression of miRNA192 downregulated by TGFβ correlates with fibrosis in human DN (25). On the other hand, expression of miRNA377 was upregulated in murine models of DN, which led to amplified fibronectin production (26).

Other mediators
Dai et al showed that high-glucose induces EMT and connective tissue growth factor (CTGF) overexpression in podocytes which can be attenuated by anti-CTGF antibody (27). On the other hand, cytochrome P450 (CYP) epoxygenases metabolize arachidonic acid into epoxyeicosatrienoic acids (EETs). TGF-β1inhibition induced by CYP2J2 expression distinguishes key function of this axis in pathophysiology DN (28). Furthermore, high glucose-induced phenotypic transition in podocytes is provoked by PTEN/PI3K/Akt pathway (29). High-mobility group AT-hook 2 (HMGA2) plays an important role in EMT during DKD, as well (30).

Role of EndoMT in diabetic kidney disease
Endothelial dysfunction has been postulated to take part in the pathogenesis of DN. Both afferent and efferent arterioles and glomerular endothelial cells (GEnC) all are damaged (31). Zeisberg et al presented the first evidence of possible EndoMT in diabetic kidney fibrosis (32). They showed that roughly half of fibroblasts expressed both endothelial marker and markers of fibroblasts and myofibroblasts simultaneously.
Advanced oxidation protein products (AOPP) are

uremic toxins formed during oxidative stress through the reaction of plasma proteins with chlorinated oxidants such as hypochlorous acid or chloramines. A study by Liang et al showed; AOPP treatment drops expression of vascular endothelial CD31 and cadherin and induces overexpression of α-smooth muscle actin and vimentin, additionally. They conclusively showed that AOPPs prompts EndoMT (33).

Rho-associated kinase 1 (ROCK1) is a protein serine/threonine kinase. It controls the actomyosin cytoskeleton and contributes to processes such as cell motility and EMT (34). Peng et al displayed that ROCK1 is induced by high glucose and it consequently stimulates EndoMT and causing amplified endothelial permeability. Therefore inhibition of ROCK1 might be a therapeutic approach for avoiding glomerular endothelial dysfunction in emerging DN (35).

Inhibitors of dipeptidyl peptidase 4 or gliptins are a category of oral hypoglycemic agents which can be used to treat diabetes mellitus type 2. The DPP-4 inhibitor linagliptin, as

Shi et al showed, amends endothelial levels of integrin β1. Furthermore, knock downing of DPP-4 results in the suppression of TGF-β receptor heterodimer formation, and EndoMT, as well (36).

Acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is a substrate of angiotensin-converting enzyme (ACE) and an endogenous anti-fibrotic molecule that has the potential of inhibition of the EndoMT through the restoration of FGF receptor (37).

Serum response factor is a member of transcription factors. This protein regulates the activity of many genes and takes part in cell differentiation. Increased serum response factor (SRF) activity provokes both EMT in podocytes (38) and EndoMT of GEnCs in DKD. Targeting SRF by small molecule inhibitors (e.g. CCG-1423) is suggested as an attractive therapeutic approach for DKD (39).

SMADs are transducer proteins that transmit extracellular signals from TGF-β ligands to the nucleus where they stimulate downstream gene transcription.

Obstruction of EndoMT by Smad3 inhibitor offers a new approach to delay the advancement of diabetic complications including DKD (40).

Human studies
EMT has also been recognized in biopsies of patients with DN (41) and also vimentin immunoreactivity was severely illustrated in atrophic diabetic tubules (42).

Li et al showed that ZO-1 and nephrin disappear in the glomeruli of human diabetic kidneys. On the other hand, FspI, is induced in glomerular podocytes (43).

Peng et al demonstrated that EndoMT occurs in the glomerular endothelium of patients with DKD, showing by a decrease in CD31 but an increase in α-SMA expression (35).

Protein C is an anticoagulant serine protease activated

by the blood coagulation pathway (44). Endothelial protein C receptor (EPCR) is a receptor for protein C that enhances its activation. EPCR delays DN progress. On the other hand, EPCR shedding through metalloproteinase ADAM17 contributes to the worsening of DKD (45).

Modifiers and drugs
A couple of agents and drugs have been studied to show their impact on EMT induced by hyperglycemia (Table 1).

Conclusion
Numerous studies, including experimental animal models and tissues from patients, undoubtedly, make obvious that EMT and EndoMT cooperate a significant role in the pathogenesis of DKD. Several studies evidently point out the explanation of molecular mechanisms implicated in EMT and EndoMT, making novel molecular targets and therapeutic approaches, available to DKD.

Authors' contribution
FD designed the study. VS collected the data. FK was the study supervisor, contributed to all aspect of the study and provided the final manuscript. All authors read and approved the paper.

Conflicts of interest
The authors declare no conflict of interest.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Table 1. List of some drugs or modifiers of EMT

Modifier name	Subject
Mycophenolate mofetil ± benazepril (46)	Rat
Chrysin (47)	RPTEC & mice
Zn (48)	NRK-52E cells
β-Casomorphin-7 (49)	NRK-52E cells
Curcumin (50)	NRK-52E cells
Resveratrol (51)	HK-2 cells
Benidipine (52)	Rat
Losartan + paricalcitol (53)	Mice
Tempol (54)	Rat
Troglitazone (55)	Primary renal proximal cell
Oxymatrine (56)	NRK52E
NSC697923 (inhibitor of UBE2N-Ueva1A complex) (57)	HK2 cells
miR-26a and miR-30c (58)	NRK52E
Mesenchymal stem cell (59)	Mice
Roscovitine (60)	NRK52E
Fucoidan (61)	Rat
eEOC & BMP5 (62)	C57/B16N mice

Abbreviations: RPTEC, human renal proximal tubular epithelial cell; NRK-52E cells, normal rat kidney tubular epithelial cell line; HK-2 cells, human tubular epithelial cells; eEOC, early endothelial outgrowth cells; BMP: bone morphogenetic protein.

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