Unleashing the pathological role of epithelial-to-mesenchymal transition in diabetic nephropathy: The intricate connection with multifaceted mechanism

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Abstract
Renal epithelial-to-mesenchymal transition (EMT) is a process in which epithelial cells undergo biochemical changes and transform into mesenchymal-like cells, resulting in renal abnormalities, including fibrosis. EMT can cause diabetic nephropathy through triggering kidney fibrosis, inflammation, and functional impairment. The diverse molecular pathways that drive EMT-mediated renal fibrosis are not utterly known. Targeting key signaling pathways involved in EMT may help ameliorate diabetic nephropathy and improve renal function. In such settings, understanding precisely the complicated signaling networks is critical for developing customized therapies to intervene in EMT-mediated diabetic nephropathy.

Key Words: Diabetes mellitus; Epithelial-to-mesenchymal transition; E-cadherin; N-cadherin; Renal fibrosis; Diabetic nephropathy

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INTRODUCTION

Chronic kidney disease (CKD) is a prevalent debilitating disorder in which renal function gradually declines over time [1]. Cardiovascular diseases account for most noncommunicable disease deaths, followed by cancers, respiratory diseases and diabetes mellitus[2]. Moreover, nephropathy due to diabetes mellitus is a leading cause of end-stage renal failure, and its mortality rate is increasing globally. Diabetic nephropathy is thought to be mediated by a variety of signaling pathways. Despite the availability of current treatments for diabetic nephropathy, such as antidiabetics and antihypertensives, the majority of patients continue to experience progressive kidney deterioration. This indicates that the major pathogenic process involved in the initiation and progression of diabetic nephropathy is still alive and unaffected by current medications. In this article, the recent developments on the pathological role of epithelial-to-mesenchymal transition (EMT) in diabetic nephropathy are presented.

INTRICATE CONNECTION BETWEEN EMT AND DIABETIC NEPHROPATHY

The process of EMT causes epithelial cells to lose their polarity and cell-to-cell adhesion characteristics and gain mesenchymal-like characteristics instead, such as increased invasiveness and migration potential[3]. In addition to its physiological role, this intricate process plays a pivotal role in pathological events, including tissue fibrosis[4]. Recent investigations have revealed partial EMT in the kidney, suggesting that epithelial cells undergo "partial EMT" to acquire some of the phenotypic features of fibroblasts rather than transforming to a "fully fibroblastic phenotype"[4]. EMT has been linked to the etiology of diabetic complications such as diabetic nephropathy, which is a major cause of end-stage renal illness. Diabetes-mediated EMT includes complex cellular and molecular alterations. EMT plays a crucial role in the development and progression of diabetic nephropathy, a common and devastating consequence of diabetes mellitus that can lead to end-stage renal disease[5]. EMT primarily affects renal tubular epithelial cells in diabetic nephropathy, resulting in renal fibrosis, inflammation, and, eventually, kidney function loss[6,7].

As EMT progresses, renal tubular epithelial cells lose their epithelial properties, such as cell-cell adhesion and apical-basal polarization[8]. They develop mesenchymal-like characteristics such as enhanced motility, invasive potential, and secretion of extracellular matrix (ECM) proteins such as collagen and fibronectin. These alterations promote the accumulation of myofibroblasts and ECM deposition, resulting in renal interstitial fibrosis. Hyperglycemia and metabolic abnormalities in the diabetic kidney activate signaling pathways such as transforming growth factor-beta (TGF-β) and Wnt/β-catenin, which are known to trigger EMT[7]. This process transforms renal tubular epithelial cells into myofibroblasts, which release ECM components and contribute to progressive fibrosis in diabetic kidney disease[7].

Overall, EMT contributes to the pathophysiology of diabetic complications by inducing tissue fibrosis and vascular dysfunction. Targeting EMT-related pathways could be a promising therapeutic option for preventing diabetes complications and improving patient outcomes. However, more studies are required to completely understand the molecular pathways underlying EMT in diabetes mellitus and to identify effective targeted therapies. Chronic hyperglycemia, coupled with other metabolic and hemodynamic variables associated with diabetes, sets off a chain reaction of molecular processes in the kidney. Proinflammatory cytokines such as TGF-β, and advanced glycation end products and reactive oxygen species are activated during these processes[7]. These variables could contribute to kidney damage and inflammation, paving the way for EMT. To initiate EMT in renal tubular epithelial cells, signaling pathways such as the TGF-β/Smad, Wnt/β-catenin, and Notch pathways need to be activated. TGF-β is a strong inducer of EMT and promotes fibrosis and tissue remodeling in diabetic kidney disease[7]. These pathways might activate various transcription factors, which may repress epithelial indicators such as E-cadherin while upregulating mesenchymal markers such as N-cadherin[9]. During EMT, cell-cell adhesion molecules such as E-cadherin are downregulated, whereas mesenchymal markers such as α-smooth muscle actin (α-SMA), fibroblast-specific protein 1, fibronectin, collagen, and vimentin are upregulated[7].

A recent study implicated the specific functional modulatory role of METTL3 in diabetic nephropathy[10], and silencing METTL3 was shown to prevent the proliferation, migration, EMT, and renal fibrosis of high glucose-induced human renal tubular cells (HK2 cells) by mediating WISP1 in m6A-dependent manner, suggesting that the METTL3/ WISP1 axis might be a novel therapeutic target for diabetic nephropathy[10]. In addition to EMT, endothelial-to-mesenchymal transition (EndMT) in glomerular endothelial cells too appears to play a significant role in diabetic nephropathy. EndMT, being a subset of EMT, may involve EMT regulators in common. While Fascin has been found to mediate EMT, a recent study reported that high glucose treatment increases fascin levels and activates EndMT in human glomerular endothelial cells (HGEcs), whereas silencing fascin inhibits EndMT in hyperglycemic HGEcs. Moreover, SirT7 has been observed to be reduced in hyperglycemic cells and the kidneys of diabetic nephropathic mice. Furthermore, inhibiting SirT7 raises fascin levels and facilitates EndMT, demonstrating an interrelationship between SirT7 and fascin levels[11]. Increased SirT7 expression reduces fascin expression, inhibits EndMT, and improves renal function in hyperglycemic cells and diabetic nephropathic mice[11].
Measures for maintaining epithelial integrity and preventing mesenchymal transition are being studied as potential therapeutic options for diabetic nephropathy. Understanding the role of EMT in diabetic nephropathy paves the way for possible therapeutic treatments. Targeting EMT-related pathways and renal fibrosis factors with TGF-β inhibitors, anti-inflammatory medications, and antioxidants might have the potential to prevent kidney damage and slow the progression of diabetic nephropathy. This contention is supported by the fact that imperatorin, a naturally occurring furanocoumarin derivative with proven antioxidant and anti-inflammatory potential, has been reported to ameliorate kidney injury in diabetic mice by regulating the TGF-β/Smad2/3 signaling axis, renal inflammation and EMT, highlighting that imperatorin might be a potential candidate for the management of diabetic nephropathy[12]. Likewise, Schisandrin B, derived from Schisandra chinensis and known for its antioxidant and anti-inflammatory properties, has been attributed to reduced renal tubular cells’ EMT and mitochondrial dysfunction in db/db mice. This is accompanied by the downregulation of TGF-β1[13]. In addition, Schisandrin B reduced TGF-β1, α-SMA, and fibronectin expression while increasing E-cadherin expression in glucose-stimulated HK2 cells, while Schisandrin B alleviated renal tubular cells’ EMT and mitochondrial dysfunction by upregulating Kielin/Chordin-like protein[13]. Furthermore, several bench investigations have suggested that the renin-angiotensin-aldosterone system (RAAS) may play a key role in renal EMT, fibrosis, and related renal disorders[14]. EMT appears to be a key pathogenic mechanism for the adverse renal effects of angiotensin II and aldosterone, the two major RAAS components. The renal RAAS-TGF-β-Smad3 pathway contributes significantly to EMT-related renal problems. In bench studies, RAAS antagonists, including losartan, telmisartan, eplerenone, and spironolactone, have shown promise in preventing renal EMT[14].

A recent study unprecedentedly proposed the concept of “ecological pathology”, which is meant to apply ecological principles and approaches to study the etiology, pathogenesis, pathological changes and outcomes of human diseases[15]. This means that the incidence and development of human diseases might be pathologically an ecological process. The concept of ecology mainly emphasizes the interaction between organisms and their surrounding environment, including biotic and abiotic interactions. Considering the pathological changes in the occurrence and development of diabetic nephropathy, this disease might also be associated with complex ecological processes. In this context, EMT-mediated CKD can be understood as a morphological and ecological adaptation of epithelial cells to external environmental stimuli.

**CONCLUSION**

EMT could contribute significantly to the development of diabetic nephropathy by promoting renal fibrosis, inflammation, and functional impairment. Targeting EMT pathways and associated mechanisms might hold potential for developing novel drugs to combat diabetic nephropathy and improve outcomes for patients afflicted with diabetes mellitus who are at risk of developing kidney issues. Understanding precisely the molecular pathways underlying EMT-mediated renal fibrosis in diabetic nephropathy is crucial for developing tailored therapies to minimize kidney damage and preserve renal function in diabetic patients. Therapeutic approaches that target vital signaling pathways involved in EMT might have the potential to arrest the course of diabetic nephropathy and lessen the burden of diabetes mellitus on kidney function. Finally, the signaling systems involved in EMT and diabetic nephropathy are complex and multifaceted. Understanding these signaling networks is critical for designing tailored therapeutics to intervene in EMT-mediated diabetic nephropathy and to prevent or delay kidney damage.

**FOOTNOTES**

**Author contributions:** Balakumar P collected the literature, conceptualized the study, critically analyzed the literature, wrote the first draft and finalized the manuscript.

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